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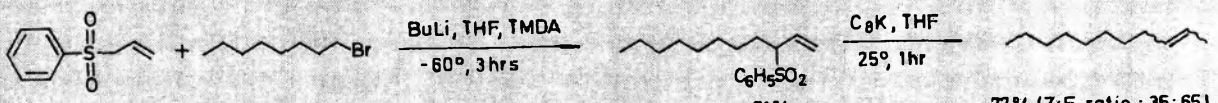

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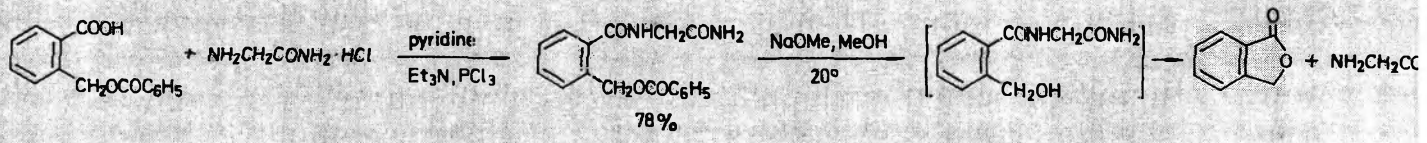

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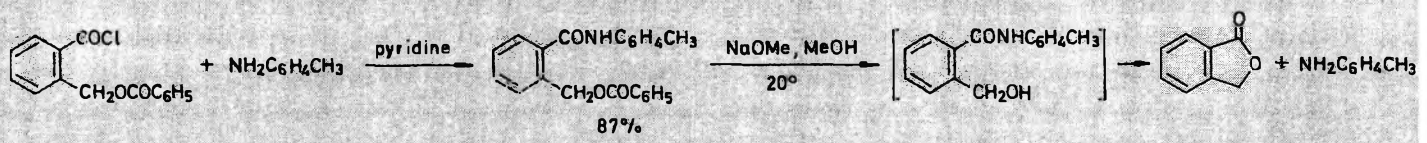

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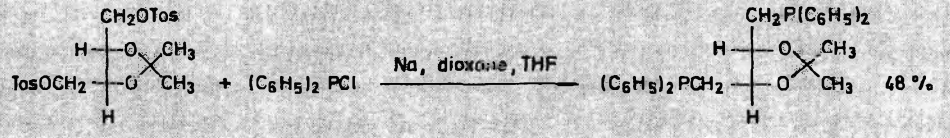

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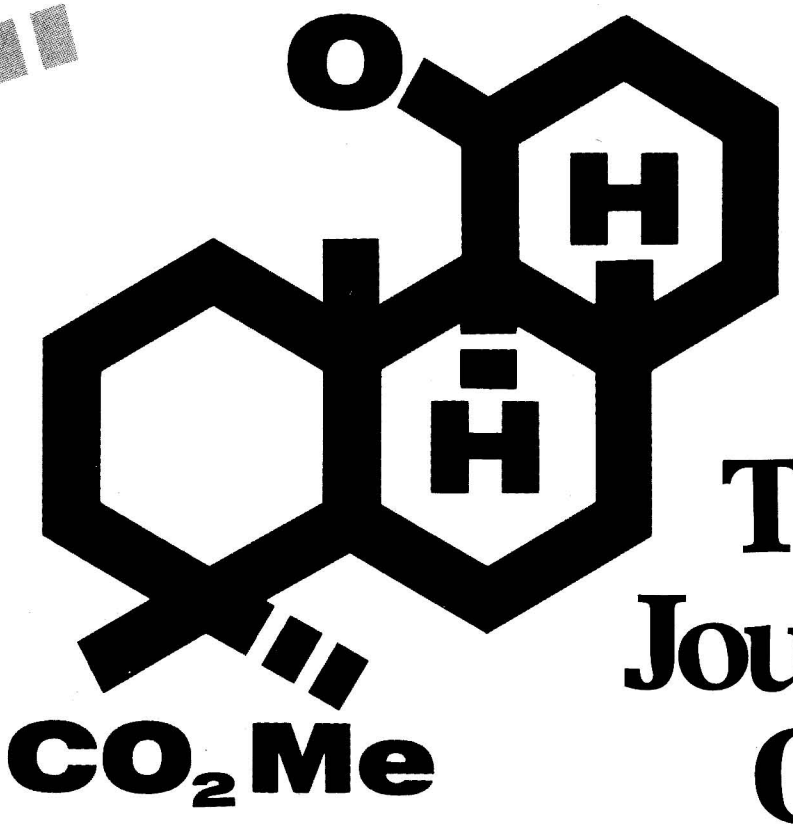

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Conversion of 2-Diazohexose Sugar Derivatives into Five-Carbon Acetylenic and Enol Ester Derivatives[1] ‡

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Received October 21, 1977

Ethyl 4,6-*O*-benzylidene-2-deoxy-2-diazo-D-*arabino*-hexonate (**1**) decomposed spontaneously with loss of nitrogen to give the 3-oxo-2-deoxy ester **4**, which on acetylation gave an enol acetate derivative **5**. Treatment of either the diazo derivative **1** or its diacetate **2** with potassium hydroxide in isopropyl alcohol, with subsequent acetylation, gave the product of chain degradation with formation of an acetylenic sugar derivative, 4-*O*-acetyl-3,5-*O*-benzylidene-1,2-dideoxy-D-*erythro*-pent-1-ynitol (**3**). Thermolysis of the acetylated diazo derivative **2** gave a mixture of the enol 3-acetate **5** and the *E* and *Z* isomers of the corresponding enol 2-acetate (**6** and **7**). The transformations observed evidently proceed through carbenoid intermediates, and the reactions may be related to previously observed photochemical transformations and alkali-catalyzed degradations of (*N*-nitroso)acetamido sugars to acetylenic products.

1-Diazo derivatives of sugars having a stabilizing carbonyl group at the adjacent position are useful as synthetic intermediates for higher-carbon ketose sugars[3] and similarly stabilized 2-diazo sugar derivatives have been prepared[4] and their reactivity studied.[5] Nonterminal diazo sugar derivatives lacking an adjacent carbonyl group but possessing considerable stability have also been prepared by pyrolysis of arylhydrazone salts[6] and by treatment of hydrazone precursors with lead tetraacetate.[7] Transient diazo intermediates have been proposed[8] in the base-catalyzed, one-carbon chain degradation[9] of 2-(*N*-nitroso)acetamido sugar derivatives to chain-terminal acetylene products. The present work was undertaken (1) to test the hypothesis[8] of the intervention of a 2-diazo intermediate in the transformation of a 2-(*N*-nitroso)acetamidohexose derivative into a 5-carbon acetylene and (2) to assess the course of thermal decomposition of 2-diazo sugar derivatives as a potential net route for transformation of 2-amino-2-deoxy sugar precursors into the corresponding 2-deoxy-3-keto sugar analogues. Compounds of the latter type are of interest in their own right,[10] provide potential intermediates for synthesis of 3-substituted 2-deoxy sugars of various types,[11] and offer a potential route for transforming such compounds as aminocyclitol antibiotics[12] into structurally modified analogues of altered biological activity.

Oxidation[13] of 2-amino-2-deoxy-D-glucose hydrochloride to the aldonic acid, followed by conversion[4] into the ethyl ester 4,6-benzylidene acetal and subsequent cautious nitrosation with sodium nitrite–aqueous acetic acid acid[5,14] gave a yellow precipitate of ethyl 4,6-*O*-benzylidene-2-deoxy-2-diazo-D-*arabino*-hexonate (**1**) that, if filtered off and dried, was stable for several months when stored at room temperature. Isolation by dichloromethane extraction[5] gave crystalline **1** having the same physical characteristics as those previously reported,[5] but the product thus isolated was unstable at room temperature; it evolved nitrogen and underwent complete decomposition during a period of 4 days. The crystalline diacetate[5] (**2**) was readily prepared from **1** and was stable on storage.

An ethereal solution of the diazo ester **1** was treated at room temperature with an excess of potassium hydroxide in isopropyl alcohol for 1 h and the product was acetylated with acetic anhydride–pyridine. These conditions are the same as those used to convert acetylated 2-deoxy-2-(*N*-nitroso)acetamidohexoses in high yield,[8,9] and acetylated alkyl 2-deoxy-2-(*N*-nitroso)acetamidohexonates[8] in moderate (~30%) yield, into 3,4,5-triacetoxy-1-pentynes retaining the stereochemical configuration at C-3 and C-4 of the amino sugar precursor. The major product from the reaction of **1** was obtained in high yield and was isolated crystalline (the net isolated yield was decreased by the necessity of chromatographic purification to remove more polar side products). This crystalline product was identified as the C_5 acetylene derivative 4-*O*-acetyl-3,5-*O*-benzylidene-1,2-dideoxy-D-*erythro*-pent-1-ynitol (**5**) on the basis of its ^1H NMR spectrum (see Table I), which was essentially first order at 60 MHz in both chloroform-*d* and benzene-d_6 and was fully supportive of a pure, single product having the structure assigned. Infrared absorptions characteristic of a terminal, acetylenic group were observed, and the mass spectrum showed a significant molecular-ion peak (*m/e* 246) together with fragment ions readily reconciled with the assigned structure **3** (see Experimental Section for details).

‡ Dedicated to Professor M. S. Newman on the occasion of his 70th birthday.

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Table I. ^{1}H NMR Data [a] for Compounds 3–7

Compd	Registry no.	Solvent	Chemical shifts of protons [b] in δ (1st order couplings, Hz, in parentheses)										
			H-1 ($J_{1,3}$)	H-2 ($J_{2,3}$)	H-3 ($J_{3,4}$)	H-4 ($J_{4,5}$)	H-5e ($J_{5e,5a}$)	H-5a ($J_{5a,6a}$)	H-6e ($J_{5a,6e}$)	H-6a ($J_{6a,6e}$)	Ph	PhCH (s)	OAc (enol) (s)	OAc (s)	$CH_2CH_3CH_2CH_3$
3	65915-35-7	$CDCl_3$	2.55 d (2.2)		4.60 dd (9.8)	5.20 m_6 (5.2)	4.52 dd (10.8)	3.65 t (10.0)[c]			7.40–7.80 m	5.60		2.17	
3		C_6D_6	2.02 d (2.1)		4.35 dd (9.8)	5.37 m_6 (5.6)	4.30 dd (10.8)	3.20 t (10.4)[c]			7.10–7.80 m	5.20		1.65	
4	65915-36-8	$CDCl_3$		3.65 s [d]			←3.45–4.35 m →				7.1–7.5 m	5.45			4.12 q 1.17 t
5	65915-37-9	$CDCl_3$		6.15 s		4.42 d (10)		5.15 m_6 (10)	4.55 q (5.2)	3.70 t (10.4)	7.40–7.80 m	5.68	2.28	2.10	4.23 q 1.28 t
5		C_6D_6		6.21 s								5.41	2.00	1.70	
6	65915-38-0	$CDCl_3$			6.05 d (8.8)	5.58 t (9.6)		5.02 m_6 (10.0)	4.50 q (4.8)	3.87 t (10.5)	7.60–7.80 m	5.77	2.28	2.10	4.40 q 1.38 t
6	65915-39-1	C_6D_6			6.05 d (8.9)	5.72 t (9.2)		5.20 m_6 (10.0)	4.35 q (5.1)	3.60 t (10.0)	7.20–7.80 m	5.55	1.82	1.68	4.05 q 0.92 t
7		$CDCl_3$			6.60 d (8.0)		← 3.40–5.40 m →				7.60–7.80 m	5.68	2.30	2.05	4.32 q 1.30 t
7		C_6D_6			6.79 d (8.4)		← 3.20–5.40 m →				7.20–7.80 m	5.42	1.90	1.78	3.95 q 0.82 t

[a] Determined at 60 MHz. [b] Multiplicities: d, doublet; t, triplet; q, quartet; m_x, multiplet of x lines. [c] $J_{4,5a}$. [d] 2-Proton singlet.

Base-catalyzed decomposition of the acetylated diazo ester **2**, with subsequent acetylation of the product, likewise gave the crystalline acetylenic derivative **3**.

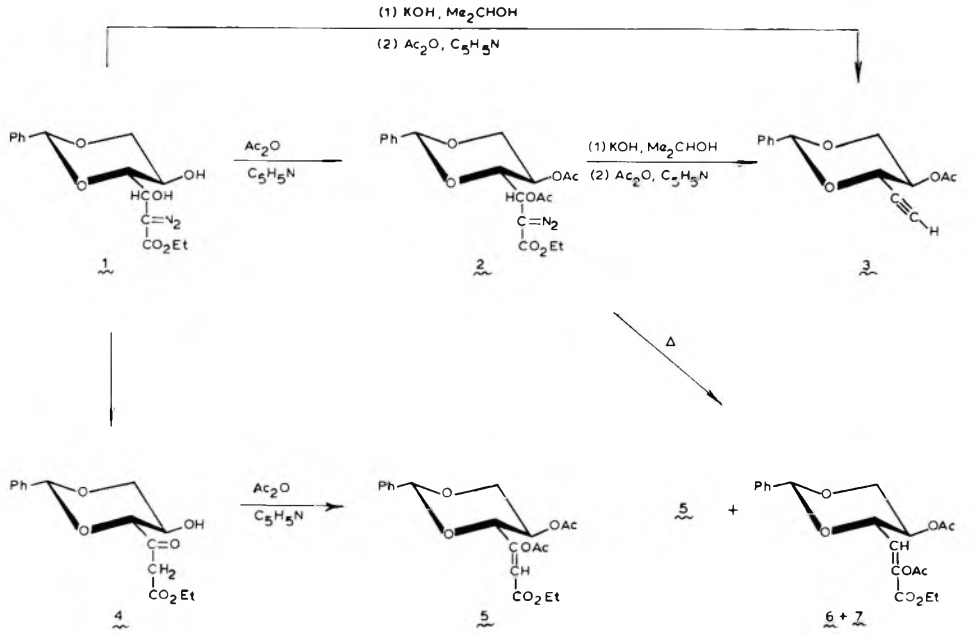
The foregoing observed conversions of the diazo derivatives **1** (or **2**) into the acetylene **3** support the idea[8] that the base-catalyzed degradation of 2-(*N*-nitroso)acetamido sugars to acetylenes in nonaqueous media takes place through a 2-diazo intermediate; in aqueous media the *N*-nitroso derivatives of 2-acetamido sugars undergo[15] conversion into 2,5-anhydroaldose groups with concomitant cleavage of glycosidic substituents.[16] Both of these reactions are useful in the sugar field; the route to acetylenic products is a useful complement to methods[17] involving ethynylation of aldehydo sugar derivatives, and the aqueous decomposition mode is of value for specific[16] fragmentation of such acetamido sugar-containing molecules as glycosaminoglycans,[18] and specific, immunological-determinant oligosaccharides of glycoproteins[19] and lipopolysaccharides.[20]

The diazo derivative **1**, as obtained by dichloromethane extraction, decomposed either in solution or in the dry state. The reaction was monitored by TLC and by disappearance of the diazo-group absorption (2119 cm^{-1}) in the infrared. Decomposition was complete after 48 h at ~25 °C and a principal, fast-migrating, reaction-product **4** was separated by chromatography on silica gel from two slower-migrating side products; it was obtained in 57% yield as an oil. Its IR spectrum showed hydroxyl (3450 cm^{-1}) and two separate carbonyl-group absorptions (1669 and 1739 cm^{-1}) and its NMR (Table I) and mass spectra (see Experimental Section) supported the assigned structure of ethyl 4,6-*O*-benzylidene-2-deoxy-D-*erythro*-hex-3-ulosonate (**4**). The presence of a 2-proton singlet at δ 3.65 (chloroform-*d*) indicated that the compound had an "isolated" methylene group at C-2; an alternative formulation as a 3-deoxy-2-keto ester would have led to multiplicity in this signal. Presumably the conversion of **1** into **4** involves loss of nitrogen and subsequent migration of H-3 to an incipient carbene at C-2 to generate the 2-ene-3-ol that subsequently ketonizes to the observed 2-deoxy-3-ketone **4**.

Acetylation of **4** with pyridine–acetic anhydride gave a mixture of two diacetylated products, presumably the geometric isomers of the structure **5**; these were separated by preparative TLC and the major one was obtained crystalline and analytically pure in 31% yield. The IR data were indicative of the enol ester structure, and cleavage of the molecular ion (*m/e* 378) between C-3 and C-4 leads to the observed fragments at *m/e* 221 and 157; further spectral details are recorded in the Experimental Section. The NMR spectrum (Table I) in chloroform-*d* was fully first order and afforded direct evidence for structure **5**; the low-field position (δ 2.28) of one of the acetyl-group signals is as expected for an enol acetate. The observation of a sharp singlet for H-2 at δ 6.15 provides clear indication that the compound has the 2-enol 3-acetate structure **5**; the proton of the enolic group would have shown the effect of vicinal coupling had the compound been the alternative 2-enol 2-acetate. It is not possible to specify with certainty the precise geometric isomerism about the C=C bond that is adopted in this crystalline isomer of **5**; attempted calculations from the chemical shift of H-2 (see later) gave ambiguous results.

The foregoing sequence of self-decomposition of **1** to give **4**, and subsequent conversion into the enol 3-acetate **5**, demonstrates a practical, net conversion of a 2-amino sugar precursor into a 2-deoxyaldos-3-ulosonic acid system.

The thermal decomposition of the acetylated diazo ester **2** was studied by heating the dry compound for 1 h at 100 °C. A mixture of three products was formed, although only two components were observed by TLC and required careful separation by preparative TLC. The faster migrating com-



ponent was found to be a single compound, isomeric with the enol acetate **5**, and it was formulated as one of the two geometric isomers (**6** or **7**) of the corresponding 2-enol 2-acetate. It showed IR absorptions similar to those observed for **5** and displayed a molecular ion (*m/e* 378) the same as that given by **5**, but distinct differences were evident in the fragmentation pattern (see Experimental Section). The NMR spectrum (Table I) provided clear differentiation of this product from **5**; the same general features were present, including a characteristic signal for the methyl protons of the enol acetate group, but the vinylic proton signal (a singlet in the spectrum of compound **5**) was observed as a wide doublet exhibiting coupling of ~9 Hz with H-4. This evidence permits assignment of the 2-enol 2-acetate structure, although it does not establish directly which one of the two possible geometric isomers (**6** or **7**) is this faster migrating component.

The slower migrating component (R_f 0.28) was found from its NMR spectrum to be a mixture of two products, the 2-enol 3-acetate **5** already described plus the geometric isomer (**7** or **6**) of the faster migrating component of the thermolysis product; the two products were present in ~7:13 ratio. The mixture having R_f 0.28 showed *m/e* 378 as the molecular ion, plus a series of fragment ions that comprised essentially the sum of the fragments observed in the separate spectra of **5** and the faster migrating (R_f 0.32) 2-enol 2-acetate. The NMR spectrum of the slower migrating component, after subtraction of all peaks assignable to compound **5**, allowed assignment of the remaining signals to the isomeric 2-enol 2-acetate (Table I); the wide, 1-proton doublet in the alkenic region (δ 6.60 in chloroform-*d*) again indicates that this signal arises from H-3, showing strong coupling to H-4, in the 2-enol 2-acetate structure.

The chemical shifts of the vinylic-proton doublets in the isomers **6** and **7** may be used for tentative attribution of geometrical isomerism by following the method of Matter et al.[21-23] for estimating these shifts in chloroform-*d* by means of the equation $\delta = 5.25 + Z_{cis} + Z_{trans} + Z_{gem}$, where the Z values are shielding constants of substituents in the locations specified. Using the published[22] values for these shielding constants, the calculated δ values for the vinylic (H-3) proton would be 6.09 ppm for the E isomer and 6.43 for the Z isomer. For the faster migrating (R_f 0.32) isomer **6**, the observed chemical shift of H-3 is 6.05 ppm, suggesting that it is the E isomer, whereas the shift of H-3 in the slower migrating 2-enol 2-acetate **7** is 6.60 ppm, suggesting that it is the Z isomer. For compound **5**, the observed shift (δ 6.15) differs considerably from values (5.40 and 5.68 ppm) calculated[21-23] for either geometric isomer.

The three products (**5**, **6**, and **7**) from thermolysis of **2** were formed in the approximate ratio of 20, 45, and 35%, showing that the carbene formed by loss of nitrogen from **2** undergoes stabilization by 3 → 2 migration of the 3-acetoxyl group more readily than 3 → 2 migration of H-3.

Experimental Section

Preparation of Ethyl 4,6-*O*-Benzylidene-2-deoxy-2-diazo-D-*arabino*-Hexonate (1). To a stirred solution of ethyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-gluconate hydrochloride (5.2 g, 15 mmol) in water (75 mL) at 0 °C was added sodium nitrite (4.2 g), and then acetic acid (2.5 mL) was added dropwise while maintaining the solution at 0 °C. A yellow precipitate appeared almost immediately. Stirring was continued for 40 min and the mixture was then extracted with dichloromethane. The dried (magnesium sulfate) extract was evaporated at 30 °C and the crystalline residue obtained was identical by IR spectrum, TLC, and other constants with the diazo derivative **1** already reported.[5]

The product thus isolated was not stable; it became pasty after several hours at room temperature, evolved nitrogen and was totally decomposed (TLC) after 96 h. To obtain a stable product, the yellow precipitate was filtered off instead of being extracted by dichloromethane. The solid was dried by lyophilization to give anhydrous **1** that could be kept for several months without special precautions. Possibly, traces of salts retained by precipitated **1** exerted a protective effect.

Acetylation of the stable, precipitated form of **1** with acetic anhydride–pyridine as already described[5] for the solvent-extracted preparation gave the diacetate **2**, identical with the product already reported.[5] This product was stable on storage at room temperature.

Base-Catalyzed Conversion of 1 (or 2) Into 3,5-*O*-Benzylidene-1,2-dideoxy-D-*erythro*-pent-1-ynitol, Isolated as Its 4-Acetate 3. A solution of **1** (642 mg, 2.0 mmol) in dry ether (100 mL) was stirred magnetically at ~25 °C and a solution of potassium hydroxide (560 mg) in isopropyl alcohol (20 mL) was added dropwise, with continued stirring, for 1 h. The solvents were evaporated off in vacuo and to the residue was added pyridine (20 mL) and acetic anhydride (4 mL); the mixture was stirred for 12 h at ~25 °C. Ice and water were added and the solution was extracted with dichloromethane. The extract was washed with water, dried (magnesium sulfate), and evaporated. There was obtained a brown oil that by TLC (1:1 petroleum ether–ethyl acetate) contained a major product, R_f 0.85, and slower migrating material. The principal product was separated by chromatography on a column of silica gel with the TLC solvent as eluent to give the pure acetylenic sugar **3** as a solid: yield 150 mg (30%); mp 102 °C; $[\alpha]_D^{20}$ −10.3° (c 0.9, dichloromethane); ν_{max}^{KBr} 3275 (≡CH), 3000, 2850, 2100 (C≡C), 1750 cm^{-1} (broad, C=O); *m/e* 246 (5, M$^{+\cdot}$), 245 (6.5), 221 (0.1, M$^{+\cdot}$ − HC≡C·), 187 (0.1, M$^{+\cdot}$ − ·OAc), 186 (4, M$^{+\cdot}$ − AcOH), 169 (1, M$^{+\cdot}$ − ·C_6H_5), 150 (2), 149 (29,

PhCH=O$^+$CH$_2$CHO), 140 (0.1, M$^{+\cdot}$ − PhCHO), 124 (2, M$^{+\cdot}$ − PhCO$_2$H), 116 (1), 115 (12, 221 − PhCHO), 109 (1), 108 (1), 107 (36, PhC$^+$HOH, 149 → 107, m* 77, calcd 76.8), 106 (7, PhCHO$^{+\cdot}$), 105 (62, Bz$^+$), 91 (12, C$_7$H$_7^+$), 90 (1), 89 (0.5), 86 (3, AcOCH=CH$_2^{+\cdot}$), 82 (7), 81 (1), 79 (3), 78 (2), 77 (10, Ph$^+$), 55 (0.5), 53 (0.5), 52 (0.5), 51 (3), 50 (1), 44 (2), 43 (100, Ac$^+$). Anal. Calcd for $C_{14}H_{14}O_4$: C, 68.29; H, 5.69. Found: C, 68.62; H, 5.78.

When the same procedure was repeated with the diacetate **2**, the acetylenic derivative **3** was also obtained, identical in all respects with the preceding product.

Decomposition of 1 to Give Ethyl 4,6-*O*-Benzylidene-2-deoxy-D-*erythro*-hex-3-ulosonate (4). The diazo derivative **1** (400 mg), as isolated by extraction with dichloromethane, decomposed either in solution or in the dry state after evaporation of dichloromethane. The progress of the reaction was monitored by observing the progressive disappearance of the diazo-group absorption in the infrared (at 2119 cm^{-1}) and by TLC (4:1 dichloromethane–ether). The starting material **1** (R_f 0.17) was progressively replaced by a major product having R_f 0.54, together with a second product having R_f 0.22, and traces of a third product, R_f 0.27. At room temperature, the decomposition of **1** in dichloromethane was complete after 48 h; the progress of the reaction did not appear substantially altered according to whether the solution had been dried (magnesium sulfate or sodium sulfate) or not. The major product (R_f 0.54) was isolated by chromatography on a column of silica gel eluted with the TLC solvent and isolated as a colorless oil identified as **4**: yield 200 mg (57%) $[\alpha]_D$ +6.1 (*c* 1.15, dichloromethane); ν_{max}^{film} 3448 (OH), 2985, 2857, 1739 (C=O), and 1669 cm^{-1}; *m/e* 294 (0.4, M$^{+\cdot}$), 293 (0.4), 276 (0.2, M$^{+\cdot}$ − H$_2$O), 250 (0.6, BzOCH$_2$COCH$_2$CO$_2$Et$^{+\cdot}$), 249 (3.7, M$^{+\cdot}$ − EtO·), 248 (0.7), 234 (0.7), 192 (1), 168 (0.7, M$^{+\cdot}$ − PhCHO), 180 (10), 179 (100, PhCH=O$^+$CH$_2$CHOHCHO), 150 (3), 149 (25, PhCH=O$^+$CH$_2$CHO), 145 (2, 250 − PhCO·), 143 (2, 250 − PhCHOH), 115 (2, EtO$_2$CCH$_2$CO$^+$), 108 (5), 107 (72, PhC$^+$HOH), 106 (40, PhCHO$^{+\cdot}$), 105 (135, PhCO$^+$), 102 (1, 179 − Ph·, m* 58.5, calcd 58.2), 92 (6), 91 (72, C$_7$H$_7^+$), 86 (15, 115 − Et·), 84 (21, 102 − H$_2$O), 79 (25), 78 (8), and 77 (32, Ph$^+$).

Ethyl 3,5-Di-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-D-*erythro*-hex-2-enonate (5). The foregoing product (**4**, 200 mg) in pyridine (10 mL) was treated with acetic anhydride (2 mL) for 24 h at ~25 °C and the mixture was then poured into water. The product was isolated by extraction with chloroform. The crude product on TLC (2:1 petroleum ether–ethyl acetate) showed two components, R_f 0.32 and 0.28, the latter being preponderant. Preparative TLC gave the pure major product as a crystalline solid: yield 80 mg (31%); mp 88–90 °C; $[\alpha]_D$ −20.4° (c 1.2, dichloromethane); ν_{max}^{KBr} 3030, 2950, 2850, 1775, 1745, 1720 (C=O), and 1675 cm^{-1} (C=C); *m/e* 378 (0.1, M$^{+\cdot}$), 377 (0.2), 336 (0.2 M$^{+\cdot}$ − C$_2$H$_2$O), 335 (0.1, M$^{+\cdot}$ − Ac·), 318 (0.5, M$^{+\cdot}$ − AcOH), 276 (1, EtO$_2$CCH=COAcCHO$^+$=CHPh), 273 (2), 272 (17, M$^{+\cdot}$ − PhCHO), 230 (2, 272 − C$_2$H$_2$O), 227 (4, 272 − EtO·), 221 (3, PhCH=O$^+$CH$_2$CHOAcCHO), 213 (1, 272 − AcO·), 212 (1, 272 − AcOH, m* 165.5, calcd 165.2), 187 (2), 186 (0.3, EtO$_2$CCH=COAcCHO$^{+\cdot}$), 185 (7, 186 − H·), 177 (2.5), 171 (4), 170 (30, 272 − AcOCH$_2$CHO, m* 106.2, calcd 106.2), 167 (2), 162 (3, 221 − AcO·), 157 (5, EtO$_2$CCH=C$^+$OAc), 149 (13, PhCH=O$^+$CH$_2$CHO), 145 (7), 124 (3), 116 (11), 115 (75, 221 − PhCHO), 107 (14, PhC$^+$HOH), 106 (6, PhCHO$^{+\cdot}$), 105 (32, Bz$^+$), 91 (7, C$_7$H$_7^+$), 87 (6), 77 (6.5, Ph$^+$), 43 (100, Ac$^+$). Anal. Calcd for $C_{19}H_{22}O_8$: C, 60.32; H, 5.82. Found: C, 59.93; H, 6.05.

Thermal Decomposition of Diazo Ester 2 to give Ethyl (*E*)- and (*Z*)-2,5-*O*-Diacetyl-4,6-*O*-benzylidene-3-deoxy-D-*erythro*-hex-2-enonates (6 and 7) and the 3-*O*-Acetyl Isomer 5. The diazo ester **2** (170 mg) in a Pyrex tube was heated in an oil bath for 1 h at 100 °C (evolution of nitrogen), whereupon TLC (2:1 petroleum ether–ethyl acetate) showed that the starting ester had disappeared and had been replaced by components having R_f 0.32 and 0.28, in approximately equal proportion. Resolution by preparative TLC gave the pure component having R_f 0.32 whose NMR spectrum indicated it to be a single compound (**6** or **7**, most probably the *E* isomer; see Discussion); it was obtained as an oil: yield 46 mg (28%); $[\alpha]_D^{20}$ −30° (*c* 0.5, dichloromethane); ν_{max}^{film} 3030, 2950, 2850, 1750 (strong, C=O), 1670 cm^{-1} (C=C); *m.e* 378 (0.5, M$^{+\cdot}$), 336 (1, M$^{+\cdot}$ − CH$_2$CO), 318 (1, M$^{+\cdot}$ − AcOH), 276 [2.5, EtO$_2$CC(OAc)=CHCH$_2$OCCOPh], 272 (5, M$^{+\cdot}$ − PhCHO), 230 (11, 272 − CH$_2$CO), 229 (78, M$^{+\cdot}$ − 149), 227 [9, EtO$_2$CC(OAc)=CHCH=CHOAc$^{+\cdot}$ − ·CH$_3$], 223 (1.5), 221 (1.5, AcOCHCH$_2$OCHPhOCH$^+$), 200 (1), 188 (6.5), 187 (69, 229 − CH$_2$CO), 185 [2, EtO$_2$CC(OAc)=CHC≡O$^+$], 170 (4, 272 − AcOCH$_2$CHO), 157· [7, EtO$_2$CC(OAc)=CH$^+$], 149 (73, PhCH=O+-CH$_2$CHO), 145 (62), 115 (7, 221 − PhCHO), 107 (32, PhC$^+$HOH), 106 (6, PhCHO$^{+\cdot}$), 105 (21, PhCO$^+$), 91 (13, C$_7$H$_7^+$), 84 (4, 157 − · CO$_2$Et), 77 (8, Ph$^+$), 43 (100, Ac$^+$).

The homogeneous product, R_f 0.28, yield 40 mg (25%), was an oil, $[\alpha]_D^{20}$ −62° (c 0.25, dichloromethane), ν_{max}^{film} 3000, 2950, 2850, 1770, 1740, and 1675 cm^{-1}, shown by its NMR spectrum to comprise a mixture of the enol ester 3-acetate **5** already described plus a second compound (**7** or **6**, most probably the *Z* isomer; see Discussion) in ~7:13 ratio. For this second enol ester 2-acetate **7** (or **6**) the estimated $[\alpha]_D^{20}$ was −84° (dichloromethane). The mass spectrum [*m/e* 378 (0.5, M$^{+\cdot}$)] was essentially a composite of those observed for **5** and the faster migrating isomer (**6**) of **7**.

The net composition of the product of thermolysis of **2** was approximately 20% **5** (R_f 0.28), 45% **6** (R_f 0.32), and 35% **7** (R_f 0.28), as estimated by NMR spectral integration of the original mixture of reaction products.

Registry No.—**1**, 35926-81-9; **2**, 35813-11-7; ethyl 2-amino-4,6-*O*-benzylidene-2-deoxy-D-gluconate hydrochloride, 40149-90-4.

References and Notes

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(2) Groupe de Chimie organique 2, École Nationale Supérieure de Chimie, Université de Clermont-Ferrand, France, at which address the work was completed.
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Synthesis of Carbocyclic Aminonucleosides

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The syntheses of the racemic carbocyclic analogues of puromycin aminonucleoside (**33**), 3′-amino-3′deoxyadenosine (**26**), and 3′-amino-3′-deoxyarabinosyladenine (**21**) are described. Acidic hydrolysis of 2-azabicyclo[2.2.1]-hept-5-en-3-one (**1**), followed by esterification and acetylation, gave methyl *cis*-4-acetamidocyclopent-2-enecarboxylate (**2a**). Reduction of **2a** with calcium borohydride gave, after acetylation, *cis*-4-acetamidocyclopent-2-enemethyl acetate (**3b**). Epoxidation of **3b** gave only *cis*-epoxide **6b**, which was opened with sodium azide to give, after acetylation, 4α-acetamido-3α-acetoxy-2β-azido-1α-cyclopentanemethyl acetate (**7a**) as the major regioisomer. Catalytic hydrogenation of **7a**, followed by immediate acetylation, gave 3α-acetoxy-2β,4α-diacetamido-1α-cyclopentanemethyl acetate (**9a**). Selective hydrolysis of the 4-acetamido group of **9a** and formation of the purine moiety at this position, followed by hydrolysis of the remaining acetamido group, gave the arabino analogue **21**. Epimerization at C-2′ gave access to ribo analogues **33** and **26**. Preliminary in vitro screening data indicate that carbocyclic 3′-amino-3′-deoxyadenosine exhibits highly significant antiviral activity.

Carbocyclic analogues of purine and pyrimidine nucleosides, in which a methylene group replaces the O atom of the ribofuranose ring, have been the object of the synthetic efforts of a number of groups.[1a,2] Since carbocyclic nucleosides lack the labile glycosidic bond, they would be expected to be stable to cleavage by phosphorylases or hydrolases, while retaining the potential for therapeutically useful interaction with other enzymes involved in nucleoside metabolism. The antitumor activity of 6-dimethylamino-9-(3′-amino-3′-deoxy-β-D-ribofuranosyl)purine (puromycin aminonucleoside) and 3′-amino-3′-deoxyadenosine has generated considerable interest in the biological properties of aminonucleosides.[1b] Our particular goal has been the hybridization of these two types of nucleosides to provide a novel class of aminocarbocyclic nucleosides with potential chemotherapeutic properties. In addition, carbocyclic puromycin would be a valuable tool in our continuing study of the precise requirements for inhibition of protein synthesis at the ribosomal level. We have previously described the interesting activity of a variety of simplified carbocyclic puromycin analogues,[3] all lacking the 5′-hydroxymethyl group.

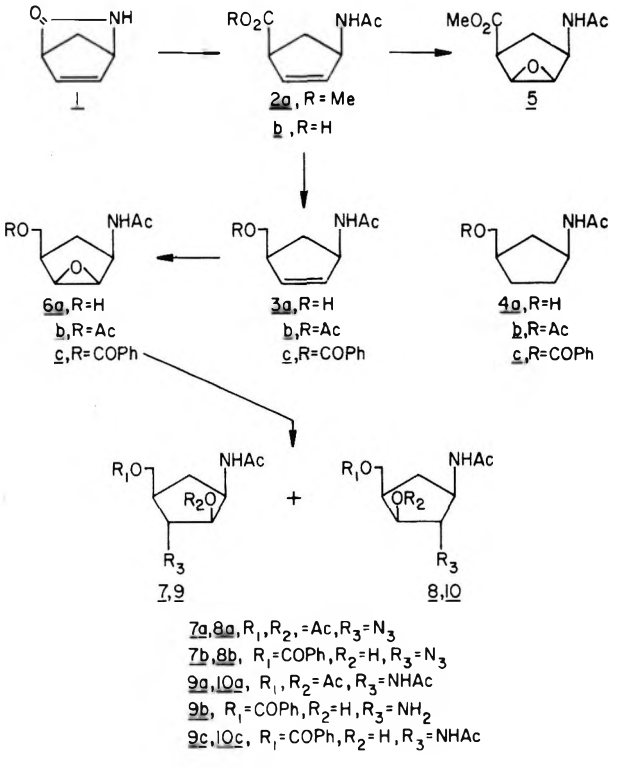
Elaboration of the lengthy, low-yield routes to carbocyclic adenosines which have been described[1a,2] seemed to us to be an extremely limited approach to the synthesis of new carbocyclic nucleosides, especially those requiring stereochemical modifications or substitutions in the cyclopentane ring. Many of the most interesting candidates for synthesis in this area, e.g., carbocyclic analogues of puromycin aminonucleoside, 3′-amino-3′-deoxyadenosine, *ara*-A, and *ara*-C, have been inaccessible. We were, therefore, impressed with the need for a simple, high-yield route to carbocyclic nucleosides using intermediates which would allow modifications to be made in a stereospecific manner in the cyclopentane ring.

The present report provides a detailed account of our preliminary communication[4] describing the development of a flexible route to 2′- and 3′-amino-(2′)3′-deoxycarbocyclic purine nucleosides. This route is also proving versatility in providing access to other carbocyclic nucleosides. For example, a preliminary account has been communicated describing the facile conversion of one of the intermediates described here (epoxide **6b**) to carbocyclic arabinosyladenine (C-*ara*-A), an adenosine deaminase resistant analogue of *ara*-A, which exhibits promising antiviral and antitumor activity.[5]

It has recently been reported that cyclopentadiene and tosyl cyanide react readily to give 3-tosyl-2-azabicyclo[2.2.1]-hepta-2,5-diene.[6a] This adduct, although quite unstable, is easily hydrolyzed to 2-azabicyclo[2.2.1]hept-5-en-3-one (**1**).[6b] The unsaturated lactam **1** offers unique possibilities as a starting material for the synthesis of a variety of carbocyclic nucleosides having the required cis orientation of the hydroxymethyl and heterocycle functions. Large-scale preparation of **1** by the literature procedure, with minor modifications, was carried out in 72% yield. The only difficulty encountered was in the synthesis of tosyl cyanide, which proved to be considerably less stable than indicated by the literature description.[7,8] A modification in the workup (see Experimental Section) avoided the violent decomposition which occasionally occurred during drying and gave a nearly quantitative yield of tosyl cyanide.

Lactam **1** was easily hydrolyzed in dilute acid. The resulting amino acid (not isolated) was esterified and then acetylated to give a high yield of methyl *cis*-4-acetamidocyclopent-2-enecarboxylate (**2a**), a stable crystalline compound (Scheme I). When the hydrolysis product from **1** was acetylated directly, the carboxylic acid **2b** was isolated. Esterification of **2b** also gave **2a**, but the overall yield was higher when esterification was carried out before acetylation.

Scheme I



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Reduction of the methyl ester function of **2a** presented an unexpected difficulty. Lithium borohydride was chosen as the reducing agent, since it is reported to reduce ester groups smoothly without attacking isolated double bonds and amides.[9] However, the samples of **3a** obtained from the reduction of **2a** with lithium borohydride under a variety of conditions (see Experimental Section) contained a significant amount of **4a,** in which the double bond had been reduced. The ratio of **3a/4a,** determined by integration of the NMR spectra, was frustratingly irreproducible. On a small scale or when older samples of lithium borohydride were used, samples of **3a** with almost perfect integration of the NMR were obtained. Larger scale reactions resulted in ratios of **3a/4a** of as high as 1:1. Possibly, deactivation of the lithium borohydride by traces of moisture was the most critical factor in lowering the extent of double bond reduction. We are unaware of previous reports of the reduction of an isolated double bond with lithium borohydride. In an attempt to facilitate separation, the mixture of **3a** and **4a** was acetylated. The resulting mixture of acetates **3b** and **4b** was an oil which could not be separated by distillation or chromatography. In the purest sample of **3b** obtained by this method (NMR integration and elemental analysis correct), the mass spectrum contained an (M + 2) ion of greater intensity than that of the molecular ion of **3b,** indicating contamination by **4b.** Benzoylation of the mixture of **3a** and **4a** was also carried out. The crystalline benzoate **3c** could be separated from contaminating **4c** (not isolated, detected by NMR) in 25–66% yield by crystallization. However, the variability of this reduction on a large scale made it desirable to find another method.

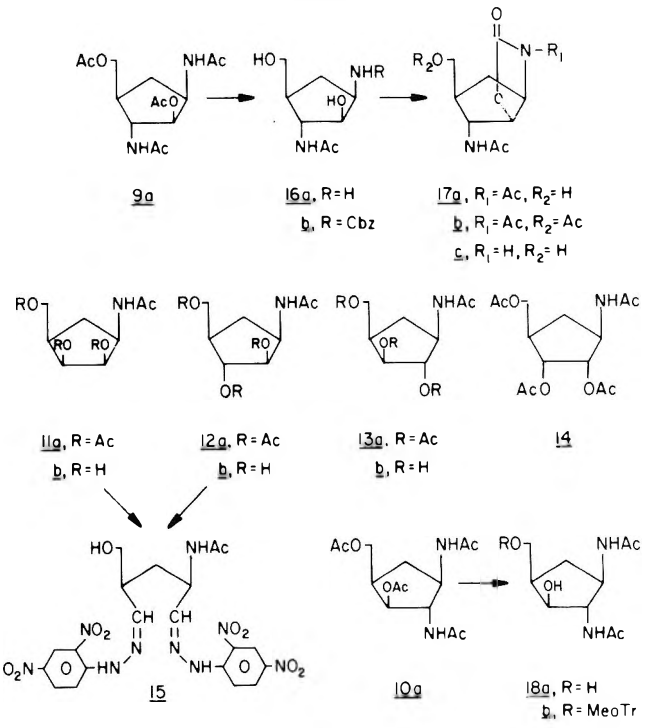
The method involving reduction of a mixed anhydride with sodium borohydride[10] was applied. Carboxylic acid **2b** was reacted with ethyl chloroformate to form a mixed anhydride (not isolated) which was then reduced to **3a** by addition to an aqueous solution of sodium borohydride. The **3a** isolated from this reaction showed no contamination by **4a.** However, the yield of **3a** was only 20–40%, with a great deal of **2b** being recovered, even after 18 h with an excess of reagents.

The reduction of **2a** with calcium borohydride was then investigated with excellent results. This reagent, easily generated in situ from sodium borohydride and calcium chloride,[11] gave reproducible high yields (94%) of **3b,** after acetylation, which showed no contamination by **4b** and solidified for the first time. Calcium borohydride has so many advantages over other reagents for the reduction of an ester, e.g., insensitivity to moisture, greater selectivity,[9,12] and ease and safety of use in large-scale reductions, that it is surprising that it is so rarely used.

Epoxidation of **3b** with *m*-chloroperbenzoic acid was highly stereoselective due to the syn-directing allylic amide group,[13] giving only the expected *cis*-epoxide **6b** (89%). The cis structure of epoxide **6b** was confirmed by later reactions. Epoxidation could also be carried out on the methyl ester **2a** or on benzoate **3c,** resulting in good yields of **5** or **6c,** respectively, presumed by analogy to be the *cis*-epoxides.

In order to generate the precursor of 3′-amino-3′-deoxycarbocyclic nucleosides, epoxide **6b** was opened with buffered sodium azide. Attack occurred predominantly at the position farthest from the acetamido group due to the inductive effect of the nitrogen,[14] giving (after acetylation) azido acetates **7a** and **8a** in a ratio of 4:1 (determined by NMR). Azide opening of epoxide **6c** resulted in azido alcohols **7b** and **8b,** also in a ratio of 4:1. This ratio was increased to 5.5:1 by hydrolysis of the ester of **6b** to alcohol **6a** prior to azide treatment. The relatively weak influence of this more distant group on the position of epoxide attack by azide is also explainable on inductive grounds.[15] When epoxide **5** was subjected to the same conditions, a complex mixture resulted, attack at both positions being approximately equally favored. The opening of **5** was also complicated by hydrolysis and lactone formation. Consideration of a route via **5** was thus abandoned due to the complexity of the epoxide opening.

Scheme II



The major azido acetate **7a** was easily separated from **8a** (not isolated) by crystallization. Catalytic hydrogenation of **7a** in ethanol with platinum catalyst, followed by acetylation, gave diacetamide **9a** in 70% yield. Hydrogenation followed by acetylation of a mixture of **7a** and **8a** gave diacetamides **9a** and **10a,** separable by chromatography. The amines formed by reduction of **7a** and **8a** cound not be characterized; their ethanolic solutions darkened rapidly in air. This was surprising, since the hydrogenation of 2α-acetamido-5β-azidocyclopentan-1α-ol under the same conditions gave an almost quantitative yield of the corresponding amine.[3d] The difference from this simpler series of compounds is that acetylation was carried out to facilitate recovery and separation of the isomeric azides **7a** and **8a.** Thus, the hydrogenation was carried out on the azido acetates, instead of the azido alcohols. Neighboring group interference by the secondary acetate being conceivable, we desired to study the hydrogenation of the corresponding azido alcohol. An attempt to convert **7a** to the corresponding azido diol by mild ammonia–methanol treatment gave an 80% yield of epoxide **6a.** The hydrogenation of azido alcohols **7b** and **8b** was therefore studied. Although in this case it was possible to characterize the free amine **9b** resulting from reduction of **7b,** solutions darkened rapidly and the yield was low (50%), unless acetylation to **9c** was carried out quickly. In the reduction of **8b,** the product turned dark red on contact with air and could be characterized only as acetamide **10c.** It was concluded that the apparent instability of the products resulting from hydrogenation of these azides is *not* associated with esterification of the adjacent hydroxyl group.

In an attempt to avoid decomposition and increase the yield of **9a,** the hydrogenation of **7a** was carried out with acetic anhydride as the solvent. Although no darkening of the product in air was noted, the yield of **9a** (64%) was not improved due to formation of a new product, **11a** (35%), a crystalline solid having the composition $C_{14}H_{21}NO_7$ (Scheme II). The opening of epoxide **6b** in dilute aqueous sulfuric acid followed by acetylation resulted in two products, **12a** and **13a,** having the same composition as **11a.**[5] Although the infrared

and high-resolution mass spectra of **11a, 12a,** and **13a** are almost identical, the NMR spectra show small differences in splitting patterns and chemical shifts. Another isomer, **14,** has been previously described as a syrup.[16] Ammonia–methanol treatment of **11a, 12a,** and **13a** gave the corresponding acetamido triols **11b, 12b, 13b.** Oxidation of these triols with 1 equiv of sodium metaperiodate resulted in the same dialdehyde, characterized as the di(2,4-dinitrophenylhydrazone) **15.** Thus **11a, 12a,** and **13a** differ only in configuration at the 2 and 3 positions, and **11a** may be assigned the lyxo stereochemistry shown in Scheme II. Corroboration of this assignment is given by acyl migration studies described below. Apparently, backside displacement of the azido group of **7a** by acetate is possible under the conditions of this hydrogenation. Prolonged (4–5 days) exposure of azide **7a** to acetic anhydride or of epoxide **6b** or diacetamide **9a** to the hydrogenation conditions in acetic anhydride gave no detectable **11a.** No **11a** was detected when reduction of the azide in ethanol was completed and then acetic anhydride added immediately before filtration of the platinum catalyst.

The best yield of **9a** was obtained by catalytic hydrogenation of **7a** in chloroform–ethanol.[17] The resulting amine hydrochloride was immediately acetylated by addition of sodium acetate and acetic anhydride, giving pure **9a** in 84% yield.

In an attempt to circumvent difficulties encountered in the catalytic reduction of **7a,** epoxide **6b** was treated with boron trifluoride etherate in acetonitrile.[18] Although this procedure gave a fair yield of **9a** on a small scale, on a preparative scale the yield was only 11% and a great deal of black tarry material resulted.

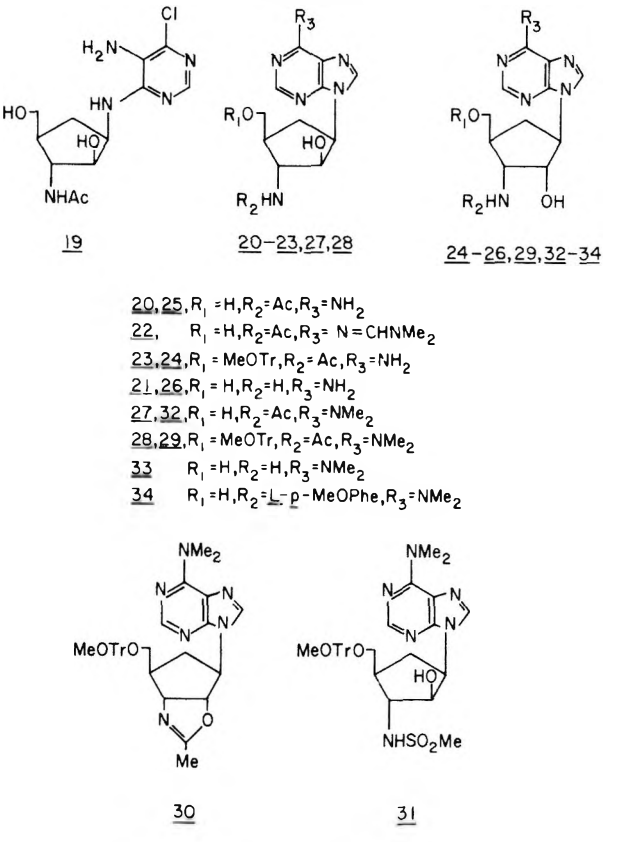
The assignment of the stereochemistry of epoxide **6a** and the structures of azides **7a** and **8a** derived from opening **6a** (or **6b**) is based, in part, on the behavior of diacetamides **9a** and **10a** in dilute hydrochloric acid. It is well known that the acid-catalyzed hydrolysis of an amide is remarkably facilitated by the presence of an adjacent *cis*-hydroxyl group, due to acyl migration.[19] As expected, mild acidic hydrolysis of **9a** resulted in monoacetamide **16a**[20] (Scheme II), one of the acetamido groups having undergone acyl migration followed by hydrolysis. The cis relationship of the amino and secondary hydroxyl groups of **16a** was further confirmed by cyclic carbamate formation: the benzyloxycarbonyl derivative **16b** cyclized to carbamate **17c,** characterized after acetylation to **17b.** The presence of the cis vicinal hydroxy and acetamido groups in **9a** also confirms the cis structure of epoxide **6a.** The *trans*-epoxide could not result in such a grouping when opened as described.

When **10a** was subjected to the same mild acidic hydrolysis conditions, neither of the acetamido groups was hydrolyzed. The resulting diacetamide **18a** was characterized as the 4-methoxytrityl derivative **18b.** When **11a, 12a,** and **13a** were subjected to this acidic treatment, the acetamido group of **11a** and **12a** was hydrolyzed, while that of **13a** was not, thus also confirming these assignments.

The selective hydrolysis of one acetamido group of **9a** is an integral part of this route to aminocarbocyclic nucleosides, making the use of different blocking groups for the two amines unnecessary. Amine **16a** was condensed with 5-amino-4,6-dichloropyrimidine and the resulting pyrimidine **19** (76%) closed with diethoxymethyl acetate (Scheme III) to the 6-chloropurine (not isolated). Reaction of the chloropurine with ammonia or dimethylamine gave **20** or **27,** respectively, isolated in good yield as crystalline solids after brief treatment with dilute acid to remove ethoxymethylidenes and acetates formed during the diethoxymethyl acetate reaction. Basic hydrolysis of **20** gave carbocyclic 3′-amino-3′-deoxyarabinosyladenine **21.**

The 6-amino group of **20** was blocked by reaction with *N,N*-dimethylformamide dimethyl acetal, giving **22.** The 5′-hydroxyl group was then tritylated by reaction with chloro(*p*-methoxyphenyl)diphenylmethane, followed by removal of the 6-*N*-(dimethylamino)methylene group with ammonia, to give the 5′-*O*-mono-*p*-methoxytrityl derivative **23.** The 5′-*O*-*p*-methoxytrityl derivative **28** was prepared by tritylation of **27.** Epimerization at C-2 was carried out via a standard method in carbohydrate chemistry,[21] sulfonation of the 2′-hydroxyl of **23** or **28,** followed by inversion with sodium acetate in hot aqueous 2-methoxyethanol. We are aware of several examples of the use of this inversion method on amino sugar nucleosides,[22] none of them involving adenine or 6-dimethylaminopurine as the heterocycle component. In contrast to the literature examples, a mesylate could not be detected (by NMR) in the mixtures resulting from treatment of **23** or **28** with 1.5 equiv of methanesulfonyl chloride in pyridine. Instead, a mixture of oxazoline, epimerized product, and starting material resulted from which, after sodium acetate hydrolysis, **24** or **29** could be isolated in good yield. The 2′-mesylates of **23** and **28** would be expected to be more reactive than the 2′-mesylates of nucleosides and are apparently displaced by the 3′-acetamido group as formed or during workup, without the sodium acetate treatment normally used for this purpose. We continued to use the sodium acetate hydrolysis to convert any oxazoline present to *cis*-acetamido alcohol. An attempt was made to characterize the oxazolines, but they proved to be decomposing slowly to the acetamido alcohols on silica gel eluted with methanol–chloroform. A quite pure sample of **30** was obtained which NMR confirmed to be oxazoline. The use of 2–3 equiv of methanesulfonyl chloride resulted in more complex dark mixtures and lower yields. In the epimerization of **28,** these complex mixtures were chromatographed. In addition to lowered yields of **29** and **30,** an additional product, **31,** was isolated (11% with 2 equiv of methanesulfonyl chloride, 26% with 3 equiv). The singlet at δ 2.80 in the NMR spectrum of **31** indicates that the acetyl group has been replaced by a methanesulfonyl group, and the absence of acetamide bands in the IR spectrum along with the presence of characteristic sulfonamide bands at 1320 and 1140 cm^{-1} supports this as-

Scheme III



sumption. The mass spectrum of **31**, while not showing a molecular ion, does contain a peak at *m/e* 369 attributable to loss of the methoxytrityl group from the molecular ion, a prominent fragmentation for trityl derivatives such as **24** and **29**. Apparently, perhaps due to the proximity of the purine, the mesylation of the 2′-hydroxyl proceeds slowly enough that a competing mesylation of the acetamide nitrogen is possible.[23] The resulting *N*-acetylsulfonamide would be hydrolyzed during workup to sulfonamide **31**. The configuration of **31** is uncertain, but since inversion and oxazoline formation would protect the nitrogen and since an *N*-acetylsulfonamide would be a poor neighboring group, it seems likely that inversion at C-2 has not occurred. The only example we have found of the use of this inversion method with a purine nucleoside having geometry comparable to that of **23** and **28** is Baker and Schaub's report of the inversion of 2-methylmercapto-6-dimethylamino-9-(2-*O*-mesyl-3-acetamido-3-deoxy-5-*O*-trityl-β-D-arabinofuranosyl)purine.[24] Unfortunately, the intermediates were not characterized sufficiently in this work to allow comparisons to be made with the present study.

Detritylation of **24** and **29** with formic acid gave the 3′-acetamido-3′-deoxycarbocyclic nucleosides **25** and **32**. Basic hydrolysis of **25** gave the ribonucleoside analogue **26**, (±)-9-[3β-amino-2β-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]adenine. Carbocyclic puromycin aminonucleoside **33** resulted on deacetylation of **32**. Carbocyclic puromycin (**34**) has been synthesized from **33**.[25]

Preliminary in vitro antiviral screening data indicate that the most active compound of this series, carbocyclic 3′-amino-3′-deoxyadenosine (**26**), exhibits highly significant activity. Virus ratings calculated as previously described[5] were 2.1 and 2.2 against Herpes simplex virus type 1 (strain HF) and vaccinia virus (strain Lederle Chorioallantoic), respectively. Further work is continuing in this laboratory and elsewhere to study the antiviral spectrum and therapeutic effects of these compounds in animals.

Experimental Section

Thin-layer chromatography (TLC) was done using 0.25-mm layers of Merck silica gel 60F-254 and column chromatography on Merck silica gel 60. Melting points were determined with a Mel-Temp apparatus and are uncorrected. UV spectra were taken with a Beckman 25 spectrophotometer, IR with a Perkin-Elmer 237B spectrophotometer, NMR with a Varian A-60D or a Varian T-60 spectrometer using an internal standard of tetramethylsilane, and mass spectra with an AEI Scientific Apparatus Limited MS-30 mass spectrometer. Low-resolution mass spectra were run on all compounds and the molecular ion and fragmentation patterns were reasonable. All evaporations were carried out at reduced pressure with a bath temperature of <50 °C. Samples were dried at 56 °C (0.1 mm) before analysis.

Tosyl Cyanide. The literature preparation of tosyl cyanide[8] gives very little detail. As difficulties were encountered when working with large quantities of the compound, as much detail as possible will be given here. A 1 M aqueous solution of sodium toluene-*p*-sulfinate or its hydrate (1 L) was prepared in a 2-L flask equipped with magnetic stirring, sintered glass gas inlet tube, thermometer, and exit tube to a trap containing 6 N sodium hydroxide. The contents of the flask was stirred vigorously and maintained at 20 °C while cyanogen chloride (Matheson) was bubbled vigorously into the solution for 30 min (solid started to form almost immediately). The gas inlet tube was disconnected and the flask was stoppered and cooled well for 30 min in an ice–salt bath. (Failure to chill well causes loss of product as an oil which passes through filter paper.) The white fluffy solid was filtered off and washed with ice water (100 mL). The damp[26] solid was immediately washed into a separatory funnel with carbon tetrachloride (500 mL). The carbon tetrachloride solution was shaken with saturated sodium chloride (100 mL), dried ($CaSO_4$) for 30 min, and evaporated to dryness (<40 °C) in the flask in which the next reaction was to be run. The white solid tosyl cyanide (consistently 98–99% yield), mp 45.5–47 °C [lit.[7] 46–48 °C], had ^1H NMR (CCl_4) and IR spectra identical with those reported.[7] The solid was used immediately for the next reaction.

2-Azabicyclo[2.2.1]hept-5-en-3-one (1). The literature procedure[6b] was modified to allow for large-scale preparation. A solution of freshly prepared tosyl cyanide (425 g, 2.35 mol) in freshly cracked cyclopentadiene (3 L) was stirred while coming to room temperature over a period of 40 min (the cyclopentadiene started out at freezer temperature, −20 °C). The resulting solution was evaporated to dryness without heating. The residue was cooled and swirled while *cold* glacial acetic acid (750 mL) was poured rapidly into the flask.[27] The resulting mixture was quickly poured into ice–water (3 L). Celite was added and the mixture filtered. The filter pad was washed with additional water (1 L). The filtrate–wash was then cooled (<20 °C) and stirred while cold 12 N sodium hydroxide was added to a pH of 8. This solution was saturated with sodium chloride and extracted with methylene chloride (3 × 3 L). A final extraction with additional methylene chloride (3 L) was carried out by allowing the layers to stir together vigorously overnight. All extracts were combined and dried ($CaSO_4$). Evaporation left a brown oil (200 g) which was purified by distillation to give 2-azabicyclo[2.2.1]hept-5-en-3-one as a pale yellow syrup which solidified on standing (184 g, 72%): bp 102–106 °C (0.25 mm); mp 50–52 °C (lit.[6b] 61%, mp 54–56 °C); IR and ^1H NMR identical with those reported.[6b]

Methyl *cis*-4-Acetamidocyclopent-2-enecarboxylate (2a). 2-Azabicyclo[2.2.1]hept-5-en-3-one (64.2 g, 0.588 mol) was dissolved in 5% hydrochloric acid (2.5 L) and the solution stirred at room temperature for 3.5 days. Sufficient 6 N sodium hydroxide was added (with cooling) to give pH 1.0. The pale yellow solution was evaporated to dryness (<50 °C). The residue was azeotroped with benzene–methanol, dried, and then refluxed in dry methanol (1 L) for 18 h. The sodium chloride was filtered off and washed with additional methanol. The filtrate–wash was evaporated to dryness and the residual yellow syrup dissolved in pyridine (500 mL). Acetic anhydride (300 mL) was added to the cooled (ice bath) solution. The solution was allowed to come to room temperature and after 1 h evaporated to dryness. The residue was dissolved in methylene chloride (500 mL), extracted with saturated sodium bicarbonate (3 × 200 mL) and saturated sodium chloride (50 mL), and dried ($CaSO_4$). Evaporation and azeotroping with toluene (3 × 200 mL) to remove pyridine left a yellow syrup (103.5 g) which solidified within a few minutes with the generation of considerable heat. The ^1H NMR spectrum of this off-white solid was identical with that of an analytical sample. Sublimation [70–80 °C (0.003 mm)] gave **2a** as white crystals (96.1 g, 89%): mp 66–67 °C; IR (KBr) 3300 (NH), 1725 (CO_2Me), 1622 br (C=C, amide 1), 1535 cm^{-1} (amide 2); ^1H NMR ($CDCl_3$) δ 6.25 (br, 1, NCH=O), 5.82 (s, $w_{1/2}$ = 2.5 Hz, 2, CH=CH), 4.97 (m, 1, CHN), 3.68 (s, 3, OCH_3), 3.6–3.4 (m, 1, $CHCO_2Me$), 1.91 (s) overlapped by 2.7–1.5 (m, 5, CH_3C=O and CH_2).

Anal. Calcd for $C_9H_{13}NO_3$ (183.21): C, 59.00; H, 7.15; N, 7.65. Found: C, 59.25; H, 7.04; N, 7.51.

This compound was also prepared by refluxing a solution of **2b** (11.85 g, 70.0 mmol) and *p*-toluenesulfonic acid (50 mg) in dry methanol (300 mL) for 18 h. The solution was evaporated to dryness and the residue dissolved in methylene choride (250 mL). This solution was extracted with half-saturated sodium bicarbonate (25 mL), dried ($CaSO_4$), and evaporated, leaving white solid (12.8 g). Crystallization from benzene–hexanes gave **2a** as white crystals (11.4 g, 89%): melting point, IR, and ^1H NMR identical with those of the analytical sample.

***cis*-4-Acetamidocyclopent-2-enecarboxylic Acid (2b).** A solution of **1** (10.1 g, 92.6 mmol) in 2 N hydrochloric acid (1 L) was stirred at room temperature for 3 days. The solution was concentrated to 150 mL and neutralized with 6 N sodium hydroxide while being cooled (ice bath). The temperature was kept at 10–15 °C with vigorous stirring while acetic anhydride (50 mL) and 6 N sodium hydroxide (sufficient to maintain basic pH) were added in alternating portions over 10 min. The solution was stirred an additional 5 min with cooling and then 5 min without cooling. The pH was adjusted to 1 with concentrated hydrochloric acid (with cooling) and the solution saturated with sodium chloride and extracted with methylene chloride (4 × 500 mL). The extracts were dried ($CaSO_4$) and evaporated, leaving white powder (14.72 g). Crystallization from acetonitrile gave **2b** as white needles (11.9 g, 76%): mp 146–147.5 °C; IR (KBr) 3300, 3069, 2950–2450 (OH, NH), 1700 sh, 1680 br (COOH), 1625, 1530 cm^{-1} (NHAc); ^1H NMR (Me_2SO-d_6) δ 12.0–11.7 (br, 1, exchanging in this solvent, COOH), 7.85 (d, *J* = 7.0 Hz, 1, NHC=O), 6.9–6.5 (m, 2, CH=CH), 5.0–4.0 (m, 1, CHN), 3.6–3.2 (m, 1, CHCOOH), 2.8–1.4 (m) with discernible singlet at 1.82 (5, CH_2, CH_3C=O).

Anal. Calcd for $C_8H_{11}NO_3$ (169.18): C, 56.79; H, 6.55; N, 8.28. Found: C, 56.98; H, 6.72; N, 8.29.

***cis*-4-Acetamidocyclopent-2-enemethyl Acetate (3b).** A mixture of calcium chloride (31.8 g, 0.286 mol) and sodium borohydride

(21.7 g, 0.572 mol) in tetrahydrofuran (600 mL) was stirred at room temperature for 1.0 h. A solution of **2a** (35.0 g, 0.191 mol) in tetrahydrofuran (500 mL) was added all at once. The resulting mixture was stirred at room temperature for 18 h. It was then cooled (ice bath) and ice water (700 mL) added dropwise (much effervescence at first). Cold 6 N hydrochloric acid (110 mL) was then added (to a pH of 1.5) and the resulting clear solution stirred at room temperature for 1.0 h. Evaporation and azeotroping with methanol (4 × 500 mL) and with pyridine (2 × 500 mL) gave a mixture of white solid and pale yellow syrup. Pyridine (250 mL) was added, and the insoluble inorganics were filtered off. Acetic anhydride (250 mL) was added to the pyridine filtrate and stirring was continued at room temperature for 18 h. After evaporation, methanol (250 mL) was added to the residual syrup and the resulting solution refluxed for 10 min. After evaporation of the methanol, the residue was stirred with methylene chloride (500 mL)–water (250 mL) while sufficient solid sodium bicarbonate was added to make the aqueous layer basic. The layers were separated and the aqueous layer was extracted with additional methylene chloride (2 × 250 mL). The combined organic layers were dried ($CaSO_4$) and evaporated. The residue was azeotroped with toluene (3 × 250 mL), leaving a yellow oil (39.1 g); ^{1}H NMR almost identical with that of an analytical sample. Distillation gave a colorless syrup (36.7 g, 98%, bp 132–134 °C (0.04 mm), which solidified to white crystals, mp 62–63 °C. Sublimation of such a sample [60 °C (0.1 mm)] gave an analytical sample of **3b** as white crystals: mp 62–63 °C; IR (neat, on syrup immediately after distillation) 3260 br (NH), 3050 (CH=CH), 1735 (OAc), 1638 (C=C, amide 1), 1530 cm^{-} (amide 2); ^{1}H NMR (CCl_4) δ 7.83 (d, J = 7.5 Hz, 1, NHC=O), 5.83 (s, $w_{1/2}$ = 2.5 Hz, 2, CH=CH), 4.93 (m, 1, CHN), 4.04 (d, J = 6.5 Hz, 2, CH_2O), 3.25–2.18 (m, 2, H-1 and H-5), 2.07 and 1.95 (both s, 6, CH_3CO_2 and CH_3CON), 1.50–1.00 (m, 1, H-5, probably the H cis to the acetamido group).

Anal. Calcd for $C_{10}H_{15}NO_3$ (197.24): C, 60.89; H, 7.67; N, 7.10. Found: C, 60.95; H, 7.97; N, 7.07.

An average yield of 94% was achieved for numerous runs of this size or larger.

Lithium Borohydride Reduction of 2a; Isolation of Mixtures of 3b and 4b or 3c and 4c. A solution of **2a** (3.40 g, 18.6 mmol) in dry tetrahydrofuran (100 mL) was added to a stirred solution of lithium borohydride (810 mg) and dry tetrahydrofuran (400 mL) under nitrogen at room temperature over a period of 1.0 h. Stirring was continued overnight. The resulting mixture (a large quantity of gummy white precipitate had formed) was cooled (ice bath) while ice water (300 mL) was added dropwise over 1.0 h. Amberlite IRA-120 (H^+) resin (5 g) was then added cautiously and the resulting mixture stirred for 2.0 h. The resin was filtered off and the filtrate evaporated to dryness. The residue was dissolved in portions of methanol (5 × 200 mL) and repeatedly evaporated to dryness. The residue was then dissolved in water (200 mL) and stirred with Amberlite IRA-400 (OH^-) resin (20 mL) for 30 min. Evaporation to dryness left colorless syrup (3.59 g) which appears from the ^{1}H NMR integration to be a mixture of **3a** and **4a**: IR (neat) CO_2Me absent; ^{1}H NMR ($CDCl_3$) δ 7.9–6.7 (m, 1, 2 partially overlapping NHC=O), 5.9–5.6 (t-like m, 1.7, CH=CH), 5.2–4.7 (m, 1, CHN), 3.9–3.3 (m, 3, CH_2O and OH, br s due to OH shifts upfield to 3.17 on heating to 60 °C), 3.1–1.0 (m) with discernible singlets at 1.98 (minor) and 1.95 (6.5, CH, all CH_2, CH_3CO). The integration of the olefinic peaks and the methylene envelope indicate, for this particular run, that the sample consists of 85% of **3a** and 15% of **4a**. The ratio of **3a**/**4a** was not reproducible (range from 1:1 to 6:1) and did not vary in any consistent way with changes in reaction conditions such as temperature, time, reversal of addition, rate of addition, or ratio of [H^-] to [**2a**].

Such mixtures of **3a** and **4a** were acetylated in acetic anhydride–pyridine (1:1) at room temperature overnight. After evaporation, the residue was dissolved in methylene chloride, extracted with half-saturated sodium bicarbonate, dried ($CaSO_4$), and evaporated, leaving a mixture of **3b** and **4b** as a colorless oil (78–86% from **2a**), chromatographically homogeneous on TLC (5% MeOH–$CHCl_3$). Two distillations of such a mixture gave a sample of **3b** as a colorless oil: bp 134–136 °C (0.1 mm); ^{1}H NMR integration and mass spectrum relative intensity ratio of $(M + 2)^+/M^+$ of 10:1 indicate contamination by **4b**.

Anal. Calcd for $C_{10}H_{15}NO_3$ (197.24): C, 60.89; H, 7.67; N, 7.10. Found: C, 6.093; H, 7.88; N, 7.35.

Benzoylation of the mixture of **3a** and **4a** gave a mixture of benzoates **3c** and **4c**. Fractional crystallization from benzene–hexanes gave **3c** as needles (25–66%): mp 84–85 °C; IR, NMR, and mass spectra as expected.

Anal. Calcd for $C_{15}H_{17}NO_3$ (259.31): C, 69.48; H, 6.61; N, 5.40. Found: C, 69.60; H, 6.71; N, 5.20.

The mother liquors contained additional **3c** contaminated by **4c** (detected by ^{1}H NMR).

Methyl 4α-Acetamido-2α,3α-epoxycyclopentane-1α-carboxylate (5). A solution of **2a** (366 mg, 2.00 mmol) and *m*-chloroperbenzoic acid (487 mg, 85%, 2.4 mmol) in carbon tetrachloride (18 mL) was refluxed for 2 h. Potassium carbonate (415 mg, 3.00 mmol) was added and the slurry added to a silica gel column packed in chloroform. Elution with chloroform gave initial fractions containing *m*-chloroperbenzoic acid followed by fractions containing **5** (370 mg). Crystallization from ethyl acetate–hexanes gave **5** as a fluffy white solid (288 mg, 73%): mp 117.5–118.5 °C; IR (KBr) 3275 (NH), 1735 (CO_2Me), 1635, 1550 (NHAc), 863, 840 cm^{-1} (epoxide); ^{1}H NMR ($CDCl_3$) δ 6.68 (d, J = 8.0 Hz, 1, NHC=O), 4.44 (q-like m, 1, CHN), 3.72 (s) overlapped by 3.7–3.4 (m, 5, CO_2Me and c-CHOCH), 3.1–2.7 (m, 1, $CHCO_2Me$), 1.99 (s) overlapped by 2.6–1.1 (m, 5, CH_3C=O, CH_2).

Anal. Calcd for $C_9H_{13}NO_4$ (199.21): C, 54.26; H, 6.58; N, 7.03. Found: C, 54.11; H, 6.71; N, 6.79.

4α-Acetamido-2α,3α-epoxycyclopentane-1α-methyl Acetate (6b). A solution of **3b** (36.7 g, 0.186 mol) and *m*-chloroperbenzoic acid (37.8 g, 85%, 0.186 mol) in carbon tetrachloride (700 mL) was refluxed for 2.0 h. The solution was concentrated to 200 mL and methylene chloride (500 mL) added. This solution was extracted with saturated sodium bicarbonate (150 mL), dried ($CaSO_4$), and evaporated, leaving **6b** as a yellow oil (40.8 g) which solidified on standing: ^{1}H NMR almost identical with that of an analytical sample. Such material was sufficiently pure for use. An analytical sample was prepared by preparative TLC (10% MeOH–$CHCl_3$), giving **6b** as a colorless oil (89%) that slowly changed to a gummy amorphorus solid on drying at 0.1 mm: mp 68–72 °C; all attempts to crystallize were unsuccessful; attempts to distill or sublime **6b** caused decomposition; IR (KBr) 3300 (NH), 1735 (OAc), 1635 br, 1540 (NHAc), 865, 830 cm^{-1} (epoxide); ^{1}H NMR ($CDCl_3$) δ 6.98 (d, J = 7.5 Hz, 1, NHC=O), 4.42 (m) overlapping 4.03 (d, J = 7.0 Hz, 3, CHN and OCH_2), 3.45 (m, 2, c-CHOCH), 2.08 and 2.02 (both s) overlapped by 2.5–0.5 (m, 9, CH_3CO_2, CH_3CON, CH, CH_2).

Anal. Calcd for $C_{10}H_{15}NO_4$ (213.24): C, 56.33; H, 7.09; N, 6.57. Found: C, 56.16; H, 6.98; N, 6.60.

4α-Acetamido-2α,3α-epoxycyclopentane-1α-methyl Benzoate (6c). Epoxidation of **3c** exactly as in the preparation of **6b** gave **6c** as white needles (90% after crystallization from benzene–hexanes): mp 138–139 °C; IR, ^{1}H NMR, and mass spectra analogous to those of **6b**.

Anal. Calcd for $C_{15}H_{17}NO_4$ (275.31): C, 65.44; H, 6.22; N, 5.09. Found: C, 65.72; H, 6.29; N, 5.10.

4α-Acetamido-2α,3α-epoxycyclopentane-1α-methanol (6a). Ammonia was bubbled through a solution of **6b** (5.62 g, 26.4 mmol) in methanol (150 mL) for 2 min at room temperature. The flask was stoppered and allowed to stand overnight. Evaporation left a yellow oil which crystallized from ethyl acetate to give white crystals (1.60 g, 35%). An analytical sample of **6a** was prepared by two recrystallizations from absolute ethanol: mp 172–173 °C; IR (KBr) 3250 br, 3000–2700 (OH, NH), 1635 br, 1565 (NHAc), 875, 830 cm^{-1} (epoxide); ^{1}H NMR (Me_2SO-d_6) δ 7.97 (d, J = 8.0 Hz, 1, NHC=O), 4.64 (t, J = 5.0 Hz, 1, CH_2OH) partially overlapping 4.5–3.8 (m, 1, CHN), 3.45 (m, 4, c-CHOCH, CH_2OH), 1.82 (s) overlapped by 2.4–0.5 (m, 6, CH_3C=O, CH_2, CH).

Anal. Calcd for $C_8H_{13}NO_3$ (171.20): C, 56.13; H, 7.65; N, 8.18. Found: C, 56.19; H, 7.74; N, 8.00.

In practice, no attempt was made to crystallize **6a**. The ammonia–methanol was evaporated to dryness and the residue used immediately in the next reaction.

4α-Acetamido-3α-acetoxy-2β-azido-1α-cyclopentanemethyl Acetate (7a) and 4α-Acetamido-2α-acetoxy-3β-azido-1α-cyclopentanemethyl Acetate (8a). A sample of **6a** prepared from **3b** (23.9 g, 0.121 mol) by epoxidation and then ammonia–methanol treatment, as described above, was stirred with sodium azide (31.5 g, 0.484 mol), ammonium chloride (6.79 g, 0.127 mol), 2-methoxyethanol (330 mL), and water (50 mL) at 75 °C for 18 h. The reaction mixture was evaporated to dryness and the residue dried by azeotroping with pyridine (2 × 200 mL). The residue was stirred with pyridine (300 mL)–acetic anhydride (200 mL) overnight. The solid was filtered off and the filtrate evaporated to dryness. The residue was dissolved in methylene chloride and extracted with saturated sodium bicarbonate (2 × 50 mL), dried ($CaSO_4$), and evaporated to dryness. The residual tan solid (32.2 g, 89% as mixture of **7a** and **8a**) was crystallized from chloroform–carbon tetrachloride, giving white prisms of **7a** (18.0 g, 50% from **3b**): mp 103–106 °C; ^{1}H NMR identical with that of an analytical sample. An analytical sample of **7a** was prepared from such a sample by crystallization from carbon tetrachloride: white prisms; mp 103–104 °C; IR (KBr) 3255, 3090 (NH),

2110 (N_3), 1745 (OAc), 1645, 1555 cm^{-1} (NHAc); ^1H NMR ($CDCl_3$) δ 6.38 (br d, J = 8 Hz, 1, NHC=O), 5.00 (m, 1, CHO), 4.8–4.2 (m, 1, CHNHCO), 4.12 (d, J = 5.5 Hz, 2, OCH_2CH) partially overlapping 4.60 (m, 1, CHN_3), 2.14, 2.13, 2.00 (all s) overlapped by 2.8–1.3 (m, 12, $3CH_3C$=O, CH, CH_2).

Anal. Calcd for $C_{12}H_{18}N_4O_5$ (298.31): C, 48.32; H, 6.08; N, 18.78. Found: C, 48.27; H, 6.12; N, 18.65.

Evaporation of the mother liquors left a yellow glass (14.0 g) which ^1H NMR showed to be a mixture of **7a** and **8a** in a ratio of ~1.2:1 (as determined by integration of the NHC=O resonances, the minor isomer's NH being slightly downfield from that of the major). Attempts to separate this mixture by column chromatography (0.5–2.5% MeOH–$CHCl_3$) gave enrichment of the major isomer **7a** in the early fractions. A pure sample of **8a** could not be obtained. Such mixtures of **7a** and **8a** could be hydrogenated to **9a** and **10a**, which were easily separated (see later). Both ^1H NMR and relative yields of **9a** and **10a** indicated the ratio of **7a** to **8a** formed in the epoxide opening to be 5.5:1.

4α-Acetamido-2β-azido-3α-hydroxy-1α-cyclopentanemethyl Benzoate (7b) and 4α-Acetamido-3β-azido-2α-hydroxy-1α-cyclopentanemethyl Benzoate (8b). A solution of **6c** (3.00 g, 10.9 mmol), sodium azide (3.78 g, 58.1 mmol), and ammonium chloride (777 mg, 14.5 mmol) in water (15 mL) and 2-methoxyethanol (40 mL) was maintained at 70 °C for 18 h. After evaporation to dryness, the residue was partitioned between water (15 mL) and methylene chloride (2 × 75 mL). The combined organic layers were dried ($CaSO_4$) and evaporated, leaving a mixture of **7b** and **8b** (2.6 g) in a ratio of 4:1 (from integration of the NH resonances in the ^1H NMR). Crystallization from benzene–hexanes gave **7b** as white crystals (1.30 g, 37%): mp 111.5–112 °C; IR and ^1H NMR analogous to those of **7a**.

Anal. Calcd for $C_{15}H_{18}N_4O_4$ (318.34): C, 56.59; H, 5.70; N, 17.60. Found: C, 56.62; H, 5.85; N, 17.73.

A small sample of the minor isomer **8b** was obtained by column chromatography of the mother liquors (5% MeOH–$CHCl_3$). Initial fractions appeared (from ^1H NMR) to be free of **7b**. This sample of **8b** was a colorless glass which could not be solidified and retained solvents on drying. Hydrogenation (see below) gave **10c** which was not contaminated by **9c**.

3α-Acetoxy-2β,4α-diacetamido-1α-cyclopentanemethyl Acetate (9a) and 2α-Acetoxy-3β,4α-diacetamido-1α-cyclopentanemethyl Acetate (10a). A. Catalytic Hydrogenation of 7a and Mixtures of 7a and 8a. 1. In Ethanol. A solution of **7a** (500 mg, 1.68 mmol) in absolute ethanol (20 mL) was shaken with prereduced platinum oxide (100 mg) under hydrogen (50 psi) overnight. The catalyst was filtered off and the filtrate evaporated to dryness. The residual glass[28] was immediately dissolved in acetic anhydride (20 mL)[29] and warmed gently on the steam bath for 2 min. Evaporation and azeotroping with toluene left a yellow glass (575 mg). Crystallization from ethanol–ethyl acetate gave **9a** as white needles (165 mg, 31%): mp 168–169.5 °C; IR (KBr) 3300 (NH), 1737 (OAc), 1653, 1553 cm^{-1} (NHAc); ^1H NMR ($CDCl_3$) δ 7.18 (br d, J = 8.0 Hz, 1, NHC=O), 6.46 (br d, J = 8.0 Hz, 1, NHC=O), 5.3–3.9 (m, 5, CHO, 2CHN, OCH_2), 2.11, 2.08, and 2.01 (all s) overlapped by 2.8–1.7 (m, 15, 4 CH_3C=O, CH, CH_2).

Anal. Calcd for $C_{14}H_{22}N_2O_6$ (314.35): C, 53.49; H, 7.05; N, 8.91. Found: C, 53.31; H, 6.97; N, 8.70.

The ethanol–ethyl acetate mother liquor darkened rapidly and TLC (10% MeOH–$CHCl_3$) showed numerous spots. Addition of acetic anhydride (20% of ethanol) to the Parr shaker immediately on opening (before filtration of the catalyst) avoided much of this decomposition. After warming gently on the steam bath for 30 min, the catalyst was filtered off and the solution evaporated to dryness. The residual colorless glass crystallized to **9a** (70%).

When a mixture of azides **7a** and **8a** was subjected to the same hydrogenation conditions and acetylation, a mixture of **9a** and **10a** was obtained as a yellow syrup. The isomers could be separated by column chromatography (2% MeOH–$CHCl_3$). The minor isomer **10a** was eluted from the column first and crystallized from chloroform–hexanes to white granules (12% from **6b**): mp 163.5–164.5 °C; mmp with **9a**, 138–147 °C; IR (KBr) 3300, 3100 (NH), 1745, 1730 (OAc), 1650, 1635, 1550 (NHAc); ^1H NMR ($CDCl_3$) δ 7.5–7.1 (m, 2, 2NHC=O), 5.4–5.3 (m, 1, CHO), 4.6–3.7 (m, 4, 2CHN, OCH_2), 2.07, 2.03, 1.98 (all s) overlapped by 3.0–1.2 (m, 15, $4CH_3C$=O, CH, CH_2).

Anal. Calcd for $C_{14}H_{22}N_2O_6$ (314.35): C, 53.49; H, 7.05; N, 8.91. Found: C, 53.47; H, 7.05; N, 8.85.

Continued elution of the column gave isomer **9a** (65% from **6b**).

2. In Acetic Anhydride: Isolation of 4α-Acetamido-2α,3α-diacetoxy-1α-cyclopentanemethyl Acetate (11a). A solution of **7a** (8.59 g, 28.8 mmol) in acetic anhydride (100 mL) was shaken with prereduced platinum oxide (500 mg) under hydrogen (50 psi) overnight. Workup as above gave a yellow syrup which crystallized from chloroform–hexanes to **9a** (5.76 g, 64%). The mother liquors contained mostly a material of greater R_f than **9a** or **10a** which could not be solidified. Further purification by column chromtography (1% MeOH–$CHCl_3$) gave **11a** as a colorless syrup (3.18 g, 35%); ^1H NMR identical with that of an analytical sample. Crystallization of such a sample from EtOAc gave white granules of **11a**: mp 115–116 °C; IR (KBr) 3270, 3080 (NH), 1735 (OAc), 1645, 1560 cm^{-1} (NHAc); ^1H NMR ($CDCl_3$) δ 5.30 (br d, J = 8.5 Hz, 1, NHC=O), 5.6–5.1 (m, 2, 2CHO), 4.8–4.0 (m, 1, CHN), 4.04 (d, J = 8.0 Hz, 2, OCH_2), 1.43, 1.37, and 1.34 (all s) overlapped by 2.8–1.2 (m, 15, $4CH_3C$=O, CH_2, CH), addition of D_2O resulted in a slow disappearance of the NH resonance; mass spectrum (20 eV, 50 °C) almost identical with that of 4α-acetamido-2β,3α-diacetoxy-1α-cyclopentanemethyl acetate,[5] high resolution confirms composition of M^+.

Anal. Calcd for $C_{14}H_{21}NO_7$ (315.33): C, 53.33; H, 6.71; N, 4.44. Found: C, 53.59; H, 6.95; N, 4.68.

3. In Chloroform–Ethanol.[17] A solution of **7a** (5.02 g, 16.8 mmol) in 5% chloroform–absolute ethanol (250 mL) was shaken with prereduced platinum oxide (250 mg) under hydrogen (50 psi) overnight. The Parr flask was opened and sodium acetate (1.38 g, 16.8 mmol) and acetic anhydride (25 mL) were added immediately. The mixture (including catalyst) was warmed gently on a steam bath for 30 min. During this time a cloudy white precipitate of sodium chloride formed. The mixture was filtered through Celite and the filter pad washed with additional hot ethanol (100 mL). The residue left after evaporation of the ethanol was triturated with refluxing chloroform and the undissolved sodium chloride filtered off. Evaporation of the chloroform left a colorless syrup that crystallized from ethanol–ethyl acetate to give **9a** as white needles (4.44 g, 84%): mp 168.5–169.5 °C; IR and NMR identical with those of the analytical sample.

B. Acid-Catalyzed Opening of 6b in Acetonitrile.[18] To a solution of **6b** (426 mg, 2.00 mmol) in dry acetonitrile (8 mL) was added boron trifluoride etherate (1.25 mL, ~10.0 mmol). The clear pale yellow solution was stirred at room temperature for 24 h. Water (8 mL) was added and stirring continued for 30 min. In a modification of the literature procedure, this solution was passed through a column of Amberlite IRA-400 (OH^-) resin (50 mL). The basic eluent (120 mL) was evaporated and the residue azeotroped dry with absolute ethanol, leaving yellow glass (458 mg). Acetic anhydride (5 mL) and pyridine (10 mL) were added. After standing overnight, the solution was evaporated, treated with refluxing ethanol, and azeotroped with toluene to give yellow glass (550 mg); TLC (10% MeOH–$CHCl_3$) shows major spot of same R_f as **9a** plus several minor spots of greater R_f. Crystallization from chloroform–hexanes gave **9a** (328 mg, 52%): mp 168–169.5 °C; NMR same as that of analytical sample.

When this reaction was run on a larger scale starting with **6b** (32.1 g, 0.151 mol), the literature workup was used (neutralization with aqueous $NaHCO_3$) and the material isolated was black tar. After extensive chromatography and crystallization, about 11% of **9a** was isolated.

Oxidation of 11b and Characterization of the Product as a Di(2,4-dinitrophenylhydrazone) (15). A solution of **11a** (158 mg, 0.500 mmol) in methanol saturated with ammonia (10 mL) was allowed to stand at room temperature overnight in a stoppered flask. Evaporation left a colorless glass (95 mg) which was dissolved in absolute ethanol (5 mL) and added all at once to a solution of sodium metaperiodate (107 mg, 0.500 mequiv) in water (2.5 mL). A white precipitate started to form within 5 min. After 3.5 h, the mixture was diluted to 20 mL with absolute ethanol and cooled (ice bath) for 30 min. The white precipitate was filtered off and washed with additional ethanol. To the filtrate–wash was added a warm solution of 2,4-dinitrophenylhydrazine (250 mg, ~20% H_2O, ~1.0 mmol) in absolute ethanol (5 mL)–concentrated hydrochloric acid (0.5 mL). An orange precipitate was filtered off, washed with ethanol, and air dried to give **15** (208 mg, 76%), mp 206–209 °C dec. Resolidification from nitromethane gave fluffy yellow solid (140 mg, 51%): mp 219–222 °C dec; IR (KBr) 3400, 3280 (NH, OH), 1650 (amide 1), 1620 (C=C), 1587 (amide 2), 1513 and 1328 cm^{-1} (NO_2).

Anal. Calcd for $C_{20}H_{21}N_9O_{10}$ (547.46): C, 43.88; H, 3.87; N, 23.03. Found: C, 43.91; H, 3.95; N, 23.24.

The same conversion was also carried out on the xylo and arabino isomers (**12a** and **13a**)[5] and the resulting phenylhydrazones gave no depression of a mixture melting point with the sample of **15** derived from **11a**.

4α-Acetamido-2β-amino-3α-hydroxy-1α-cyclopentanemethyl Benzoate (9b): Acetylation to 9c. A solution of **7b** (2.45 g, 7.70 mmol) in absolute ethanol (20 mL) was shaken with prereduced platinum oxide (250 mg) under hydrogen (50 psi) for 18 h. Filtration

and evaporation left yellow gum (2.5 g) that crystallized from chloroform–hexanes to white granules of **9b** (1.17 g, 52%): mp 174–178 °C; IR (KBr) 3300 br, 3065 (OH, NH), 1712 (benzoate), 1640, 1535 (NHAc), 1595 cm^{-1} (C=C).

Anal. Calcd for $C_{15}H_{20}N_2O_4$ (292.34): C, 61.63; H, 6.90; N, 9.58. Found: C, 61.39; H, 7.04; N, 9.63.

Although crystalline **9b** was stable, mother liquors darkened rapidly. Acetylation of **9b** by refluxing in methanol–acetic anhydride (1:1) for 30 min gave **9c** as white needles (89% after crystallization from ethyl acetate): mp 200–202 °C; IR (KBr) 3330, 3260, 3075 (OH, NH), 1708 (benzoate), 1660, 1640, 1550 cm^{-1} (2NHAc); ^1H NMR (Me_2SO-d_6) δ 8.0–7.2 (m, 7, C_6H_5 and 2NHC=O), 5.00 (br s, 1, OH), 4.20 (d, J = 6.0 Hz) overlapped by 4.4–3.5 (m, 5, $CHCH_2O$, CHO, 2 CHN), 1.83 and 1.80 (both s) overlapped by 2.3–1.3 (m, 9, $2CH_3CO$, CH_2, CH).

Anal. Calcd for $C_{17}H_{22}N_2O_5$ (334.38): C, 61.06; H, 6.63; N, 8.38. Found: C, 61.27; H, 6.70; N, 8.37.

3β,4α-Diacetamido-2α-hydroxy-1α-cyclopentanemethyl Benzoate (10c). Hydrogenation of **8b** exactly as for **7b** gave a colorless glass that turned red on contact with air. Immediate acetylation (as for **9c**) gave **10c** as white granules (70% after crystallization from ethyl acetate): R_f on TLC (5% MeOH–$CHCl_3$) greater than that of **9c**; mp 190–191 °C; IR, NMR, and mass spectra similar to those of **10c.**

Anal. Calcd for $C_{17}H_{22}N_2O_5$ (334.38): C, 61.06; H, 6.63; N, 8.38. Found: C, 61.22; H, 6.88; N, 8.35.

2β-Acetamido-4α-amino-3α-hydroxy-1α-cyclopentanemethanol (16a). A solution of **9a** (5.75 g, 18.3 mmol) in 2 N hydrochloric acid (220 mL) was maintained at 70 °C for 1.0 h. After evaporation, the residue was dried by evaporation of portions of absolute ethanol and toluene, leaving the hydrochloride of **16a** as a hygroscopic white solid foam; ^1H NMR (CD_3OD) shows only once acetyl group. The solid foam was dissolved in methanol and passed through a column of Amberlite IRA-400 (OH^-) resin (100 mL). The basic methanol eluent (600 mL) was evaporated, leaving **16a** which was pure enough for use as an intermediate as a colorless glass (3.60 g, contains solvent). Attempts to solidify **16a** or to remove traces of solvent by drying were unsuccessful.

2β-Acetamido-4α-benzyloxycarbonylamino-3α-hydroxy-1α-cyclopentanemethanol (16b). A sample of crude hydrochloride of **16a** prepared by hydrolysis of **9a** (1.00 g, 3.18 mmol) as described above was dissolved in dry dimethylformamide (20 mL). The solution was cooled (ice bath) and triethylamine (1.2 mL, 8.4 mmol) and carbobenzoxy chloride (0.53 mL, 4.8 mmol) were added. The ice bath was removed and stirring continued for 1.0 h. Ice water (20 mL) was added and stirring continued for 20 min. The resulting mixture (some white solid formed) was evaporated to a glass. After trituration with ether (2 × 20 mL), a white solid remained (931 mg, 91%): mp 142–148 °C; IR identical with that of an analytical sample. Resolidification of such a sample from methylene chloride gave an analytical sample of **16b** as white powder: mp 152.5–153.5 °C; IR (KBr) 1688 (Cbz), 1640, 1537 cm^{-1} (NHAc); ^1H NMR (Me_2SO-d_6) δ 7.98 (br d, J = 7.5 Hz, 1, NHC=O), 7.37 (br s, 5, C_6H_5), 6.63 (br d, J = 7.5 Hz, 1, NHC=O), 5.07 (s) overlapped by 5.0–4.7 (m, 3, OCH_2Ph and OH), 4.3–3.0 (m, 6.4, CHO, 2CHN, OCH_2CH, OH, and contaminating H_2O in solvent), 1.68 (s) overlapped by 2.3–1.0 (m, 6, CH_3C=O, CH_2, CH).

Anal. Calcd for $C_{16}H_{22}N_2O_5$ (322.37): C, 59.61; H, 6.88; N, 8.69. Found: C, 59.37; H, 6.88; N, 8.65.

2β,4α-Diacetamido-3α-hydroxy-1α-cyclopentanemethyl Acetate 3,4-Carbamate (17b). To a solution of **16b** (200 mg, 0.653 mmol) in dry dimethylformamide (3 mL) was added a 1.5 N solution of sodium methoxide in dry methanol (0.1 mL). The solution was stirred at 100 °C for 1.5 h and evaporated, and the residual colorless glass was extracted with ether (3 × 20 mL) and dried. This crude **17c** was only partially acetylated in acetic anhydride–methanol, giving a mixture of **17a** and **17c** (~1:1 from TLC and NMR). Acetylation was completed in acetic anhydride (10 mL)–pyridine (10 mL) at room temperature overnight. Evaporation and trituration of the residue with carbon tetrachloride (20 mL) left chromatographically homogeneous white powder (160 mg, 82%): mp 172–178 °C; IR and R_f identical with an analytical sample of **17b.** Resolidification of such a sample from methylene chloride–carbon tetrachloride gave white powder: mp 168–174 °C effervesces; IR (KBr) 3250, 3080 (NH), 1770 (urethane C=O), 1735 (OAc), 1697 ($AcNCC_2$), 1635 and 1540 cm^{-1} (NHAc); ^1H NMR (Me_2SO-d_6) δ 8.10 (br d, J = 8.0 Hz, 1, NHC=O), 5.0–3.7 (m, 5, CHO, 2CHN, CH_2O), 2.40 (s, CH_3CONCO_2–), 2.02 and 1.88 (both s, CH_3CO_2 and CH_3CONH) overlapped by 2.4–1.0 (m, total 12, 3Ac, CH, CH_2).[30]

Anal. Calcd for $C_{13}H_{18}N_2O_6$ (298.30): C, 52.34; H, 6.08; N, 9.39. Found: C, 52.18; H, 6.10; N, 9.42.

Hydrolysis of 10a to 3β,4α-Diacetamido-2α-hydroxy-1α-cyclopentanemethanol (18a): Characterization of 18a as the 4-Methoxytrityl Derivative (18b). A solution of **10a** (200 mg, 0.636 mmol) in 2 N hydrochloric acid (10 mL) was maintained at 70 °C for 1.0 h. The solution was evaporated and the residual glass azeotroped dry by evaporation of portions of absolute ethanol and toluene, and dried. Since the resulting glass still contained HCl, it was dissolved in methanol and stirred with Amberlite IRA-400 (OH^-) resin (10 mL). Evaporation of the methanol left a colorless glass (147 mg, 100% as **18a**) which was hygroscopic and could not be solidified: ^1H NMR (CD_3OD) δ 4.62 (br s, 4, MeOH due to exchangeable protons, 2NHC=O and 2OH), 4.2–3.3 (m, 5, CH_2O, CHO, 2 CHN), 1.78 and 1.74 (both s) overlapped by 3.0–0.9 (m, 9, $2CH_3C$=O, CH_2, CH).

Such a sample of **18a** obtained from the hydrolysis of **10a** (200 mg, 0.636 mmol) as described above was dissolved in dry pyridine (5 mL) and stirred with 4-methoxytrityl chloride (236 mg, 0.763 mmol) for 2 days. The solution was poured into ice water (5 mL), neutralized with sodium bicarbonate, and extracted with methylene chloride (3 × 10 mL). The combined organic layers were dried ($CaSO_4$) and evaporated, leaving pale yellow solid foam (300 mg): TLC (5% MeOH–$CHCl_3$) shows one major band plus several minor greater R_f bands. The foam was chromatographed on two 20 × 20 cm silica gel F254 preparative plates (2 mm) developed in 10% MeOH–$CHCl_3$. Extraction of the major band gave **18b** as a colorless glass which solidified to a white powder on trituration with carbon tetrachloride (164 mg, 51%): mp 158–160 °C effervesces; IR (KBr) 3400 sh, 3260, 3060 (OH, NH), 1650 br, 1550 br cm^{-1} (NHAc); ^1H NMR ($CDCl_3$) δ 7.6–6.7 (m, 15, $2C_6H_5$, OC_6H_4, NHC=O), 6.40 (d, J = 6.0 Hz, 1, NHC=O), 4.43 (br s, 1, OH), 3.78 (s) overlapped by 4.2–3.5 (m, 6, OMe, CHO, 2CHN), 3.30 (d, J = 5.8 Hz, 2, OCH_2CH), 1.95, 1.87 (both s) overlapped by 2.7–1.2 (m, 9, $2CH_3CO$, CH, CH_2).

Anal. Calcd for $C_{30}H_{34}N_2O_5$ (502.62): C, 71.69; H, 6.82; N, 5.57. Found: C, 71.58; H, 6.62; N, 5.36.

5-Amino-4-*N*-[3β-acetamido-2α-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]amino-6-chloropyrimidine (19). A solution of **16a** from the hydrolysis of **9a** (5.77 g, 18.4 mmol) as described above, 5-amino-4,6-dichloropyrimidine (6.10 g, 37.2 mmol), and triethylamine (12.7 mL, 91 mmol) in 1-butanol (90 mL) was refluxed under nitrogen for 24 h. The solution was evaporated to dryness and the residue stirred vigorously with water (150 mL)–chloroform (75 mL). The aqueous layer was separated and extracted with additional chloroform (3 × 25 mL). The aqueous layer was stirred briefly with Amberlite IRA-400 (OH^-) resin (40 mL). Evaporation left **19** as cream-colored powder (5.21 g): TLC (20% MeOH–$CHCl_3$) shows one major spot plus a minor contaminant at slightly greater R_f.[31] One resolidification from absolute ethanol gave chromatographically homogeneous **19** as a cream-colored powder (4.45 g, 77%), mp 239–240 °C dec. An analytical sample was prepared by resolidification of such a sample from absolute ethanol–ether, giving **19** as an off-white powder: mp 254–256 °C dec (varies with rate of heating); IR (KBr) 3450–3050 (OH, NH), 1645 br (amide 1), 1585 br, 1570, 1560 (C=C, C=N), 1540 br cm^{-1} (amide 2); ^1H NMR (Me_2SO-d_6) δ 7.93 (d, J = 7.5 Hz, 1, NHC=O) 7.62 (s, 1, pyrimidine CH), 6.40 (d, J = 6.5 Hz, 1, OH), 5.4–3.0 (m, 10, NH_2, NH, OH, CH_2O, CHO, 2CHN, H_2O in solvent), 1.83 (s) overlapped by 2.4–1.2 (m, 6, CH_3C=O, CH, CH_2).

Anal. Calcd for $C_{12}H_{18}N_5O_3Cl$ (315.77): C, 45.64; H, 5.75; Cl, 11.23; N, 22.18. Found: C, 45.52; H, 5.95; Cl, 11.09; N, 22.07.

9-[3β-Acetamido-2α-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]adenine (20). A mixture of **19** (1.76 g, 5.57 mmol) and diethoxymethyl acetate (20 mL) was stirred at room temperature overnight and then at 100 °C for 1.0 h. The solution was evaporated to a yellow foam which showed numerous spots on TLC (10% MeOH–$CHCl_3$). The foam was shaken with liquid ammonia (100 mL) in a stainless steel bomb at room temperature for 3 days. Evaporation left a yellow glass which was dissolved in 1 N hydrochloric acid (100 mL) and maintained at 60 °C for 45 min. The solution was evaporated to dryness and the residue was dissolved in methanol and passed through a column of Amberlite IRA-400 (OH^-) resin (50 mL). Evaporation of the basic methanol eluent (500 mL) left orange glass mixed with solid. Crystallization from absolute ethanol gave **20** as white granules (967 mg, 54%): mp 218–222 °C dec; UV max (ε × 10^{-3}) 258 nm (14.5) in 0.1 N HCl, 260 nm (14.6) in H_2O, 260 nm (14.8) in 0.1 N NaOH; IR (KBr) 3360, 3160 (OH, NH), 1670, 1607, 1570 (C=C, C=N), 1650, 1545 cm^{-1} (NHAc); ^1H NMR (Me_2SO-d_6) δ 8.08 (s) overlapping 8.1–7.9 (m, 3, purine H-2 and H-8, NHC=O), 7.07 (br s, 1.5, exchanges in this solvent, NH_2), 5.5–3.1 (m, 9, 2 OH, CHO, 2CHN, CH_2O, H_2O), 1.89 (s) overlapped by 2.5–1.3 (m, 6, CH_3C=O, CH, CH_2); mass spectrum essentially the same as that of stereoisomer **25.**

Anal. Calcd for $C_{13}H_{18}N_6O_3 \cdot H_2O$ (324.35): C, 48.14; H, 6.22; N, 25.91. Found: C, 48.07; H, 6.34; N, 25.68.

Column chromatography of the mother liquor contents (20–30% MeOH–$CHCl_3$) gave additional **20** (397 mg, 22% after crystallization from absolute ethanol): melting point and TLC same as those of the analytical sample.

9-[3β-Acctamido-2α-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]-6-dimethylaminopurine (27). A sample of **19** (3.76 g, 11.9 mmol) was reacted with diethoxymethyl acetate as described above. The resulting crude chloropurine was refluxed with 40% aqueous dimethylamine (75 mL) for 3 h. After evaporation the residue was dissolved in 1 N hydrochloric acid (60 mL) and maintained at 65 °C for 45 min. After evaporation, the residue was dissolved in methanol (300 mL) and stirred with Amberlite IRA-400 (OH^-) resin (100 mL) for 10 min. Evaporation left white solid (3.73 g). Crystallization from absolute ethanol gave white granules of **27** (2.96 g, 74%): mp 257–258.5 °C; IR (KBr) 3450, 3280, 3085 (OH, NH), 1665, 1560 (NHAc), 1603 cm^{-1} (C=C, C=N); mass spectrum (70 eV, 200 °C) *m/e* 334 (5.3, M^+), 164 (81.0, BH_2^+), 163 (100, BH^+), almost identical with the spectrum of stereoisomer **32.**

Anal. Calcd for $C_{15}H_{22}N_6O_3$ (334.39): C, 53.88; H, 6.63; N, 25.13. Found: C, 53.71; H, 6.88; N, 25.01.

The mother liquors contained more **27** and a lower R_f contaminant. Additional **27** (~5%) could be isolated by column chromatography. No attempt was made to identify the lower R_f impurity.

5′-*O*-(4-Methoxytrityl) Derivative (23) of 20. A solution of **20** (1.89 g, 5.84 mmol) and dimethylformamide dimethyl acetal (3.5 g, 29 mmol) in dry dimethylformamide (25 mL) was stirred at room temperature overnight. After evaporation, the residue was triturated with absolute ethanol (15 mL) until white solid formed. The mixture was diluted with ether (100 mL) and analytical quality **22** was filtered off (2.0 g, 95%): mp 227–231 °C dec; IR (KBr) 3280, 3100, 3050 (OH, NH), 1680, 1595 br (C=C, C=N), 1635 and 1540 cm^{-1} (NHAc).

Anal. Calcd for $C_{16}H_{23}N_7O_3$ (361.42): C, 53.17; H, 6.41; N, 27.13. Found: C, 52.90; H, 6.44; N, 27.09.

A solution of **22** (1.99 g, 5.51 mmol) and chloro(*p*-methoxyphenyl)diphenylmethane (2.04 g, 6.60 mmol) in dry pyridine (50 mL) was stirred at room temperature in the dark for 24 h, at which time TLC (10% MeOH–$CHCl_3$) showed no **22** left. The solution was concentrated to a small volume and methylene chloride (50 mL), ice water (20 mL), and excess sodium bicarbonate were added. After vigorous stirring, the organic layer was separated and the aqueous layer extracted with additional methylene chloride (2 × 100 mL). The combined methylene chloride layers were dried ($CaSO_4$) and evaporated, leaving pale yellow solid foam (3.90 g). Such a sample (3.06 g) was stirred with concentrated ammonium hydroxide–water–pyridine (1:1:1, 150 mL) overnight. The white precipitate which formed was filtered off, washed with water (50 mL), and dried, leaving **23** as a white powder (2.10 g, 66% from **22**): collapses to a semiopaque glass at 150–154 °C, turns red at ~220 °C, becomes completely fluid at ~240 °C. Resolidification of such a sample from chloroform gave an analytical sample of **23** as a white powder: melting point, same as before resolidification; IR (KBr) 3410 br (OH, NH), 1635 very br, 1600 sh, 1560 sh cm^{-1} (NHAc, C=C, C=N); ^1H NMR (1:1 $CDCl_3$–CD_3OD) δ 8.08, 8.01 (both s, 2, purine H-2 and H-8), 7.4–6.5 (m, 14.4, $2C_6H_5$, OC_6H_4, partially exchanged NHC=O), 4.58 (br s), overlapped by 5.5–4.2 (m, 8, HDO from exchangeable protons, CHO, 2CHN, H_2O in solvent), 3.98 (br d, J = 4.5 Hz, 2, CH_2O), 3.75 (s, 3, OCH_3), 1.97 (s) overlapped by 2.6–1.8 (m, 6, CH_3C=O, CH_2, CH).

Anal. Calcd for $C_{33}H_{34}N_6O_4$ (578.68): C, 68.49; H, 5.92; N, 14.52. Found: C, 68.41; H, 5.99; N, 14.56.

Evaporation of the ammonium hydroxide–pyridine filtrate left a yellow glass (0.75 g), which solidified to a white powder on trituration with chloroform (680 mg, 21%); melting point and TLC (5% MeOH–$CHCl_3$) same as the analytical sample of **23.**

5′-*O*-(4-Methoxytrityl) Derivative (28) of 27. Methoxytritylation of **27** as described for the preparation of **23** gave crude **28** as a white solid on evaporation of the methylene chloride. Trituration with chloroform gave chromatographically homogeneous **28** (92–94%): melting point shrinks to glass at 118–130 °C, becoming fluid at ~160 °C; very difficult to handle when dry due to static; IR and NMR identical with those of an analytical sample.[32] Crystallization from methanol gave **28** as white granules: mp 195–196 °C; IR (KBr) 3400 (br), 3280, 3060 (OH, NH), 1640, 1555 (NHAc), 1600 br cm^{-1} (C=C, C=N); ^1H NMR (Me_2SO-d_6) δ 8.10, 7.72 (both s, 2, purine H-2 and H-8) 7.9–6.5 (m, 15, $2C_6H_5$, OC_6H_4, NHC=O), 5.4–4.8 (m, 2, OH, CHO), 4.2–3.8 (m, 2, 2CHN), 3.72 (s, 3, OCH_3), 3.44 (s, 5.8, $N(CH_3)_2$) partially overlapping 3.4–2.9 (m, 3.2, CH_2O, H_2O in solvent), 1.90 (s) overlapped by 2.4–1.4 (m, 6, CH_3C=O, CH_2, CH); mass spectrum (70 eV, 120 °C) *m/e* 606 (0.4, M^+), 333 (77.6, M^+ – MeOTr), 273 (MeOTr), 190 (14.8, $^+BHCH{=}CH_2$), 164 (38.1, BH_2^+), 163 (54.3, BH^+), 134 (17.7, BH^+ – NCH_3).

Anal. Calcd for $C_{35}H_{38}N_6O_4$ (606.74): C, 69.29; H, 6.31; N, 13.85. Found: C, 69.25; H, 6.25; N, 13.64.

Epimerization of 23 to 24. A stirred mixture of **23** (1.83 g, 3.17 mmol) and dry pyridine (25 mL) was cooled (ice bath) while methanesulfonyl chloride (0.37 mL, 4.8 mmol) was added. Stirring was continued for 3 days at room temperature. During this period, solid **23** slowly dissolved. TLC (10% MeOH–$CHCl_3$) showed two major spots at greater R_f than **23** and many minor spots. Ethanol (4 mL) was added and stirring was continued for several hours. The solution was evaporated to dryness and the residual brown glass dissolved in methylene chloride (100 mL). This solution was extracted with saturated sodium bicarbonate (15 mL), dried ($CaSO_4$), and evaporated to dryness, leaving tan solid foam (2.0 g). The foam was dissolved in 2-methoxyethanol (47.5 mL)–water (2.5 mL). Sodium acetate (1.30 g, 15.8 mmol) was added and the solution maintained at 60–65 °C overnight. At this point, TLC (10% MeOH–$CHCl_3$) showed one major spot at R_f slightly lower than that of **23.** The solution was evaporated to dryness and the residue dried by azeotroping with absolute ethanol, leaving yellow solid foam (3.30 g). Column chromatography (10% MeOH–$CHCl_3$) gave numerous impurities of greater R_f than **23** (0.29 g), followed by unreacted **23** (0.16 g, 9%), followed by **24** as white solid (1.22 g, 67%), sufficiently pure for use. Resolidification of such a sample from methanol gave **24** as white powder: softens at 160 °C, turns clear with effervescence at ~200 °C; IR (KBr) 3345, 3200, 3060 (OH, NH), 1660 very br, 1595, 1565 cm^{-1} (NHAc, C=C, C=N); ^1H NMR (1:1 $CDCl_3$–CD_3OD) δ 8.07, 8.00 (both s, 2, purine H-2 and H-8), 7.6–6.6 (m, 14, 2 C_6H_5, OC_6H_4), 4.67 (br s) overlapped by 5.5–4.0 (m, 10, HDO from exchangeable protons, CHO, 2CHN, CH_2O), 3.73 (s, 3, OCH_3), 1.97 (s) overlapped by 2.8–1.8 (m, 6, CH_3C=O, CH_2, CH).

Anal. Calcd for $C_{33}H_{34}N_6O_4$ (578.68): C, 68.49; H, 5.92; N, 14.52. Found: C, 68.56; H, 5.98; N, 14.53.

Epimerization of 28 to 29. A mixture of **28** (5.02 g, 8.27 mmol) and dry pyridine (65 mL) was stirred and cooled (ice bath) while methanesulfonyl chloride (0.97 mL, 12.4 mmol) was added. Stirring was continued for 3 days at room temperature. The same workup described for the epimerization of **23** gave red solid foam (5.22 g); TLC (10% MeOH–$CHCl_3$) shows at least five spots having R_f greater than **28** and one spot with the same R_f as **28**; ^1H NMR ($CDCl_3$) looks like complex mixture, no indication of mesylate. Treatment with sodium acetate as described above followed by column chromatography (1–2% MeOH–$CHCl_3$) gave **30** as a pale yellow solid foam (2.50 g, 51%): ^1H NMR ($CDCl_3$) δ 8.33 (s, 1, purine H-8), 7.74 (s, 1, purine H-2), 7.6–6.7 (m, 14, $2C_6H_5$, OC_6H_4), 5.38 (dd, $J_{2,1}$ = 6.5 Hz, $J_{2,3}$ = 10.0 Hz, 1, CHO), 5.9–4.1 (m, 2, 2CHN), 3.80 (s, 3, OCH_3), 3.57 (s) overlapped by 3.4–3.1 (m, 8, $N(CH_3)_2$, OCH_2), 2.7–2.1 (m, 3, CH, CH_2), 2.02 (s, 3, CH_3C=O). Several attempts to further purify this material by chromatography on silica gel preparative plates (5% MeOH–$CHCl_3$) gave slow conversion of the higher R_f **30** to a material having the same R_f as **28** or **29.**[33]

Continued elution of the column (2–4% MeOH–$CHCl_3$) gave **29** as a pale yellow solid foam (2.11 g, 40%); same R_f as **28** (10% MeOH–$CHCl_3$); NMR same as analytical sample. An analytical sample of **29** was obtained as a white solid foam by rechromatography on preparative plates (10% MeOH–$CHCl_3$): IR (KBr) 3280 br, 3050 (NH, OH), 1680 sh, 1650, 1560 (NHAc), 1600 br cm^{-1} (C=C, C=N); ^1H NMR ($CDCl_3$) δ 8.16 (s, 1, purine H-2), 7.71 (s, 1, purine H-8), 7.6–6.6 (m, 14, $2C_6H_5$, OC_6H_4), 6.63 (d, J = 7.0 Hz, 1, NHC=O), 5.39 (br s, 1, OH), 4.8–3.8 (m, 3, CHN, 2CHO), 3.77 (s, 3, OCH_3), 3.49 (s) overlapped by 3.7–2.9 (m, 8, $N(CH_3)_2$, OCH_2), 1.93 (s) overlapped by 2.7–1.2 (m, 6, CH_3C=O, CH_2, CH); mass spectrum almost identical with that of stereoisomer **28.**

Anal. Calcd for $C_{35}H_{38}N_6O_4 \cdot 2H_2O$ (642.77): C, 65.40; H, 6.59; N, 13.08. Found: C, 65.63; H, 6.56; N, 13.10.

Detritylation of such samples of **29** to **32** (see below) indicate contamination by a few percent of **28.** Attempts to effect complete epimerization by using 2 equiv of methanesulfonyl chloride resulted in formation of a new product **31** (11%); with 3 equiv of methanesulfonyl chloride, the yield of **31** rose to 26% and the **29** isolated was still contaminated by unreacted **28.** Use of more methanesulfonyl chloride also resulted in more decomposition; the reactions were darker and less of the starting material was accounted for, with the dark material staying on the silica gel columns. A sample of **31** was separated from **29** and **30** by chromatography on preparative plates (10% MeOH–$CHCl_3$). Extraction of the band having R_f between that of **29** and **30** gave **31** as a pale yellow solid foam: IR (KBr) 3260 br (OH, NH), 1595 br (C=C, C=N), 1320, 1140 cm^{-1} (-SO_2NH-); ^1H NMR ($CDCl_3$) δ 8.10 (s, 1, purine H-2), 7.55 (s) overlapped by 8.0–6.6 (m, 15, purine H-8, $2C_6H_5$, C_6H_4), 6.3 (m, 1, OH) partially overlapping 5.49 (d, J = 6.0 Hz, 1, $NHSO_2CH_3$), 3.73 (s, OCH_3) and 3.45 (s, $N(CH_3)_2$) over-

lapped by 4.8–3.2 (m, 14, CHO, 2CHN, CH_2O), 2.80 (s) overlapped by 3.0–1.4 (m, 6, $NHSO_2CH_3$, CH, CH_2); mass spectrum (70 eV, 100 °C) *m/e* (relative intensity) no M^+, 369 (4.0, $M^+ - MeOTr$), 273 (100, MeOTr), 164 (90.6, BH_2^+), 163 (28.3, BH^+), 134 (49.7, $BH^+ - NCH_3$).

Anal. Calcd for $C_{34}H_{38}N_6O_5S \cdot \frac{1}{2}H_2O$ (651.80): C, 62.65; H, 6.03; N, 12.89; S, 4.92. Found: C, 62.86; H, 6.17; N, 12.91; S, 4.68.

9-[3β-Acetamido-2β-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]adenine (25). A solution of **24** (931 mg, 1.61 mmol) in 97% formic acid (25 mL) was stirred at room temperature for 4 h and then diluted with 1:1 toluene–1-butanol (50 mL). The solution was concentrated to a small volume, diluted with additional toluene–1-butanol (50 mL), and reconcentrated. This process was repeated again, and then the residue was evaporated to dryness, leaving a white powder. After extraction with hexane (100 mL) the powder was dissolved in methanol (400 mL) and stirred with Amberlite IRA-400 (OH^-) resin (20 mL). Evaporation left chromatographically homogeneous **25** as a glass (457 mg, 93%). Crystallization of such a sample from absolute ethanol gave **25** as white granules (85%): R_f (20% MeOH–$CHCl_3$) same as **20**; mp 153–154 °C effervesces; UV max ($\epsilon \times 10^{-3}$) 258 nm (14.2) in 0.1 N HCl, 260 nm (14.4) in H_2O, 260 nm (14.7) in 0.1 N NaOH; IR (KBr) 3500–3050 (NH, OH), 1673, 1607 (C=C, C=N), 1635, 1565 cm^{-1} (NHAc); ^1H NMR (Me_2SO-d_6) δ 8.13, 8.07 (both s, 2, purine H-2 and H-8), 7.67 (d, 1, NHC=O), 7.10 (br s, 2, NH_2), 6.5–3.0 (m, 7.5, 2OH, CHO, 2CHN, CH_2O, H_2O in solvent), 1.90 (s) overlapped by 2.5–1.1 (m, 6, CH_3C=O, CH, CH_2); mass spectrum (70 eV, 175 °C) *m/e* (relative intensity) 306 (M^+), 275 (1.8, $M^+ - CH_2OH$), 162 (33.3, $^+BHCH{=}CH_2$), 154 (30.9 $M^+ - B - H_2O$), 136 (100, BH_2^+), 135 (24.4, BH^+).

Anal. Calcd for $C_{13}H_{18}N_6O_3$ (306.34): C, 50.97; H, 5.92; N, 27.44. Found: C, 50.94; H, 6.18; N, 27.41.

9-[3β-Acetamido-2β-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]-6-dimethylaminopurine (32). Detritylation of samples of **29** or mixtures of **29** and **30** and workup, as described for the preparation of **25**, gave **32** (often contaminated by a few percent of **27**) as a solid foam (89%). Two crystallizations from absolute ethanol–ethyl acetate were sufficient to remove any contaminating **27** (detectable at a lower R_f on TLC with 20% MeOH–$CHCl_3$), giving **32** as white granules (76%): mp 169–170 °C; UV max ($\epsilon \times 10^{-3}$) 268 nm (18.2) in 0.1 N HCl, 276 nm (18.4) in H_2O, 276 nm (18.5) in 0.1 N NaOH; IR (KBr) 3325, 3245, 3060 (OH, NH), 1650, 1550 (NHAc), 1595 cm^{-1} (C=C, C=N); mass spectrum (70 eV, 250 °C) *m/e* (relative intensity) 334 (3.4, M^+), 303 (1.9, $M^+ - CH_2OH$), 190 (22.6, $^+BHCH{=}CH_2$), 164 (100, BH_2^+), 163 (58.9, BH^+).

Anal. Calcd for $C_{15}H_{22}N_6O_3$ (334.39): C, 53.88; H, 6.63; N, 25.13. Found: C, 54.15; H, 6.56; N, 24.92.

9-[3β-Amino-2α-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]adenine (21). A solution of **20** (250 mg, 0.771 mmol) in 0.5 N barium hydroxide (10 mL) was refluxed under nitrogen for 6 h. The solution was then neutralized with CO_2 and the precipitated $BaCO_3$ removed by filtration through Celite. The filtrate was evaporated to dryness, leaving a white solid foam (225 mg) which appears from IR to be the acetic acid salt of **21**. The foam was dissolved in MeOH and stirred with Amberlite IRA-400 (OH^-) resin (10 mL). Evaporation left white solid foam which solidified from absolute ethanol, giving **21** as white powder (134 mg, 66%):[34] R_f (20% MeOH–$CHCl_3$) lower than that of **20**; mp 199–201 °C; UV max ($\epsilon \times 10^{-3}$) 258 nm (14.3) in 0.1 N HCl, 260 nm (14.9) in H_2O, 260 nm (14.9) in 0.1 N NaOH; IR (KBr) 3480, 3320, 3180, 3120 (OH, NH_2), 1680, 1650, 1605, 1570 cm^{-1} (C=C, C=N, NH_2); mass spectrum (70 eV, 200 °C) *m/e* (relative intensity) 264 (0.3, M^+), 233 (0.7, $M^+ - CH_2OH$), 216 (1.6, $M^+ - CH_2OH - NH_3$), 215 (2.0, $M^+ - CH_2OH - H_2O$), 190 (6.2, B + 56), 178 (6.4, $^+BHCH{=}CHOH$), 162 (32.4, $^+BHCH{=}CH_2$), 136 (87.5, BH_2^+), 135 (16.6, BH^+), 112 (100, $M^+ - B - H_2O$).

Anal. Calcd for $C_{11}H_{16}N_6O_2$ (264.30): C, 49.99; H, 6.10; N, 31.80. Found: C, 49.92; H, 6.09; N, 31.81.

9-[3β-Amino-2β-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]adenine (26). A solution of **25** (165 mg, 0.539 mmol) in 0.5 N barium hydroxide (10 mL) was refluxed under nitrogen for 2 h, at which time TLC (20% MeOH–$CHCl_3$) showed one spot at R_f lower than **25**. The solution was diluted with ethanol (5 mL) and neutralized with carbon dioxide. The barium carbonate was removed by filtration through Celite. Evaporation of the filtrate and drying by evaporation of several portions of absolute ethanol left a white solid foam (169 mg, 94%), the acetic acid salt hemihydrate of **26**:[35] UV max ($\epsilon \times 10^{-3}$) 258 nm (14.4) in 0.1 N HCl, 260 nm (14.5) in H_2O, 260 nm (14.8) in 0.1 N NaOH; IR (KBr) 3500–3050, 2800–2500 (OH, NH_2, NH_3^+), 1650 br, 1600 (C=C, C=N), 1575, 1520, 1410 br cm^{-1} ($-NH_3^+OAc^-$); mass spectrum (20 eV, 100 °C) *m/e* (relative intensity), 265 (1.4), 264 (0.3, M^+ of free base), 233 (0.8, $M^+ - CH_2OH$), 216 (4.9, $M^+ - CH_2OH - NH_2$), 162 (16.9, $^+BHCH{=}CH_2$), 136 (74.1, BH_2^+), 135 (13.2, BH^+), 112 (78.3, $M^+ - B - H_2O$), 60 (89.2), 45 (100), 43 (92.8).

Anal. Calcd for $C_{11}H_{16}N_6O_2 \cdot CH_3CO_2H \cdot \frac{1}{2}H_2O$: C, 46.84; H, 6.35; N, 25.21. Found: C, 47.07; H, 6.43; N, 24.96.

9-[3β-Amino-2β-hydroxy-4α-(hydroxymethyl)cyclopent-1α-yl]-6-dimethylaminopurine (33). Hydrolysis of **32** (632 mg, 1.89 mmol) exactly as described for the synthesis of **26** gave the acetic acid salt hemihydrate of **33** as a white solid foam (649 mg, 95%):[35] TLC (20% MeOH–$CHCl_3$) one spot at R_f lower than that of **32**; UV max ($\epsilon \times 10^{-3}$) 268 nm (19.3) in 0.1 N HCl, 276 nm (19.5) in H_2O, 276 nm (19.6) in 0.1 N NaOH; IR (KBr) 3500–3050, 2800–2400 (OH, NH_2, NH_3^+), 1600 br, 1560, 1410 cm^{-1} (C=C, C=N, $-NH_3^+OAc^-$); mass spectrum (70 eV, 150 °C) *m/e* (relative intensity) 293 (0.8), 292 (0.6, M^+ of free base), 244 (6.5, $M^+ - H_2O - HCHO$), 190 (16.0, $^+BHCH{=}CH_2$), 164 (51.8, BH_2^+), 163 (33.5, BH^+), 134 (28.9, $BH^+ - NCH_3$), 112 (40.2, $M^+ - B - H_2O$), 60 (61.6), 45 (100), 43 (93.4).

Anal. Calcd for $C_{13}H_{20}N_6O_2 \cdot CH_3CO_2H \cdot \frac{1}{2}H_2O$: C, 49.85; H, 6.97; N, 23.26. Found: C, 49.67; H, 7.05; N, 22.98.

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Registry No.—**1**, 61865-48-3; **2a**, 61865-49-4; **2b**, 65898-96-6; **3a**, 65942-42-9; **3b**, 61865-50-7; **3c**, 65969-56-4; **4a**, 65898-97-7; **4b**, 65898-98-8; **5**, 65898-99-9; **6a**, 61865-52-9; **6b**, 62357-71-5; **6c**, 65899-00-5; **7a**, 61865-53-0; **7b**, 65899-01-6; **8a**, 61865-65-4; **8b**, 65899-02-7; **9a**, 61865-54-1; **9b**, 65899-03-8; **9c**, 65899-04-9; **10a**, 61865-66-5; **10c**, 65899-05-0; **11a**, 65841-40-4; **11b**, 65941-41-5; **15**, 65942-43-0; **16a**, 61865-55-2; **16a** HCl, 65941-42-6; **16b**, 61865-63-2; **17a**, 65898-88-6; **17b**, 65898-89-7; **17c**, 65898-90-0; **18a**, 61865-67-6; **18b**, 61865-68-7; **19**, 61865-56-3; **20**, 61865-57-4; **21**, 61914-36-1; **22**, 61865-58-5; **23**, 61865-59-6; **24**, 61914-32-7; **25**, 61914-33-8; **26**, 61865-69-8; **27**, 61865-60-9; **28**, 61865-61-0; **29**, 61914-34-9; **30**, 65898-91-1; **31**, 65942-44-1; **32**, 61914-35-0; **33**, 61865-71-2; 2-(hydroxymethyl)-4-acetamidopentanedial, 65898-92-2; 4α-acetamido-3β-amino-2α-hydroxy-1α-cyclopentanemethyl benzoate, 65898-93-3; 5-amino-4,6-dichloropyrimidine, 5413-85-4; (±)*N*-acetyl-9-[β-(3α-amino-2α-hydroxy)cyclopentyl]-6-dimethylaminopurine, 65898-94-4; 3α-hydroxy-2β,4α-bis(3-chloro-4-aminopyrimidin-6-yl)-1α-cyclopentanemethanol, 65898-95-5.

References and Notes

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(20) Alternatively, the ester groups of **9a** could be removed with ammonia–methanol to give the diacetamido diol, which could then be treated with hydrochloric acid to give **16a**. Benzoate **9c**, when subjected to the same treatment with hydrochloric acid, was hydrolyzed to a monoacetamide which retained the benzoyl blocking group on the primary hydroxyl. Thus, neighboring-group participation by the primary hydroxyl group does not account for the acid lability of one of the acetamido groups of **9a**.
(21) L. Goodman, *Adv. Carbohyd. Chem.*, **22**, 109 (1967), and references cited therein.
(22) F. W. Lichtenthaler and P. Emig in "Synthetic Procedures in Nulceic Acid Chemistry", Vol. 1, W. W. Zorbach and R. S. Tipson, Ed., Interscience, New York, N.Y., 1968, pp 232–235, and references cited therein.
(23) When the inversion of **28** was attempted with 2 equiv of tosyl chloride in pyridine at room temperature for 5 days, most of the **28** was recovered.
(24) B. R. Baker and R. E. Schaub, *J. Am. Chem. Soc.*, **77**, 5900 (1955).
(25) R. Vince and S. Daluge, manuscript in preparation.
(26) Repeated attempts to dry this solid in a vacuum desiccator for a few hours or overnight resulted in loss of the product. The solid turned from a white fluffy material to a shrunken tan mass no longer soluble in CCl_4. Although it was occasionally possible to dry samples of tosyl cyanide, especially in smaller runs, the unpredictability of this decomposition led to changing the workup. Another person in this lab reported an explosion of sufficient force to blow the top off a large vacuum desiccator when drying a 100-g sample of tosyl cyanide.
(27) Failure to adequately cool in one run resulted in generation of considerable heat; **1** was separated with difficulty in low yield (~30%) from black tarry material by column chromatography.
(28) Attempts to characterize the free amine were unsuccessful as it appears to decompose on contact with air. Solutions darkened rapidly and attempts to solidify the material gave only colloidal yellow solid that turned to gum on contact with the air. Immediately after opening the Parr shaker, TLC (20% MeOH–$CHCl_3$) showed one major spot and one minor lower R_f spot. However, after a few hours, numerous new spots started to appear.
(29) An attempt to carry out the acetylation with acetic anhydride–pyridine gave tar. Apparently the free amine is base sensitive.
(30) In order to confirm spectral assignments, a sample of (±)-9-[β-(3α-amino-2α-hydroxy)cyclopentyl]-6-dimethylaminopurine 2′,3′-carbamate[3a] was acetylated in acetic anhydride–pyridine and the *N*-acetyl derivative characterized: 74% (from ethyl acetate–hexanes); mp 142–143 °C; IR (KBr) 1790 (urethane C=O, appears at 1779 before acetylation), 1705 cm^{-1} ($AcNCO_2$); ^1H NMR (Me_2SO-d_6) δ 2.40 (s, CH_3CONCO_2–). Anal. C, H, N.
(31) Preparative TLC (15% MeOH–$CHCl_3$) of such mother liquor contents gave a pure sample of the greater R_f impurity as a pale yellow solid foam (3%). Elemental analysis, mass spectrum, and NMR agree for $C_{14}H_{16}N_8O_2Cl_2 \cdot CH_3CO_2Et$ (ethyl acetate used to obtain foam). Apparently, hydrolysis of **9a** results in a small amount of diamine which reacts with two molecules of 5-amino-4,6-dichloropyrimidine.
(32) The chloroform mother liquors contained, in addition to more **28**, a higher R_f product. Purification of a portion of such material by chromatography on preparative plates developed in 15% MeOH–$CHCl_3$ gave a colorless glass (~5%) which NMR ($CDCl_3$) showed to be a di-4-methoxytrityl derivative.
(33) The oxazoline intermediate formed in the epimerization of **23** is hydrolyzed completely to **24** by sodium acetate, but the same hydrolysis conditions here leave a considerable amount of unhydrolyzed oxazoline. When the hydrolysis of the crude reaction products was carried out for longer periods (2–3 days) at 65 °C or at reflux temperature overnight, the reaction mixture turned dark brown and the combined yield of **29** and **30** was lower, but the ratio of **29**/**30** was greater. In practice such mixtures of **29** and **30** were not separated, but converted by formic acid treatment to **32** (see below).
(34) TLC (20% MeOH–$CHCl_3$) of the mother liquor showed a mixture of unhydrolyzed **20** and **21**.
(35) An attempt was made to characterize the free base by neutralization of the acetic acid salt with Amberlite IRA-400 (OH^-) resin as for the synthesis of isomer **21**. The gummy material isolated could not be solidified and appeared to decompose slowly in air. This behavior has been noted with other *cis*-aminocyclopentanols, in contrast to the stable, solid trans isomers.[3g]

Convenient Synthesis of Some Purine 8,5′-Imino Cyclonucleosides

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Synthesis of some purine 8,5′-imino and aminimino cyclonucleosides was achieved starting from 2′,3′-*O*-isopropylidene-5′-*O*-tosyl-8-bromoadenosine (**1**) and anhydrous hydrazine. **1** with anhydrous hydrazine in ethanol gave 8,5′-aminimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (**2a**), which was oxidatively converted to the corresponding 8,5′-imino cyclonucleoside (**2b**). The *N*-amino group in **2a** was quantitatively protected with hot acetic acid and phthalic anhydride to afford the 8,5′-acetamidimino (**2c**) and 8,5′-phthalimidimino analogues (**8**), respectively. Acidic treatment of **2a** and **2b** gave the parent cyclonucleosides **4a–b**. On the other hand, treatment of **2a**, **2c**, and **8** with nitrous acid gave the corresponding inosine analogues **5**, **7**, and **9**. Dephthaloylation of **9** with methanolic hydrazine gave 8,5′-aminimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (**10**) as a 1:1 complex with the released phthalazine-1,4-dione. Treatment of **5** and **10** with 90% trifluoroacetic acid gave the corresponding parent hypoxanthine analogues **6** and **11**, while the treatment of a mixture of **10** and **11** with methanol–concentrated hydrochloric acid (3:1) gave the derivative of 2,5′-aminimino-bridged AICA riboside (**12**).

In recent years a large number of cyclonucleosides have been synthesized as basic models for gaining insight into the relationship between conformation and biological activity[1] or physicochemical properties.[2] Limiting the viewpoint to the synthesis in the purine series, the accumulated data have demonstrated the possibility of bonding the 8 position of the base with $C_{2'}$, $C_{3'}$, and $C_{5'}$ of the sugar through a heteroatom (O, S, or limitedly N)[3] or directly with $C_{5'}$.[4] Although the synthesis of oxygen- and sulfur-bridged nucleosides has been and continues to be elaborated for various purine nucleosides,[3c,5] the recorded synthesis of nitrogen isostere is quite limited. The hitherto known four compounds of this class are all 8,2′-imino cyclonucleosides obtainable by heating 8-amino-2′-*O*-triisopropylbenzenesulfonyladenosine with base[3b] or of preformed 8-aminopurinenucleosides with diphenyl carbonate.[3c]

8-Aminoadenosine is known to exhibit significant inhibition of sarcoma 180 ascites cells and is resistant toward adenosine deaminase.[6] 8-Aminopurinenucleosides also attracted much interest because of their structural similarity to a paralytic marine toxin, saxitoxin.[7] These findings gave an impetus to the extensive synthesis of a variety of 8-aminopurinenucleosides and their analogues.[8]

In view of these facts, synthesis of purine 8,5′-iminonucleosides and analogues which are restricted in anti conformation seemed to be of primary importance, and we herein describe a simple and effective synthesis of this class of compounds from 2′,3′-*O*-isopropylidene-5′-*O*-tosyl-8-bromoadenosine (**1**)[9] and hydrazine as the nitrogen source.

To circumvent the formidable N^3,$C_{5'}$ cyclization of **1** (this excludes a priori the application of the methods used for the synthesis of 8,2′-imino purinenucleosides), **1** was treated with

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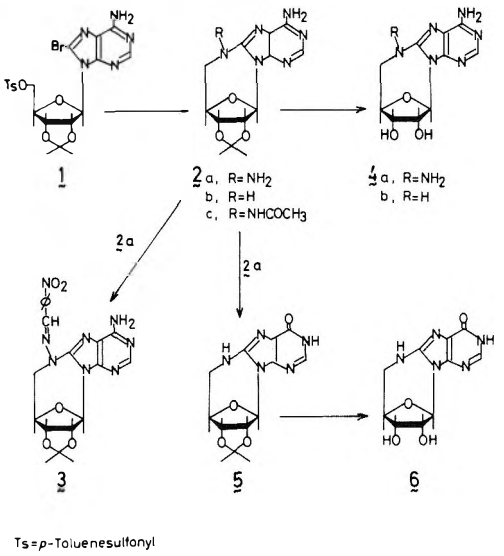
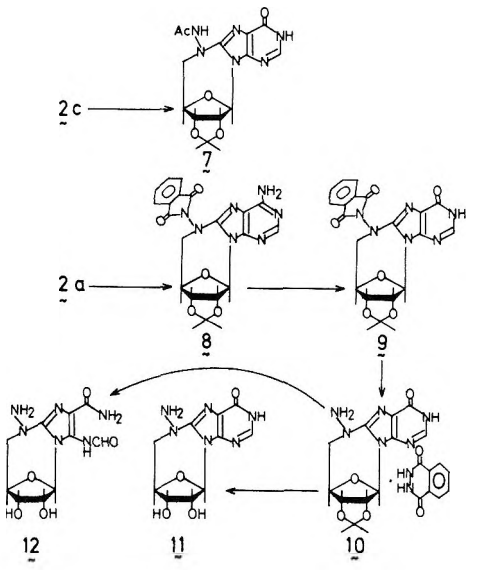
Scheme I



Scheme II



a large excess of hydrazine at ambient temperature to afford 8,5′-aminimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (**2a**) as crystals in 90% yield (Scheme I). Its structure was easily deduced from the UV absorption at 272 nm comparable with those of 8-aminoadeninenucleosides[8b,c] and the ^{1}H NMR spectrum, in which two amino signals appeared at 4.92 and 6.81 ppm, the former being assigned to the hydrazino group. The other signals were also consistent with the proposed structure. The presence of a 1,1-disubstituted hydrazino structure was further confirmed by the preparation of its *p*-nitrobenzylidene derivative (**3**) (see Experimental Section). In this series of work, synthesis of parent 8,5′-aminimino-bridged compounds was also intended, since it was conceived that this type of compounds represents analogues of 8-aminopurinenucleosides retaining a "naked" amino group in the anti conformation and hence interesting substrates for biological survey. **2a** was quantitatively oxidized to 8,5′-imino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (**2b**) with iodine pentoxide in 85% THF. The oxidative elimination of the *N*-amino group was tried in various ways. Thus, lead tetraacetate, mercuric oxide, potassium permanganate, and sodium metaperiodate also proved to be applicable using the standard procedures, giving the same compound in moderate to good yields, but the iodine pentoxide procedure seemed to be the most simple and time-saving. The structure of **2b** was fully confirmed by the spectroscopic data described in the Experimental Section. An attempt to deacetonate **2a** with hot 80% acetic acid failed, giving instead a good yield of 8,5′-acetamidimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (**2c**). It was found afterward that **2a** could be quantitatively converted to **2c** using hot acetic acid and this compound appeared to be a hopeful intermediate for the transformation of the base moiety. Deprotection of **2a** and **2b** to 8,5′-aminimino-9-(5′-deoxy-β-D-ribofuranosyl)adenine (**4a**) and 8,5′-imino-9-(5′-deoxy-β-D-ribofuranosyl)adenine (**4b**) was achieved by the use of more stronger acids. The general analysis and spectroscopic data confirmed their structures (see Experimental Section).

We next attempted to synthesize the hypoxanthine analogues of **4a,b** as the first step of base transformation starting from the same key intermediate (**2a**). Thus, the conventional diazotization converted **2a** into 8,5′-imino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (**5**) in 72% isolated yield in one step.[10] Desopropylidenation of **5** with 90% trifluoroacetic acid proceeded smoothly to give the parent compound 8,5′-imino-9-(5′-deoxy-β-D-ribofuranosyl)hypoxanthine (**6**). We next challenged the synthesis of 8,5′-aminimino-9-(5′-deoxy-β-D-ribofuranosyl)hypoxanthine (**11**) (Scheme II) starting from the above obtained protected nucleoside (**2c**). **2c** was treated with nitrous acid to give 8,5′-acetamidimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (**7**), deacetylation of which, however, met with difficulty when several kinds of acids and bases were applied. Selective deisopropylidenation using 90% trifluoroacetic acid seemed to have occurred in terms of TLC, but gave no isolable crystalline product.[11] We then selected phthalic anhydride as a protecting agent mainly from a consideration on crystallinity and stepwise deprotection. Thus, **2a** was converted to 8,5′-phthalimidimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (**8**) using the standard method and the latter diazotized to obtain 8,5′-phthalimidimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (**9**); both steps proceeded almost quantiatively. The location of the phthalimino group in both compounds was evident from the lack of an *N*-amino signal in the NMR spectra. Treatment of **9** with 0.2 M methanolic hydrazine at room temperature gave a 84% isolated yield of 8,5′-aminimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (**10**) as a 1:1 complex with the released phthalazin-1,4-dione.[12] Several trials for removing the phthalazin from the complex were unsuccessful, especially because both components contain the similar lactam group, excluding the conventional separation method using aqueous base. Accordingly, the complex was directly submitted to acid treatment, after which **11** was fortunately isolated as crystalline hydrochloride hemi-methanolate. The pyrimidine part in such an 8-aminohypoxanthine system appeared to be particularly sensitive to acid as shown by an experiment using aqueous hydrochloric acid. Thus, the treatment of a mixture of **10** and **11** with a mixture of concentrated hydrochloric acid and methanol (1:3) at room temperature yielded 2,5′-aminimino-1-(5′-deoxy-β-D-ribofuranosyl)-5-*N*-formylamino-imidazole-4-carboxamide (**12**) as hydrochloride, which would, however, be another interesting substrate when compared with the recently exploited 2-substituted derivatives of 5-amino-1-β-D-ribofuranosylimidazole-4-carboxamide (AICA riboside).[13] The ring-opened structure of **12** was supported by the extensive bathochromic shift of the major UV absorption as compared with the closed structure.[14]

At this point, some comments on the optical and mass spectroscopic behavior of these compounds are in order. CD spectra[15] of **4a,b, 6, 11,** and **12** (Figures 1 and 2) show strong positive Cotton effects in the 255–270-nm region and reinforce the typical anti conformation of these compounds. The

Table I. Principal Mass Spectral Peaks in the Spectra of Purine 8,5′-Aminimino and Imino Cyclonucleosides (4a, 4b, and 6)[a]

Compound	M	M − 29 (*b*)	M − 57 (*c*)	M − 87 (*d*)	M − 88 (*e*)	M − 88 − X (*f*)	M − 101 (*g*)	*a*	*a* + 1
4a	279	250	222	- - -	191	175	178	165	166
	(100)	(2.0)	(4.1)		(3.3)	(14.3)	(8.7)	(57)	(11.8)
4b	264	235	207	177	176	175	163[b]	150	151
	(100)	(6.7)	(17.9)	(3.9)	(8.0)	(21.7)	(30.6)	(72.4)	(50)
6	265	236	208	178	177	176	164	151	152
	(65.7)	(9.3)	(21.1)	(4.1)	(11.3)	(34.7)	(29.7)	(100)	(83)

[a] The upper number represents the *m/e* of a given ion; the lower is the intensity relative to the base peak. [b] The same ion also occurs in the spectrum of **4a** in a relative intensity of 35.1%.

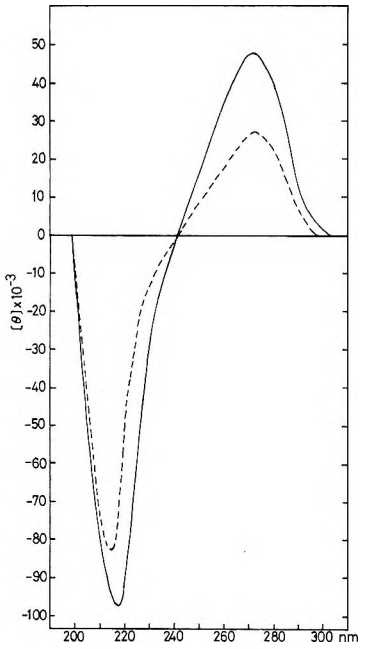


Figure 1. CD spectra of 8,5′-aminimino-9-(5′-deoxy-β-D-ribofuranosyl)adenine (**4a**) (—) and 8,5′-imino-9-(5′-deoxy-β-D-ribofuranosyl)adenine (**4b**) (- - -) in methanol.

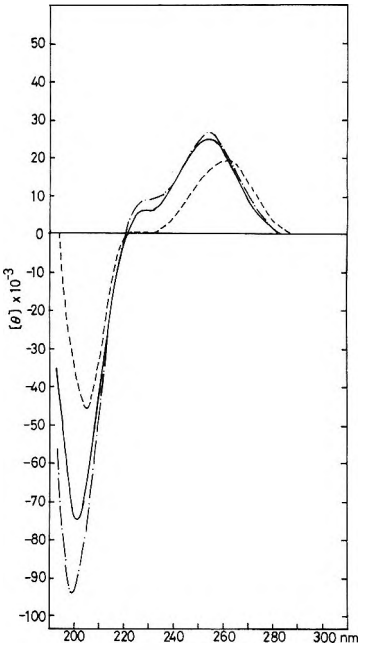
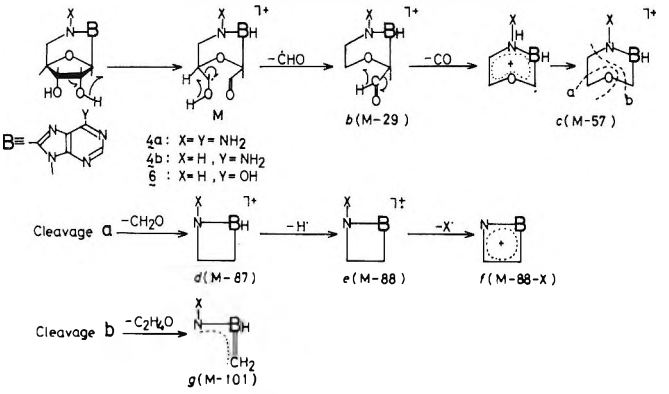
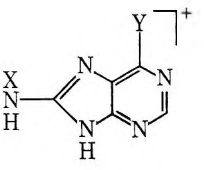


Figure 2. CD spectra of 8,5′-imino-9-(5′-deoxy-β-D-ribofuranosyl)-hypoxanthine (**6**) (- - -) in water, and 8,5′-aminimino-9-(5′-deoxy-β-D-ribofuranosyl)hypoxanthine hydrochloride (**11**) (—) and 2,5′-aminimino-1-(5′-deoxy-β-D-ribofuranosyl)-5-*N*-formylaminoimidazole-4-carboxamide hydrochloride (**12**) (· - · - · - ·) in methanol.

spectrum of **12** (this seems to be the first example recorded for a nucleoside with an opened base) suggests the applicability of the empirical rule of circular dichroism to nucleosides with such an opened base structure. The mass spectra of available samples, **4a,b** and **6** were also recorded[16] and compared with those of the other oxygen- and sulfur-bridged adenosine 8-cyclonucleosides.[17] Although high resolution measurements were not conducted, the marked spectral correlation between these compounds and the known fragmentation patterns of purine and pyrimidine cyclonucleosides[17-19] permit some crude generalizations of the principal cleavage processses. The plausible fragmentation pathways in the upper mass range and the relative peak intensities are given in Scheme III and Table I. As is generally observed with cyclonucleosides,[17-19] the three compounds show the high stability of the molecular ion radicals: in two (**4a** and **4b**) of the three the molecular ions appeared as base peaks. The observation of abundant 8-amino and 8-aminimino purine radicals is also in agreement with the previous observation.[17] These ions, which seem to have formed by mechanisms involving a double hydrogen transfer, are formulated as *a* according to the precedent literature[17] and given in the table with the one mass unit higher ions (*a* + 1). Notably, M − 29 and M − 57 ion peaks shown by our three compounds lack from the spectra of 8,5′-*O*- and *S*-cycloadenosines,[17] while M − 59 and M − 77

Scheme III. Mass Spectral Fragmentations of Purine 8,5′-*N*-Cyclonucleosides (4a, 4b, and 6)





a

X = Y = NH_2
X = H; Y = NH_2
X = H; Y = OH

ions observed for one of the latter were mostly absent or negligible in the spectra of our compounds. Appreciable amounts of M − 89 (corresponding to M − 88 − X in Table I) and M − 101 ions were found also in our case. The common apparition of M − 29 and M − 57 ions in the spectra of **4a,b** and **6** suggests a different start of fragmentation, and this could be rationalized by initial cleavage between $C_{2'}$ and $C_{3'}$ with the concurrent shift of a hydroxyl hydrogen to the base (probably triggered by favorable ionization at 8-imino nitrogen) (Scheme III). Subsequent ejections of an aldehyde radical and a ketone would give ion c (M − 57). Indeed, in the spectra of pyrimidine O^6,5′-cyclonucleosides,[18] somewhat similar seven-membered heterocyclic fragment (M − 59) and M − 29 ion were observed. Thus, the slight discrepancy of the fragmentations of our purine 8-*N*-cyclonucleosides from those of pyrimidine O^6,5′-cyclonucleosides and 8,5′-*O*- and *S*-cycloadenosines seems to be conditioned by the presence of a more ionizable 8-imino group.[20] Cleavage of ion c along the dotted line a and b would reasonably generate the fused imidazole cation *f* and *g* ions (or its closed alternative).

The above exemplified aminimino bridging synthetic method would provide a new and in principle versatile route to a variety of purine 8,5′- and as yet unknown 8,3′-imino cyclonucleosides, especially when the precursors with a leaving group at $C_{5'}$ or $C_{3'}$ are heat-sensitive.[21] Furthermore, the strong nucleophilicity and the oxidant-sensitive nature of the introduced *N*-amino group would permit its highly selective protection or its complete elimination to an imine with a wide variety of oxidants which can specifically transform the base or sugar moiety. Further studies along this line are under way.

Experimental Section

8,5′-Aminimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (2a). To a stirred suspension of **1** (6.02 g, 11.14 mmol) in ethanol (76 mL) was added 100% hydrazine monohydrate (24 mL). After 4 h, the resulting solution was left at room temperature for 2 days. The mixture was evaporated and the residue repeatedly co-evaporated with ethanol to remove excess hydrazine. The obtained pasty residue was partitioned between chloroform (300 mL) and water (30 mL). The separated chloroform layer was dried over sodium sulfate and evaporated to give a powder, which was recrystallized from a mixture of ethanol and chloroform to afford 3.024 g (90.10%) of fine needles (7–10 h reaction usually gave satisfactory yields of 80 to 85%): mp 232–234 °C; λ_{max}^{MeOH} (ε) 215 (27 100) and 272 nm (21 800); ^{1}H NMR (100 MHz, Me_2SO-d_6) δ 1.29 and 1.47 (each 3 H, s, isopropylidene methyls), 3.44–3.69 (2 H, m, 5′-methylene), 4.58 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{2'}$ or $H_{3'}$), 4.64 (1 H, d, J = 1 Hz, $H_{4'}$), 4.92 (2 H s, N–NH_2, D_2O exchangeable), 4.97 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{3'}$ or $H_{2'}$), 6.14 (1 H, s, $H_{1'}$), 6.81 (2 H, br s, 6-amino group, D_2O exchangeable) and 8.05 (1 H, s, H_2).

Anal. Calcd for $C_{13}H_{17}N_7O_3$: C, 48.89; H, 5.37; N, 30.71. Found: C, 48.94; H, 5.33; N, 30.70.

***p*-Nitrobenzylidene Derivative of 2a (3).** A mixture of **2a** (100 mg, 0.313 mmol), *p*-nitrobenzaldehyde (47.5 mg, 0.314 mmol), and granules of calcium chloride (50 mg) in ethanol (5 mL) was heated to reflux. After 1 h and 40 min, further *p*-nitrobenzaldehyde (47.5 mg) was added and the mixture heated for further 30 min. Then, further *p*-nitrobenzaldehyde (47.5 mg) and calcium chloride (20 mg) were added. After a total of 3.5 h, the mixture was cooled and adjusted to pH 8 with a mixture of methanol and concentrated ammonium hydroxide (3:1), and the yellow precipitate was collected by suction. Recrystallization from methanol gave 89 mg (63%) of yellow needles (**3**): mp 290–291 °C; λ_{max}^{MeOH} (ε) 211 (25 500) and 273 nm (24 900); ^{1}H NMR (60 MHz, Me_2SO-d_6) δ 1.26 and 1.48 (each 3 H, s, isopropylidene), 3.60–3.82 (2 H, m, 5′-methylene), 4.46–4.88 (4 H, m, $H_{2'}$, $H_{3'}$, $H_{4'}$, and –N=CH–), 6.20 (1 H, s, $H_{1'}$), 7.23 (2 H, br s, D_2O exchangeable, 6-amino group), 7.85–8.39 (4 H, m, phenyl protons), and 8.82 (1 H, s, H_2).

Anal. Calcd for $C_{20}H_{20}O_5N_8$: C, 55.09; H, 4.46; N, 24.77. Found: C, 53.15; H, 4.55; N, 24.80.

8,5′-Imino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (2b). To a stirred solution of **2a** (1 g, 3.13 mmol) in 85% THF (64 mL) was added at 0 °C iodine pentoxide (1.1 g, 3.3 mmol). After stirring at this temperature for 30 min and then at room temperature for another 30 min, the mixture was neutralized with a mixture of methanol and concentrated ammonium hydroxide (3:1) and evaporated. The residue was taken into water (40 mL) and repeatedly extracted with chloroform until the aqueous phase indicated no product on a TLC plate. The combined chloroform solution was decolorized with 10% sodium thiosulfate solution, dried over sodium sulfate, and evaporated to give homogeneous crystals. Recrystallization from ethanol gave 1 g (95%) of **2b** as an ethanolate of mp 184–186 °C. This product also solvates with chloroform or ethyl acetate. λ_{max}^{MeOH} (ε) 211 (31 300) and 272 nm (21 600); ^{1}H NMR (100 MHz, Me_2SO-d_6, solvent signals excluded) δ 1.28 and 1.47 (each 3 H, s, isopropylidene methyls), 3.08–3.51 (2 H, m, 5′-methylene), 4.56 (1 H d, $J_{2',3'}$ = 6 Hz, $H_{2'}$ or $H_{3'}$), 4.63 (1 H, m, $H_{4'}$), 4.87 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{3'}$ or $H_{2'}$), 6.11 (1 H, s, $H_{1'}$), 6.64 (2 H, br s, 6-amino group, D_2O exchangeable), 6.96 (1 H, br d, J = 4 Hz, –NH–, D_2O exchangeable), and 8.01 (1 H, s, H_2).

Anal. Calcd for $C_{13}H_{16}N_6O_3 \cdot C_2H_5OH$: C, 51.42; H, 6.33; N, 23.98. Found: C, 51.32; H, 6.44; N, 23.73.

8,5′-Acetamidimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (2c). Compound **2a** (500 mg, 1.57 mmol) in acetic acid (20 mL) was heated at 95–100 °C for 3. 5 h. The solvent was evaporated and the crystalline residue repeatedly co-evaporated with ethanol to remove the residual acetic acid. Recrystallization from ethanol gave 565 mg (quantitative) of needles (**2c**), which did not melt below 290 °C: λ_{max}^{MeOH} (ε) 212 (28 300) and 270 nm (20 400); ^{1}H NMR (100 MHz, Me_2SO-d_6) δ 1.29 and 1.48 (each 3 H, s, isopropylidene methyls), 1.92 (3 H, s, acetyl), 3.44–3.78 (2 H, m, 5′-methylene), 4.62 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{2'}$ or $H_{3'}$), 4.67 (1 H, br s, $H_{4'}$), 5.21 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{3'}$ or $H_{2'}$), 6.18 (1 H, s, $H_{1'}$), 6.81 (2 H, br s, 6-amino group, D_2O exchangeable), 8.07 (1 H, s, H_2), and 10.34 (1 H, s, –N–NH–COMe, D_2O exchangeable).

Anal. Calcd for $C_{15}H_{19}O_4N_7$: C, 49.85; H, 5.31; N, 27.14. Found: C, 49.90; H, 5.34; N, 26.93.

8,5′-Aminimino-9-(5′-deoxy-β-D-ribofuranosyl)adenine (4a). Compound **2a** (500 mg, 1.57 mmol) in a mixture of methanol (15 mL) and concentrated hydrochloric acid (7 mL) was warmed at 45–50 °C for 18 h. The mixture was evaporated and the residual solid repeatedly co-evaporated with warm methanol to remove excess hydrogen chloride. The finally obtained powder was dissolved in methanol (120 mL), neutralized with anion exchange resin, IRA-410 (OH form) (20 mL). The resin was filtered and eluted with methanol (200 mL). The methanol solution was once filtered with Norit and evaporated to give a practically homogeneous solid, which was recrystallized from methanol to colorless needles (**4a**): mp 243–245 °C; yield 230 mg (53%); λ_{max}^{MeOH} (ε) 213 (27 500) and 272 nm (20 800); ^{1}H NMR (100 MHz, Me_2SO-d_6) δ 3.20–3.63 (2 H, m, 5′-methylene), 4.03 (1 H, t, $J_{2',3'} = J_{2' \text{ or } 3',OH}$ = 6 Hz, $H_{2'}$ or $H_{3'}$, collapsed to a doublet with J = 6 Hz on D_2O addition), 4.34 (1 H, br t, $J_{2',3'} = J_{3' \text{ or } 2',OH}$ = 6 Hz, $H_{3'}$ or $H_{2'}$, collapsed to d with J = 6 Hz on D_2O addition), 4.47 (1 H, s, $H_{4'}$), 4.93 (2 H, br s, –N–NH_2, D_2O exchangeable), 5.24 (1 H, br d, J = 6 Hz, 2′- or 3′-OH, D_2O exchangeable), 5.44 (1 H, br d, J = 6 Hz, 3′- or 2′-OH, D_2O exchangeable), 6.07 (1 H, s, $H_{1'}$), 6.76 (2 H, br s, 6-amino group, D_2O exchangeable), and 8.05 (1 H, s, H_2).

Anal. Calcd for $C_{10}H_{13}O_3N_7$: C, 43.01; H, 4.69; N, 35.11. Found: C, 43.30; H, 4.67; N, 34.94.

8,5′-Imino-9-(5′-deoxy-β-D-ribofuranosyl)adenine (4b) A solution of **2b** (200 mg, 0.66 mmol) in 90% CF_3CO_2H (8 mL) was left at room temperature for 5 h. The total was evaporated and the residue co-evaporated with methanol to remove the residual acid. The residual paste was taken into methanol (20 mL) and neutralized with anion-exchange resin, IRA-410 (8 mL). The subsequent workup as in the case of **4a** gave 50 to 60% yield of **4b** as colorless needles: mp 290–295 °C (dec); λ_{max}^{MeOH} (ε) 210 (25 200) and 272 nm (17 600); ^{1}H NMR (100 MHz, Me_2SO-d_6) δ 3.06–3.46 (2 H, m, 5′-CH_2), 3.99 (1 H, t, $J_{2',3'} = J_{2' \text{ or } 3',OH}$ = 6 Hz, $H_{2'}$ or $H_{3'}$, collapsed to d on D_2O addition), 4.27 (1 H, t, $J_{2',3'} = J_{3' \text{ or } 2',OH}$ = 6 Hz, $H_{3'}$ or $H_{2'}$, collapsed to d on D_2O addition), 5.22 (1 H, br d, J = 6 Hz, 2′- or 3′-OH, D_2O exchangeable), 5.44 (1 H, br d, J = 6 Hz, 3′- or 2′-OH, D_2O exchangeable), 6.06 (1 H, s, $H_{1'}$), 6.62 (2 H, br s, 6-amino group, D_2O exchangeable), 6.94 (1 H, br d, J = 4 Hz, NH bridge, D_2O exchangeable) and 8.03 (1 H, s, H_2).

Anal. Calcd for $C_{10}H_{12}O_3N_6$: C, 45.45; H, 4.58; N, 31.81. Found: C, 45.57; H, 4.79; N, 31.74.

8,5′-Imino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (5). Sodium nitrite (324 mg, 4.7 mmol) was added at 0 °C to a solution of **2a** (300 mg, 0.94 mmol) in 80% acetic acid (19 mL). The mixture was left at 0 °C overnight and then at room temperature for another 5 h. After evaporating the solvent, the residue was digested with a small volume of ice–water and the insoluble part

collected by suction and air dried. Recrystallization from a large amount of methanol gave 207 mg (72.2%) of powder-like crystals (**5**): mp above 300 °C; λ_{max}^{MeOH} (ϵ) 261 (19 400) and 288 nm (9200, sh); ^{1}H NMR (100 MHz, Me_2SO-d_6) δ 1.28 and 1 46 (each 3 H, s, isopropylidene methyls), 3.00–3.46 (2 H, m, 5′-methylene), 4.59 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{2'}$ or $H_{3'}$), 4.65 (1 H, s, $H_{4'}$, overlapped on the signal at 4.59 ppm), 4.85 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{3'}$ or $H_{2'}$), 6.03 (1 H, s, $H_{1'}$), 6.97 (1 H, br d, J = 5 Hz, –NH– bridge, D_2O exchangeable), 7.87 (1 H, s, H_2), and 12.16 (1 H, br s, –NHCO– in the base).

Anal. Calcd for $C_{13}H_{15}O_4N_5$: C, 51.14; H, 4.95; N, 22.94. Found: C, 51.09; H, 4.92; N, 23.13.

8,5′-Imino-9-(5′-deoxy-β-D-ribofuranosyl)hypoxanthine (6). A solution of **5** (65 mg, 0.213 mmol) in 90% trifluoroacetic acid (4 mL) was left at room temperature for 24 h, and then thoroughly evaporated. Co-evaporation with ethanol was also carried out. The residue was dissolved in methanol (25 mL), neutralized with Amberlite IRA-93 resin (OH form, weakly basic), and filtered. The resin was eluted with methanol (200 mL) and the combined methanol solution was evaporated to give a crystalline solid, which was recrystallized from aqueous methanol to afford 30 mg (53.1%) of powdery crystals (**6**): mp above 300 °C, λ_{max}^{MeOH} 261 nm (ϵ 20 600); ^{1}H NMR (100 MHz, Me_2SO-d_6) δ 3.02–3.42 (2 H, m, 5′-methylene), 4.00 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{2'}$ or $H_{3'}$), 4.24 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{3'}$ or $H_{2'}$), 4.47 (1 H, br s, $H_{4'}$), 5.30 (2 H, br s, D_2O exchangeable, hydroxyls), 5.98 (1 H, s, $H_{1'}$), 6.96 (1 H, br d, J = 4 Hz, D_2O exchangeable, NH bridge), and 7.88 (1 H, s, H_2). Low-field measurement was omitted.

Anal. Calcd for $C_{10}H_{11}O_4N_5$: C, 45.28; H, 4.18; N, 26.41. Found: C, 45.44; H, 4.37; N, 26.64.

8,5′-Acetamidimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (7). Sodium nitrite (310 mg, 4.5 mmol) was added at 0 °C to a solution of **2c** (540 mg, 1.5 mmol) in 90% acetic acid (20 mL), and the mixture was left at 0 °C for 24 h. The solvent was evaporated, and the residue was washed with a small volume of water and extracted with hot acetone (5 × 30 mL). Evaporation of acetone and recrystallization of the residual solid from methanol gave 400 mg (74%) of colorless powdery crystals which did not melt below 300 °C: λ_{max}^{MeOH} 259 nm (ϵ 19 200).

Anal. Calcd for $C_{15}H_{18}O_5N_6$: C, 49.72; H, 5.01; N, 23.20. Found: C, 49.46; H, 5.04; N, 23.18.

8,5′-Phthalimidimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)adenine (8). A mixture of **2a** (319 mg, 1 mmol) and phthalic anhydride (200 mg, 1.35 mmol) in chloroform (10 mL) was heated to reflux at 70 °C for 4 h. The mixture was evaporated and the residual solid filtered with a small volume of methanol. Recrystallization from a mixture of methanol and chloroform gave 420 mg (93.3%) of colorless prisms (**8**): mp above 300 °C; λ_{max}^{MeOH} (ϵ) 215 (63 900) and 269 nm (20 300); ^{1}H NMR (60 MHz, Me_2SO-d_6) δ 1.33 and 1.50 (each 3 H, s, isopropylidene methyls), 4.13 (2 H, m, 5′-methylene), 4.71–4.80 (2 H, m, $J_{2',3'}$ = 6 Hz, $H_{2'}$ or $H_{3'}$ and $H_{4'}$), 5.16 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{3'}$ or $H_{2'}$), 6.22 (1 H, s, $H_{1'}$), 6.88 (2 H, br s, 6-amino group, D_2O exchangeable), and 7.94–8.05 (5 H, m, H_2 and phthaloyl protons).

Anal. Calcd for $C_{21}H_{19}O_5N_7$: C, 56.12; H, 4.26; N, 21.82. Found: C, 56.07; H, 4.40; N, 22.01.

8,5′-Phthalimidimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine (9). A solution of **8** (700 mg, 1.56 mmol) in 80% acetic acid (33 mL) was treated with sodium nitrite (747 mg, 10.83 mmol) and the total was left at 0 °C for 2 days. The solvent was evaporated off and the residue repeatedly co-evaporated with ethanol. Digestion of the residue with a small amount of water gave a practically pure solid, which was collected and recrystallized from methanol to afford 665 mg (95%) of needles (**9**): mp above 300 °C; λ_{max}^{MeOH} (ϵ) 256 (21 400) and 279 nm (13 400, sh); ^{1}H NMR (60 MHz, Me_2SO-d_6) δ 1.3 and 1.45 (each 3 H, s, isopropylidene methyls), 4.02 (2 H, m, 5′-methylene), 4.70–4.80 (2 H, $H_{2'}$ or $H_{3'}$ and $H_{4'}$), 5.07 (1 H, d, $J_{2',3'}$ = 6 Hz, $H_{2'}$ or $H_{3'}$), 6.12 (1 H, s, $H_{1'}$), 7.93 (5 H, s, phthaloyl and H_2) and 12.21 (1 H, br s, D_2O exchangeable, NH).

Anal. Calcd for $C_{21}H_{18}O_6N_6$: C, 56.00; H, 4.03; N, 18.66. Found: C, 55.68; H, 4.21; N, 18.71.

8,5′-Aminimino-9-(5′-deoxy-2′,3′-*O*-isopropylidene-β-D-ribofuranosyl)hypoxanthine–Phthalazin-1,4-dione Complex (10). Compound **9** (165 mg, 0.366 mmol) was dissolved in 0.2 M methanolic hydrazine by slight warming and the solution was left at room temperature overnight. The solvent and excess hydrazine were evaporated and the residue repeatedly co-evaporated with ethanol. Recrystallization from methanol gave 135 mg (76%) of homogeneous crystals of the complex (**10**): mp above 290 °C (dec at 280 °C); λ_{max}^{MeOH} (ϵ) 260 (19 100) and 283 nm (10 600, sh); ^{1}H NMR (60 MHz, Me_2SO-d_6) δ 1.27 and 1.42 (each 3 H, s, isopropylidene methyls), 4.56–4.98 (5 H, m, $H_{2'}$, $H_{3'}$, $H_{4'}$ and –N–NH_2), 6.02 (1 H, s, $H_{1'}$), and 7.76–8.17 (5 H, m, phthalyl and H_2).

Anal. Calcd for $C_{13}H_{16}O_4N_6$ + $C_8H_6O_2N_2$: C, 52.28; H, 4.60; N, 23.23. Found: C, 52.47; H, 4.71; N, 23.34.

The homogeneity of this product was confirmed by TLC using silica gel and the solvent mixtures, chloroform/methanol, 9:1 and 92:8.

Hydrochloride of 8,5′-Aminimino-9-(5′-deoxy-β-D-ribofuranosyl)hypoxanthine (11). A solution of **10** (300 mg, 0.62 mmol) in 90% trifluoroacetic acid (12 mL) was left at room temperature for 26 h and then at 0 °C overnight. The mixture was evaporated below 35 °C and repeatedly co-evaporated with ethanol and/or methanol. The residue was dissolved in methanol (70 mL), neutralized with anion-exchange resin, IRA-93, and filtered. The resin was thoroughly washed with methanol and the combined methanol solution was evaporated to give a powder, which was shown by TLC (silica gel, 8:2 mixture of chloroform and methanol) to be a mixture of two compounds, the faster moving of which seemed to be phthalazin-1,4-dione. The total was swirled with warm water (30 mL) and a small amount of the insoluble part was filtered off. The aqueous filtrate was concentrated in vacuo to ca. 10 mL and repeatedly extracted with ethyl acetate until the faster moving substance was removed. The aqueous layer was evaporated and co-evaporated with methanol to give a homogeneous gum, which resisted crystallization. Hence, the gum was again dissolved in dry methanol (ca. 100 mL), acidified with a saturated dioxane solution of hydrogen chloride, and evaporated. The semi-solid residue was repeatedly co-evaporated with methanol to give a powder, which was recrystallized from a small volume of methanol at room temperature (by spontaneous evaporation) to afford very gradually 65.5 mg (32%) of **11** as colorless powdery crystals, decomposition at 165 °C: λ_{max}^{MeOH} (ϵ) 260 (15 000) and 290 nm (inflection).

Anal. Calcd for $C_{10}H_{12}O_4N_6$·HCl·½MeOH: C, 37.90; H, 4.54; N, 25.26. Found: C, 37.65; H, 4.67; N, 25.38.

Hydrochloride of 2,5′-Aminimino-1-(5′-deoxy-β-D-ribofuranosyl)-5-*N*-formylaminoimidazole-4-carboxamide (12). A solution of **10** (62 mg, 0.194 mmol) in 90% trifluoroacetic acid (2 mL) was left at room temperature for 22 h. TLC with an aliquot of the reaction mixture using silica gel and 30% ethanol in benzene showed the presence of a single product corresponding to **11** with a tiny amount of the starting material. The mixture was worked up as in the case of **6**, involving treatment with IRA-93 resin. However, purification of the finally obtained powdery mixture proved to be difficult. Hence, the total was suspended in a mixture of concentrated hydrochloric acid and methanol (1:3) (10 mL) and stirred at room temperature overnight. TLC with an aliquot (after neutralization with IRA-93 resin) showed the conversion of the major part of **11** to another substance. The total was evaporated and repeatedly co-evaporated with methanol, and the residue was recrystallized from methanol to give 30 mg (46.3%) of **12** as colorless needles, decomposition at 260–270 °C. λ_{max}^{MeOH} (ϵ) 216 (21 100) and 277 nm (12 400).

Anal. Calcd for $C_{10}H_{14}O_5N_6$·HCl: C, 35.88; H, 4.52; N, 25.11. Found: C, 35.93; H, 4.54; N, 24.98.

Registry No.—**1**, 20789-78-0; **2a**, 65879-28-9; **2b**, 65879-29-0; **2c**, 65879-30-3; **3**, 65879-31-4; **4a**, 65879-32-5; **4b**, 65879-33-6; **5**, 65879-34-7; **6**, 65879-35-8; **7**, 65879-36-9; **8**, 65879-37-0; **9**, 65879-38-1; **10**, 65879-40-5; **11** HCl, 65879-41-6; **12** HCl, 65879-42-7; *p*-nitrobenzaldehyde, 555-16-8; phthalic anhydride, 85-44-9.

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(10) One referee has called in question of the conversion of 2a to 5 since, he believes, 2a should rapidly react to give an *N*-diazonium hydroxide. Whatever intermediate may have formed (*N*-diazonium hydroxide or *N*-nitroso compound), the thermodynamic product obtained by us must be 5 on the basis of the combustion data, UV, CD (the positive Cotton effect), NMR, and mass spectral data (abudant M^+ ion etc.). The guanidin type structure seems to particularly stabilize the $C_{5'}$–N–C_8 bond of our compounds, in contrast to the oxidation or diazotization reactions of many *N*-amino alicyclic amines.
(11) The crystallization process was hampered by strong solvation with protic solvents to form a gelatine.
(12) Some spectral comparisons between 9 and 10: 9 absorbs at 256 (ε 21 400) and 279 nm (ε 13 400, sh), while 10 absorbs at 260 (ε 19 100) and 283 nm (ε 10 600, sh) (see Experimental Section). The ^{1}H NMR spectrum of 9 indicated the resonance of the lactam NH at 12.21 ppm and that of the phthaloyl group at 7.93 ppm (overlayed on the H_2 signal) as a sharp singlet (accidentally conditioned by steric and electronic factors in the nucleoside molecule). On the other hand, the spectrum of 10 exhibited the phthaloyl resonance at 7.76–8.17 ppm as a complex multiplet and no lactam resonances for both inosine base and phthalazin-1,4-dione under the same measurement conditions (60 MHz, Me_2SO-d_6). This latter finding seems to suggest complex formation by hydrogen bonding between the molecules.
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Purine *N*-Oxides. 67. Redox and Rearrangement Reactions of 1,7-Dimethylguanine 3-Oxide with Anhydrides[1]

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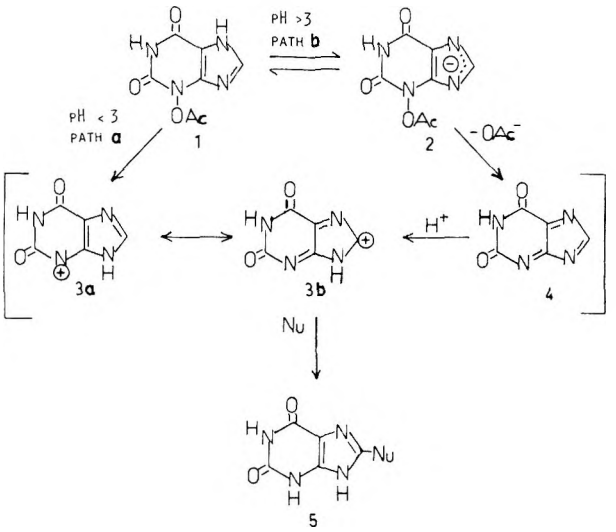
Acetylation of 1,7-dimethylguanine 3-oxide in aqueous or methanolic solution produces an intermediate that undergoes an extremely rapid intermolecular reaction with the solvent under ambient conditions to yield 8-substitution products of 1,7-dimethylguanine. This reaction occurs despite the presence of an alkyl group at N-7 that prevents delocalization of a positive charge generated at N-3 to the C-8 position. Added nucleophiles, even at high concentrations, do not react to yield 8-substitution products. Iodide and bromide ions undergo a redox reaction with the intermediate to afford 1,7-dimethylguanine and iodine or bromine. The extent of 8 substitution with water and the reduction by bromide ion are inversely affected by variations in the concentrations of bromide ion, indicating that the two reactions are competitive and proceed from a single intermediate. A delocalized nitrenium ion is proposed as the common intermediate. Accompanying the 8-substitution reaction is a competitive, slower reaction that results in loss of UV absorption. This reaction can be enhanced at the expense of the 8-substitution reaction by the use of trifluoroacetic anhydride. Oncogenicity assays in rats show that 1,7-dimethylguanine 3-oxide does not induce tumors.

A number of *O*-acyl esters of purine 3-oxides[2–6] undergo a spontaneous N-3 elimination–C-8 substitution reaction that parallels those observed with some oncogenic *N*,*O*-diacyl aromatic hydroxylamines.[7–12] As part of studies to elucidate the mechanism of tumor induction by N-oxidized purines, the reactions of one ester, 3-acetoxyxanthine (**1**, Scheme I), were examined in detail. Those studies[13] indicated that the 8-substitution reaction of **1** can proceed by either of two routes (Scheme I) depending upon the pH of the medium. A relatively slow S_Ni' reaction (path a) is observed in the pH range 0 to 3, while the faster path b, requiring ionization of the imidazole proton, predominates at pH's above 3. Interference with delocalization of the positive charge in the common intermediate **3** by a substituent at N-7 was found to inhibit the 8-substitution reaction by both routes.[3,13] A second spontaneous reaction of **1**, reduction to xanthine, was observed only in conjunction with the 8-substitution reaction via path b. The presence of iodide ion greatly enhanced the reduction of **1**, and the enhanced reduction was accompanied by oxidation of iodide to iodine. It was suggested[13] that the redox reaction with iodide ion was correlated with the spontaneous reduction of **1** and proceeded via the same intermediate. A radical anion, presumed to form by homolysis of the N–O bond of **2**, was suggested as the common intermediate. However, recent evidence[14] indicates that oxidation of iodide can also occur in conjunction with path a and thus cannot proceed solely via a radical from **2**.

Scheme I



One member of the purine *N*-oxide series, 1,7-dimethylguanine 3-oxide (**6**, Scheme II), appeared to react anoma-

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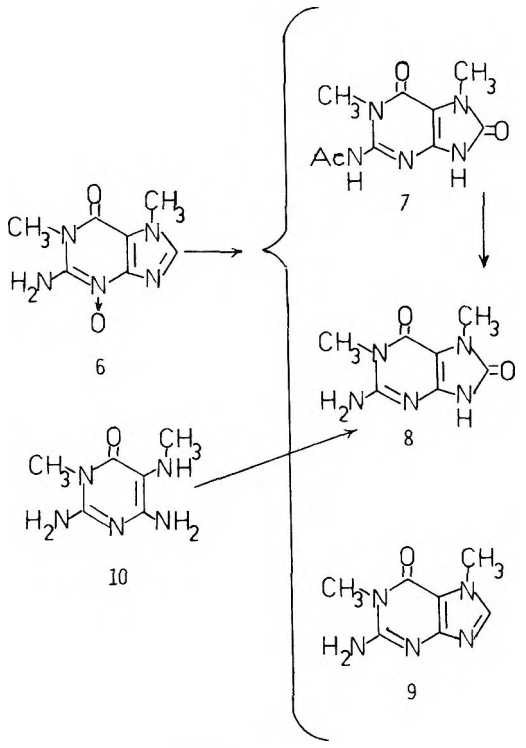
Table I. Reaction Parameters for the Rearrangement of 1,7-Dimethylguanine 3-Oxide with Acetic Anhydride

pH	7, %	9, %	Recovery, %	λ_{max},[a] nm	Apparent pseudo-first-order rate constant, min^{-1} k_1	k_2
2				265		
3	21		21	265	2×10^{-1}	
4	18		18	242	4×10^{-2}	6×10^{-2}
5	50	5	55	244	2×10^{-2}	5×10^{-4}
6				242	8×10^{-2}	3×10^{-4}
7	45	6	51	260	6×10^{-2}	7×10^{-3}
8				255	3×10^{-2}	3×10^{-4}

[a] Absorption maximum of the intermediate immediately after addition of acetic anhydride.

Scheme II



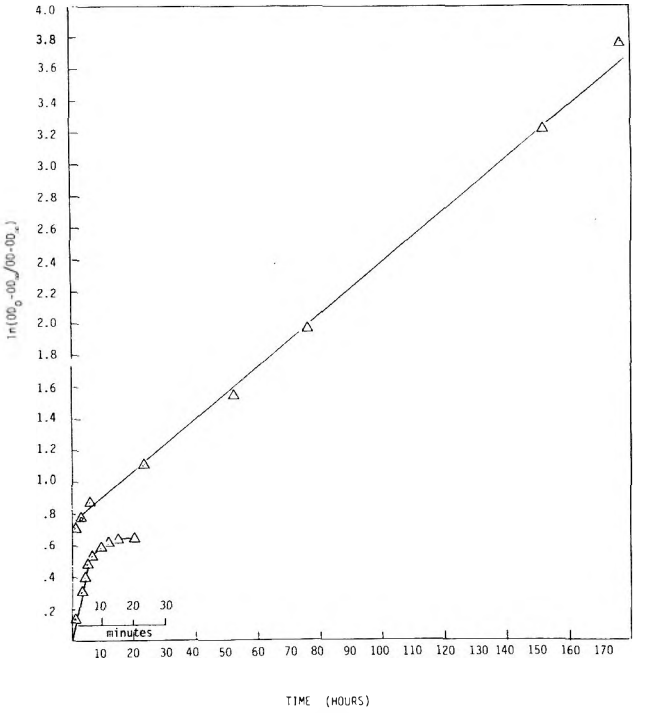


Figure 1. Pseudo-first-order plot for the reaction of 1,7-dimethylguanine 3-oxide with acetic anhydride at pH 6.

lously. Formation of its ester in situ was reported to generate a species that could oxidize iodide ion readily, but it did not yield an 8-substitution product with other nucleophiles.[5] Since a 3-*O*-acyl derivative of **6** could not ionize in the imidazole ring to afford a radical anion comparable to that proposed as an intermediate in the redox reaction of **1**, it appeared that a study of the reactions of acylated **6** would be uniquely helpful in delineating the mechanism of the redox reaction of esters of purine *N*-oxides. We now report that in the presence of acetic anhydride, **6**, although possessing a substituent at N-7, nevertheless reacts very rapidly under ambient conditions with water or with methanol to afford 8-substitution products. We present proof of structures of the products of the reaction, data on the mechanism, and evidence on the redox properties of the reaction intermediate.

Results

The addition of acetic anhydride to a solution of **6** yielded 2-*N*-acetyl-1,7-dimethyl-8-oxo-9*H*-guanine (**7**; 29%) (Scheme II), 1,7-dimethyl-8-oxo-9*H*-guanine (**8**; 2.5%), a small amount of 1,7-dimethylguanine (**9**), and traces of a fourth, unidentified, product. The assignments of **7** and **8** were confirmed by independent synthesis of **8** from 2,6-diamino-3-methyl-5-methylamino-4-oxopyrimidine (**10**). To examine the kinetics of the reaction, the UV spectral changes of the reaction of **6** in buffered solutions at pH's 2–8 were monitored. Upon addition of acetic anhydride to each of the solutions, there was an immediate change in the UV spectrum to that of an intermediate, the absorption maximum of which varied with pH (Table I). At pH 2 only reversion to the spectrum of **6** was observed. At pH's above 2 there was a gradual change in the spectrum to that of **7**, but with significant loss (~50%) of optical density. Treatment of the spectral changes as a pseudo-first-order decomposition gave plots that were linear only for the first few minutes of reaction. This was followed by a period of nonlinear change, and then at pH's 4–8 the change became linear again and remained so for the rest of the reaction (Figure 1). Apparent pseudo-first-order rate constants were calculated for the two linear portions of the plots (Table I). When the course of the reaction at pH 7 was monitored chromatographically, the reaction of **6** to **7** was found to be nearly complete within the first few minutes of reaction. No reaction was observed between **7** and acetic anhydride under the conditions for rearrangement, but **8** reacted to yield an unstable acetyl derivative with UV absorption different from that of **7**. It quickly reverted to **8** with no loss of optical density. Treatment of the spectral changes for that reaction, as a pseudo-first-order reaction, gave good linear plots for the entire course of the reaction and apparent pseudo-first-order

Table II. NMR Spectral Parameters (δ) during the Reaction of 1,7-Dimethylguanine 3-Oxide (6) with Anhydrides

Time	C-8		NCH_3		NCH_3					
T_0[a]	8.04		4.00		3.54					
30 s[b]	↓8.07[c]	4.09[d]	↓4.00	3.66[d]	↑3.57[c]		3.42[d]			
3 min[b]	↓8.09	↓4.09	↓4.03	↓3.66	↑3.57		3.43		3.12[d]	
10 min[b]					↑3.54			3.15[d]	↑3.11	2.95[d]
4 h[b]					3.55			↑3.16	3.13	2.95
5 days[b]					3.55	3.46[d]	3.41[d]		3.12	
7[a]			3.55		3.55					
8[a]			3.32		3.27					

Time	C-8				NCH_3			NCH_3		
T_0[e]	7.99				3.88			3.37		
10 min[f]		4.09	4.03	3.98		3.43	3.39		3.33	
7[g]					3.40			3.37		
8[g]					3.30			3.25		

[a] Spectrum taken in D_2O containing 2 drops of CD_3CO_2D with DSS as a reference. [b] Reaction of 5 mg of 7 in D_2O containing 2 drops of CD_3CO_2D and 20 μL of acetic-d_6 anhydride with DSS as a reference. [c] Increase (↑) or decrease (↓) in relative intensity of the band from previous reading. [d] New band. [e] Spectrum taken in Me_2SO-d_6 with Me_4Si as a reference. [f] Reaction of 5 mg of 7 in Me_2SO-d_6 with 50 μL of $(CF_3CO_2)_2O$ with Me_4Si as a reference. [g] Spectrum taken in Me_2SO-d_6 after addition of 50 μL of $(CF_3CO_2)_2O$ with Me_4Si as a reference.

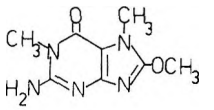
rate constants of 0.15, 0.2, and 0.3 min^{-1} for pH's 2, 5, and 8, respectively.

The kinetic data indicate that 6 undergoes two competing reactions with acetic anhydride: (a) a very rapid ($k \sim 10^{-2}$ min^{-1}) rearrangement to 7 (and 8), and (b) a slower reaction ($k \sim 10^{-4}$ min^{-1}) that leads to the decomposition of 6 to non-UV-absorbing compounds. These conclusions were supported by an NMR study of the reaction of 6 with acetic-d_6 anhydride in D_2O containing CD_3CO_2D (pD ~ 5). Addition of acetic-d_6 anhydride to a solution of 6 in D_2O caused a rapid decrease in the signal intensities of the C-8 hydrogen and one of the NCH_3 groups of 6 (Table II). The signal of the second NCH_3 group of 6 increased in intensity since it appeared at the same position as the two coincident NCH_3 signals of 7. Three signals at δ 4.01, 3.66, and 3.42 appeared briefly, but they were absent by 10 min. These bands are probably attributable to *N*-methyl groups of acetylated intermediates in the rearrangement of 6 to 7. Paralleling the slower changes in UV absorption, changes in several bands were apparent for several days in the NMR spectra; these must reflect changes in the NCH_3 bands of intermediates associated with the slow reaction leading to loss of UV absorption.

The reaction of 6 with $(CF_3CO)_2O$ did not yield 7 or 8, but instead induced an extremely rapid reaction that destroyed the purine chromophore. When the reaction of 6 with $(CF_3CO)_2$ in Me_2SO-d_6 was followed by NMR spectroscopy, the reaction was complete in 10 min (Table II) and two groups of signals were present. Little absorbance due to the NCH_3 groups of 7 or 8 was evident.

Under the conditions for rearrangement of 6, the structurally related compounds 1,7-dimethyl-3-hydroxyxanthine,[15] 3-hydroxy-7-methylguanine,[15] and 2-amino-6-methoxypurine 3-oxide[15] failed to yield 8-substitution products. The 3-acetoxy-7-methylguanine (λ_{max} 267 nm) generated in situ did afford a second product (λ_{max} 282 nm), but this slowly hydrolyzed to 3-hydroxy-7-methylguanine and is presumably the 2-*N*-acetyl derivative.

Reaction of Acetylated 6 with Other Nucleophiles. In agreement with an earlier report using pyridine,[5] 6 in the presence of aqueous acetic anhydride showed no evidence of undergoing 8 substitution with azide ion (1 M) or with methionine (0.05 M), both of which are quite reactive with 1.[3] However, when 6 was reacted with acetic anhydride in methanol, 1,7-dimethyl-8-methoxyguanine (11) and its 2-*N*-acetyl derivative were obtained.



11

The reaction of acetylated 6 at pH 7 in the presence of 3 M NaBr afforded a large quantity of 9 and some 2-*N*-acetyl-1,7-dimethylguanine, but no 7 and no 8-bromo derivative of 9 were present. The absence of the latter was confirmed by synthesis and characterization of 8-bromo-1,7-dimethylguanine and careful chromatographic examination of the reaction mixture for it. At pH 5 there was an inverse correlation of the yields of 7 and 9 which was directly related to changes in the bromide ion concentration (Table III). In the absence of bromide ion little reduction of 6 to 9 occurs, but in the presence of 3 M NaBr no 8-substitution product (7) was detectable and 9 was obtained in 55% yield. There was little variation in the overall recovery over the range of 0 to 3 M NaBr. This indicates that only the portion of 6 that yields 7 is diverted to 9 in the presence of bromide ion. Bromide ion apparently has no effect on the slower reaction that results in destruction of 6. Addition of acetic anhydride to a concentrated solution of 6 in 3 M NaBr caused the transient appearance of a red color. The solution showed absorption maxima at 405 and 470 nm, which correspond to the maxima for bromine and tribromide ion. These results demonstrate that the enhanced reduction of 6 to 9 in the presence of bromide ion is part of a redox reaction that also results in oxidation of bromide ion to bromine. This is the first evidence that esters of purine *N*-oxides can oxidize bromide ion.

The reaction of acetylated 6 in the presence of 1 M iodide ion at pH 7 also resulted in diversion from the formation of 7 to a mixture of 9 (33%) and its 2-*N*-acetyl derivative (19%). This recovery (52%) is slightly less than the yield of triiodide ion (81%) produced in the reaction but is comparable to the yield of 9 obtained from the reaction of 6 in 3 M NaBr (Table III). These data thus demonstrate that the oxidation of iodide ion is correlated with the reduction of 6 to 9.

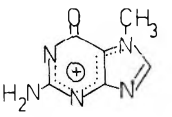
Discussion

The rapid reaction of acetylated 1,7-dimethylguanine 3-oxide under ambient conditions to yield the 8-substituted derivatives 7 and 11 is unusual since such reactions have been observed with esters of other 7-substituted purine 3-oxides

Table III. The Effect of Bromide Ion on the Reaction of 1,7-Dimethylguanine 3-Oxide (6) with Acetic Anhydride at pH 5

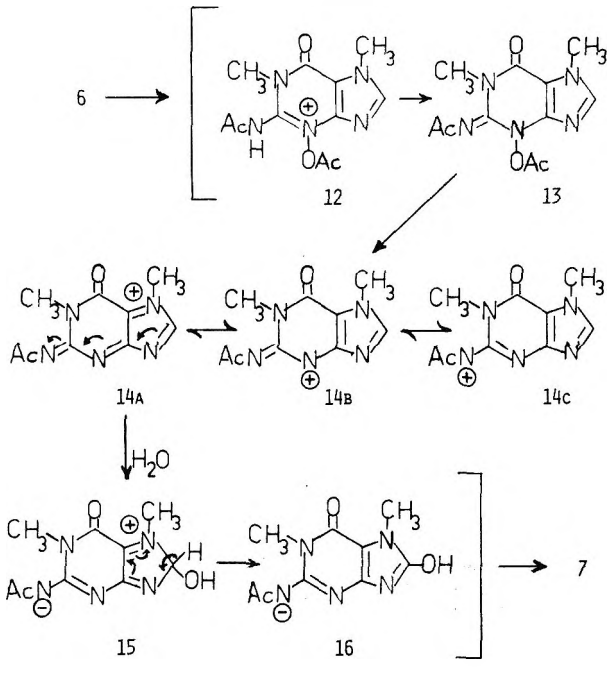
Product	Yield of products, % [Br^-], M 0	0.1	0.5	3
2-*N*-Acetyl-1,7-dimethyl-8-oxo-9*H*-guanine (7)	50	41	18	0
1,7-Dimethylguanine (9)	6	21	34	55
Total recovery	56	62	52	55

only under more vigorous conditions, if at all.[16] The rate of reaction of acetylated **6** to **7** is comparable to that for the reaction of 3-acetoxyxanthine (**1**) via path b.[13] However, the mechanism for the reaction of **6** must differ somewhat from either of those proposed[13] for the elimination–substitution reactions of **1** (paths a and b, Scheme I) since a delocalized cation (**3**) which is common to both paths is precluded by the 7-methyl group of **6**. The presence of both the 1-methyl and 2-amino groups of **6** is essential for rearrangement. Both 1,7-dimethyl-3-hydroxyxanthine and 3-hydroxy-7-methylguanine readily form neutral 3-acetoxy derivatives,[5] but neither undergoes a **3** to **8** rearrangement. The formation of **11** from the reaction of **6** with acetic anhydride in methanol clearly demonstrates that the reaction of **6** is intermolecular. A plausible mechanism for the rearrangement of **6** that accommodates the accumulated observations involves acetylation to **12** (Scheme III), ionization and tautomerization of **12** to the neutral **13**, and ionization of **13** to the delocalized cation **14** (**a**–**c**). The electron-withdrawing effect of the positive charge in the imidazole ring of **14a** must render the 8 position susceptible to attack by basic solvents to afford the Michael addition product **15**, but not susceptible to attack by nucleophiles in general. Ionization of the hydrogen at C-8 of **15** would permit rearomatization of **15** to **16**, a tautomer of **7**. The rearrangement of **13** but not the structurally related 1,7-dimethyl-3-acetoxyxanthine indicates that the 2-amino group plays a significant role in stabilizing the cationic intermediate **14** and encouraging ionization of **13**. Resonance contributors analogous to **14** are conceivable for a cation from 3-acetoxy-7-methylguanine, i.e., **17**, but there are two significant differences between **14** and **17**. (a) The extension in conjugation provided by **14c** is linear to that of the other resonance contributors of **14**. This contrasts with the nearly perpendicular relationship of any charge density at N-1, the resonance contributor to **17** comparable to **14c**, to the remainder of the resonance system of **17**. This suggests that the former cation should be more stable than the latter, and the difference in resonance stabilization may be sufficient enough to permit ionization to **14**, but not to **17**. (b) Only **14a** contains an imine function at C-2 that is also in linear conjugation with C-8 and is oriented appropriately to provide stabilization to a Michael adduct by a base at C-8 of **14a**. These two factors, both unique to a cation from **6**, must play a significant role in determining whether an N-3 elimination–C-8 substitution reaction can occur under mild conditions in a compound for which direct allylic delocalization of the positive charge is blocked by a 7 substituent.[17] The observation that acetylation appears to occur at pH 2, but rearrangement to **7** does not follow, suggests that an ionization that is essential for the reaction does occur, but only at pH's above 3. This agrees with the proposed mechanism.



17

Scheme III



With the demonstration that acetylated **6** can undergo an elimination–substitution reaction, a consistent picture emerges on the reactions of *O*-esters of purine *N*-oxides: they either undergo a 3 to 8 rearrangement *and* oxidize iodide ion or exhibit neither reaction. The high reactivity with a variety of nucleophiles at C-8 of all esters in the series that do rearrange,[3-5] with the single exception of **13**, provides strong support for the participation of a carbonium ion, e.g., **3b**, in the 8-substitution reaction. Recent evidence[14] indicates that there is sufficient electron deficiency at the allylic N-3 position to permit certain nucleophiles to react at N-3 of **3a**. It was proposed[14] that oxidation of iodide ion by **1**, with concomitant formation of xanthine, occurs by formation of a reactive *N*-iodo intermediate at the nitrenium ion and subsequent reaction of this with a second iodide ion to afford iodine and the parent purine. The demonstration that acetylated **6** can undergo both 8-substitution and redox reactions and that the two reactions are competitive (Table III) provides strong evidence that they occur from a single delocalized cation, viz., **14**. The observation of redox reactivity with acetylated **6** indicates that there must be sufficient contribution from **14b** or **14c** to permit iodide and bromide ions to react at an electron-deficient nitrogen to form reactive *N*-halo intermediates that undergo subsequent reaction to **9** and iodine or bromine. The fact that there is a correlation between the yields of I_3^- and of **9** indicates that the iodide-mediated reduction is part of a redox reaction and is not due to a heavy atom induced spin inversion to the nitrenium triplet[18] and reduction of that species by hydrogen abstraction.[19] Acetylated intermediates of **6** cannot form anions comparable to **2** (Scheme I) from **1**, and in contrast to the ~25% reduction of **1** via path b,[13,14] little spontaneous reduction of **6** accompanies its rearrangement to **7**. The inability of intermediates from **6** to form an anion comparable to **2** precludes the formation of a radical anion, such as that previously suggested[13] as an intermediate in the spontaneous reduction of **1** to xanthine, and the possibility of such a species being an intermediate in the redox reaction with iodide ion. Thus, data on the reactions of acetylated **6** complement those from recent studies on the reactions of **1**[14] and support the conclusion that redox reactions observed with *O*-esters of purine *N*-oxides occur via reactions at nitrenium ions and not via radical intermediates. This conclusion may

also explain the reduction reactions observed with acylated intermediates from other heterocyclic *N*-oxides, e.g., 1,5-naphthyridine 1-oxide,[20] in the presence of bromide or iodide ions.

In parallel with the chemical studies, **6** was assayed in vivo for its oncogenic potential. Administration of 1.2 mg of **6** subcutaneously three times per week for 8 weeks induced no tumors. By comparison, the tumor incidence was 35% (7/20) in rats treated similarly with approximately the same molar equiv of 3-hydroxyguanine (1.0 mg).[21]

Experimental Section

General. UV spectra were determined with a Unicam SP800A recording spectrophotometer and NMR spectra with a Jeol 100-Hz spectrometer. The elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., or Schwarzkopf Microanalytical Laboratory, Woodside, N.Y. An ISCO UA-2 analyzer with a coordinated fraction collector was used to monitor all column eluates.

Reaction of 1,7-Dimethylguanine 3-Oxide (6) with Acetic Anhydride. A 1.52-g sample of **6**, purified as described,[15] was dissolved in 34 mL of H_2O, 6 mL of acetic anhydride was added, and the pH of the solution was adjusted from 2.5 to 4.5 with 1 N NaOH. The reaction was allowed to proceed for 2 weeks, and then the precipitate that had formed was collected, washed with acetone, and air dried; yield 420 mg. This was chromatographically homogeneous 2-*N*-acetyl-1,7-dimethyl-8-oxo-9*H*-guanine (**7**): mp, gradual decomposition at >180 °C; mass spectrum (CI), *m/e* 238 (M + 1), 194, 166, 153; UV λ_{max} ($\epsilon \times 10^{-3}$) pH 1, 265 nm (7.8), 296 (5.5); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 12, 228 nm (22.3), 284 (9.2); NMR (Me_2SO-d_6) δ 2.12 (s, 3, $NCOCH_3$), 3.40 (s, 6, $2NCH_3$), 10.62 (s, 1, NH), 11.62 (s, 1, NH).

An analytical sample was recrystallized from CH_3OH–EtOH and dried at 120 °C over P_2O_5 for 4 h under vacuum.

Anal. Calcd for $C_9H_{11}H_5O_3$: C, 45.57; H, 4.67; N, 29.52. Found: C, 45.54; H, 4.67; N, 29.05.

The filtrate was evaporated to dryness under vacuum. A solution of the residue was applied to a 25 × 200 mm Dowex 50 (H^+), 200–400 mesh, column that was eluted with H_2O, 1 N HCl, and finally 2 N HCl in 60% aqueous CH_3OH; 25-mL fractions were collected. Fractions showing similar UV absorption spectra were combined and the solvents removed under vacuum. Water (fractions 1–12) eluted an additional 75 mg of **7**; the total yield of **7** was 495 mg (29%).

Fractions 73–79 (1 N HCl) contained a small amount, too little for structure identification, of an unknown material: UV λ_{max} pH 1, 240, 285 nm; UV λ_{max} pH 12, 292 nm. Fractions 82–92 contained 35 mg (2.5%) of 1,7-dimethyl-8-oxo-9*H*-guanine (**8**): mp, gradual decomposition above 240 °C; mass spectrum (CI), *m/e* 197 (M + 2), 196 (M + 1); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 1, 250 nm (10.9), 291 (9.9); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 7, 250 nm (10.6), 293 (9.9); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 13, 225 nm (37.2), 260 sh (7.2), 294 (11.6); NMR (Me_2SO-d_6) δ 3.27 (s, 3, NCH_3), 3.32 (s, 3, NCH_3), 6.94 (s, 2, NH_2), 10.99 (s, 1, NH).

An analytical sample was recrystallized from H_2O and dried at 80 °C over P_2O_5 under vacuum for 2 h.

Anal. Calcd for $C_7H_9N_5O_2$: C, 46.07; H, 4.65; N, 35.88. Found: C, 42.75; H, 4.63; N, 35.68.

This product, **8**, was also obtained by treatment of **7** with $NaOCH_3$ in CH_3OH.

Continued elution of the column with 2 N HCl eluted **9** (2%), which was identified from its UV spectra.[22]

Synthesis of 1,7-Dimethyl-8-oxo-9*H*-guanine (8). 2,6-Diamino-3-methyl-5-methylamino-4-oxopyrimidine (**10**) was prepared from 1,7-dimethylguanosinium iodide by a sequence of reactions similar to that reported for the synthesis of 2,6-diamino-4-hydroxy-5-methylaminopyrimidine·2HCl from 7-methylguanosine.[23] 1,7-Dimethylguanosinium iodide[24] (10 g) was dissolved in 50 mL of 28% NH_4OH. The solvent was removed under vacuum, and the flask was left under vacuum for several days. The residue was then dissolved in methanolic HCl, and the solution was warmed slightly. Progress of the reaction was monitored by UV spectra of aliquots. The solvents were removed, and the residue was chromatographed over a 2.5 × 15 cm Dowex 50 (H^+) column that was eluted first with 60% aqueous CH_3OH and then with 1 N HCl in 60% aqueous CH_3OH to elute **10** as the dihydrochloride. The product was recrystallized from CH_3OH–EtOAc: yield 2.6 g (32%); mp 250–251 °C dec; NMR (Me_2SO-d_6) δ 2.64 (s, 3, NCH_3), 3.22 (s, 3, NCH_3), 6.56, 7.64, 11.31 (broad, exchangeable, NH's); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 1, 223 sh nm (13.5), 262 (13.9); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 7, 212 nm (22.5), 277 (9.7); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 12, 211 nm (22.7), 279 (11.0).

An analytical sample was recrystallized from CH_3OH–EtOAc and dried at 120 °C for 3 h over P_2O_5.

Anal. Calcd for $C_6H_{11}N_5O$·2HCl·0.5H_2O: C, 28.70; H, 5.61; N, 27.89. Found: C, 28.82; H, 5.32; N, 27.62.

A mixture of **10**·2HCl (100 mg, 10 mmol) and urea (130 mg) was heated at 180 °C for 4 days; progress of the reaction was monitored by UV spectra of aliquots. A solution of the reaction mixture was chromatographed over Dowex 50 (H^+), 200–400 mesh, to obtain **8**; yield 55 mg (68%). The chromatographic and NMR, UV, and mass spectral properties of the synthetic sample were identical with those of the product from the reaction of **6**.

Reaction of 6 with Acetic Anhydride in Methanol. To a solution of **6** (470 mg, 2.2 mmol) in 900 mL of CH_3OH was added 18 mL of acetic anhydride. Progress of the reaction was followed by TLC (silica gel; $CHCl_3$–CH_3OH, 9:1). After 5 h no **6** remained, and three new components (R_f 0.4, 0.47, and 0.56) were present. Removal of ~300 mL of solvent under reduced pressure induced precipitation of material which was collected (130 mg) and found to contain a single chromatographically homogeneous component (R_f 0.47). Further reduction in volume to ~200 mL yielded more (75 mg) of the same product, which was identified as 1,7-dimethyl-8-methoxyguanine (**11**): mp, gradual decomposition at >240 °C; mass spectrum (CI), *m/e* 210 (M + 1); NMR (Me_2SO-d_6) δ 3.31 (s, 3, NCH_3), 3.57 (s, 3, NCH_3), 3.77 (s, 3, OCH_3), 4.06 (s, 2, NH_2); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 1, 212 sh nm (15.2), 251 sh (8.1), 274 (12.1); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 7, 217 nm (25), 245 (6.7), 285 (9.5).

An analytical sample was recrystallized from CH_3OH–EtOAc and dried at 120 °C for 3 h over P_2O_5.

Anal. Calcd for $C_8H_{11}N_5O_2$·H_2O: C, 42.28; H, 5.76; N, 30.80. Found: C, 42.75; H, 5.28; N, 31.16.

The structure of **11** was confirmed by heating a sample in 0.1 N HCl for 2 h, which converted the sample into **8**, as shown by comparison of the UV and NMR spectra and chromatographic properties in three solvent systems of the hydrolysis product with those of an authentic sample of **8**.

Reduction of the remaining reaction solution to a small volume, application of the solution to preparative silica gel TLC plates (developed in $CHCl_3$–CH_3OH, 4:1, v/v), and elution of the three bands (R_f 0.35, 0.45, and 0.7) yielded additional 1,7-dimethyl-8-methoxyguanine (R_f 0.45) (23 mg); the total yield of **11** was 228 mg (51%).

Elution of the band at R_f 0.7 gave 2-*N*-acetyl-1,7-dimethyl-8-methoxyguanine: yield 8.5 mg (1.5%); mp 219–220 °C; NMR (Me_2SO-d_6) δ 2.099 (s, 3, $COCH_3$), 3.38 (s, 3, NCH_3), 3.66 (s, 3, NCH_3), 4.08 (s, 3, OCH_3), 10.51 (s, 1, exchangeable, NH); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 1, 217 nm (26.5), 261 (10.6), 278 sh (7.9); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 7, 220 nm (32.8), 263 (10.7), 277 sh (7.5); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 12, 218 nm (28.3), 261–277 (10.7).

An analytical sample was recrystallized from CH_3OH–EtOAc and dried at 120 °C over P_2O_5 for 3 h.

Anal. Calcd for $C_{10}H_{13}N_5O_3$·H_2O: C, 44.60; H, 5.62; N, 26.01. Found: C, 44.77; H, 5.22; N, 26.15.

The band at R_f 0.35 was **9**, 6.7 mg (2%); the overall recovery from **6** was 54%.

Reaction of 6 with Acetic Anhydride in the Presence of 3 M NaBr. To a solution of **6** (600 mg) in 40 mL of 0.5 N pH 7.0 phosphate buffer containing 12.3 g of NaBr was added 2.4 mL of acetic anhydride. The reaction was allowed to proceed overnight, and then the solvents were removed. A solution of the residue was applied to a 25 × 200 mm Dowex 50, 200–400 mesh, column. Elution with H_2O afforded a product, the UV absorption of which was not identical with that of **7**. The fractions containing the product were combined, reduced in volume, and then neutralized with BioRad AG-3 in the basic form. The eluate was reduced to a small volume and applied to a preparative silica gel TLC plate that was developed in $CHCl_3$–CH_3OH (19:1). Two UV-absorbing bands were present at R_f 0.1 and 0.2. The former was **9**. Elution of the latter afforded 95 mg of 2-*N*-acetyl-1,7-dimethylguanine: mp 252–254 °C; NMR (Me_2SO-d_6) δ 2.10 (s, 3, $COCH_3$), 3.39 (s, 3, NCH_3), 3.95 (s, 3, NCH_3), 8.15 (s, 1, C-8–H), 10.59 (s, 1, NH); mass spectrum (CI), *m/e* 222 (M + 1), 206 (M + 1 − O), 179 (M + 1 − $COCH_3$), 163 (M + 1 − O, $COCH_3$); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 1.0, 260 nm (11.2); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 7.0, 216 nm (23), 261 (9.7); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 13, 265–270 nm (10.1).

Anal. Calcd for $C_9H_{11}N_5O_2$: C, 48.86; H, 5.01; N, 31.66. Found: C, 48.88; H, 4.94; N, 31.69.

The structure was confirmed by acetylating a sample of 1,7-dimethylguanine. The synthetic and isolated samples showed identical chromatographic and UV, NMR, and mass spectral properties.

Synthesis of 8-Bromo-1,7-dimethylguanine. A solution of 8-bromoguanosine (1.0 g, 2.8 mM) and 0.75 mL of $(CH_3)_2SO_4$ (8 mM) in 5 mL of Me_2SO was allowed to stir in a sealed flask at room tem-

perature; progress of the reaction was monitored by TLC (silica gel; CH_3CN–H_2O–28% NH_4OH, 7:2:1). After 5 days $KHCO_3$ (975 mg, 8.4 mM) and 0.7 mL of $(CH_3)_2SO_4$ were added, and the reaction was continued for another week. The reaction mixture was then diluted with 10 mL of 50% aqueous CF_3COOH and allowed to stir for 4 days. It was then applied to a 20 × 150 mm Dowex 50 (H^+) column that was eluted with water, 60% aqueous CH_3OH, 1 N HCl in 60% aqueous CH_3OH, and finally with 2 N HCl in 60% aqueous CH_3OH, which eluted the major product; 25-mL fractions were collected. Fractions (72–83) containing the major product were combined, and the solvents were removed under vacuum. The residue was dissolved in CH_3OH, neutralized with AG-1 (HCO_3^-), and recrystallized (charcoal) to afford 8-bromo-1,7-dimethylguanine, yield 390 mg (50%, calculated as hydrate): mp, gradual decomposition at >257 °C; NMR (Me_2SO-d_6) δ 3.46 (s, 3, NCH_3), 3.84 (s, 3, NCH_3), 7.03 (s, 2, exchangeable, NH_2); mass spectrum (CI), *m/e* 260 (M + 1, Br = 81), 258 (M + 1, Br = 79); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 1, 217 nm (19.1), 253 sh (8.2), 272 (12.8); UV λ_{max} ($\epsilon \times 10^{-3}$) pH 7, 216 nm (23.5), 237 sh (8.8), 276 (14.2).

An analytical sample was recrystallized from CH_3OH–H_2O and dried over P_2O_5 at 120 °C under vacuum for 3 h.

Anal. Calcd for $C_7H_8N_5BrO \cdot 0.5H_2O$: C, 31.47; H, 3.39; N, 26.22; Br, 29.91. Found: C, 31.40; H, 3.26; N, 25.77; Br, 29.05.

8-Bromo-1,7-dimethylguanine was eluted from a 9 × 250 mm Dowex 50 (H^+) column by 2 N HCl in 60% CH_3OH as a discrete band well before **9**. It could be readily identified and distinguished from **7**, **8**, and **9** by its UV spectra and was not detectable in the mixture of products from the reaction of **6** with acetic anhydride in the presence of 3 M NaBr at pH 7.

Kinetic Analyses. Aliquots were removed from solutions containing weighed samples of **6** (2.5 mg, 11 μmol), dissolved in 9.9 mL of buffer immediately after the addition of 0.1 mL (1.05 mmol) of acetic anhydride, and added to 1 mm path-length cells that were then stoppered. The UV spectral changes were monitored under ambient conditions (23 °C) with a Unicam SP800A spectrophotometer. Buffers (pH) employed were 10^{-2} M HCl (2), 10^{-3} M HCl (3), 0.1 M formate (4), 0.1 M acetate (5), 0.1 M succinate (6), and 0.5 M phosphate (7 and 8). Rate constants in Table I were obtained from plots of $\ln(OD_0 - OD_\infty)/(OD - OD_\infty)$ vs. time using data from the spectral changes at the maximum of the acetylated intermediate at each pH (Table I). After reactions were complete, the product compositions in the remaining solutions were determined for the pH's shown in Table I by chromatography over a 9 × 100 mm column containing Dowex 50 (H^+), 200–400 mesh. Yields were calculated from elution volumes and known ε values.

The product composition of aliquots withdrawn at various times from a reacting solution of **6** at pH 7 was determined by the same method. The initial aliquot, taken immediately after adding acetic anhydride to the reaction, contained 40% of **7**. The yield of **7** increased slightly in later aliquots, e.g., 46% after 2 h, but was little changed after 7 days of reaction (48%). Small amounts (3–8%) of **8** and **9**, which were often poorly resolved, were present throughout the later phase of the reaction. The fourth, unidentified, UV-absorbing product was still detectable after a week of reaction.

Reaction of 6 with Acetic Anhydride in the Presence of 1 M KI. This reaction was performed, as described above, using 0.1 M phosphate buffer (pH 7) containing 1 M KI. The quantity of I_3^- was determined spectrophotometrically at 352 nm (ε 26 500)[5] in a 0.1 mm path-length cell. Quantities of the products were determined chromatographically.

Assays for oncogenicity were carried out as described[21] using groups of 20 CD rats (Charles River Breeding Laboratories, Wilmington, Mass.). Compounds were homogenized in 0.5% carboxymethylcellulose in 0.85% NaCl and injected subcutaneously in the intrascapular area. The experiment was terminated after the 18th month. Autopsies were performed on all animals, and suspicious masses were prepared histologically and examined microscopically.

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Registry No.—**6**, 30345-29-0; **7**, 65879-10-9; **8**, 65879-11-0; **9**, 26758-00-9; **10**·2HCl, 65879-12-1; **11**, 65879-13-2; 1,7-dimethylguanosinium iodide, 26758-44-1; urea, 57-13-6; 2-*N*-acetyl-1,7-dimethyl-8-methoxyguanine, 65879-14-3; 2-*N*-acetyl-1,7-dimethylguanine, 65879-15-4; 8-bromoguanosine, 4016-63-1; 8-bromo-1,7-dimethylguanine, 65879-16-5.

References and Notes

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(16) The 3-acetyl ester of 3-hydroxy-7-methylxanthine only undergoes hydrolysis in water.[13] However, reaction of 3-hydroxy-7-methylxanthine with methane-sulfonyl chloride in dimethylformamide does afford 8-substitution products.[3] The 3-methylsulfate ester of 7,9-dimethyl-3-hydroxyxanthine will also rearrange to 7,9-dimethyluric acid, but only upon heating.[3]
(17) The fact that the 3-methylsulfate ester of 3-hydroxy-7-methylxanthine undergoes an 8-substitution reaction in dimethylformamide suggests that the presence of a more effective leaving group than acetate and a highly polar solvent can also facilitate the formation of a cation from an ester of a 7-substituted 3-hydroxypurine and permit an 8-substitution reaction.
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Synthesis of Lecithin Analogues by Means of Cyclic Enediol Phosphates. Derivatives of 1-Octadecanol and of Cholesterol

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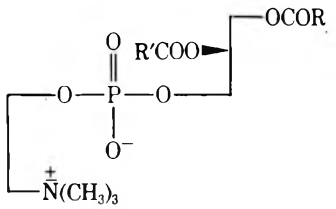
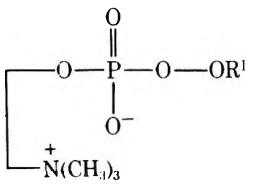
Alkylphosphorylcholines have been synthesized as analogues of the natural phospholipid lecithin (phosphatidylcholine). The synthesis involves three steps: (1) reaction of the lipophilic alcohol, 2-methyl-1-propanol, 1-octadecanol, or cholesterol, with 1,2-dimethylethenylene phosphorochloridate in the presence of triethylamine; (2) triethylamine-catalyzed reaction of the hydrophilic alcohol choline chloride with the alkyl 1,2-dimethylethylene phosphate generated in the first step; and (3) removal of the 1-methylacetonyl blocking group from the alkyl(1-methylacetonyl)phosphorylcholine chloride produced in the second step. The hydrolysis is performed in aqueous acetonitrile, in the presence of triethylamine, and gives the alkylphosphorylcholine zwitterion as a crystalline monohydrate after silica gel chromatography. A second method of synthesis reverses the sequence in which the choline chloride and the lipophilic alcohols are phosphorylated and affords the same alkylphosphorylcholines but in lower yields than the first method.

The phospholipids of biological membranes are phosphodiesters, $(R^IO)(R^{II}O)P(O)OH$, derived from a lipophilic and a hydrophilic alcohol. In the natural lipids, the lipophilic moiety, R^IOH, is a fatty acid ester of glycerol or dihydroxyacetone, or a fatty acid amide of the aminodiol sphingosine.[2] The hydrophilic moiety ($R^{II}OH$), which in conjunction with the phosphate constitutes the polar head group of the molecule, is derived from polyfunctional alcohols such as choline, ethanolamine, serine, *N*-(2-hydroxyethyl)alanine, glycerol, and *myo*-inositol. Lecithin (phosphatidylcholine) is widely distributed in biomembranes and is being extensively employed as the source of the phospholipid bilayer in studies of model membranes by the black film and vesicle techniques.[3] This paper describes the synthesis of several alkyl phosphorylcholines, 1, in which the diglyceride moiety, R^IOH, of lecithin is replaced by simpler lipophilic groups. Compounds of this type are being sought for research into the bilayer-forming properties of unnatural phospholipid analogues.



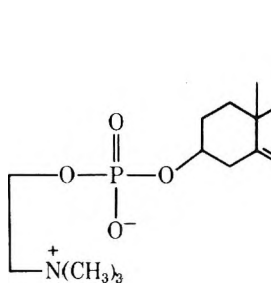
lecithin



1a. $R^I = (CH_3)_2CHCH_2$

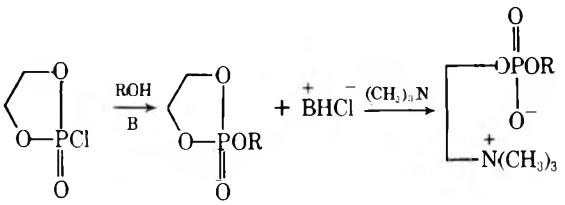
b. $R^I = CH_3(CH_2)_{16}CH_2$

One of the lecithin analogues included in the present study is 3-cholest-5-enylphosphorylcholine (**1c**). Cholesterol is present in conjunction with phospholipids in plasma membranes, and it has been suggested that the steroid reduces the area occupied by lecithin at the air–water interface due to mechanical obstruction of the tilting of the lipid molecules.[4] There is evidence that cholesterol influences the packing of phospholipid molecules and the permeability of model membranes made from them.[4] It appeared of interest to replace cholesterol by the "cholesterollecithin", **1c**, in such studies, and also to compare its behavior with that of the recently synthesized optically active[5] and racemic[6] phosphatidylcholesterol, where the steroid is linked to the lipophilic diglyceride group rather than to the hydrophilic choline group. The bilayer-forming properties of these two types of phospholipid analogues are described elsehwere.



1c

Scheme I



Several syntheses of phosphatidylcholine have been reported,[7-11] and an ingenious method to introduce the choline cation into phosphodiesters (Scheme I) has been recently introduced by Chabrier et al.[12] (Scheme I).

The general synthetic method utilized in the present work is summarized in Scheme II.[13,14] The first of the two phosphorus–oxygen bonds in the phosphodiester is established (step 1) by means of a derivative of the 1,2-dimethylethenylenedioxyphosphoryl group, abbreviated X=P(O)–. Either one of the two alcohols being phosphorylated, R^IOH (lipophilic) or $R^{II}OH$ (hydrophilic), can play the role of the "first alcohol" or R^IOH, in the scheme. The second P–O bond is established (step 2) as a result of the amine-catalyzed phosphorylation of the "second alcohol" or R^2OH by the alkyl cyclic enediol phosphate generated in step 1. The desired phosphodiester is obtained by hydrolysis of the 1-methylacetonyl (Acn) blocking group. The conversion of the two alcohols into the phosphodiester can be achieved as a "one-, two-, or three-step" syntheses, according to the number of intermediates isolated and purified.

Scheme II[a]

$$R^1OH + X{=}P(O)Y + B \rightarrow X{=}P(O)OR^1 + Y^-BH^+ \quad (1)$$

$$R^2OH + X{=}P(O)OR^1 \rightarrow (R^1O)(R^2O)P(O)OAcn \quad (2)$$

$$(R^1O)(R^2O)P(O)OAcn + H_2O \rightarrow (R^1O)R^2O)P(O)OH + Acn \cdot OH \quad (3)$$

[a] Acn = $CH(CH_3)COCH_3$.

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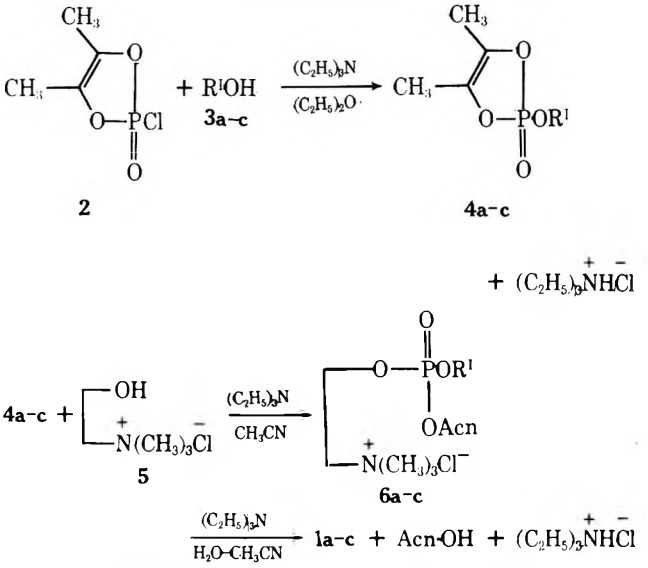
Scheme III[a]



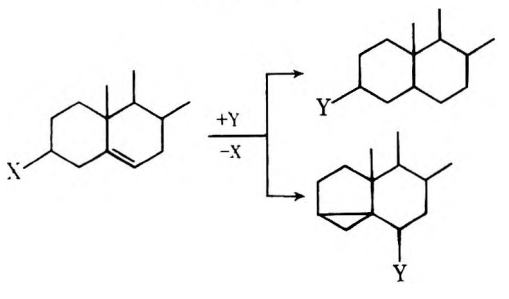
[a] a, $R^I = (CH_3)_2CHCH_2$; b, $R^I = CH_3(CH_2)_{16}CH_2$; c, R^I = 3-cholest-5-enyl; Acn = $CH(CH_3)COCH_3$.

Results

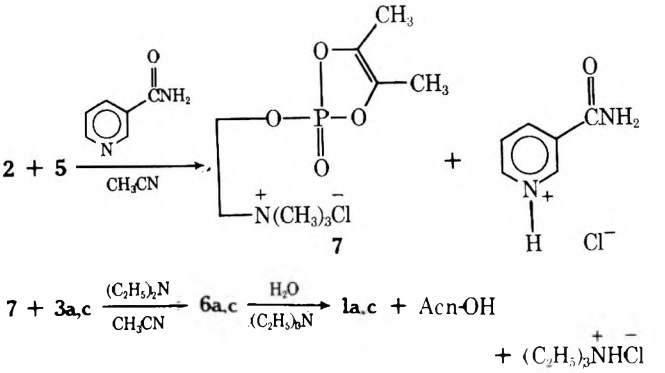
Lipophilic Alcohols (R^IOH) as "First Alcohol" (R^IOH) in the Phosphorylation Sequence. Procedure 1. Three alcohols of increasing lipophilicity, 2-methyl-1-propanol (**3a**), 1-octadecanol (**3b**), and cholesterol (**3c**), are converted into the corresponding alkyl phosphorylcholine zwitterions, **1a–c**, following the sequence of reactions shown in Scheme III. The first step is the phosphorylation of the alcohol by the cyclic enediol phosphorochloridate,[15,16] **2**, and proceeds in virtually quantitative yield; the alkyl cyclophosphate, **4a–c**, is isolated but is not purified. The second step is the phosphorylation of choline chloride (**5**) by the alkyl cyclophosphate, **4a–c**. This reaction yields an acyclic phosphotriester derivative of choline chloride, **6a–c**, which is directly hydrolyzed to the desired alkyl phosphorylcholine zwitterion, **1a–c**. The procedure involves two laboratory operations, since only the alkyl cyclophosphate, **4a–c**, is isolated, although not purified. The zwitterions, **1a–c**, are isolated in 70, 53, and 52% yields, respectively, based on the first alcohol, **3a–c**, after silica gel chromatography. Two of the zwitterions, **1a** and **1c**, are obtained as stable monohydrates, **1a** $\cdot H_2O$ and **1c** $\cdot H_2O$, which retain water even after prolonged drying under vacuum; however, the third zwitterion, **1b**, which contains the octadecyl group is easily dehydrated under comparable conditions.

The structures of the zwitterions, **1a–c**, rest on elemental analysis and ^{31}P and ^1H NMR spectrometry. The structure of 3-cholest-5-enylphosphoryl-choline, **1c**, is also supported by ^{13}C-NMR spectrometry. The key structural features are carbon atoms C3, C5, and C6, and their chemical shifts and multiplicities are those expected from the values found in the parent cholesterol molecule.[17] The ^{13}C parameters of the choline moiety have the values expected from those found for choline chloride.[18] The optical rotation of the zwitterion **1c** is $[\alpha]^{25}_D$ −15.2° (c 1.0, CH_3OH), while that of cholesterol is $[\alpha]^{25}_D$ −39.5° (c 1.3, $CHCl_3$).

Scheme IV



Scheme V



Scheme VI

$$R^2OH + X{=}P(O)OR^1 \rightarrow X{=}P(O)OR^2 + R^1OH \quad (4)$$

$$X{=}P(O)OR^1 + R^1OH \rightarrow (R^1O)_2P(O)OAcn \quad (5)$$

$$X{=}P(O)OR^2 + R^2OH \rightarrow (R^2O)_2P(O)OAcn \quad (6)$$

A careful scrutiny of the structure of the zwitterion derived from cholesterol, **1c**, is mandatory in view of the occurrence of the *i*-cholesterol rearrangement (Scheme IV) during nucleophilic displacements at C3 of certain cholesterol derivatives.[19,20] It is apparent that this rearrangement does not play a significant role in the preparation of the alkyl cyclophosphate, **4c**, and in the subsequent phosphorylation of choline chloride (**5**) by the phosphate, **4c**, at least under the specified conditions, in spite of the relatively high-energy content of the alkyl cyclic enediol phosphate, **4c**.

Hydrophilic Alcohol ($R^{II}OH$ = Choline Chloride) as "First Alcohol" (R^IOH) in the Phosphorylation Sequence. Procedure 2. The flexibility of the present phosphodiester synthesis in the field of lecithin analogues would be increased by the utilization of choline chloride in the first step of the phosphorylation sequence. This procedure has been utilized in the alternate preparation of 2-methyl-1-propyl- and 3-cholest-5-enylphosphorylcholine **1a** and **1c**, as shown in Scheme V.[21]

Although this procedure 2 is feasible, the zwitterions are obtained in significantly lower yields than in procedure 1, e.g., 43 and 37% for **1a** and **1c**, respectively. The reason for this decrease in efficiency is shown in Scheme VI. A nucleophilic displacement with ring retention, instead of ring opening, in the second step of the synthesis (eq 4 in Scheme VI) decreases the yield of the desired *unsymmetrical* dialkyl-1-methylacetonyl phosphate (eq 2 in Scheme II), since the transesterification reaction permits the formation of undesirable *symmetrical* dialkyl-1-methylacetonyl phosphates (eq 5 and 6, Scheme VI). In one case, substantial amounts (ca. 17%) of one of these symmetrical triesters, di-(2-methyl-1-propyl)-1-methylacetonyl phosphate, was isolated in the corresponding synthesis according to procedure 2.

Experimental Section

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Reactions involving derivatives of the 1,2-dimethylethenylenedioxyphosphoryl group must be carried out under strictly anhydrous conditions. Choline chloride was recrystallized from anhydrous ethanol and was kept 24 h at 20 °C (0.2 mm). Cholesterol was anhydrous grade. δ ^{31}P in ppm vs. H_3PO_4 = 0; positive values are down-field from the reference compound; τ ^1H in ppm vs. Me_4Si = 10; ^1H-decoupled δ ^{13}C in ppm to low field of Me_4Si = 0; all spectra at ~30 °C.

2-Methyl-1-propylphosphorylcholine Monohydrate ($1a \cdot H_2O$). Procedure 1. A solution of 2-methyl-1-propanol (2.13 g, 28.8 mmol)

and triethylamine (2.19 g, 1 molar equiv) in diethyl ether (20 mL) was added dropwise to a stirred ether solution (80 mL) of 1,2-dimethylethenylene phosphorochloridate[15b] (**2**; 4.85 g, 28.8 mmol) at 20 °C After 2 h at 20 °C, the alkylammonium salt was filtered and washed with ether (3 × 20 ml). The combined ether solution was evaporated to yield the cyclic phosphate **4a** (6.2 g, 100% yield, after 1 h at 20 °C (0.2 mm)). A solution of the cyclic phosphate **4a** (4.82 g, 28.2 mmol) in acetonitrile (100 mL) was treated with choline chloride (3.94 g, 28.2 mmol, added at once), followed by triethylamine (7.86 mL, 2 molar equiv), at 20 °C. The heterogeneous mixture was stirred for 24 h at 20 °C, at which point it had become homogeneous and contained the alkyl-1-methylacetonylphosphorylcholine chloride, **6a**. Water (200 mL) was added to the acetonitrile solution, and the mixture was stirred for 24 h at 20 °C. The solution was evaporated at 40 °C (20 mm, and 0.2 mm), the residue was dissolved in chloroform (20 mL), and the solution was applied to a column (4 × 52 cm) containing silica gel 60 (400 g, Merck Catalogue No. 7734, packed in $CHCl_3$). Elution with $CHCl_3$ (2 L) and with mixtures of $CHCl_3/CH_3OH$ (99/1, 2 L; 95/5, 2 L; 90/10, 2 L; 80/20, 2 L; 50/50, 1.5 L) removed impurities. The alkyl phosphorylcholine, **1a**, appeared in 4 L of methanol; the solvent was evaporated and the residue was kept 12 h at 20 °C (0.2 mm) to give 4.03 g (70%) of **1a**. ^{1}H-NMR spectra (in CD_3OD) revealed that this material could be nearly anhydrous or could contain variable amounts of water depending on the degree of exposure of the sample to atmospheric moisture. The zwitterion, **1a**, was converted into its monohydrate by addition of moist acetone (20 mL) to a methanol (5 mL) solution of the chromatographed product (4.0 g). The crystals were filtered and dried for several hours at 20 °C (0.2 mm) to yield **1a**·H_2O, mp 225–230 °C (with decomposition after losing water at ca. 120 °C); δ ^{31}P = −0.6 ppm (CD_3OD); τ ^{1}H = 9.05 (doublet, J = 7 Hz), 8.00, 6.72 (singlet) 6.32, 5.70, and 5.11 (singlet) ppm in CD_3OD. Anal. Calcd for $C_9H_{22}O_4NP$·H_2O: C, 42.0; H, 9.4; N, 5.4; P, 12.0; H_2O, 7.0. Found: C, 42.2; H, 9.5; N, 5.4; P, 12.0; H_2O, 6.9 (K. Fischer method).

1-Octadecylphosphorylcholine (1b). Procedure 1. This compound was prepared by the procedure described above, with the following variations. From 1-octadecanol (6.52 g) and triethylamine (2.44 g) in diethyl ether (20 mL), and the phosphorochloridate **2** (4.06 g) in diethyl ether (100 mL), there was obtained the cyclic phosphate **4b** as a white solid. From **4b**, choline chloride (3.29 g), and triethylamine (4.77 g) in acetonitrile (500 mL), after stirring for 36 h at 20 °C, there was obtained a solution of the alkyl 1-methylacetonylphosphorylcholine chloride, **6b**. The solution was evaporated at 30 °C (30 mm), the residue was dissolved in water (200 mL) and acetonitrile (100 mL), and the mixture was treated with triethylamine (4.77 g) and stirred for 10 h at 70 °C. The residue obtained after evaporation was purified by chromatography to give 5.55 g (53%) of **1b**. Crystallization of the crude product (4.26 g) from acetone (30 mL) and methanol (4 mL) gave the *anhydrous* zwitterion **1b**, melting with decomposition at ca. 235 °C (after 12 h at 20 °C (0.2 mm)); δ ^{31}P = 0.0 ppm (CD_3OD); τ ^{1}H = 8.67, 6.70 (singlet), 6.30, and 5.76 ppm in CD_3OD. Anal. Calcd for $C_{23}H_{50}O_4NP$: C, 63.4; H, 11.6; N, 3.2; P, 7.1. Found: C, 63.3; H, 11.9, N, 3.1; P, 7.1; H_2O, 0.6 (K. Fischer method).

3-Cholest-5-enylphosphorylcholine Monohydrate (1c·H_2O). Procedure 1. From cholesterol (4.42 g) and triethylamine (1.16 g) in diethyl ether (20 mL), and the phosphorochloridate **2** (1.93 g) in diethyl ether (100 mL), after 6 h of reaction time at 20 °C, there was obtained the cyclic phosphate **4c** as a white solid, following the procedure described above. A suspension of the cyclic phosphate **4c** in acetonitrile (250 mL) and dichloromethane (250 mL) was treated with choline chloride (1.60 g) and triethylamine (2.32 g) at 20 °C. Reaction time to the alkyl 1-methylacetonylphosphorylcholine chloride, **6c**, was 36 h at 20 °C. The solution was evaporated at 30 °C (30 mm), the residue was dissolved in water (100 mL) and acetonitrile (50 mL), and the mixture was treated with triethylamine (2.31 g) and stirred for 10 h at 70 °C. The residue obtained after evaporation of the resulting solution was purified by silica gel chromatography as described above (the impurities were removed using 3 L of each of the indicated solvent mixtures; the desired product was obtained in 3 L of methanol). The alkyl phosphorylcholine **1c** was obtained as a powder (3.26 g, 52% yield) and was recrystallized from methanol (2 mL) and moist acetone (20 mL). The crystals melted with decomposition at ca. 230 °C after drying for 1 h at 20 °C (0.2 mm) and had the composition of the monohydrate **1c**·H_2O; $[\alpha]^{25}_D$ −15.2° (c 1.0 in CH_3OH); δ ^{31}P = −1.4 ppm (CD_3OD); τ ^{1}H = 9.00, 6.80 (singlet), 6.30, 5.70, and 5.18 (singlet) ppm (CD_3OD); main δ ^{13}C = 76.8 (doublet, J_{COP} = 6 Hz, C3), 122.8 (singlet, C6), and 141.6 (singlet, C5) ppm, in the 3-cholest-5-enyl group, and 54.6 [triplet, J_{CN} = 3.4 Hz, $(CH_3)_3N$], 60.1 (doublet, J_{COP} = 4.9 Hz, CH_2OP), and 67.4 (multiplet, CH_2N) ppm, in the choline group (in CD_3OD). Lit. for cholesterol: δ ^{31}C = 71.0 (C3), 120.9 (C6), and 141.7 (C5) ppm (in pyridine-d_5); Lit. for choline chloride δ ^{13}C = 54.8 (triplet, J_{CN} = 4.1 Hz), 56.6 (singlet, CH_2OH), and 68.3 (triplet, J_{CN} = 3.0 Hz, CH_2N) ppm (in D_2O). Anal. Calcd for $C_{32}H_{58}O_4NP$·H_2O: C, 67.5; H, 10.6; N, 2.5; P, 5.4; H_2O, 3.2. Found: C, 67.8; H, 10.7; N, 2.3; P, 5.4; H_2O, 4.6 (K. Fischer method).

1,2-Dimethylethenylenedioxyphosphorylcholine Chloride (7). Choline chloride (5.33 g, 38.2 mmol) was added to a solution of 1,2-dimethylethenylene phosphorochloridate (6.43 g, 38.2 mmol) in acetonitrile (100 mL) containing nicotinamide (4.66 g, 1 molar equiv) in suspension, at 20 °C. The mixture was stirred for 24 h at 20 °C, and was filtered. The filtrate was evaporated (30 °C (20 mm and 0.2 mm)). The residue was dissolved in dichloromethane (100 mL) and was kept for 12 h at −20 °C and filtered to remove the last traces of nicotinamide hydrochloride. The filtrate was evaporated, the residue was redissolved in dichloromethane (100 mL), and the solution was diluted with diethyl ether (20 mL) and kept 12 h at −20 °C. The crystalline choline chloride cyclophosphate ester (7) was filtered and dried at 20 °C (0.2 mm). This substance is sensitive to moisture and unlike choline chloride is relatively soluble in dichloromethane and in acetonitrile; it has the following spectral properties: δ ^{31}P = +10.4 ppm ($CDCl_3$); τ ^{1}H = 8.00 (apparent singlet, $CH_3C{=}CCH_3$), 6.42 (singlet), 5.75, and 5.37 ppm ($CDCl_3$).

1,2-Dimethylethenylenedioxyphosphorylcholine 1,2-Dimethylethenylenephosphate. A salt analogous to the chloride 7 was made as described above, but utilizing as reagent bis(1,2-dimethylethenylene) pyrophosphate X=P(O)·O·(O)P=X. The cyclophosphate salt of the choline cyclophosphate ester has the following spectral properties; δ ^{31}P = +10.3 (triplet, J_{POCH_2} = 6.8 Hz), and +11.8 (singlet) ($CDCl_3$); τ ^{1}H = 8.24 (singlet), 8.10 (singlet), 6.60 (singlet), 5.84, and 5.30 ppm ($CDCl_3$).

3-Cholest-5-enylphosphorylcholine Monohydrate (1c·H_2O). Procedure 2. A dichloromethane (20 mL) solution of cholesterol (5.99 g, 15.5 mmol) and triethylamine (3.14 g, 1 molar equiv) was added, dropwise, to a dichloromethane (50 mL) solution of 1,2-dimethylethenylenedioxyphosphorylcholine chloride (**7**; 4.21 g, 1 molar equiv), at 20 °C. The solution was stirred for 20 h at 20 °C and was evaporated. The residue was dissolved in water (100 mL) and acetonitrile (50 mL), and the mixture was treated with triethylamine (3.14 g) and stirred for 16 h at 70 °C. The solution was evaporated, and the residue was purified by column chromatography as described under procedure 1. The alkyl phosphorylcholine **1c** was obtained in 37% yield (3.22 g) and was converted into the monohydrate **1c**·H_2O, mp 230 °C dec, $[\alpha]^{25}_D$ −15.8° (c 1.16, CH_3OH), for characterization.

2-Methyl-1-propylphosphorylcholine Monohydrate (1a·H_2O). Procedure 2. From 2-methyl-1-propanol and the choline chloride cyclophosphate **7**, there was obtained the alkyl phosphorylcholine, **1a**·H_2O, in 43% yield. A by-product of this reaction is di(2-methyl-1-propyl)-1-methylacetonyl phosphate, isolated in 17% yield.

Registry No.—**1a**, 21991-72-0; **1b**, 65956-63-0; **1c**, 65956-64-1; **2**, 21949-38-2; **3a**, 78-83-1; **3b**, 112-92-5; **3c**, 57-88-5; **4a**, 16764-09-3; **4b**, 65956-65-2; **4c**, 65956-66-3; **5**, 67-48-1; **6a**, 65956-67-4; **6b**, 65956-68-5; **6c**, 65956-69-6; **7**, 65956-59-4; 1,2-dimethylethenylenedioxyphosphorylcholine 1,2-dimethylethenylenephosphate, 65956-61-8; bis(1,2-dimethylethenylene) pyrophosphate, 55894-84-5; bis(2-methyl-1-propyl)-1-methylacetonyl phosphate, 65956-62-9;

References and Notes

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(21) Nicotinamide is used as the proton acceptor in the first step in order to minimize the solubility of the base hydrochloride in the acetonitrile solvent. The latter is used in place of ether to maximize the solubility of choline chloride (**5**).

Formation of 14α-Cardenolides from 21-Acetoxy-20-keto Steroids

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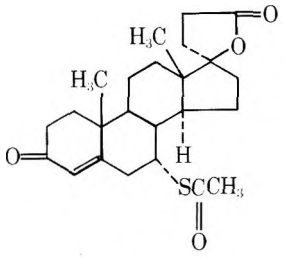
The Emmons–Horner condensation of diethyl cyanomethylenephosphonate with 21-acetoxy-20-keto steroids has been studied. The reaction with 21-acetoxypregnenolone gives a 20-cyanomethylene steroid as a single isomer. The 3-enol ethers of deoxycorticosterone acetate, 11-dehydrocorticosterone acetate, and corticosterone diacetate react similarly. Δ^1-Corticosterone acetate reacts directly with the ylide only at C-20 to form the corresponding 20-cyanomethylene derivative. These modified corticoids undergo ready dehydrogenation to form 1,4-, 4,6-, and 1,4,6-unsaturated ketones. When these cyanomethylene derivatives react with 1 equiv of *p*-toluenesulfonic acid in refluxing aqueous ethanol, transesterification of the 21-acetate and hydrolysis of the nitrile occurs to form a cardenolide ring in high yield. These mild conditions are compatible with a wide variety of other functional groups in the steroid. The corresponding cardanolides have been prepared by ketalization of the 3-ketone and subsequent hydrogenation and deketalization.

We were interested in preparing cardenolides and cardanolides related to the known anti-aldosterone steroid, Spironolactone **1**. If the usual hormonal steroid stereochemistry is introduced into the cardenolides (i.e., C/D-trans) and, additionally, when the requisite 3-keto-4-ene grouping is present, the structural similarity between **2** and **1** becomes apparent.[1]



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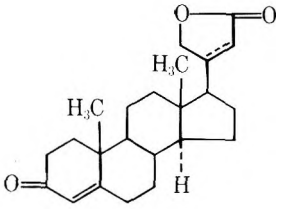
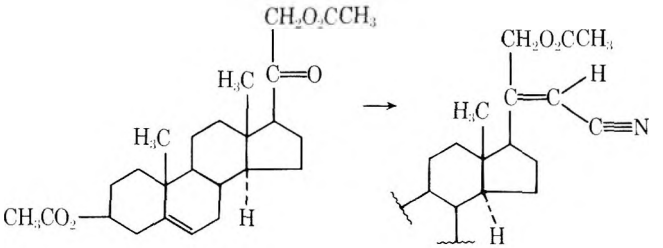


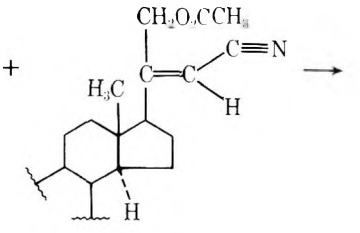
2 ($\Delta^{20,22}$)

31

An apparently simpler reaction, proceeding in very high yield, for the formation of the steroid cardenolide ring was described by Fritsch.[2] This involved the reaction of a 21-hydroxy-20-ketone moiety with the anion of trimethyl phosphonoacetate in a modified Horner–Emmons reaction to yield directly the cardenolide ring in yields of greater than 95%.[3] When this reaction was attempted using deoxycorticosterone, we were never able to achieve yields of more than 25%, and this particular reaction appeared to be limited in its applicability. Similar observations were reported by Yoshii and Ozaki on the same condensation with 21-hydroxypregnenolone.[4] During the time that these studies were in progress, Pettit reported on the formation of cardenolides from 21-acetoxy-20-ketones and diethyl cyanomethylenephosphonate.[5] The reaction between 21-acetoxypregnenolone acetate **3** and the Horner–Emmons ylide formed a mixture of 20-cyanomethylene isomers **4** and **6** which were not separated, but the crude reaction mixture was directly reacted with hydrochloric acid to form the iminocardenolide hydrochloride **5** and the pure (*E*)-cyanomethylene isomer **6**. Compound **5** could then be hydrolyzed in refluxing hydrochloric acid to give the cardenolide **7**. The assignment of stereochemistry for **6** was based on repeated



3 **6**



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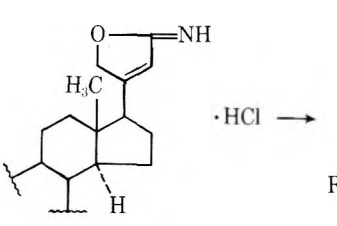

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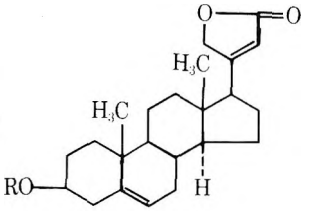

7, R = $OCCH_3$
8, R = H

unsuccessful attempts to convert it into the cardenolide **7**.[5]

The enol ether **9** of deoxycorticosterone was prepared using standard methods and condensed with the anion of diethyl cyanomethylenephosphonate to give the enol ether **10** which could be hydrolyzed in aqueous acetic acid to the enone **11** in an overall yield of 58%. When basic hydrolysis of the 21-acetate in **11** was attempted only extensive degradation occurred and this approach to the 21-hydroxy compounds was abandoned. As a consequence, acid-catalyzed transesterification

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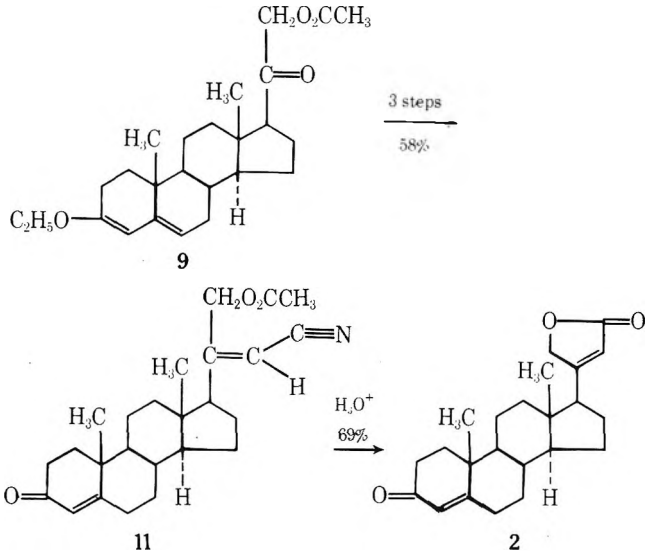


was attempted using *p*-toluenesulfonic acid in absolute methanol. Only a small amount of a new product was formed and the yield was a function of the amount of catalyst present. The product was isolated and identified as the known cardenolide **2**.[2] The probable mechanism involved transesterification of **11** to the 21-hydroxy compound which adds to the nitrile to form the imino lactone and which, in turn, is hydrolyzed to the cardenolide **2** and ammonia by the water of hydration of the tosyl acid. The liberated ammonia neutralizes the acid, thereby stopping both the hydrolysis and the transesterification. When 1.1 equiv of acid was used in aqueous ethanol, **11** was smoothly converted into **2** in 69% yield without detectable intermediates.

Because of this facile conversion of the cyanomethylene steroid into a cardenolide, we reinvestigated the reaction with 21-acetoxypregnenolone acetate **3**.[5] Condensation with the ylide gave, again, only a single isomer in 75% yield which was identical with that reported by Pettit for the *E* isomer **6**. Acid-catalyzed transesterification and hydrolysis gave the known 3β-hydroxycardenolide **8** in 95% yield, which was also acetylated to the known **7**.[5] Since we did not detect any isomerization of the cyanomethylene compound during the hydrolysis and no evidence was obtained for any intermediate, the cyanomethylene compound possesses the *Z* configuration (**4**) and Pettit's results were apparently due to incomplete hydrolysis of the cyanomethylene compound **4** into the imino lactone **5**. We were unable to find any of the *E* isomer **6**.

The 11β-acetate and 11-keto derivatives of deoxycorticosterone were also converted into their enol ethers and subsequently into their 20-cyanomethylene derivatives. The data are presented in Scheme I and the yields given are for the overall conversion of 20-keto enones into the 20-cyanomethylene enones. As the formation of the enol ether of corticosterone acetate was very difficult, the 1,4-dienone **12** was prepared on the assumption that the 3-ketone would be sufficiently deactivated to allow exclusive reaction with the ylide at the 20-ketone. In practice this was observed and the 11β-hydroxy-20-cyanomethylene derivative **13** was obtained in 78% yield. Conversion to the 11β-hydroxydienone cardenolide **14** was readily accomplished with aqueous tosyl acid in 65% yield without any evidence for the dienone–phenol rearrangement.[6]

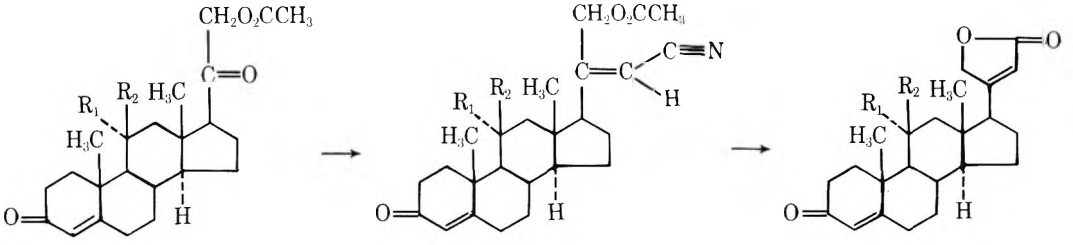
An advantage to isolating the 20-cyanomethylene derivatives as their 3-enol ethers is their facile conversion to the 4,6-dienone or the 1,4,6-trienone by dichlorodicyanobenzoquinone (DDQ) oxidation in aqueous acetone and benzene, respectively.[7] For example, the enol ether of compound **11** was oxidized to the 4,6-dienone **15** and the 1,4,6-trienone **16** in 75 and 43% yields, respectively. The 1,4-dienone **14** was obtained in 43% yield from the enone **11** via DDQ oxidation in refluxing benzene. Similarly, the cardenolide **2** was oxidized to its 1,4-dienone **18** and its 3-enol ether was converted to the 1,4,6-trienone **19**. This time, however, the 4,6-dienone cardenolide **20** was synthesized from the corresponding 4,6-dienone-20-cyanomethylene compound **15** by tosyl acid hydrolysis, indicating the stability of the linear dienone system to these reaction conditions.

The tosyl acid hydrolysis of the 21-acetoxy-20-cyanomethylene grouping into a cardenolide has thus been shown to proceed under very mild conditions and alcohol, acetate, ketone, enone, and 1,4- and 4,6-dienone functions are stable to the reaction conditions effecting this conversion.

The reduction of the cardenolide **2** to the 3β-hydroxy-4-ene **21**, without affecting the cardenolide double bond, was accomplished using lithium aluminum tri-*tert*-butoxide hydride. This reaction was also reported by Ruschig using sodium borohydride.[8] Reaction of **21** with methylene iodide under Simmons–Smith conditions furnished the 4β,5β-cyclopropane **22**.[9] Oxidation of the cyclopropylcarbinol to the 4β,5β-cyclopropyl ketone **24** was readily accomplished using silver carbonate on Celite.[10]

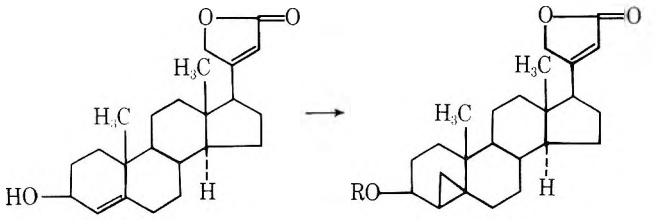
To protect the enone function of **2** during catalytic reduction of the cardenolide double bond, the ketal **29** was formed using the ethylene glycol vacuum distillation technique.[11] Hydrogenation of compound **29** over palladium on carbon gave the cardanolide ketal **30**. Hydrolysis of the ketal was effected by 2.8 M perchloric acid in aqueous tetrahydrofuran,[12] but TLC indicated that the product **31** was contaminated with a small amount of starting material **2** and chromatography was necessary to isolate pure **31** in 85% overall yield from the ketal **2**. A similar series of reactions on the 11-ketocardenolide **26** gave the corresponding cardanolide **32**. While the hydroge-

Scheme I

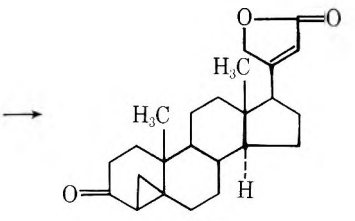


R_1	R_2			
H	H		11 (58%)	2 (69%)
O			25 (76%)	26 (56%)
H	O_2CCH_3		27 (31%)	28 (65%)
H	OH[a]		13 (78%)[a]	14 (65%)[a]

[a] $\Delta^{1,4}$-Dienone as starting material and reaction products.

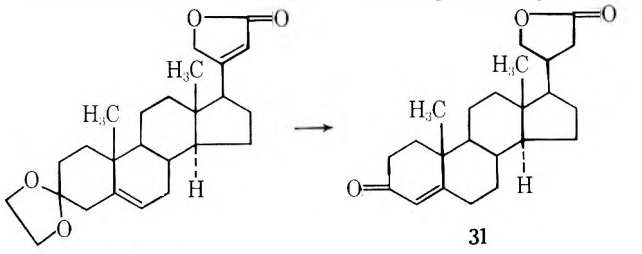


21 22, R = H 23, R = $OCCH_3$



24

nation of 20(22)-noncholenic acid esters was reported to be nonstereospecific,[13] the similar hydrogenation of 14α-cardenolides is either stereospecific or highly stereoselective in forming the (20*R*)-20β-cardanolide.[14] Since both TLC and NMR indicated that cardanolide **31** is a pure compound, it



29 31

probably possesses the 20*R* configuration, but in the absence of additional information this assignment and that of the other 14α-cardanolides prepared in this work has to be considered tentative.

Dehydrogenation of the cardanolide enone **31** and its enol ether with DDQ, analogous to the dehydrogenation of the cardenolide 2, gave the cross conjugated 1,4-dienone **33,** the linear 4,6-dienone **34,** and the 1,4,6-trienone **35.**

Experimental Section

General. Melting points were run on a Thomas-Hoover Unimelt Capillary Apparatus and are uncorrected. IR spectra were run in potassium bromide, unless otherwise stated, on a Beckman IR-12.Ultraviolet spectra were run in methanol on a Beckman DK-2a spectrometer, and optical rotations were run in chloroform on a Perkin-Elmer Model 141 polarimeter. NMR spectra were recorded on a Varian A-60 spectrometer and were run in deuteriochloroform using tetramethylsilane as an internal standard. The NMR spectra are reported in chemical shift (δ) followed by a first order analysis of the signal shape: s, singlet; d, doublet; t, triplet; q, quartet; and m, multiplet. The multiplicity is followed by the coupling constant in hertz, where appropriate, and then the integrated signal intensity. Microanalyses were determined by the Searle Laboratories Microanalytical Service under the direction of Mr. E. Zielinski; chromatographies were performed under the supervision of Mr. R. Nicholson and hydrogenations were conducted under the supervision of Mr. M. Scaros.

The Reaction of 3β,21-Dihydroxy-5-pregnen-20-one Diacetate (3) with Diethyl Cyanomethylphosphonate. To a suspension of 0.83 g of sodium hydride (50% dispersion in mineral oil) in 25 mL of 1,2-dimethoxyethane was added 5.8 g of diethyl cyanomethylphosphonate (Aldrich) in 10 mL of solvent. After reaction had ceased, 10.0 g (24 mmol) of 21-acetoxypregnenolone acetate **3,** Searle Chemicals, in 50 mL of the same solvent was added via an addition funnel. After stirring at room temperature for 1 h, the solution was heated to ca. 80 °C and allowed to cool. This heating was subsequently found to be unnecessary. The reaction mixture was poured into water and then stirred magnetically. After crystallization was complete, the material was filtered and dissolved in methylene chloride. The methylene chloride solution was dried with sodium sulfate and evaporated and the residue was crystallized from ethyl acetate–ether to yield 7.9 g (18 mmol, 75%) of **4** [3β,21-dihydroxy-24-norchola-5,20(22)-diene-23-nitrile diacetate], mp 175–177 °C (lit.[5] mp 182–185 °C), whose spectral characteristics agreed with Pettit's published values.

The Conversion of 4 into the Cardenolide 8. Compound **4** (1.00 g, 2.27 mmol) was suspended in 50 mL of 95% ethanol (containing 5% methanol) and an additional 5 mL of distilled water was added. The mixture was stirred and after the addition of 0.5 g of *p*-toluenesulfonic acid monohydrate brought to reflux. Due to the slower, but still significant, hydrolysis of the 3β-acetate it was necessary to reflux the mixture for 39 h to complete both hydrolyses. The conversion to the cardenolide ring, however, was complete after 16 h. Upon cooling the reaction mixture, a substantial precipitate was evident in the flask and after the addition of 50 mL of distilled water the precipitate was filtered and dried to yield 750 mg (2.11 mmol, 93%) of the cardenolide **8,** 3β,21-dihydroxy-5,20(22)-norcholadieno-23,21-lactone, mp 239–249 °C (lit. mp 240–245 °C), $[\alpha]_{589}^{25}$ −63°, $[\alpha]_{365}^{25}$ −208° (c 1.00, chloroform), whose spectral properties were identical with the published values.

A portion of **8** was acetylated in quantitative yield with acetic anhydride–pyridine (1:4:5 w/v/v equivalents), using 4-*N*,*N*-dimethylaminopyridine as a catalyst.[15] Dilution of the acetylation mixture with distilled water gave the 3β-acetate **7:** mp 162–163 °C (lit. mp 170–172,[5] 153–154 °C[16]), $[\alpha]_{589}^{25}$ −57°, $[\alpha]_{365}^{25}$ −197° (c 1.00, chloroform). The spectral values of **7** were identical with Pettit's published values.[5]

The Enol Ether of Deoxycorticosterone Acetate 9. Deoxycorticosterone acetate (60 g, 161 mmol, Searle Chemicals) was dissolved in a solution of 180 mL of dioxane, 120 mL of ethanol, and 75 mL of triethyl orthoformate at 0 °C, 3.6 g (18.9 mmol) of *p*-toluenesulfonic acid monohydrate was added, and the solution was stirred at 0 °C for 15 min. The suspension (solids present) was then poured into 3 L of a 2% pyridine–water solution at 0 °C. The precipitate was filtered and washed with 300 mL of 2% pyridine/water to give 48.6 g (121 mmol, 75%) of the enol ether: mp 124–129 °C; UV 239 nm (ϵ) 18 300); IR 1735 (C-20 ketone), 1755 cm^{-1} (acetoxy carbonyl); NMR δ 5.20 (m, 2 H, C-4, 6 H), 4.81 (d, J = 17.0 Hz, 1 H, C-21 H), 4.47 (d, J = 17.0 Hz, 1 H, C-21 H), 2.15 (s, 3 H, acetoxy methyl H), 0.99 (s, 3 H, C-19), 0.70 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 74.81; H, 9.36.

The Emmons–Horner Condensation of the Enol Ether of Deoxycorticosterone Acetate. Diethyl cyanomethylphosphonate (8.8 g; 50 mmol) was dissolved in 50 mL of tetrahydrofuran and added, under N_2, to a slurry of 2.5 g of NaH (50% in mineral oil) in 50 mL of tetrahydrofuran at 10–15 °C. To the clear yellow-orange solution was added 20 g (50 mmol) of the enol ether of deoxycorticosterone acetate dissolved in 50 mL of tetrahydrofuran. The solution was stirred at room temperature for 24 h and then added to 1 L of 0.25 M HCl and warmed (30–35 °C) for 2 h, filtered, and washed with water and 2% pyridine/methanol. The crude product was then digested in boiling 2% pyridine/methanol, cooled, and filtered to give 14.8 g (35 mmol, 70%) of the cyanomethylene derivative **10:** mp 132–136 °C; UV 232.5 nm (ϵ 27 000); IR 2230 (C≡N), 1755 cm^{-1} (acetoxy carbonyl); NMR δ 5.50 (s, 1 H, cyanomethylene H), 5.12 (m, 2 H, C-4,6), 4.81 (d, J = 8.0 Hz, 1 H, C-21 H), 4.22 (d, J = 8.0 Hz, 1 H, C-21 H), 2.17 (s, 3 H, acetoxy methyl H), 0.99 (s, 3 H, C-19), 0.65 (s, 3 H, C-18). Anal. Calcd for $C_{27}H_{37}NO_3$: C, 76.56; H, 8.81; N, 3.31. Found: C, 76.58; H, 8.90; N, 2.95.

The Formation of the Cyanomethylene Enone 11. 10 (6.0 g; 14.2 mmol) was dissolved in 40 mL of 60% acetic acid by heating on a steam bath for 30 min. The solution was cooled, diluted with water, and filtered. The crude product was dissolved in hot methanol, cooled, diluted with water, and filtered to give 4.62 g (11.7 mmol, 82.6%) of the enone **11,** [21-(acetyloxy)-3-oxo-24-norchola-4,20(22)-diene-23-nitrile]: mp 167–169 °C; UV 232.5 nm (ϵ 26 000); IR 2220 (C≡N), 1755 (acetoxy carbonyl), 1675 cm^{-1} (C-3 ketone); NMR δ 5.72 (s, 1 H, C-4 H), 5.38 (s, 1 H, cyanomethylene H), 4.92 (d, J = 14.0 Hz, 1 H, C-21 H), 4.63 (d, J = 14.0 Hz, 1 H, C-21 H), 1.98 (s, 3 H, acetoxymethyl H), 1.18 (s, 3 H, C-19), 0.67 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{33}NO_3$: C, 75.91; H, 8.41; N, 3.54. Found: C, 75.54; H, 8.63; N, 3.42.

DDQ Dehydrogenation of the Cyanomethylene Enone 11. 11 (1.0 g; 2.53 mmol) was dissolved in 25 mL of dry benzene with stirring under nitrogen. To this solution was added, at room temperature, 0.72 g (3.1 mmol, 1.25 equiv) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 25 mL of dry benzene. The solution was heated at reflux for 20 h and then cooled, concentrated, and filtered. The remaining solution was then reduced to dryness and the residue was chromatographed over 40 g of Woelm neutral aluminum oxide (activity grade

III). Elution with ethyl acetate–benzene gave 0.48 g (1.22 mmol, 48.2%) of the 3-keto-1,4-dienone **17** [21-(acetyloxy)-3-oxo-24-norchola-1,4,20(22)-triene-23-nitrile]: mp 144.5–146.5 °C; UV 220 nm (ε 23 000); IR 2220 (C≡N), 1755 (acetoxy carbonyl), 1670 cm^{-1} (C-3 ketone); NMR δ 7.03 (d, J = 10.0 Hz, 1 H, C-2 H), 6.22 (d, J = 10.0 Hz, 1 H, C-1 H), 6.08 (s, 1 H, C-4 H), 5.39 (s, 1 H, cyanomethylene H), 4.92 (d, J = 14.0 Hz, 1 H, C-21 H), 4.64 (d, J = 14.0 Hz, 1 H, C-21 H), 2.12 (s, 3 H, acetoxymethyl H), 1.22 (s, 3 H, C-19), 0.68 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 76.40; H, 8.08; N, 3.64.

DDQ Dehydrogenation of the Enol Ether 10. 10 (3.0 g; 7.08 mmol) was dissolved in 150 mL of 95% aqueous acetone. DDQ (1.71 g; 7.44 mmol) was dissolved in 30 mL of 95% aqueous acetone and added dropwise with stirring. The reaction mixture was stirred for 10 min and then reduced to dryness at 25 °C under vacuum. The residue was slurried in 30 mL of benzene and filtered; the filter cake was washed with an additional 15 mL of benzene. The clear yellow solution was chromatographed over 150 g of Woelm neutral aluminum oxide (activity grade III). Elution with ethyl acetate–benzene (50:50) gave, after crystallization from ethyl acetate–diethyl ether, 2.10 g (5.34 mmol, 75.4%) of the 3-keto-4,6-dienone **15** [21-(acetyloxy)-3-oxo-24-norchola-4,6,20(22)-triene-23-nitrile]: mp 167–169 °C; UV 282.5 nm (ε 26 500); IR 2220 (C≡N), 1755 (acetoxy carbonyl), 1665 cm^{-1} (C-3 ketone); NMR δ 6.17 (s, 2 H, C-6, 7 H), 5.70 (s, 1 H, C-4 H), 5.46 (s, 1 H, cyanomethylene H), 4.97 (d, J = 14.0 Hz, 1 H, C-21 H), 4.68 (d, J = 14.0 Hz, 1 H, C-21 H), 2.17 (s, 3 H, acetoxy methyl H), 1.13 (s, 3 H, C-19), 0.70 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{31}NO_3$: C, 76.30; H, 7.94; N, 3.56. Found: C, 76.36; H, 7.99; N, 3.55.

DDQ Dehydrogenation of the Enol Ether 10 in Aprotic Solvents. 10 (1.0 g; 2.36 mmol) was dissolved in 25 mL of dry benzene and added rapidly, under nitrogen, to 1.14 g (4.96 mmol) of DDQ in 40 mL of dry benzene. The reaction mixture was stirred vigorously at room temperature for 20 min, diluted with 20 mL of dichloromethane, and filtered. The organic solution was evaporated to dryness and chromatographed over 40 g of Woelm neutral aluminum oxide (activity grade III). Elution with ethyl acetate–benzene (50:50) gave, after crystallization from ethyl acetate–hexane, 400 mg of trienone **16** [21-(acetyloxy)-3-oxo-24-norchola-1,4,6,20(22)-tetraene-23-nitrile] (1.01 mmol, 42.6%): mp 155–158 °C; UV 299 nm (ε 12 800); IR 2220 (C≡N), 1755 (acetoxy carbonyl), 1660 cm^{-1} (C-3 ketone); NMR δ 7.08 (d, J = 10.0 Hz, 1 H, C-2 H), 6.29 (d, J = 10.0, 1 H, C-1 H), 6.09 (m, 3 H, C-4, 6,7 H), 5.45 (s, 1 H, cyanomethylene H), 5.98 (d, J = 14.0 Hz, 1 H, C-21), 4.68 (d, J = 14.0 Hz, 1 H, C-21 H), 2.16 (s, 3 H, acetoxymethyl H), 1.22 (s, 3 H, C-19), 0.75 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{29}NO_3$: C, 76.69; H, 7.43; N, 3.56. Found: C, 76.68; H, 7.38; N, 3.48.

Acid-Catalyzed Conversion of the 21-(Acetyloxy)-20-cyanomethylene Grouping in 11 into the Cardenolide Ring. 11 (3.0 g; 7.58 mmol) was dissolved in 150 mL of ethanol and 7.5 mL of water, and then 1.65 g (8.3 mmol) of p-toluenesulfonic acid monohydrate was added. The solution was heated at reflux for 24 h, cooled to room temperature, and concentrated under vacuum to approximately 35 mL. The solution was diluted with water, chilled, filtered and washed with cold ethanol to give 1.86 g (5.25 mmol, 69.1%) of the cardenolide **2** [21-hydroxy-3-oxo-24-norchola-4,20(22)-dieno-23,21-lactone]: mp 226–227.5 °C; UV 224 nm (ε 22 000); IR 1760 (C-22 carbonyl), 1670 cm^{-1} (C-3 ketone); NMR δ 5.87 (d, 1 H, C-21 H), 5.75 (s, 1 H, C-4 H), 4.78 (s, 2 H, C-23), 1.22 (s, 3 H, C-19), 0.70 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 78.12; H, 8.63.

DDQ Dehydrogenation of the Cardenolide 2. Compound **2,** 1.90 g (5.36 mmol), was dissolved in 50 mL of dry benzene with stirring under nitrogen. DDQ, 1.56 g (6.75 mmol), was dissolved in 50 mL of dry benzene and added dropwise. The solution was refluxed 24 h, cooled, concentrated, and filtered. The filtrate was reduced to dryness and the residue was chromatographed over 60 g of Woelm neutral aluminum oxide (activity grade III) to give 400 mg of the 1,4-dienone **18** [21-hydroxy-3-oxo-24-norchola-1,4,20(22)-trieno-23,21-lactone] (1.13 mmol, 21.2%): mp 287–290 °C; UV 218 nm (ε 25 000); IR 1755 (C-22 carbonyl), 1665 cm^{-1} (C-3 ketone); NMR δ 7.06 (d, J = 11.0 Hz, 1 H, C-1 H), 6.20 (J = 11.0 Hz, 1 H, C-2 H), 6.08 (s, 1 H, C-4), 5.84 (d, 1 H, C-21), 4.74 (s, 2 H, C-23), 1.25 (s, 3 H, C-19), 0.73 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 78.41; H, 7.90.

The Enol Ether of the Cardenolide 2. Compound **2,** 2.00 g (5.64 mmol), was dissolved in a solution of 6.0 mL of dioxane, 4.0 mL of ethanol, and 2.5 mL of triethyl orthoformate at 0 °C. p-Toluenesulfonic acid monohydrate (120 mg) was added and the solution was stirred at 0 °C for 15 min. The solution was poured into 100 mL of a 2% pyridine–water solution at 0 °C. The precipitate was filtered, slurried in 20 mL of hot 2% pyridine–methanol, cooled, and filtered to give 1.54 g (4.03 mmol, 71.5%) of the enol ether: mp 173.5–182.5 °C; UV 224.5 (ε 24 300); NMR δ 5.86 (d, 2 H, C-21), 5.20 (m, 2 H, C-4 H + C-6 H), 4.79 (s, 2 H, C-21 H), 1.00 (s, 3 H, C-19), 0.68 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{34}O_3$: C, 78.49; H, 8.96. Found: C, 77.58; H, 8.97.

Dehydrogenation of the Cardenolide 3-Enol Ether. The enol ether of compound **2,** 1.33 g (3.48 mmol), was dissolved in 35 mL of dry benzene and added rapidly through a dropping funnel to 1.75 g (7.71 mmol) of DDQ in 60 mL of dry benzene. The solution was stirred under nitrogen at room temperature for 15 min and then diluted with 30 mL of dichloromethane. The solution was filtered and the green gummy residue extracted with dichloromethane. The organic was evaporated to dryness and chromatographed over 50 g of Woelm neutral aluminum oxide (activity grade III). Elution with ethyl acetate–benzene (50:50) gave, after crystallization from ethyl acetate, 310 mg (0.885 mmol, 25.4%) of the trienone **19** [21-hydroxy-3-oxo-24-norchola-1,4,6,20(22)-tetraeno-23,21-lactone]: mp 207.5–211.5 °C; UV 298.5 nm (ε 13 000); IR 1740 (C-22 carbonyl), 1650 cm^{-1} (C-3 ketone); NMR δ 7.12 (d, J = 10.5 Hz, 1 H, C-1 H), 6.29 (d, J = 10.5 Hz, 1 H, C-2 H), 5.92 (s, 1 H, C-21), 4.82 (s, 2 H, C-23), 1.22 (s, 3 H, C-19), 0.77 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{26}O_3$: C, 78.82; H, 7.48. Found: C, 78.42; H, 7.51.

The Preparation of the Cardenolide Linear 4,6-Dienone 20 from 15. Compound **15,** 500 mg (1.27 mmol), was dissolved in 100 mL of methyl alcohol with stirring and then 500 mg (2.63 mmol) of p-toluenesulfonic acid monohydrate was added. The solution was stirred at reflux for 24 h, cooled, concentrated, diluted with water, and filtered. The crude product was recrystallized from methyl alcohol to give 260 mg (0.739 mmol, 58.2%) of dienone **20** [21-hydroxy-3-oxo-24-norchola-4,6,20(22)-trieno-23,21-lactone]: mp 287–290 °C; UV 283 nm (ε 26 500); IR 1760 (C-22 carbonyl), 1670 cm^{-1} (C-3 ketone); NMR δ 6.16 (s, 2 H, C-6, 7 H), 5.88 (s, 1 H, C-21 H), 5.70 (s, 1 H, C-4 H), 4.79 (s, 2 H, C-23), 1.04 (s, 3 H, C-19), 0.72 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 77.97; H, 8.00.

The Formation of 4β,5β-Methylene Cardenolides. A solution of 5 g of cardenolide **2** in 150 mL of dry tetrahydrofuran was cooled in an ice bath and reacted with 6 g of lithium tri-*tert*-butoxyaluminum hydride until TLC indicated disappearance of the enone. The reaction mixture was poured into water and the mixture was acidified with concentrated hydrochloric acid. The suspension was extracted with chloroform, dried with the sodium sulfate, and evaporated. The residue was triturated with ether to yield 4.1 g of the allylic alcohol **21** which was not characterized except to note the presence of the cardenolide ring (1785, 1760 cm^{-1}) and a hydroxyl group (3500 cm^{-1}) and the absence of an enone in the IR spectrum.[8]

A mixture of 4.0 g (11.2 mmol) of the allylic alcohol **21,** 7.0 g of zinc–lead couple, and 5 mL of methylene iodide was stirred magnetically. Since the reaction was not self-initiating, a few crystals of iodine were added and the temperature held between 40 and 45 °C by intermittent cooling. After the reaction had subsided, stirring was continued overnight. The reaction mixture was then partitioned between chloroform and dilute hydrochloric acid. The aqueous layer was extracted with chloroform and the combined organic solutions were dried with sodium sulfate. The residue, after removal of solvent, was chromatographed over 400 g of silica. Elution with ethyl acetate–benzene (1:4) returned 75 mg of starting material which was followed by 1.42 g (3.84 mmol, 34%) of **22** [3′,4α-dihydro-3β-hydroxycyclopropa(4,5)-5β-24-norchola-4,20(22)-dieno-23,21-lactone]: mp 177–179 °C (ethyl acetate–petroleum ether); IR 1790, 1760, 1750, 1730 cm^{-1}; UV 220 nm (end, ε 16 000); NMR δ 5.85 (m, 1 H), 4.75 (m, 2 H), 4.40 (m, 1 H), 0.98 (s, 3 H), 0.82 (s, 3 H), 0.3 to −0.15 (m, cyclopropyl). Anal. Calcd for $C_{24}H_{34}O_3$: C, 77.80; H, 9.25. Found: C, 77.64; H, 9.36.

A portion (367 mg) of **22** was acetylated using 3.5 mL of acetic anhydride in 5 mL of pyridine and 20 mL of methylene chloride. After standing overnight, the methylene chloride was removed and the residue was poured into water and extracted with chloroform. The organic solution was washed with water and dilute hydrochloric acid, dried with sodium sulfate, and evaporated. The residue was crystallized from ether–petroleum ether to yield 347 mg of the 3β-acetate **23:** mp 124–125 °C; IR 1785, 1755, 1735, 1635 cm^{-1}; UV 220 nm (end, ε 17 000); NMR δ 5.87 (m, 1 H), 5.32 (m, 1 H), 4.80 (m, 2 H), 2.03 (s, 3 H), 0.98 (s, 3 H), 0.63 (s, 3 H), 0.13 (m, cyclopropyl H). Anal. Calcd for $C_{26}H_{36}O_4$: C, 75.69; H, 8.79. Found: C, 75.62; H, 8.84.

The Oxidation of the Cyclopropylcarbinol 22 to the Cyclopropyl Ketone 24. A solution of 502 mg (1.36 mmol) of compound **22** in 125 mL of refluxing toluene was oxidized with 25 g of silver carbonate on Celite[10] until TLC indicated conversion to the cyclopropylenone **24** (16 h). The mixture was filtered and the residue was washed with hot ethyl acetate. The combined organic solutions were

evaporated and the noncrystalline residue was chromatographed on a short silica gel column. Elution with ethyl acetate–benzene (1:3 and 1:1) yielded 375 mg (1.02 mmol, 75%) of the cyclopropylenone **24** [3′,4α-dihydro-3-oxocyclopropa(4,5)-5β-24-norchola-4,20(22)-dieno-23,21-lactone]: mp 188–190 °C (ethyl acetate–petroleum ether); IR 1785, 1750, 1680, 1625 cm^{-1}; UV 220 nm (end, ε 17 500); NMR δ 5.88 (m, 1 H), 4.78 (m, 2 H), 1.10 (s, 3 H), 0.83 (s, 3 H). Anal. Calcd for $C_{24}H_{32}O_3$: C, 78.22; H, 8.75. Found: C, 78.42; H, 8.96.

Ketalization of the Cardenolide 2. Compound **2**, 2.0 g (5.64 mmol), was suspended in 200 mL of ethylene glycol and 100 mg of *p*-toluenesulfonic acid monohydrate was added with stirring. Ethylene glycol (140 mL) was distilled under reduced pressure (0.6 mm at 65–70 °C). The pot residue was cooled to 20 °C and 0.3 mL of pyridine was added, followed by 100 mL of water. The solution was cooled to 10 °C and filtered to give 2.1 g (5.27 mmol, 93.4%) of the ketal **29**: mp 163.5–173.5 °C; IR 1765 cm^{-1} (C-22 carbonyl); NMR δ 5.85 (s, 1 H, C-21 H), 5.37 (m, 1 H, C-6 H), 4.76 (s, 2 H, C-23), 3.97 (s, 4 H, 3-ketal), 1.05 (s, 3 H, C-19), 0.67 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{34}O_4$: C, 75.34; H, 8.60. Found: C, 75.28; H, 8.68.

The Hydrogenation of the Cardenolide Ring in the Ketal 29. A solution of 6.60 g (16.6 mmol) of **29** in 300 mL of dioxane was hydrogenated over 0.7 g of 5% palladium on carbon at 2 psi. After 98 h, 15.4 mmol of H_2 had been consumed and the uptake stopped. The catalyst was removed and the solution was reduced to dryness to give 7.1 g (17.7 mmol, 107%) of ketal **30**: mp 208–231 °C; IR 1785 cm^{-1} (C-22 ketone); NMR δ 5.35 (m, 1 H, C-6 H), 4.51 (d, J = 6.0 Hz, 1 H, C-23 H), 4.31 (d, J = 6.0 Hz, 1 H, C-23 H), 3.94 (s, 4 H, 3-ketal), 1.04 (s, 3 H, C-19), 0.71 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{36}O_4$: C, 74.96; H, 9.06. Found: C, 72.68; H, 8.80.

The Deketalization of the Ketal 30 to the Cardanolide 31. Ketal **30**, 3.0 g (7.5 mmol), was dissolved in 45 mL of tetrahydrofuran at room temperature and 112.5 mL of 2.66 M (300 mmol) perchloric acid was added. The reaction mixture was then stirred for 10 min and 225 mL of water was added over a 10-min period. Another 75 mL of water was added and the solution was extracted with 2 × 150 mL of benzene–ether (2:1). The organic layer was washed with 0.5 N sodium bicarbonate and water, dried over sodium sulfate, filtered, and reduced to dryness. The crude material was crystallized from methyl alcohol–water to give 2.42 g (6.79 mmol, 90.6%) of **31** with a trace of **2**. The mixture (1.5 g) was chromatographed over Woelm neutral aluminum oxide (activity grade III). Elution with ethyl acetate–benzene (5:95) gave 1.1 g (65%) of pure **31**: mp 154–159 °C; UV 243 nm (ε 16 000); IR 1785 (C-22 carbonyl), 1680 cm^{-1} (C-3 ketone); NMR δ 5.75 (s, 1 H, C-4 H), 4.42 (m, 1 H, C-23 H), 3.86 (m, 1 H, C-23 H), 1.20 (s, 3 H, C-19), 0.75 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.36; H, 8.98.

The 3-Enol Ether of the Cardanolide 31. Ketone **31**, 2.0 g (5.61 mmol), was partially dissolved in a solution of 6 mL of dioxane, 4 mL of ethanol, and 2.5 mL of triethyl orthoformate at 0 °C. To this stirred suspension was added 0.12 g of *p*-toluenesulfonic acid monohydrate and the solution was stirred for 15 min at 0 °C. The solution was poured into 100 mL of a 2% pyridine–water mixture of 0 °C. The product precipitated as a paste and was extracted with chloroform. The chloroform was dried over sodium sulfate, filtered, and reduced to dryness. The residue was crystallized from 1% pyridine–methanol to give 1.82 g (4.73 mmol, 84.3%) of the enol ether. The compound was not further characterized.

DDQ Dehydrogenation of the Cardanolide Enol Ether. The enol ether of compound **31**, 0.58 g (1.5 mmol), was dissolved in 30 mL of 95% aqueous acetone. DDQ (0.36 g, 1.58 mmol) was dissolved in 6 mL of 95% aqueous acetone and added dropwise with stirring to the above solution. After the addition, the solution was stirred for 10 min and then reduced to dryness under vacuum at 25 °C. Residual water was removed by azeotroping with benzene, then 10 mL of benzene was added and the solution was cooled and filtered. The organic filtrate was reduced to dryness and the residue was chromatographed over Woelm netural aluminum oxide (activity grade III). Elution with ethyl acetate–benzene (5:95) gave 328 mg (0.925 mmol, 61.7%) of a 3-keto-4,6-dienone **34** [21-hydroxy-3-oxo-4,6-norcholadieno-23,21-lactone]: mp 186–193 °C; UV 283 nm (ε 26 500); IR 1785 (C-22 ketone), 1670 cm^{-1} (C-3 ketone); NMR δ 6.12 (s, 2 H, C-6, 7 H), 5.67 (s, 1 H, C-4 H), 4.42 (m, 1 H, C-23 H), 3.89 (m, 1 H, C-23 H), 1.13 (s, 3 H, C-19), 0.80 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 78.23; H, 8.52.

The Cardanolide 1,4,6-Trienone 35. The enol ether of **31**, 0.77 g (2.00 mmol), was dissolved in 20 mL of dry benzene and added rapidly, through a dropping funnel, to 0.93 g (4.1 mmol) of DDQ in 40 mL of dry benzene. The solution was stirred under nitrogen at room temperature for 15 min and then diluted with dichloromethane. The solution was filtered and the filter cake was washed until it became a dry green powder. The organic was evaporated to dryness and chromatographed over Woelm neutral aluminum oxide (activity grade III). Elution with ethyl acetate–benzene (20:80) gave 142 mg (0.403 mmol, 20.1%) of the trienone **35** [21-hydroxy-3-oxo-1,4,6-norcholatrieno-23,21-lactone]: mp 199–203 °C; UV 299 nm (ε 13 100); IR 1785 (C-22 carbonyl), 1665 cm^{-1} (C-3 ketone); NMR δ 7.08 (d, J = 10.0 Hz, 2 H, C-1 H), 6.27 (d, J = 10.0 Hz, 1 H, C-2 H), 6.10 (s, 1 H, C-4 H), 6.02 (m, 2 H, C-6, 7 H), 4.43 (m, 1 H, C-23 H), 3.96 (m, 1 H, C-23 H), 1.22 (s, 3 H, C-19), 0.83 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{28}O_3$: C, 78.37; H, 8.01. Found: C, 78.69; H, 8.13.

Dehydrogenation of the Cardanolide Enone 31. Cardanolide **31**, 1.00 g (2.81 mmol), was dissolved in 25 mL of dry benzene with stirring under nitrogen. To this solution was added dropwise, at room temperature, 0.79 g of DDQ (3.5 mmol, 1.25 equiv) in 25 mL of dry benzene. The solution was refluxed 24 h, cooled, concentrated, and filtered. The solution was reduced to dryness and the residue was chromatographed over 60 g of E. Merck neutral alumina. Elution with ethyl acetate–benzene (5:95) gave, after crystallization from ethyl acetate–hexane, 410 mg (1.16 mmol, 41.3%) of 3-keto-1,4-dienone **33** [21-hydroxy-3-oxo-1,4-norcholadieno-23,21-lactone]: mp 185–188 °C; UV 243 nm (ε 16 000); IR 1780 (C-22 carbonyl), 1665 cm^{-1} (C-3 ketone); NMR δ 7.08 (d, J = 10.0 Hz, 1 H, C-1 H), 6.24 (d, J = 10.0 Hz, 1 H, C-2 H), 6.09 (s, 1 H, C-4 H), 4.42 (m, 1 H, C-23 H), 3.87 (m, 1 H, C-23 H), 1.28 (s, 3 H, C-19), 0.79 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.84; H, 8.78.

The 20-Cyanomethylene Derivative 25 of 11-Dehydrocorticosterone. Corticosterone acetate was oxidized to the 11-ketone (21-hydroxypregn-4-ene-3,11,20-trione acetate) using Jones reagnet; this product was converted into its 3-enol ether as described for deoxycorticosterone acetate. Reaction with diethyl cyanomethylphosphate followed by acid hydrolysis gave **25** in 75.7% yield from the enol ether: mp 160–163 °C; UV 231 nm (ε 27 500); IR 1755 (acetoxycarbonyl), 1720 (C-11 ketone), 1680 cm^{-1} (C-3 ketone); NMR δ 5.73 (s, 1 H, C-4 H), 5.39 (s, 1 H, cyanomethylene-H), 4.90 (d, J = 16.0 Hz, 1 H, C-21 H), 4.63 (d, J = 16.0 Hz, 1 H, C-21 H), 2.13 (s, 3 H, acetoxymethyl-H), 1.42 (s, 3 H, C-19), 0.64 (s, 1 H, C-18). Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.95; N, 3.42. Found: C, 73.21; H, 7.95; N, 3.37.

Hydrolysis and Lactonization of the Cyanomethylene Derivative 25 of 11-Dehydrocorticosterone. Compound **25** was converted, in 56% yield, into the cardenolide **26**, as described for compound **11**: mp 264–267 °C; UV 223 nm (ε 23 600); IR 1755 (acetoxy ketone), 1715 (C-11 ketone), 1675 cm^{-1} (C-3 ketone); NMR δ 5.91 (s, 1 H, C-21 H), 5.77 (s, 1 H, C-4 H), 4.78 (s, 2 H, C-23), 1.44 (s, 3 H, C-19), 0.68 (s, 3 H, C-18). Anal. Calcd for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 74.64; H, 7.61.

Hydrogenation of 26. Compound **26** was converted into its ketal in a manner analogous to the one employed for compound **2** and hydrogenated in the same manner as **29**. Hydrolysis of the ketal with perchloric acid gave the 11-oxo derivative of **31** in 33.2% yield from **26**: mp 263–266 °C; UV 237 nm (ε 14 600). Anal. Calcd for $C_{23}H_{30}O_4$: C, 74.58; H, 8.16. Found: C, 74.19; H, 8.10.

11β-Acetoxy-21-hydroxy-3-oxo-4,20(22)-norcholadieno-23,21-lactone 28. The 11β-acetate of corticosterone acetate was prepared by acetylation of corticosterone using acetic anhydride and a catalytic amount of *p*-toluenesulfonic acid. The acetoxy ketone was converted into its enol ether which was subjected to the action of the anion of diethyl cyanomethylphosphonate; this gave the 20-cyanomethylene 3-enol ether derivative **31**, which upon hydrolysis afforded compound **27** in 31% yield. The compound was converted directly to the cardenolide with only NMR data used for structure confirmation: NMR δ 5.70 (s, 1 H, C-4 H), 5.40 (s, 2 H, C-11 H + cyanomethylene H), 4.88 (d, J = 14 Hz, 1 H, C-21 H), 4.62 (d, J = 14 Hz, 1 H, C-21 H), 2.12 (s, 3 H, C-21 acetoxymethyl H), 2.04 (s, 3 H, C-11 acetoxymethyl H), 1.17 (s, 3 H, C-19), 0.80 (s, 3 H, C-18).

Compound **27** was converted into the cardenolide **28** (in 65% yield) in the same manner as compound **11**: mp 213–217 °C; UV 227 nm (ε 21 500); IR 1755 (11-acetoxy ketone), 1740 (C-22 carbonyl), 1675 cm^{-1} (C-3 ketone); NMR δ 5.85 (s, 1 H, C-21 H), 5.71 (s, 1 H, C-4 H), 5.43 (m, 1 H, C-11 H), 4.71 (s, 2 H, C-23), 2.06 (s, 3 H, C-11 acetate), 1.30 (s, 3 H, C-19), 0.82 (s, 3 H, C-18). Anal. Calcd for $C_{25}H_{32}O_5$: C, 72.79; H, 7.82. Found: C, 72.84; H, 7.94.

The Condensation of the Cyanomethylenephosphonate with Δ¹-Corticosterone Acetate. In a flamed three-necked flask equipped with a magnetic stirring bar, nitrogen inlet, rubber septum inlet, and an addition funnel was placed 255 mg of a 50% sodium hydride dispersion in mineral oil. After adding 5 mL of dry tetrahydrofuran (benzophenone ketyl), stirring was started and 0.97 mL (5.87 mmol) of diethyl cyanomethylenephosphonate was injected with a syringe. After gas evolution ceased, 1.00 g (2.59 mmol) of Δ¹-corticosterone

acetate [11β,21-dihydroxypregna-1,4-dien-3,20-dione 21-acetate] in 10 mL of dry tetrahydrofuran was added via the addition funnel, and the funnel was washed with an additional 10 mL of solvent. TLC indicated the reaction was complete after 2 h and the solution was poured into water and adjusted to a pH of ca. 4 with acetic acid. From this aqueous suspension, 821 mg (2.01 mmol, 78%) of **13** slowly crystallized: mp 187–194 °C (ethyl acetate–cyclohexane); IR 3400, 2220, 1750, 1665, 1615, 1605 cm^{-1}; UV 213 nm (ε 25 000); NMR δ 7.35 (d, J = 10 Hz, 1 H), 6.28 (dd, J = 10, 2 Hz, 1 H), 6.04 (s, 1 H), 5.43 (s, 1 H), 4.95 (d, J = 14.5 Hz, 1 H), 4.67 (d, J = 14.5 Hz, 1 H), 4.45 (m, 1 H), 2.13 (s, 3 H), 1.48 (s, 3 H), 0.95 (s, 3 H). Anal. Calcd for $C_{25}H_{31}NO_4$: C, 73.32; H, 7.63; N, 3.42. Found: C, 73.07; H, 7.89; N, 3.37.

The Formation of the Cardenolide 14 from the 1,4-Dien-3-one 13. To a solution of **13** (350 mg, 0.86 mmol) in 50 mL of ethanol was added 2.5 mL of distilled water and 0.5 g of *p*-toluenesulfonic acid monohydrate. The reaction mixture was refluxed for 16 h, cooled, and diluted with 150 mL of distilled water. The precipitate was filtered, dried, and crystallized from methylene chloridine–ethyl acetate–petroleum ether to yield 205 mg (0.57 mmol, 65%) of cardenolide **14** as the monohydrate: mp 256–269 °C; IR 3450, 1780, 1750, 1660, 1625, 1660 cm^{-1}; UV 220 nm (ε 21 000), 244 (sh, 15 500); NMR (Me_2SO-d_6) δ 7.37 (d, J = 10 Hz, 1 H), 6.17 (dd, J = 10, 2 Hz, 1 H), 5.95 (m, 2 H), 4.83 (d, 2 H), 4.57 (d, exchanges with D_2O), 4.23 (m, 1 H), 1.40 (s, 3 H), 0.86 (s, 3 H). Anal. Calcd for $C_{23}H_{28}O_4 \cdot H_2O$: C, 71.48; H, 7.82. Found: C, 71.63; H, 7.64.

Registry No.—**2**, 14030-39-8; **2** enol ether, 53287-13-1; **3**, 1693-63-6; **4**, 66007-63-4; **7**, 23330-61-2; **8**, 19637-05-9; **9**, 2739-50-6; **10**, 65970-05-0; **11**, 65970-06-1; **12**, 58652-04-3; **13**, 65970-17-4; **14**, 65970-18-5; **15**, 65970-08-3; **16**, 65970-09-4; **17**, 65970-07-2; **18**, 6747-92-8; **19**, 66007-62-3; **20**, 53287-14-2; **21**, 24366-43-6; **22**, 65970-10-7; **23**, 65970-11-8; **24**, 65970-12-9; **25**, 65970-13-0; **26**, 65970-14-1; **27**, 65970-15-2; **28**, 65970-16-3; **29**, 65969-98-4; **30**, 65969-99-5; **31**, 65970-00-5; **31** 3-enol ether, 65970-01-6; **31** 11-oxo derivative, 65970-04-9; **33**, 66007-61-2; **34**, 65970-02-7; **35**, 65970-03-8; diethyl cyanomethylphosphonate, 2537-48-6; deoxycorticosterone acetate, 56-47-3.

References and Notes

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New Zearalenone Related Macrolides and Isocoumarins from an Unidentified Fungus

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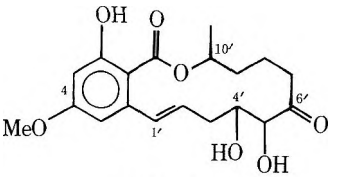
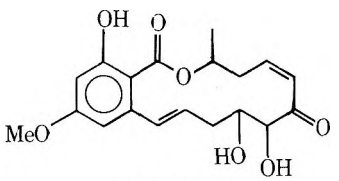
The isolation and characterization of four new zearalenone-like macrolides and three isocoumarins from an unidentified fungus, Lederle Culture Z1640, are reported. By altering the fermentation conditions this organism could be forced to produce curvularin macrolides. X-ray studies on a di-*p*-chlorobenzoyl derivative of LL-Z1640-1 showed this metabolite to be (4′*S*,5′*S*)-4′,5′-dihydroxyzearalenone 4-methyl ether.

Lederle culture Z1640 was selected for study on the basis that crude extracts of shaker-flask fermentations inhibited the growth and motility of the ciliated protozoan *Tetrahymena pyriformis*. Stirred fermentations of this unidentified fungus yielded three zearalenone[1] related metabolites LL-Z1640-1, -2, and -4. Surface fermentation yielded LL-Z1640-4 and -3 as the predominant products. In an attempt to obtain the corresponding diphenolic compounds still cultures were incubated in the presence of D,L-ethionine.[2] Under these conditions the mycelium was blanched from the normal very dark color and workup yielded curvularin and dihydrocurvularin[3] and none of the larger macrolides.



LL-Z1640-1



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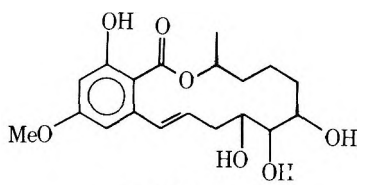

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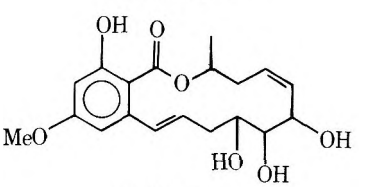


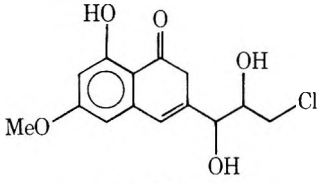
LL-Z1640-4

0022-3263/78/1943-2339$01.00/0

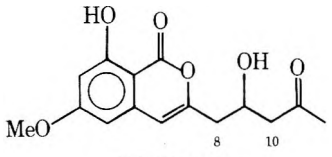
The culture failed to produce spores under a number of conditions and consequently its identity has not been established. Based on the dark-colored mycelium it exhibits, it likely belongs in the family *Dematiaciae* of the class *Deuteromyces*.

The uterotropic and anabolic properties of zearalenone are well known.[1a] Macrolides **1** through **4** revealed no particularly interesting activities except perhaps some antiviral effects associated with **4**. The presence of the phenolic esters may be responsible for this lack of activity. In our hands all attempts to remove this ether by classical methods resulted in degradation.

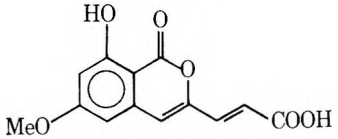
In one fermentation where very little of the macrolides was observed, three new isocoumarins LL-Z1640-**5**, -**6**, and -**7** were produced. Components **6** and **7** were obtained in some quantity whereas only a very minor yield of **5** was recovered (see Experimental Section).



LL-Z1640-**5**



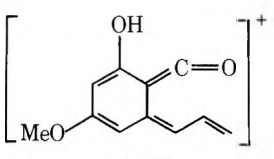
LL-Z1640-**6**



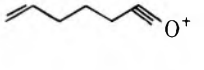
LL-Z1640-**7**

Characterization of Macrolides. Macrolide **1**, $C_{19}H_{24}O_7$, was shown to be a β resorcylate by characteristic UV maxima at 232, 270, and 311 nm (ϵ 30 900, 12 000, and 6 100). The NMR spectrum included signals indicative of a secondary methyl (δ 1.40, J = 6 Hz), a methoxy (δ 3.82) two aromatic protons (δ 6.40), and a trans double bond (eight-line pattern at δ 5.95 and a broadened doublet at δ 7.05, J = 15 Hz). An exchangeable 1 H singlet at δ 12.0 is assigned to the chelated phenolic hydrogen. The IR spectrum shows carbonyl bands at 1710 and 1655 cm^{-1} attributed to the ketone and hydrogen-bonded lactone groupings. A positive reaction with periodate and the ready formation of an acetonide indicated the vicinal glycol moiety.

The mass spectrum of the acetonide, $C_{22}H_{28}O_7$, provided decisive evidence for the structure of the macrocyclic portion. The base peak at *m/e* 190 and the second most abundant ion at *m/e* 97 are consistent only with the glycol–ketone system as depicted in **1**.



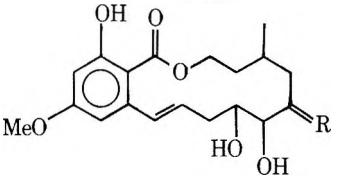
m/e 190



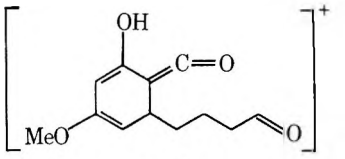
m/e 97

Lactone **2**, $C_{19}H_{22}O_7$, exhibited an UV spectrum almost identical to that of **1** except the 233 nm maxima had an ϵ of 38 200 cm^{-1} requiring the presence of an additional chromophore. The IR spectrum is also closely related to that of **1** except the 6′ ketone band is now at 1680 cm^{-1} consistent with its being part of an α,β-unsaturated system. This was supported by the NMR spectrum which showed the additional trans vinyl proton signals. The mass spectrum of the easily formed acetonide, $C_{22}H_{26}O_7$, showed in this case an *m/e* 95 ion as the base peak while the *m/e* 190 ion is only 16% of the former. The *m/e* 95 ion is consistent with the position of an additional site of unsaturation in the $C_{6'}$–$C_{11'}$ unit.

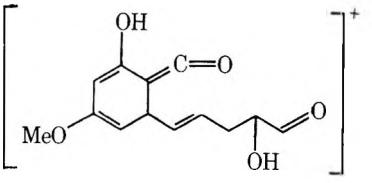
Hydrogenation of both **1** and **2** gave **8** as shown by mp, mmp, and IR spectrum. Examination of the mass spectrum of **8** revealed significant differences from that of **1**, **2**, and their



8, R = O
9, R = H, OH



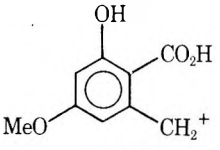
m/e 221



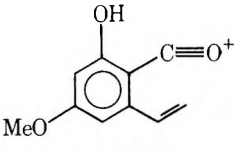
m/e 251

acetonides in that strong ions at *m/e* 221 and 251 are observed rather than the characteristic *m/e* 190 ion seen in the spectra of the parent compounds.

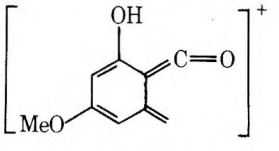
Other significant fragmentation ions are observed at *m/e* 182, 177, and 164 with structures as shown. The *m/e* 97 ion expected from the $C_{6'}$–$C_{11'}$ chain is surprisingly only 4% that of the base peak at *m/e* 128.



m/e 182



m/e 177



m/e 164

Lactones **3** and **4** showed UV spectra similar to those of the corresponding ketones although their IR spectra are devoid of the $C_{6'}$ ketone absorption. Reduction of **3** and **4** gave **9** indicating the only difference between them to be the double bond between $C_{7'}$ and $C_{8'}$ in **4**. Sodium borohydride reduction of **1** gave two triols, one of which was identical to **3** thus interrelating all four macrolides.

Macrolide **4** was further characterized by the formation of its acetonide **10**. Although the acetonides of **1** and **2** were crystalline, that of **4** was an oil despite considerable effort to crystallize it. Oxidation of **10** with Jones reagent yielded the crystalline ketone **11**. The IR spectrum of **11** has a strong band at 1735 cm^{-1} indicating the structure of **11** to be as indicated. Further verification was obtained from the NMR spectrum

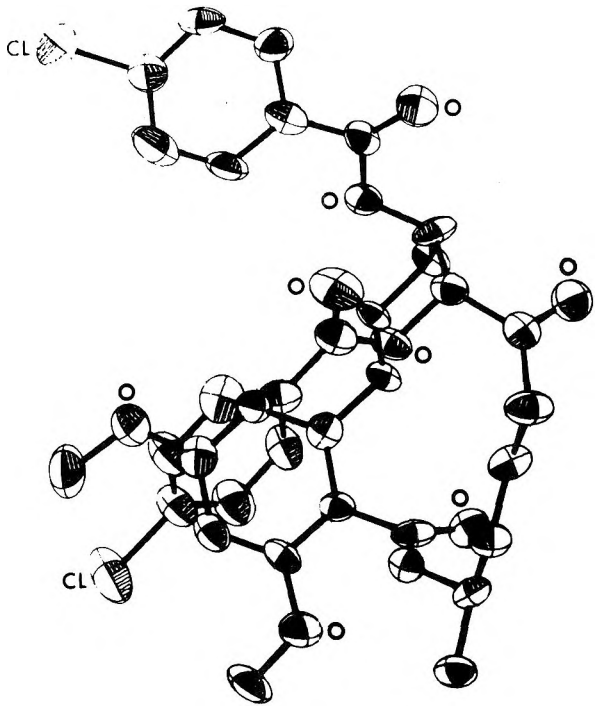
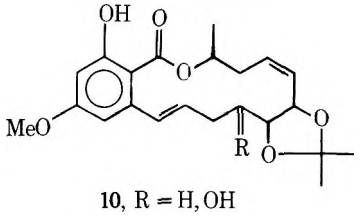


Figure 1.

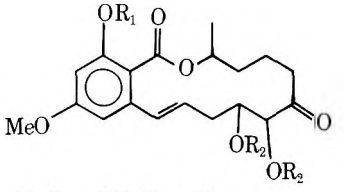
of **12** which showed a 1 H doublet at ϵ 4.65 (J = 8 Hz) assigned to $H_{5'}$ which is split only by $H_{6'}$. Compound **12** which is the



10, R = H, OH
11, R = O

2-methyl ether of **1** upon treatment with *p*-chlorobenzoyl chloride in pyridine gave the nicely crystalline **13**.

X-Ray Crystallography. Prismatic crystals of **13**, suitable for X-ray analysis, yielded the following data: from diffractometer measurements on 25 reflections in the range 20 < θ



12, R_1 = CH_3; R_2 = H
13, R_1 = CH_3, R_2 = C(O)-*p*-ClPh

< 30 °C (Cu Kα λ 1.5418 Å) a = 10.257 (3), b = 11.147 (4), c = 28.287 (11) Å; orthorhombic crystals, space group $P2_12_12_1$, C = 4; d_{obsd} = 1.336 g cm^{-3}, d_{calcd} = 1.343 g cm^{-3}; linear absorption coefficient μ = 22.6 cm^{-1}; crystal size 460 × 230 × 320 m elongated along the a axis.

Intensity data were collected on a computer controlled Enraf-Nonius CAD-3 diffractometer using the θ–2θ scan method with Ni-filtered Cu Kα radiation. In the range 3 < θ < 60 °C, 2753 independent reflections were measured of which 1736 were classified as observed by the criterion $I > 2\sigma(I)$ where $\sigma(I)$ was determined from counting statistics. No absorption corrections were applied.

A trial structure consisting of two chlorine atoms and 40 nonhydrogen atoms was obtained using the MULTAN[4] program for direct-phase determination. Isotropic refinement

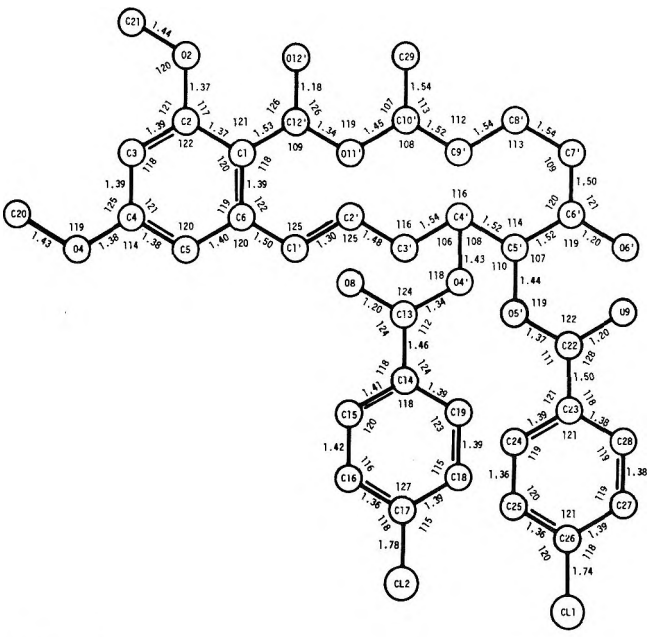


Figure 2.

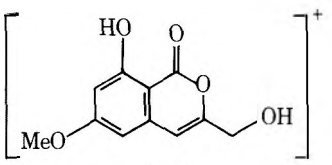
treating all atoms except the chlorines as carbon gave $R = [\Sigma||F_o| - |F_c||/\Sigma|F_o|] = 0.22$. The remaining atoms of the molecule were then found in a difference electron density map. After assigning oxygen atoms on the basis of chemistry and refined isotropic temperature parameters further refinement (isotropic and anisotropic) led to R = 0.10 for observed reflections. Coordinates for all hydrogens (except on the methyl groups) were calculated and peaks corresponding to them were found in a difference map. Hydrogens were included, but not refined, in final refinement calculations; the last difference map contained no significant peaks. The anomalous dispersion effects of chlorine and oxygen were included in a series of anisotropic refinement calculations for the two enantiomers of the structure. Reliability indices of R = 0.076 and R = 0.080 were obtained which by the Hamilton[5] test are significantly different. In the structure corresponding to R = 0.076 the configurations at atoms $C_{4'}$, $C_{5'}$, and $C_{10'}$ are all S. The same configuration at $C_{10'}$ was found in the structure of 8′-hydroxyzearalenone.[6]

Lists of coordinates and anisotropic temperature parameters for the nonhydrogen atoms and torsion angles in the structure are available as supplementary data and appear in the microfilm edition. Bond distances and angles are shown in Figure 1 (a list of structure factors has been bound into *J. Org. Chem.* **43** (1978), held in the library at Lederle Laboratories; copies may be obtained from the Librarian).

All calculations were made using the X-RAY SYSTEM (1972)[7] set of crystallographic programs; atomic scattering factors and dispersion corrections were taken from the International Tables for X-ray Crystallography.[8]

A survey of contact distances <4.0 Å in the unit cell revealed no unusually close interactions. The conformation of the molecule is shown in Figure 2. The torsion angle $O_{4'}$–$C_{4'}$–$C_{5'}$–$O_{5'}$ is −57° corresponding to a left-handed rotation looking along $C_{4'}$–$C_{5'}$; this agrees with the result obtained from circular dichroism studies on this compound.

Characterization of Isocoumarins. The isocoumarin **5**, $C_{13}H_{13}O_6Cl$, has the structure shown on the basis of NMR, UV, IR, and mass spectral data. A 2,4-dihydroxyisocoumarin moiety is indicated by comparison of the UV spectrum with that of the known metabolite diaporthin.[9] The NMR of **5** shows signals attributable to the phenolic hydroxy proton at δ 11.04, the meta aromatic hydrogens as 1 H doublets at δ 6.4 and 6.5 (J = 2 Hz), the methoxy signal at δ 3.88, and the vinyl



m/e 221

proton as a sharp 1 H singlet at δ 6.58. The chloromethyl protons resonate as a 2 H doublet at δ 3.80 (J = 4 Hz) and the two remaining hydrogens at δ 4.15 and 4.45 as broad multiplets. A positive reaction with periodate confirmed the presence of the vicinol glycol moiety. The base peak in the mass spectrum occurs at *m/e* 221 which is represented as shown.

Likewise the low-field NMR signals in the spectrum of **6** are essentially identical to the corresponding ones of diaporthin. The terminal methyl signal resonates at δ 1.20 and two overlapping doublets at δ 2.65 and 2.69 (J = 5.5 Hz) are assigned to the C_8 and C_{10} methylene protons. The C_9 carbinyl proton signal is seen as a five-line pattern at δ 2.47 while the C_9 hydroxyl proton signal resonates as an exchangeable signal at δ 3.60. Prominent fragmentation ions in the mass spectrum appear at *m/e* 274, 232, and 206 consistent with the assigned structure.

The most polar isocoumarin **7** exhibited a UV spectrum similar to that of **5** and **6** but each maximum was shifted bathochromically with absorption at 259, 304, 313, 342, and 355 sh nm (ε 43 300, 11 800, 12 300, 15 500, and 11 800). The NMR spectrum showed signals indicative of the isocoumarin moiety but in addition signals representing an AB pair at δ 6.14 and 6.32 (J = 13 Hz) were present which were assigned to the trans olefinic protons of the double bond of the side chain. The acidic nature was indicated by its solubility in sodium bicarbonate.

Biosynthesis. A polyketide pathway from acetate is the most likely biogenetic origin of zearalenone metabolites.[1e] A similar route has been proposed for the curvularins.[3a] The close relationship of zearalenone, curvularin, and isocoumarins such as diaporthin each produced by different fungi is well known. It is noteworthy that culture Z1640 is capable of producing metabolites of each type depending on the fermentation conditions.

Experimental Section

TLC was carried out on Brinkmann silica gel plates. NMR spectra were obtained with a Varian A-100 instrument. Mass spectra were obtained with an AEI MS9 mass spectrometer. IR and UV spectra were run on an Infracord and Cary 11 spectrophotometers, respectively. CD curves run on a Jasco spectropolarimeter were supplied by Professor K. Nakanishi of Columbia University. Solvents and solutions were dried over anhydrous $MgSO_4$. Melting points were taken on a Thomas hot-plate apparatus and are uncorrected.

Isolation of Macrolides. Culture Z1640 was grown from a slant in a medium consisting of 3% corn steep liquor, 3% glucose, 1% proflo, and 0.5% $CaCO_3$ with pH adjusted to 6.5 before sterilization. Second stage inoculum was added to a 300-L fermenter containing the medium NH_4 tartrate 0.2%, $MgSO_4 \cdot 7H_2O$ 0.05%, KH_2PO_4 0.1%, KCl 0.05%, $FeSO_4 \cdot 7H_2O$ 0.001%, glucose 5%, and corn steep liquor 1% with pH adjusted to 6.0. Fermentation occurred at 28 °C with air supply at 0.5 v/v/min and impeller speed at 215 rpm. Harvesting was carried out after 11 days and the pH was usually below 5.5.

The ethyl acetate extract (400 L) of the culture filtrate (pH 4.2) from two 300-L 11-day fermentations was concentrated to a dark viscous residue. This was taken up in methanol and washed with heptane and reconcentrated to dryness. Trituration with ether provided a semicrystalline mass which was slurried in a methanol–methylene chloride mixture and the soluble portion was absorbed into the top of an acid-washed silica gel column (5.5 × 75 cm) packed in methylene chloride. The column was developed with 5% methanol–methylene chloride and monitored at 275 nm by an UV spectrum. Combination of the appropriate fractions and concentration to dryness gave on tituration with ether 842 mg of crude **2**. Recrystallization from ethyl acetate–hexane gave the analytical sample: mp 172–176 °C; $[\alpha]_D$ −75.9° (c 0.41, MeOH); IR (KBr) 3500, 1690, 1640, 1610, 1575 and 970 cm^{-1}; UV (MeOH) 233, 271, and 314 nm (ε 38 200, 11 400, and 5 960); mass spectrum *m/e* (%, composition) 362 (M, 42, $C_{19}H_{22}O_7$), 344 (2, $C_{19}H_{20}O_6$), 249 (7, $C_{13}H_{13}O_5$), 219 (41, $C_{12}H_{11}O_4$), 190 (100, $C_{11}H_{10}O_3$), and 95 (61, C_6H_7O). Anal. Calcd for $C_{19}H_{22}O_7$: mol wt 362.1365. Found: mol wt (mass spectrum) 362.1377.

That portion of the above-mentioned semicrystalline mass which was insoluble in the methanol–methylene chloride system was filtered off to give 40 g of semicrystalline material which by silica gel TLC (chloroform–methanol, 85:15) was composed of two materials with R_f's of 0.60 and 0.25. Ten grams of this mixture was dissolved in methanol–acetone and adsorbed onto silica gel. The solvent was then removed on a rotary evaporator and the silica gel was poured onto the top of a silica gel column (5.5 × 75 cm) packed in methylene chloride. The column was developed with 5% methanol–methylene chloride and monitored at 275 nm. This gave a single broad band resulting in 9 g of a crystalline mixture of **1**, **2**, and **4** as shown by TLC. Rechromatography over the same size column resolved the charge into a crystalline mixture of **1** and **2** and 2.9 g of essentially pure **4**. Fractional crystallization of **1** from benzene/hexane gave the analytical sample: mp 151–153 °C; $[\alpha]_D$ −80° (c 0.48, MeOH); IR (KBr) 3550, 1710, 1645, 1610, 1570, and 970 cm^{-1}; UV (MeOH) 232, 270, and 311 nm (ε 30 900, 12 000, 6 100); *m/e* (%, composition) 364 (M, 25, $C_{19}H_{24}O_7$), 346 (1, $C_{19}H_{22}O_6$), 249 (13, $C_{13}H_{13}O_5$), 219 (32, $C_{12}H_{11}O_4$), 190 (100, $C_{11}H_{10}O_3$), and 97 (13, C_6H_9O). Anal. Calcd for $C_{19}H_{24}O_7$: mol wt 364.1522. Found: mol wt (mass spectrum) 364.1504.

Recrystallization of **4** from ethyl acetate–hexane gave crystals: mp 193–195 °C; $[\alpha]_D$ −102° (c 0.49, MeOH): IR (KBr) 3500, 1645, 1620, and 1570 cm^{-1}; UV (MeOH) 236, 272, and 316 (ε 21 840, 9 100, and 4 000); *m/e* (%, composition) 364 (M, 16, $C_{19}H_{24}O_7$), 346 (12, $C_{19}H_{22}O_6$), 328 (7, $C_{19}H_{20}O_5$), 267 (16, $C_{13}H_{15}O_6$), 249 (36, $C_{13}H_{13}O_5$), 219 (19, $C_{12}H_{11}O_4$), 190 (100, $C_{11}H_{20}O_3$), and 97 (42, C_6H_9O). Anal. Calcd for $C_{19}H_{24}O_7$: mol wt 364.1522; Found: mol wt (mass spectrum) 364.1536.

A second crop from the above mother liquors provided an additional 283 mg of **4**.

Acetonide of 2. A mixture of 200 mg of **2** in 5 mL of 2,2-dimethoxypropane was treated with a few milligrams of *p*-toluenesulfonic acid and warmed gently on the steam bath until solution was complete. After standing overnight at room temperature, the solution was diluted with chloroform, washed with 5% sodium bicarbonate and brine, and dried (magnesium sulfate) and the solvent was removed to give a crystalline residue. Recrystallization from ethyl acetate/hexane gave 100 mg of crystals: mp 164–165 °C; $[\alpha]_D$ −71.3° (c 0.59, MeOH); IR 3500, 1704, 1645, 1570, 990, and 970 cm^{-1}; *m/e* (% composition) 402 (M, 2, $C_{22}H_{26}O_7$), 190 (15, $C_{11}H_{10}O_3$), and 95 (100, C_6H_7O). Anal. Calcd for $C_{22}H_{26}O_7$: mol wt 402.1678. Found: mol wt (mass spectrum) 402.1670.

Acetonide of 1. Treatment of **1** with 2,2-dimethoxypropane in the same manner as for **2** gave crystals: mp 187–188 °C; IR (KBr) 3500, 1720, 1650, 1620, and 1570 cm^{-1}; *m/e* (%, composition) 404 (M, 55 $C_{22}H_{28}O_7$), 190 (100, $C_{11}H_{10}O_3$), and 97 (92, C_6H_9O). Anal. Calcd for $C_{22}H_{28}O_7$: mol wt 404.1835. Found: mol wt (mass spectrum) 404.1830.

Acetonide of 4. A crude mixture of 2.5 g of LL-Z1640 crystalline solids containing primarily **1** and **4** by TLC was heated with 60 mL of 2,2-dimethoxypropane in the presence of a few crystals of *p*-toluenesulfonic acid. Upon solution the solvent was evaporated off and the residue was chromatographed over 100 g of acid-washed silica gel using a 50:50 hexane/ethyl acetate solvent system. About 1.9 g of the acetonide of **1** was obtained, mp 181–183 °C, as indicated by IR and NMR. The second product (1 g) eluted was an oil which by TLC was a single compound **10**: *m/e* (%, composition) 404 (M, 30, $C_{22}H_{28}O_7$), 249 (10, $C_{13}H_{13}O_5$), 219 (9, $C_{12}H_{11}O_4$), 193 (17, $C_{10}H_9O_4$), and 190 (23, $C_{11}H_{10}O_3$). Anal. Calcd for $C_{22}H_{28}O_7$: mol wt 404.1833. Found: mol wt (mass spectrum) 404.1833.

About 600 mg of this oil was dissolved in 75 mL of ether and stirred overnight with a solution of 2 g of potassium dichromate in 0.2 mL of concentrated sulfuric acid and 6 mL of water. The ether phase was evaporated to give 450 mg of residue which was chromatographed over 50 g of acid-washed silica gel using 10% ethyl acetate in hexane. This gave in addition to unreacted starting material **10** 95 mg of crystalline **11**: mp 169–170 °C; $[\alpha]_D$ −77° (c 0.67, ethyl acetate–methanol 30:70); *m/e* (%, composition) 402 (M, 10, $C_{22}H_{26}O_7$), 190 (68, $C_{11}H_{10}O_3$), 189 (100, $C_{11}H_9O_3$), and 167 (13, $C_{10}H_{15}O_2$). Anal. Calcd for $C_{22}H_{26}O_7$: C, 65,66; H, 6.51. Found: C, 65.73; H, 6.64.

Hydrogenation of 1 and 2. A solution of 32 mg of **1** in methanol was stirred in a hydrogen atmosphere in the presence of 10 mg of 10% palladium on charcoal until the hydrogen uptake ceased (~1 mmol). The mixture was filtered through diatomaceous earth and the filtrate was evaporated to dryness in vacuo giving a crystalline residue of **8**.

Recrystallization from benzene/hexane gave the analytical sample: mp 160–161 °C; $[\alpha]_D$ +30.5° (c 0.47, MeOH); IR (KBr) 1705, 1645, 1630, and 1580 cm^{-1}; UV (MeOH) 218, 265, and 305 nm (ϵ 21 400, 10 800, and 4 390); *m/e* (%, composition) 366 (M, 47, $C_{19}H_{26}O_7$), 251 (44, $C_{13}H_{15}O_5$), 221 (45, $C_{12}H_{13}O_4$), 193 (40, $C_{11}H_{13}O_3$), 192 (53, $C_{11}H_{12}O_3$), 182 (39, $C_9H_{10}O_4$), 177 (39, $C_{11}H_{13}O_2$ and $C_{10}H_9H_3$), 164 (48, $C_9H_8O_3$), 129 (75, $C_7H_{13}O_2$), 128 (100, $C_7H_{12}O_2$). Anal. Calcd for $C_{19}H_{26}O_7$: mol wt 366.1678. Found: mol wt (mass spectrum) 366.1689.

A 50-mg sample of **2** was hydrogenated in the same manner as above to give **8** identical to that obtained from **1** by IR, mp, and mmp.

Sodium Borohydride Reduction of 1. Macrolide **1** (25 mg) in methanol was treated with a few milligrams of sodium borohydride and the reaction was allowed to stand at room temperature overnight. Acidification followed by extraction with ethyl acetate gave by silica gel TLC (methanol/chloroform 15:85) two compounds. The minor component by this TLC system was identical to **3**. The IR of the crystalline mixture was very similar to that of **3**.

Hydrogenation of 4. A solution of 50 mg of **4** in ethanol was hydrogenated over 10 mg of 10% palladium on charcoal. After the uptake was complete (slight excess of 2 mol), the reaction mixture was filtered through diatomaceous earth, concentrated to dryness, and crystallized from benzene/hexane to give crude **9**. Recrystallization from benzene/hexane gave the analytical sample: mp 146–148 °C; IR (KBr) 1640, 1615, and 1575 cm^{-1}; *m/e* (%, composition) 368 (M, 42, $C_{19}H_{10}O_7$), 251 (26, $C_{13}H_{15}O_5$), 221 (98, $C_{12}H_{13}O_4$), 206 (25, $C_{12}H_{14}O_3$), 192 (52, $C_{11}H_{12}O_3$), 182 (100, $C_9H_{15}O_4$), 177 (72, $C_7H_{13}O_5$), 164 (69, $C_9H_8O_3$), and 99 (81, $C_6H_{11}O$). Anal. Calcd for $C_{19}H_{28}O_7$: mol wt 368.1833. Found: mol wt (mass spectrum) 368.1824.

Preparation of 12 and 13. About 1 g of **1** was refluxed in acetone overnight in the presence of 2 g of K_2CO_3 and 5 mL of CH_3I. About 250 mg of **12**, mp 162–164 °C, was obtained following silica gel chromatography: CD (MeOH) $\Delta\epsilon$ (325) 0, (310) −0.02, (300) 0, (285) +0.05, (275) +0.02, (245) +0.22, (232) 0, (220) −0.17, and (215) −0.10. About 210 mg of **12** in 2 mL of pyridine was treated with 0.5 mL of *p*-chlorobenzoyl chloride at room temperature overnight. Water was added and the mixture was extracted with ether. The ether extract was treated with 6 M HCl, 5% Na_2CO_3, and brine, dried, and concentrated to a solid. Preparative TLC using 20% EtOAc in benzene gave **13**: mp 159–161 °C; yield 117 mg; NMR ($CDCl_3$) δ 5.26 (1 H, m, $H_{10'}$), 5.92 (1 H, m, $H_{5'}$), and 6.06 [1 H, d ($J_{4'5'}$ = 4 Hz), $H_{4'}$] CD (MeOH) $\Delta\epsilon$ (325) 0, (295) −1.8, (285) 0, (260) +16.8, (250) 0, (245) −8.0, and (230) 0; mass spectra, molecular ions at 656 and 654.

Surface Fermentation of Culture Z1640. Slants of LL-Z1640 were used to inoculate Erlenmeyer flasks each containing 50 mL of a medium consisting of corn steep liquor 2%, cerelose 4%, $(NH_4)_2SO_4$ 1%, KH_2PO_4 0.6%, and $CaCO_3$ 0.05% with the pH adjusted to 6.2 with a potassium hydroxide solution. The Erlenmeyers were incubated at 28 °C on a rotary shaker for 6 days. Each Erlenmeyer flask was then used to inoculate two Fernbach flasks, each containing 1 L of medium consisting of NH_4 tartrate 0.2%, $MgSO_4 \cdot 7H_2O$ 0.05%, KH_2PO_4 0.1%, glucose 5.0%, corn steep liquor 1.0% in aqueous solution with pH adjusted to 6.5 with sodium hydroxide. Fermentation at ambient temperature was allowed to continue for 8 to 9 weeks. At this time a thick black matte covered the surface of the medium in each Fernbach flask. The liquid layer was drained off and the matte was reflooded with fresh medium and these reflooded flasks were harvested at the end of 4 to 5 weeks.

Workup included extraction with half-volume of ethyl acetate, concentration of the solvent extract, followed by silica gel chromatography.

From 5 L of surface fermentation 800 mg of crude solids were obtained by extraction with ethyl acetate. Silica gel chromatography yielded 400 mg of **4**. Further chromatography of the mother liquors from this and other similar preparations yielded a small amount (100 mg) of **3**: mp 175 °C; $[\alpha]_D$ −112° (c 0.28, MeOH); IR (KBr) 3500, 1640, 1605, and 1575 cm^{-1}; UV (MeOH) 235, 272, and 315 nm (ϵ 26 580, 11 350, and 5 490); *m/e* (%, composition) 366 (M, 14, $C_{19}H_{26}O_7$), 348 (2, $C_{19}H_{24}O_6$), 330 (2, $C_{19}H_{22}O_5$), 219 (8, $C_{12}H_{13}O_4$), 190 (100, $C_{11}H_{26}O_3$), and 99 (30, $C_6H_{11}O$). Anal. Calcd for $C_{19}H_{26}O_7$: mol wt 366.1678. Found: mol wt (mass spectrum) 366.1661.

Still fermentations were set in Fernbachs using the same medium except that D,L-ethinoine at a concentration of 200 μg/mL of medium was added at the time of inoculation. Incubation was again allowed to proceed for about 8 weeks. The mattes in these flasks were almost white in color and workup in the described manner yielded only curvularin and dehydrocurvularin as shown by mp, NMR, IR, and mass spectral data.

Isolation of Isocoumarins. A 1000-L fermentation (11 days) was extracted with ethyl acetate (400 L) at pH 5. The concentrate was defatted by partitioning between methanol/heptane. The methanol layer was concentrated to dryness to give 125 g of a dark oily residue. This was chromatographed over an acid-washed silica gel (1000 g) column (in methylene chloride) and developed with a gradient between methylene chloride/25% ether–methylene chloride. The eluate was monitored at 275 nm by UV. Compound **6** was obtained from the first band and was obtained crystalline after concentration to dryness of the appropriate fractions and crystallization from ethyl acetate/hexane. This gave 1.34 g of **6**: mp 95–98 °C; $[\alpha]_D$ +4.4° (c 0.23, $CHCl_3$); UV 237 (sh), 243, 256 (sh), 277, 286 (sh), and 325 nm (ϵ 49 850, 56 450, 13 700, 7 400, 4 930, and 7 120); *m/e* (% composition) 292 (M, 4, $C_{15}H_{16}O_6$), 274 (35, $C_{15}H_{14}O_5$), 232 (69, $C_{13}H_{12}O_4$), and 206 (100, $C_{11}H_{10}O_4$). Anal. Calcd for $C_{15}H_{16}O_6$: mol wt 292.0942; Found: mol wt (mass spectrum) 292.0947.

The next zone to be eluted off the column gave 2.9 g of **7** after concentration to dryness and crystallization from ethyl acetate/hexane: mp 192–194 °C; IR 3500, 1680, 1640, 1615, and 1570 cm^{-1}; UV 260, 305 (sh), 313, 342, and 354 nm (sh) (ϵ 47 160, 11 790, 12 315, 15 460, and 11 290); *m/e* (%, composition) 262 (M, 100, $C_{13}H_{10}O_6$), 244 (18, $C_{13}H_8O_5$), and 216 (12, $C_{12}H_8O_4$). Anal. Calcd for $C_{13}H_{10}O_6$: mol wt 262.0476. Found: mol wt (mass spectrum) 262.0461.

Finally a mixture of mainly **1** and a little **5** (4.1 g) was obtained from the last 275-nm band. Column chromatography over silica gel with a gradient elution [methylene chloride/methylene chloride (10% methanol)] gave after fractional crystallization from methylene chloride/ether 1.09 g of crude **1** and a little **5**. Preparative TLC (silica gel; ethyl acetate/chloroform 1:1) of 150 mg of the above material gave 5 mg of **5** after elution of the plate with acetone, concentration to dryness, and crystallization from ethyl acetate/hexane: mp 158–160 °C; IR (KBr) 3500, 1680, 1625, and 1575 cm^{-1}; UV 236 (sh), 244, 257 (sh), 276, 286 (sh), and 325 nm (ϵ 48 000, 54 000, 11 700, 6 600, 4 500, and 11 700); *m/e* (%, composition) 300 (M, 9, $C_{13}H_{13}O_6Cl$), and 221 (100, $C_{11}H_9O_5$). Anal. Calcd for $C_{13}H_{13}O_6Cl$: mol wt 300.0420; Found: mol wt (mass spectrum) 300.0413.

Acknowledgments. We wish to thank W. Fulmor, L. M. Brancone, and associates for the spectral and analytical data and Dr. G. Van Lear for certain mass spectral results. We are grateful to A. J. Shay, M. Dann, and J. D. Korshalla for large scale fermentations and processing. Finally, we acknowledge Dr. F. Durr for in vitro antiviral testing and Dr. H. Tresner and Mrs. J. H. Korshalla for classification studies on Z1640.

Registry No.—**1**, 66018-37-9; **1** acetonide, 66036-83-7; **2**, 66018-38-0; **2** acetonide, 66018-39-1; **3**, 66018-40-4; **4**, 66018-41-5; **5**, 66018-42-6; **6**, 66018-43-7; **7**, 66018-44-8; **8**, 66018-45-9; **9**, 66018-46-0; **10**, 66018-47-1; **11**, 66018-48-2; **12**, 66018-49-3; **13**, 66018-50-6.

Supplementary Material Available: Atomic coordinates and torsion angles from the X-ray analysis of **13** (2 pages). Ordering information is given on any current masthead page.

References and Notes

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An Amine Solvent Modification of the Kostanecki–Robinson Reaction. Application to the Synthesis of Flavonols[1]

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A modification of the Kostanecki–Robinson reaction for synthesis of flavonoid compounds is described. In the modified method, an anhydrous tertiary amine (usually triethylamine or *N*-ethylmorpholine) is used as solvent. Application of the amine solvent modification to galangin 3-methyl ether (**2**), tamarixetin (**5**), and 5,7-dihydroxy-3-methoxy-3′,4′-methylenedioxyflavone (**7**) is reported. The 7-piperonylate of **7** (**6**) is isolable when sodium bicarbonate is used as base in the isolation procedure. Interaction of protocatechuic anhydride tetraacetate with ω-methoxyphloroacetophenone in triethylamine yields 2-methyl-3-methoxy-5,7-dihydroxychromone (**11**).

The Kostanecki–Robinson (Allan–Robinson)[2] reaction is an important synthetic method for flavonoid substances. Although widely used, it has certain disadvantages: low yields inherent in any fusion procedure, and formation of 3-aroylflavones, especially at temperatures above 200 °C.[3] The 3-aroyl group often can be removed under alkaline conditions, which, however, also can effect yield-lowering ring opening of the γ-pyrone moiety (ring C) of the flavone.[4] Kuhn and Löw[5] modified the K–R reaction by substituting a catalytic amount of triethylamine for the stoichiometric quantity of benzoate salt and ran the reaction at 160 °C. The Kuhn–Löw modification makes many complex hydroxyflavones and flavonols accessible in modest yield and still is useful.[6] A second major flavone synthesis involves the Baker–Venkataraman rearrangement,[7] followed by cyclization of an intermediate diaroylmethane derivative. Inasmuch as a dibenzoylmethane has been isolated as a K–R reaction product,[8] the Baker–Venkataraman (B–V) rearrangement is an intermediate step therein. In the present paper, we describe an amine solvent modification of the K–R reaction and its application to the synthesis of several flavonols.

In this work, an *anhydrous* tertiary amine is used in sufficient quantity to provide a homogeneous reaction medium. Experiments on the synthesis of galangin 3-methyl ether (5,7-dihydroxy-3-methoxyflavone (**2**)) from ω-methoxyphloroacetophenone (**1**) and benzoic anhydride are summarized in Table I. The theoretical quantity of anhydride for aroylation of all phenolic hydroxyl groups of **1** was employed. It is evident that the yield of **2** decreases with increase in boiling point of the amine solvent. The amine solvent method differs from the Kuhn–Löw procedure in use of the amine in sufficient quantity to provide homogeneity of the medium, and the reflux temperature of the amine controls the reaction temperature.

Application of the amine solvent procedure to more complex flavonols in which the side phenyl (ring B) contains hydroxyl groups necessitates use of blocking groups. The acetyl block would be useful because of its ease of removal. In the attempted synthesis of 2′,5,7-trihydroxy-3-methoxyflavone by K–R fusion of **1** with salicylic anhydride diacetate and sodium acetylsalicylate at 250 °C, no flavone was obtained but instead 5,7-dihydroxy-3-methoxy-2-methylchromone.[9] However, synthesis of several derivatives of quercetin was achieved with the diacetate of isovanillic anhydride.[10] Accordingly, in a projected synthesis of quercetin 3-methyl ether, synthesis of protocatechuic anhydride tetraacetate (**10**) was investigated. The tetraacetate **10** was obtainable only under a narrow range of experimental conditions, specifically by reacting protocatechuyl chloride diacetate with a stoichiometric quantity of water and pyridine in ethyl ether. Use of **10** in reaction with **1**, however, gave 5,7-dihydroxy-3-methoxy-2-methylchromone with either *N*-ethylmorpholine or triethylamine as solvent. Acetyl migration to a phenolic hydroxyl group of **1** evidently occurred, even at the low reflux temperature of triethylamine.

With the acetyl block contraindicated, mesyl blocked protocatechuic acids were investigated. Dimesylprotocatechuic acid was obtained in this laboratory several years ago,[11b] but all attempts to convert it to the anhydride have been unsuccessful. Mesylisovanillic acid also was available[11a] and has been converted to the anhydride (**4**) by a slight modification of the method of Brewster and Ciotti.[12] Reaction of **4** with ω-benzoyloxyphloroacetophenone (**3**) in anhydrous triethylamine gave tamarixetin (quercetin 4′-methyl ether (**5**)) in 69% yield. The intermediate mesyl-blocked quercetin derivative was not isolated, since the alkaline conditions used in obtaining **5** effected hydrolysis of the 3′-mesyloxy group, as well as of the aroyloxy groups of the crude product. *p*-Mesyloxybenzoic anhydride,[11c] although soluble in *N*-ethylmorpholine, unaccountably gave unsatisfactory results upon attempted reaction with **1**.

Synthesis of other flavonols with the quercetin oxygenation pattern has been investigated. Piperonylic anhydride is available by interaction of piperonylic acid with mesyl chloride–pyridine[12] and was reacted with **1** in anhydrous *N*-ethylmorpholine. The product isolated in 82% yield by using sodium bicarbonate as the only base in the isolation was 5-hydroxy-3-methoxy-3′,4′-methylenedioxy-7-piperonyloxyflavone (**6**). Hydrolysis of the 7-piperonyloxy group of **6** was carried out in 5% alcoholic potassium hydroxide to give the known 5,7-dihydroxy-3-methoxy-3′,4′-methylenedioxyflavone (**7**)[13] in 72% yield for the two-step synthesis. Attempts to remove the methylene group to give quercetin 3-methyl ether were not successful. Use of concentrated sulfuric acid and phloroglucinol[14] caused irreversible alteration of the product.

3,4-(Diphenylmethylenedioxy)benzoic acid has been obtained previously in this laboratory[15] and was converted to the anhydride (**8**) with mesyl chloride–pyridine.[12] Interaction of **8** with **1** in *N*-ethylmorpholine, followed by an isolation procedure in which the only base employed was sodium bicarbonate, gave 5-hydroxy-7-[(3,4-diphenylmethylenedioxy)benzoyloxy]-3′,4′-diphenylmethylenedioxy-3-methoxyflavone (**9**) in 75% yield. Reaction of **9** with sulfuric acid in aqueous acetic acid gave a flavonoid substance (positive magnesium–hydrochloric acid test),[16] the NMR spectrum of which contained a complex of peaks from δ 6.5 to 7.5 (integrating for 15 aromatic protons), and indicated incomplete removal of the 3′,4′-diphenylmethylene group. Cleavage of the diphenylmethylene group from gallic acid derivatives in dilute acetic acid previously has been demonstrated.[17]

Inasmuch as **10** gave a 2-methylchromone derivative, **1** and **3** tris(3,4-diacetoxybenzoates) (**12** and **13**, respectively) were prepared and subjected to several base–solvent combinations[18] in the B–V rearrangement. From **12** in triethylamine containing benzoic acid, a flavonoid product was obtained in

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minute yield. The rearrangement product of **13** in potassium acetate–acetic acid gave a positive flavonoid test,[16] but the infrared spectrum showed other substances present. The tris(3,4-dimesyloxybenzoates) of **1** and **3** then were prepared (**14** and **15**, respectively). Attempted rearrangement of **14** in a pyridine–potassium hydroxide mixture gave no detectable flavonoid. Rearrangement of **15** in potassium acetate–acetic acid resulted, in low yield, in a product which gave a positive flavonoid test.[16] The product was not quercetin and may have been a partially *O*-aroylated derivative.

Experimental Section

All melting points were taken by the capillary tube method and are uncorrected. NMR spectra were observed with the aid of a Varian A-60 spectrometer, with tetramethylsilane as internal standard. Infrared spectra were determined on a Perkin-Elmer Model 237 spectrophotometer.

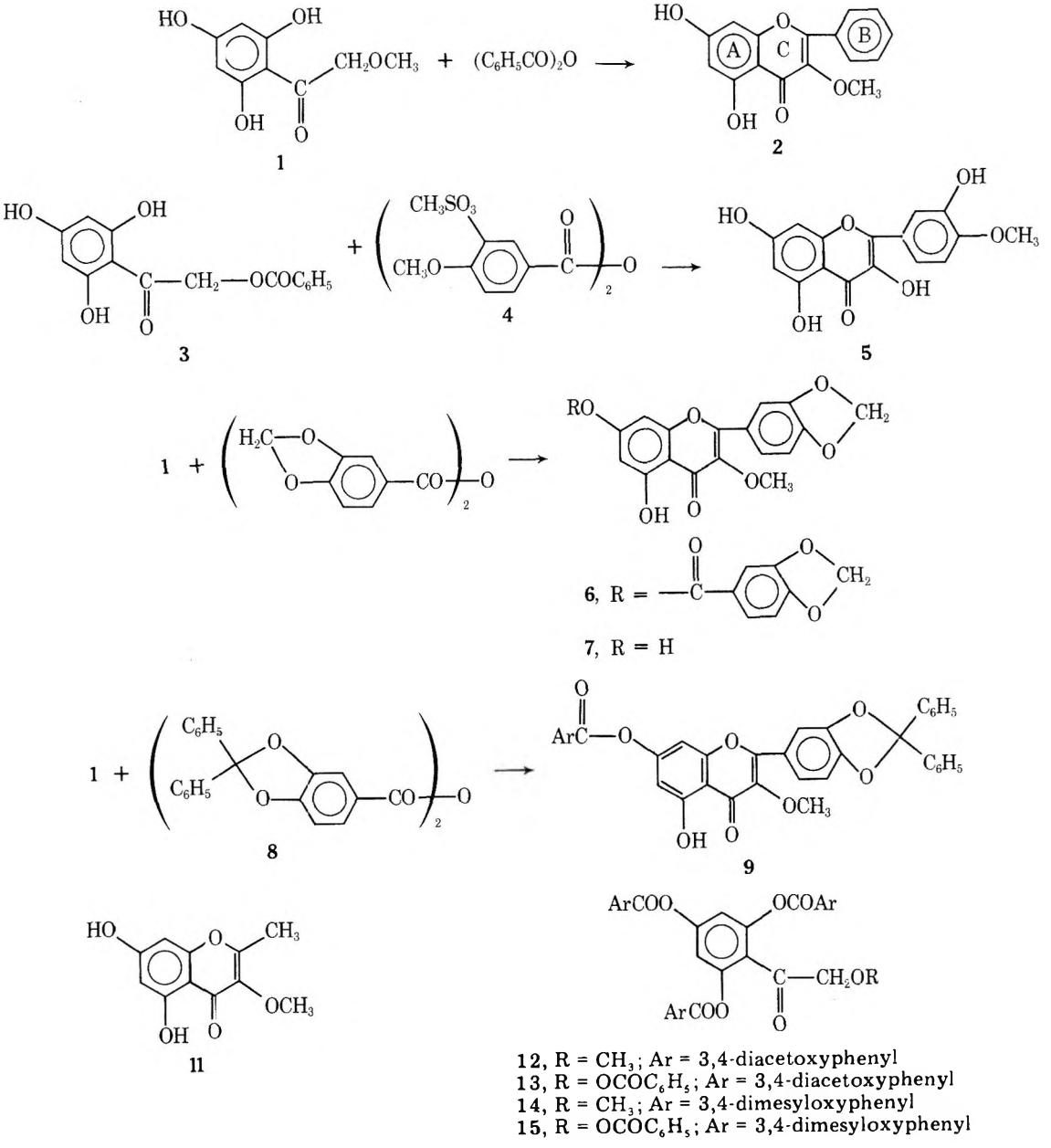
Galangin 3-Methyl Ether (2). ω-Methoxyphloroacetophenone (5 g) and benzoic anhydride (17 g) were heated under reflux in triethylamine (purified twice by distillation from phenyl isocyanate)[19a] for 4.5 h. Just enough amine was used to effect complete solution. After reflux, the solution was permitted to cool, 25 mL of absolute ethanol was added, and reflux was continued for 30 min. The solution was diluted to 250 mL with water and triethyl amine and ethanol were removed by rotary evaporation in vacuo. The remaining aqueous solution was diluted with 250 mL of water and saturated with solid carbon dioxide. The crude product was recrystallized from absolute ethanol to give galangin 3-methyl ether (**2**): mp 293 °C (lit.[20] mp 299 °C), 5.2 g yield (75%). Demethylation of 3.2 g of **2** with 20 mL of hy-

Table I. Synthesis of Galangin 3-Methyl Ether by the Amine Solvent Modification of the Kostanecki–Robinson Reaction

Amine	Bp of amine, °C	% yield of galangin 3-methyl ether[a]
$(C_2H_5)_3N$[b]	86	75[d]
$(CH_3CH_2CH_2)_3N$[b]	156	60[e]
N-Ethylpiperidine[c]	130.8	65[f]
$(CH_3CH_2CH_2CH_2)_3N$[c]	214	8.5[e]

[a] Lit. mp 299 °C; cf. ref 20. [b] Just enough amine used to insure complete solution; see Experimental Section for procedure. [c] Solution incomplete; 75 mL of amine used with 6.8 g of benzoic anhydride and 2 g of ω-methoxyphloroacetophenone. [d] Mp of product, 293 °C. [e] Mp of product, 295 °C. [f] Mp of product, 290 °C.

Scheme I



driodic acid (specific gravity 1.7) in 50 mL of glacial acetic acid at reflux for 6 h gave 2.8 g (83%) of galangin, mp 219 °C (lit.[21] mp 214–215 °C).

Isovanillic Anhydride Dimesylate (4). To a cold solution (0–5 °C) of isovanillic acid mesylate[11a] (24.6 g) in 50 mL of pyridine was added 11.4 g of mesyl chloride over 30 min with constant stirring. The reaction mixture was kept in an ice chest for 1 h and then stood at room temperature overnight. Solid material separated, and the suspension was added with vigorous stirring to 500 mL of 6 N hydrochloric acid containing 500 g of ice. The light tan product remained suspended in the acid solution for 1 h and was collected, washed well with water, and air dried. The product was recrystallized from benzene–petroleum ether (bp 30–60 °C) (1:1 vol) to give 21.2 g (90%) of anhydride, mp 161 °C. Anal. Calcd for $C_{18}H_{18}O_{11}S_2$: C, 45.57; H, 3.82; S, 13.52. Found: C, 45.73; H, 3.81; S, 13.51.

Quercetin 4′-Methyl Ether (Tamarixetin (5)). To 2.88 g of ω-benzoyloxyphloroacetophenone[21] suspended in 50 mL of triethylamine (twice distilled from phenyl isocyanate)[19a] was added, with vigorous stirring, 14.22 g of isovanillic anhydride dimesylate. The reaction mixture was refluxed overnight with constant stirring and then cooled to 50 °C. Absolute ethanol (50 mL) was added and reflux was continued 1 h. After cooling, the brown solution was added to 400 mL of 12 N hydrochloric acid containing 600 g of ice. The resulting yellow precipitate was collected, washed with 500 mL of 1 N hydrochloric acid and then with 500 mL of water, and dissolved in 150 mL of 25% aqueous dimethyl sulfoxide. To the resulting solution at 10 °C was added, dropwise, a potassium hydroxide solution (5 g in 10 mL of water) at such a rate that the temperature did not exceed 20 °C. After standing at room temperature 4 h, the solution was diluted to 1 L and saturated with solid carbon dioxide. The resulting precipitate, mp 251–252 °C, was recrystallized from ethanol to give 2.18 g (69%) of quercetin 4′-methyl ether (**5**), mp 257–258 °C (lit.[10] mp 256–258 °C). The quercetin 4′-methyl ether was acetylated by the method of Freudenberg[22] to give the tetraacetate, mp and lit.[10] mp 202 °C.

Piperonylic Anhydride. This substance was prepared from 16.6 g of piperonylic acid in 150 mL of pyridine at 0 °C by adding 11.4 g of methanesulfonyl chloride by the general method described for isovanillic anhydride dimesylate: yield 14.0 g (89%); mp and lit.[23] mp 156 °C.

5-Hydroxy-3-methoxy-3′,4′-methylenedioxy-7-piperonyloxyflavone (6). ω-Methoxyphloroacetophenone (5 g) and piperonylic anhydride (25 g) were suspended in 250 mL of anhydrous *N*-ethylmorpholine.[19b] The solids quickly dissolved on refluxing, which was continued 6 h. To the cooled solution was added 300 mL of ethanol. The mixture was refluxed 1 h, cooled to ca. 50 °C, and poured onto ice–concentrated hydrochloric acid. The product was collected, washed well with water, and stirred with 1 L of saturated sodium bicarbonate and the mixture was filtered. Piperonylic acid was recovered on acidification of the filtrate. The precipitate was washed with water, air dried, and crystallized from ethanol/acetone (9/1 vol) to give 9.8 g (82%) of the title compound: mp 212 °C; NMR (Me_2SO-d_6) δ 3.82 (s, 3, OCH_3), 6.14 and 6.18 (overlapping s, 4, OCH_2O groups), 6.96 [d(pair), 2, H_6 and H_8], 7.00 (s, 1, H_2' or H_2 of piperonyloxy), 7.13 (s, 1), 7.6 (m, 4, H_5', H_6', H_5, and H_6 of piperonyloxy), 12.33 (s, 1, 5-OH). Anal. Calcd for $C_{25}H_{16}O_{10}$: C, 63.03; H, 3.39. Found: C, 63.20; H, 3.22.

5,7-Dihydroxy-3-methoxy-3′,4′-methylenedioxyflavone (7). A suspension of 5-hydroxy-3-methoxy-3′,4′-methylenedioxy-7-piperonyloxyflavone (5 g) in 5% alcoholic KOH solution (150 mL) was refluxed 4 h. The solution was poured onto ice–concentrated HCl to give a pale yellow solid, which was washed with water, lixiviated with saturated $NaHCO_3$, washed again with water, and air dried. Crystallization from acetone gave the title compound (2.9 g), mp 274–275 °C (lit.[13] mp 275 °C).

3,4-(Diphenylmethylenedioxy)benzoic Anhydride (8). To 68 g of 3,4-diphenylmethylenedioxybenzoic acid,[15,24] mp 182.5–184 °C, in dry pyridine (400 mL) was added 22.8 g of mesyl chloride. After standing 45 min, the mixture was poured onto ice and 400 mL of concentrated HCl. The precipitate was collected, washed well with water, and dried in vacuo at 95 °C. Crystallization from benzene gave the title anhydride in a 52.5-g (79.4%) yield. Recrystallization from benzene and subsequent drying in vacuo for several weeks gave the analytical sample: mp 122.5–125 °C; IR (KBr) 1770 and 1700 cm^{-1} (anhydride CO groups). Anal. Calcd for $C_{40}H_{26}O_7 \cdot C_6H_6$: C, 79.30; H, 4.63. Found: C, 78.92, 78.99; H, 4.65, 4.63.

5-Hydroxy-7-[(3,4-diphenylmethylenedioxy)benzoyloxy]-3′,4′-diphenylmethylenedioxy-3-methoxyflavone (9). To a suspension of ω-methoxyphloroacetophenone (1.0 g) in anhydrous *N*-ethylmorpholine[19b] (50 mL) was added 9.5 g of 3,4-(diphenylmethylenedioxy)benzoic anhydride. The solids dissolved upon heating and the resulting solution was refluxed 2.5 h. After cooling to ca. 50 °C, 35 mL of ethanol was added and the mixture was refluxed an additional hour. The reddish solution was poured onto ice and 150 mL of concentrated hydrochloric acid to give a light-tan solid, which was collected, washed well with water, and suspended in 500 mL of saturated sodium bicarbonate. The insoluble material was collected, washed with water, and air dried. Crystallization from ether–petroleum ether gave the pale yellow title compound, mp 165–170 °C dec, in a 3.93-g (75%) yield. The substance gave a dark green color with alcoholic ferric chloride: NMR ($CDCl_3$) δ 3.74 (s, 3, OCH_3), 6.5 to 7.5 (complex series of multiplets, integrating for 28 aromatic protons), 12.55 (s, 1, 5-OH). Anal. Calcd for $C_{49}H_{32}O_{10}$: C, 75.37; H, 4.14. Found: C, 75.01; H, 4.19.

Protocatechuic Acid Anhydride Tetraacetate (10). To protocatechuyl chloride diacetate[25] (25.6 g) in 250 mL of absolute ether were added, dropwise, over 1 h, 16.1 mL of reagent pyridine. The ether solution was stirred vigorously during pyridine addition and then 10 additional h. The reaction mixture was open to the air at all times. Precipitation started immediately and continued several hours. The product was collected, air dried, and recrystallized repeatedly from the minimal quantity of 2:1 by vol acetone–petroleum ether (bp 30–60 °C). The title anhydride crystallized as needles, mp 109 °C, in a 17.7-g yield (81%). The product was stored over phosphorus pentoxide in a vacuum desiccator until used. Any deviation from above conditions caused a marked diminution in yield: IR (KBr) 1775 and 1725 cm^{-1} (anhydride CO groups). Anal. Calcd for $C_{22}H_{18}O_{11}$: C, 57.64; H, 3.96. Found: C, 57.62; H, 4.29.

5,7-Dihydroxy-3-methoxy-2-methylchromone (11). A mixture of 1.98 g of ω-methoxyphloroacetophenone, 13.74 g of protocatechuic anhydride tetraacetate, and 100 mL of anhydrous triethylamine[19a] was refluxed for 5 h with vigorous stirring. After removing 75 mL of triethylamine, absolute ethanol (100 mL) was added and reflux was continued for 30 min. Then 100 mL of 5% potassium hydroxide solution were added dropwise and reflux was continued for 30 min. Organic solvents were removed by distillation in vacuo and the title compound was isolated by saturating the resulting aqueous solution with solid carbon dioxide in a 0.96-g (48%) yield; mp, lit.[9], and mmp 225 °C.

ω-Methoxyphloroacetophenone Tris(3,4-diacetoxybenzoate) (12). To analytically pure ω-methoxyphloroacetophenone (1.98 g) in 50 mL of reagent pyridine was added, rapidly with vigorous stirring, 7.68 g of protocatechuyl chloride diacetate, mp 55 °C. The pyridine solution stood overnight and was neutralized; product was isolated by pouring the solution over 500 g of ice and 500 mL 6 N hydrochloric acid. While still moist it was dissolved in 200 mL of 95% ethanol and added to 1 L of 0.5 N hydrochloric acid containing 1 kg of crushed ice. The product separated as a fine white powder and was collected (with difficulty) by filtration, washed with 500 mL of water, and air dried. Crystallization from aqueous acetic acid (charcoal) gave the title compound, mp 110 °C with softening at 80 °C, in a 7.96-g (93%) yield. Anal. Calcd for $C_{42}H_{34}O_{20}$: C, 58.74; H, 3.99. Found: C, 58.75; H, 3.99.

Rearrangement of **12** (8.58 g) in 50 mL of anhydrous triethylamine containing 1.2 g of benzoic acid by reflux for 4 h followed by addition of 100 mL of absolute ethanol and further reflux gave an orange solution. Addition of an alkaline solution (10 g of potassium hydroxide in 50 mL of water) and heating on a steam bath 30 min, followed by removal of organic solvents, gave a residual aqueous solution which after dilution to 250 mL was saturated with solid carbon dioxide. There resulted 50 mg of flavonoid material: mp 330 °C (positive ferric chloride and magnesium–HCl[16] tests); IR (KBr) ca. 1745 (ester CO) and 1655 cm^{-1} (flavonoid CO).

ω-Benzoyloxyphloroacetophenone Tris(3,4-diacetoxybenzoate) (13). To ω-benzoyloxyphloroacetophenone (3) (2.88 g) in 25 mL of dry pyridine was added rapidly 9.84 g of protocatechuyl chloride diacetate. After 10 h at room temperature, the mixture was added, dropwise, to 1 kg of crushed ice in 1 L of 2 N hydrochloric acid, and the acidic suspension was permitted to stand until the ice melted. The white precipitate was collected, washed well with water, and air dried. Crystallization from 95% ethanol gave the title compound in a 9.02-g (94%) yield, mp 110 °C. Anal. Calcd for $C_{48}H_{36}O_{21}$: C, 60.76; H, 3.82; acetyl, 27.22. Found: C, 60.35; H, 3.96; acetyl, 26.21.

Rearrangement of 9.48 g of **13** in 200 mL of glacial acetic acid containing 50 g of anhydrous potassium acetate by refluxing for 12 h gave a red solution, which was added dropwise to 2 L of an ice–water mixture, with vigorous stirring. The light-tan product was recrystallized from 75% aqueous ethanol: yield 1.2 g; mp 130–135 °C [positive ferric chloride and Mg–HCl[16] tests (red color)]. Solution in 50 mL of dimethyl sulfoxide and addition of potassium hydroxide (10 g in 10 mL of water) gave an exothermic reaction. The mixture was cooled

to maintain a temperature under 25 °C. After ca. 30 min, 250 mL of 6 N hydrochloric acid was added, and the resulting solution was cooled in ice 2 h to give 430 mg of a flavonoid substance: mp 210 °C (positive $FeCl_3$ test and red color with Mg–HCl);[16] IR (KBr) 1705 (CO), and ca. 1645 cm^{-1} (flavonoid CO).

ω-Methoxyphloroacetophenone Tris(3,4-dimesyloxybenzoate) (14). To 1.98 g of ω-methoxyphloroacetophenone in 30 mL of reagent pyridine was added rapidly 9.84 g of protocatechuyl chloride dimesylate.[11b] The reaction mixture stood at room temperature 3 days. The heterogeneous mixture then was added slowly with vigorous stirring to 1.5 L of 6 N hydrochloric acid containing 1.5 kg of ice. The precipitate was collected, washed successively with 500 mL of 1 N hydrochloric acid and 500 mL of water, and dried in vacuo over P_2O_5. Recrystallization from the minimal quantity of ethanol–acetone (95/5 vol) gave the title ester in a 10.5-g (97%) yield, mp 80 °C. Anal. Calcd for $C_{36}H_{34}O_{26}S_6$: C, 40.22; H, 3.19. Found: C, 40.09; H, 3.41.

Attempted rearrangement of **14** in 50 mL of pyridine containing 5.6 g of potassium hydroxide at room temperature gave only water soluble products. No flavonoids could be detected.

ω-Benzoyloxyphloroacetophenone Tris(3,4-dimesyloxybenzoate) (15). ω-Benzoyloxyphloroacetophenone[21] (2.88 g) was reacted with 9.84 g of protocatechuyl chloride dimesylate,[11b] as described in the preceding section. Recrystallization of crude product from ethanol–acetone (95/5 vol) gave (10.3 g, 89%) mp 120 °C. Anal. Calcd for $C_{42}H_{36}O_{27}S_6$: C, 43.28; H, 3.11; S, 16.49. Found: C, 43.09; H, 3.38; S, 16.22.

Rearrangement of **15** (11.64 g) in 30 mL of glacial acetic acid containing 10 g of anhydrous potassium acetate at reflux for 48 h gave a red solution, which upon cooling set to a semisolid mass. Solution of the latter in 100 mL of acetic acid–sulfuric acid (20 mL), with removal of inorganic salts by filtration, gave a reddish orange filtrate which was heated gently for 2 h, diluted with 250 mL of water, and cooled in an ice chest overnight. A light yellow solid crystallized at the surface and was collected (negative $FeCl_3$ and Mg–HCl[16] tests, positive blue fluorescence in concentrated H_2SO_4): IR (KBr) 1665 cm^{-1} (flavonoid CO). This substance in 15 mL of dimethyl sulfoxide was added to potassium hydroxide (1 g) in 20 mL of water, permitted to stand 4 h at room temperature, added to 100 mL of 6 N hydrochloric acid, and cooled in an ice chest. The precipitated product (110 mg) gave positive $FeCl_3$ and Mg–HCl[16] tests.

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Synthesis and Molecular Structure of *exo*-7-Phenyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane

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The dimer of methyl vinyl ketone, when treated with phenylmagnesium bromide, was converted to the exo and endo isomers of 7-phenyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane. The x-ray crystallographic examination of the exo isomer provides the first detailed structural data for this interesting bicyclic ketal series. The method of synthesis and the x-ray structural data are provided.

From the observation that 6,8-dioxabicyclo[3.2.1]octane constitutes the major structural framework of the aggregating sex pheromones for three pernicious bark beetles (brevicomin (**2**), (*Dendroctonus brevicomis*),[1] frontalin (**3**), (*D. frontalis*),[2] and multistriatin (**4**), (*Scolytus multistriatus*)[3]) has evolved an interest in the detailed structures of bicyclic ketals in this series. The additional realization that other natural products have this basic skeletal system has resulted in the motivation for a systematic analysis of these structures.[4]

We were most fortunate that as part of a general investigation directed toward syntheses in this series, a suitable solid sample, *exo*-7-phenyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]-octane (**6**), was available. Addition of the dimer **5** of methyl vinyl ketone to a solution of phenylmagnesium bromide re-

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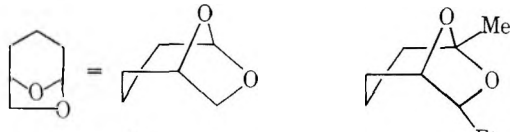
Table I. Bond Angles (deg) with Standard Deviations in Parentheses

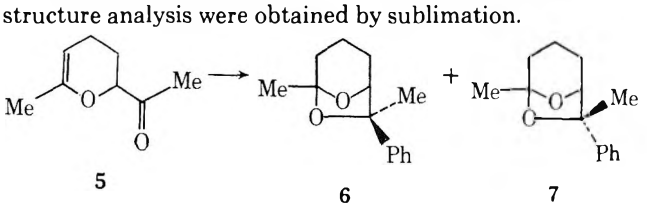
C(2)–C(1)–O(8)	109.1 (3)	O(6)–C(7)–C(10)	109.3 (3)
C(2)–C(1)–C(7)	116.9 (4)	O(6)–C(7)–C(11)	109.7 (3)
C(2)–C(1)–H1	109 (2)	C(10)–C(7)–C(11)	109.0 (3)
O(8)–C(1)–C(7)	100.3 (3)	C(5)–O(6)–C(7)	107.9 (3)
O(8)–C(1)–H1	108 (2)	C(5)–C(9)–H9(1)	115 (2)
C(7)–C(1)–H1	113 (2)	C(5)–C(9)–H9(2)	107 (2)
C(1)–C(2)–C(3)	112.2 (4)	C(5)–C(9)–H9(3)	114 (2)
C(1)–C(2)–H2(1)	105 (2)	H9(1)–C(9)–H9(2)	103 (3)
C(1)–C(2)–H2(2)	110 (2)	H9(1)–C(9)–H9(3)	110 (3)
C(3)–C(2)–H2(1)	108 (2)	H9(2)–C(9)–H9(3)	107 (3)
C(3)–C(2)–H2(2)	112 (2)	C(7)–C(10)–H10(1)	112 (3)
H2(1)–C(2)–H2(2)	109 (3)	C(7)–C(10)–H10(2)	114 (2)
C(2)–C(3)–C(4)	112.8 (4)	C(7)–C(10)–H10(3)	118 (2)
C(2)–C(3)–H3(1)	108 (2)	H10(1)–C(10)–H10(2)	106 (3)
C(2)–C(3)–H3(2)	110 (2)	H10(1)–C(10)–H10(3)	100 (3)
C(4)–C(3)–H3(1)	114 (2)	H10(2)–C(10)–H10(3)	106 (3)
C(4)–C(3)–H3(2)	110 (2)	C(7)–C(11)–C(12)	122.4 (4)
H3(1)–C(3)–H3(2)	100 (3)	C(7)–C(11)–C(16)	120.3 (4)
C(3)–C(4)–C(5)	111.3 (4)	C(12)–C(11)–C(16)	117.3 (4)
C(3)–C(4)–H4(1)	109 (2)	C(11)–C(12)–C(13)	121.7 (4)
C(3)–C(4)–H4(2)	112 (2)	C(11)–C(12)–H12	120 (2)
C(5)–C(4)–H4(1)	104 (2)	C(13)–C(12)–H12	119 (2)
C(5)–C(4)–H4(2)	112 (2)	C(12)–C(13)–C(14)	119.8 (4)
H4(1)–C(4)–H4(2)	108 (3)	C(12)–C(13)–H13	121 (2)
C(4)–C(5)–O(8)	109.7 (3)	C(14)–C(13)–H13	119 (2)
C(4)–C(5)–O(6)	108.0 (3)	C(13)–C(14)–C(15)	119.2 (5)
C(4)–C(5)–C(9)	115.5 (4)	C(13)–C(14)–H14	116 (2)
O(8)–C(5)–O(6)	104.1 (3)	C(15)–C(14)–H14	124 (2)
O(8)–C(5)–C(9)	109.0 (4)	C(14)–C(15)–C(16)	121.2 (4)
O(6)–C(5)–O(9)	110.0 (3)	C(14)–C(15)–H15	118 (2)
C(1)–O(8)–C(5)	102.5 (3)	C(16)–C(15)–H15	121 (2)
C(1)–C(7)–O(6)	100.7 (3)	C(11)–C(16)–C(15)	120.8 (4)
C(1)–C(7)–C(10)	115.9 (4)	C(11)–C(16)–H16	115 (2)
C(1)–C(7)–C(11)	111.9 (3)	C(15)–C(16)–H16	124 (2)

Table II. Torsion Angles in Degrees

H1–C(1)–C(7)–C(11)	38	O(8)–C(1)–C(2)–C(3)	−55.7
H1–C(1)–C(7)–C(10)	88	C(1)–O(8)–C(5)–O(6)	39.8
C(5)–O(6)–C(7)–C(11)	101.7	O(8)–C(5)–O(6)–C–(7)	−13.2
C(5)–O(6)–C(7)–C(10)	−138.9	C(5)–O(6)–C(7)–C(1)	−16.4
C(2)–C(1)–C(7)–C(11)	165.9	O(6)–C(7)–C(1)–O(8)	40.1
C(2)–C(1)–C(7)–C(10)	40.1	C(7)–C(1)–O(8)–C(5)	−49.7
O(8)–C(1)–C(7)–C(11)	−76.3	O(6)–C(7)–C(1)–C(2)	−77.6
O(8)–C(1)–C(7)–C(10)	157.9	C(7)–C(1)–C(2)–C(3)	57.2
C(7)–O(6)–C(5)–C(9)	−129.8	C(7)–O(6)–C(5)–C(4)	103.4
C(1)–O(8)–C(5)–C(9)	157.1	O(6)–C(5)–C(4)–C(3)	−54.8
C(3)–C(4)–C(5)–C(9)	−178.3	C(16)–C(11)–C(7)–C(1)	−58.7
C(1)–C(2)–C(3)–C(4)	36.6	C(16)–C(11)–C(7)–O(6)	−169.5
C(2)–C(3)–C(4)–C(5)	−37.2	C(16)–C(11)–C(7)–C(10)	70.9
C(3)–C(4)–C(5)–O(8)	58.0	C(12)–C(11)–C(7)–C(1)	122.8
C(4)–C(5)–O(8)–C(1)	−75.5	C(12)–C(11)–C(7)–O(6)	12.0
C(5)–O(8)–C(1)–C(2)	73.7	C(12)–C(11)–C(7)–C(10)	−107.7



sulted in the formation of **6** and the endo isomer **7** in the ratio of 3:1. It is important to emphasize, at this point, that the expected tertiary alcohol was not formed. Indeed, we have observed that for the addition of any Grignard or organolithium reagent to **5**, even in the absence of acid (other than water) during workup, only the ketal is isolated.[5] The exo isomer **6** crystallized from the reaction mixture and could be recrystallized from ethanol–water. Crystals suitable for x-ray structure analysis were obtained by sublimation.



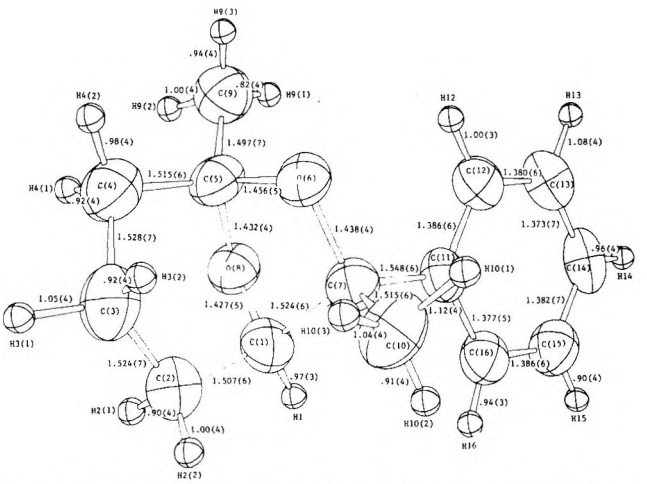


Figure 1. ORTEP drawing of *exo*-7-phenyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane. The hydrogen atoms are represented by arbitrary spheres and the probability level for the thermal ellipsoids is 0.5.

The details of the x-ray determination are presented in the Experimental Section. An ORTEP drawing of **6**, with measured bond lengths, is presented in Figure 1. Tables I–IV provide the important structural data, including bond angles, dihedral angles, and coordinate system. The stereoview is presented in Figure 2.

Experimental Section

Preparation of 6 and 7. To an ether solution of phenylmagnesium bromide (0.01 mol) was slowly added 1.4 g (0.01 mol) of **5**. The reaction mixture was stirred and at various time intervals 10-mL portions were analyzed by GLC for **5**. When this had been consumed, water was carefully added, to hydrolyze the salts. the ether solution was filtered, dried, and reduced in volume to give the crude product in about 90% yield. GLC analysis (SE-30) indicated two products in the ratio of 3:1

Table III. Equations of Planes and Dihedral Angles

	A[a]	B	C	D	Σ
(1) C(7),C(11),C(12), C(13),C(14),C(15),C(16)	−0.2961	0.7632	0.5729	13.465	3.6×10^{-4}
(2) C(1),C(5),C(7),O(6)	0.4494	0.2907	−0.8448	5.514	2.5×10^{-2}
(3) C(1),C(5),O(8)	0.1240	0.8835	−0.4517	13.890	
(4) C(1),C(2),C(4),C(5)	−0.4739	0.7564	0.4510	10.021	1.5×10^{-4}
(5) C(2),C(3),C(4)	−0.2017	0.9793	−0.0178	13.436	
(6) C(1),C(2),O(8)	−0.8790	0.4730	0.0609	0.011	
(7) C(2),C(3),C(5),O(8)	−0.0448	0.9686	0.2447	15.894	6.2×10^{-2}
(8) C(3),C(4),C(5)	−0.7108	0.6712	0.2105	6.218	

Dihedral Angles, deg

(1)–(2)	66.8	(4)–(5)	34.1
(2)–(3)	46.0	(6)–(7)	59.2
(2)–(4)	68.0	(7)–(8)	42.8
(3)–(4)	66.1		

[a] The equation of the plane is $Ax + By + Cz - D = 0$, where A, B, and C are direction cosines, D is the perpendicular distance from the plane to the origin, and is the sum of the squares of the deviations of the atoms from the least-square plane. The coordinate system is described by x along a, y along the b, and z along the c axes.

Table IV. Positional and Thermal Parameters and Standard Deviations[a]

Atom	x/a	y/b	z/c	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
C(1)	0.36049 (16)	0.65013 (16)	0.5479 (6)	0.00128 (8)	0.00169 (9)	0.0237 (11)	0.00001 (6)	−0.0003 (3)	0.0010 (3)
C(2)	0.34420 (20)	0.61410 (19)	0.6984 (7)	0.00234 (11)	0.00184 (9)	0.0273 (14)	−0.00027 (8)	−0.0015 (3)	0.0011 (3)
C(3)	0.28513 (19)	0.60192 (19)	0.6948 (7)	0.00214 (11)	0.00206 (10	0.0284 (14)	−0.00044 (9)	0.0016 (3)	0.0013 (3)
C(4)	0.26374 (17)	0.59651 (18)	0.5083 (7)	0.00156 (9)	0.00189 (10)	0.0263 (13)	−0.00017 (8)	0.0006 (3)	−0.0002 (3)
C(5)	0.28938 (15)	0.63526 (17)	0.3829 (6)	0.00116 (7)	0.00182 (9)	0.0224 (11)	−0.00010 (7)	−0.0001 (2)	−0.0006 (3)
O(8)	0.34489 (11)	0.62738 (11)	0.3824 (4)	0.00132 (5)	0.00168 (6)	0.0238 (7)	0.00005 (5)	0.0006 (2)	−0.0003 (2)
C(7)	0.33251 (15)	0.70354 (16)	0.5360 (6)	0.00111 (7)	0.00156 (8)	0.0202 (10)	0.00002 (6)	−0.0001 (2)	−0.0002 (3)
O(6)	0.28280 (10)	0.68789 (10)	0.4579 (4)	0.00110 (5)	0.00137 (5)	0.0269 (8)	0.00001 (4)	0.0002 (2)	−0.0002 (2)
C(9)	0.26989 (20)	0.63419 (19)	0.1965 (7)	0.00222 (10)	0.00216 (10)	0.0281 (14)	0.00001 (9)	−0.0004 (3)	−0.0009 (3)
C(10)	0.32249 (18)	0.73094 (18)	0.7108 (7)	0.00186 (9)	0.00233 (10)	0.0243 (12)	−0.00027 (8)	−0.0007 (3)	−0.0012 (3)
C(11)	0.36092 (16)	0.74130 (15)	0.4105 (6)	0.00137 (8)	0.00110 (7)	0.0211 (11)	0.00017 (6)	0.0006 (3)	−0.0003 (2)
C(12)	0.33643 (17)	0.76395 (17)	0.2653 (7)	0.00149 (8)	0.0280 (12)	0.00016 (7)	0.00016 (7)	0.0000 (3)	0.0003 (3)
C(13)	0.36245 (20)	0.79918 (18)	0.1545 (6)	0.00216 (11)	0.00156 (9)	0.0233 (12)	0.00041 (8)	0.0005 (3)	0.0010 (3)
C(14)	0.41411 (20)	0.81190 (17)	0.1881 (7)	0.00220 (11)	0.00129 (8)	0.0274 (14)	0.00000 (8)	0.0019 (3)	0.0006 (3)
C(15)	0.43906 (17)	0.78943 (18)	0.3304 (7)	0.00153 (9)	0.00162 (9)	0.0287 (13)	−0.00005 (7)	0.0010 (3)	−0.0002 (3)
C(16)	0.41319 (17)	0.75512 (17)	0.4422 (6)	0.00162 (9)	0.00149 (8)	0.0206 (11)	0.00003 (7)	0.0000 (3)	0.0002 (3)
H1	0.3990 (12)	0.6530 (12)	0.547 (4)	3.42					
H2(1)	0.3629 (13)	0.5814 (14)	0.677 (4)	4.46					
H2(2)	0.3549 (12)	0.6284 (13)	0.810 (4)	4.46					
H3(1)	0.2781 (13)	0.5708 (13)	0.774 (4)	4.45					
H3(2)	0.2667 (13)	0.6277 (13)	0.756 (4)	4.45					
H4(1)	0.2743 (13)	0.5609 (13)	0.459 (4)	3.98					
H4(2)	0.2262 (13)	0.5988 (13)	0.505 (4)	3.98					
H9(1)	0.2879 (14)	0.6534 (14)	0.120 (4)	4.73					
H9(2)	0.2750 (13)	0.5992 (14)	0.152 (4)	4.73					
H9(3)	0.2362 (14)	0.6414 (13)	0.186 (4)	4.73					
H10(1)	0.3020 (13)	0.7668 (13)	0.693 (4)	4.38					
H10(2)	0.3523 (13)	0.7393 (13)	0.773 (4)	4.38					
H10(3)	0.2992 (13)	0.7139 (13)	0.795 (4)	4.38					
H12	0.3005 (13)	0.7567 (12)	0.243 (4)	3.74					
H13	0.3436 (12)	0.8165 (13)	0.045 (4)	4.10					
H14	0.4304 (13)	0.8345 (12)	0.106 (5)	3.91					
H15	0.4731 (12)	0.7978 (12)	0.349 (4)	4.03					
H16	0.4286 (11)	0.7405 (12)	0.552 (4)	3.47					

[a] The form of the anisotropic temperature expression is $\exp[-(\beta_{11}h^2 + \beta_{22}k^2 + \beta_{33}l^2 + 2\beta_{12}hk + 2\beta_{13}hl + 2\beta_{23}kl)]$.

(peak areas). The mass spectral molecular weights and the NMR spectra of the two products were compatable with structures **6** and **7**, respectively. Calcd for **6**, $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.93; H, 8.35. Found for **7**, $C_{14}H_{18}O_2$: C, 77.10; H, 8.14.

The major product of this reaction crystallized from the reaction mixture and could be recrystallized from ethanol–water, mp 54–55 °C. Room temperature sublimation was effective for purification. However, crystals most suitable for x-ray analysis were obtained by slow crystallization (ca. 1 month) from the sublimate.

The NMR spectrum ($CDCl_3$) exhibited a multiplet centered at δ 7.2 (5 H, aromatic), a singlet at δ 4.3 (1 H, methine), a multiplet centered at δ 1.7 (6 H, ring protons), a singlet at δ 1.8 (3 H, methyl), and a singlet at δ 1.4 (3 H, methyl).

The density of a crystal, measured by floation in H_2O/H_2SO_4, was 1.173 g/cm^3.

Crystallographic Data Collection. A needle-shaped crystal fragment was sealed in a glass capillary to prevent sublimation during exposure to x rays. Preliminary Weissenberg and Buerger precession photographs indicated a tetragonal space group with systematic absences of hkl, $h + k + l \neq 2n$; $hk0$, $h(k) \neq 2n$; and $00l$, $l \neq 4n$.

Unit cell dimensions, refined by least squares from 14 independent 2θ values, obtained with a GE XRD-490 diffractometer using Ni filtered Cu Kα radiation and a scintillation counter, are: $a = b = 25.433(4)$, $c = 7.498$ (2) Å, and space group $I4_1/a$.

The crystal fragment was mounted along the c axis which was roughly parallel to its long dimension. Its approximate dimensions

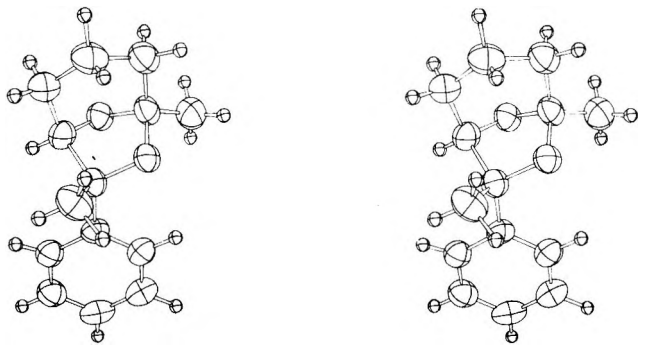


Figure 2. Stereoview of *exo*-7-Phenyl-5,7-dimethyl-6,8-dioxabicyclo[3.2.1]octane.

were 1.4 mm in length and 0.25 mm in average diameter, but no clearly defined faces could be discerned. Intensity data were collected out to a 2θ of 120° using automatic θ–2θ step scans with backgrounds counted at both extremes of the scan range. Three standard reflections were measured at 50 reflection intervals and showed no significant change. Of the 2043 reflections scanned, 1061 were considered observed based on the criterion $I > 3\sigma(I)$; unobserved data were not included in structure refinement. Lorentz and polarization corrections were applied in the normal manner,[6] and weights were calculated according to the method of Stout and Jensen:[7] $w(F) = [(k/4LpI)(\sigma^2(I) + (0.03I)^2)]^{-1}$. Scattering factors for non-hydrogen atoms were taken from Cromer and Mann;[8] the scattering factor curve for hydrogen was that of Stewart, Davidson, and Simpson.[9] No corrections were made for absorption and extinction.

Structure Analysis and Refinement. The structure was solved by direct methods using the program MULTAN.[6] The positions of the non-hydrogen atoms were first refined isotropically then anisotropically using full-matrix least-squares procedures minimizing $\Sigma w(\Delta F)^2$. A difference Fourier map revealed all the hydrogen atoms except those of the two methyl groups. The hydrogen atoms were assigned the refined isotropic temperature factors of the atoms to which they are bound and after three additional cycles of refinement a second difference Fourier map gave the positions of the methyl hydrogens. Subsequent refinement of positional parameters for all atoms and anisotropic thermal parameters for non-hydrogen atoms produced a final R factor of 5.5% [$R = (\Sigma||F_o| - |F_c||)/\Sigma|F_o|$]. The weighted R_w was 6.5% ($R_w = [\Sigma w(\Delta F)^2]^{1/2}/[\Sigma wF_o^2]^{1/2}$, and S, the standard deviation of an observation of unit weight, was calculated to be 2.16 ($S = [\Sigma w\Delta F^2/(m-n)]^{1/2}$, where m is the number of observations and n is the number of parameters).

Discussion

The results of this study provide a precise knowledge of the basic atomic skeletal features for this series, which should be useful in other studies. For example, Gore et al. recently reported on the analysis of frontalin and multistriatin by the lanthanide shift reagent experiment.[10] As necessary input data for the study it was necessary to rely on structural coordinate data generated without benefit of x-ray results. The unusually long europium–oxygen distances[11] associated with the lowest agreement factors for this work may be a consequence of the derived coordinate system.[12] Also, some NMR coupling constant correlations with C-7 substitution[13] have not yet been rationalized. It would appear that ring deformation as a result of increasing size of endo-C-7 substituents could qualitatively be invoked; however, a quantitative explanation is not yet possible. Because of the intimate relationship of coupling constants to dihedral angles, the x-ray data reported here may find application in studies of the bicyclic ketal series which rely on coupling constant analyses.

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Registry No.—**5,** 28450-02-4; **6,** 65899-46-9; **7,** 65899-47-0; phenyl bromide, 108-86-1.

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(6) Computer programs used were by F. R. Ahmed and co-workers (NRC-2, Data Reduction; NRC-8, Fourier for Distorted and Undistorted Nets; and NRC-12, Scan of Interatomic Distances and Angles; National Research Council, Ottawa, Ontario, Canada), Busing and Levy (ORFLS), Carroll K. Johnson (ORTEP), and Germaine, Main, and Woolfson (MULTAN, 1972 version). These programs were locally modified for use with the XDS Sigma 7 computer. Other programs were written locally by G. D. Smith, C. N. Caughlan, and R. D. Larsen.
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Diastereomeric 10,11-Epoxyerythromycins B and the Preparation of 10-*epi*-Erythromycin B[1]

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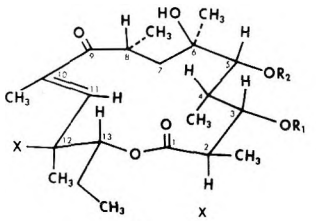
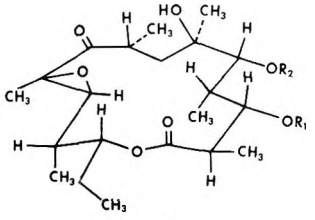
Epoxidation of 10,11-anhydroerythromycin B (**1b**) with either *m*-chloroperbenzoic acid or alkaline hydrogen peroxide gave, after reduction of the resulting *N*-oxide to the free amine, 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**). Catalytic hydrogenation of **2** gave a mixture of 10-*epi*-erythromycin B (**3**) and erythromycin B (**4d**). Sodium borohydride reduction of **1b** followed by epoxidation of the resulting allylic alcohol **12** with m-chloroperbenzoic acid gave, after reduction of the resulting *N*-oxide to the free amine, 9(*R*)-dihydro-10,11-anhydro-10(*R*),-11(*R*)-epoxyerythromycin B (**13**). The latter (**13**) readily rearranged to 9(*R*)-dihydro-6,10(*R*)-epoxy-11-*epi*-erythromycin B (**14**). Jones oxidation of both **13** and **14** gave 6,10(*S*)-epoxy-11-*epi*-erythromycin B (**16a**). Albright–Goldman oxidation of **13** gave the 2′-*O*-acetyl-4″-oxo enol ether **17**, which was converted to 8,9:10,11-dianhydro-10(*S*),11(*R*)-epoxyerythromycin B 6,9-hemiacetal (**18**) by methanolysis and sodium borohydride reduction.

We have previously reported studies of the chemistry of the erythromycin antibiotics which have been directed toward chemical and stereochemical modification of the erythromycin lactone rings.[2] Our general approach has involved initial introduction into the lactone rings of functionalizable sites of unsaturation. The present report is concerned with selective preparation from 10,11-anhydroerythromycin B (**1b**)[2a] of diastereomeric 10,11-epoxyerythromycins and some of their characteristic reactions, including the catalytic reduction of 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) to 10-*epi*-erythromycin B (**3**).



	X
1a	OH
1b	H



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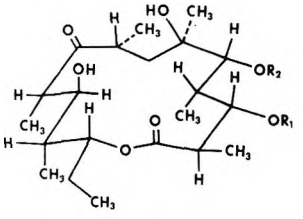

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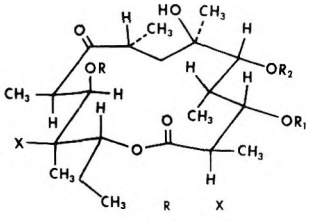
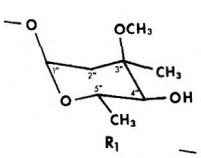
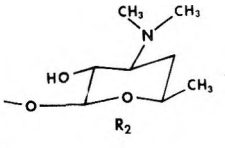


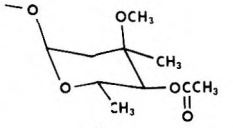
	R	X
4a	SO_2CH_3	OH
4b	SO_2CH_3	H
4c	H	OH
4d	H	H



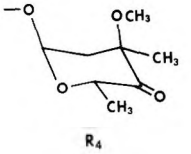
R_1



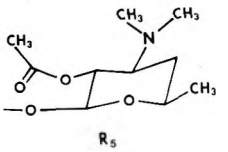
R_2



R_3



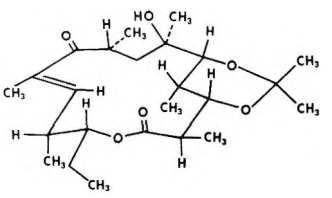
R_4



R_5

NMR and CD studies[4] of the erythromycin antibiotics have shown that the solution conformation of their aglycone rings is essentially identical with that found in the crystal for the hydriodide dihydrate of erythromycin A (**4c**).[6] Assignment of geometry to the 10,11-double bonds of the 10,11-anhydroerythromycins A and B (**1a** and **1b**), formed by base-catalyzed elimination of the elements of methanesulfonic acid from the corresponding 11-*O*-methanesulfonylerythromycins A and B[2a] (**4a** and **4b**, respectively), is based on the assumption of trans elimination of the antiperiplanar C_{10} protons and C_{11} methanesulfonate groups. The newly introduced trans double bonds of **1a** and **1b** are accommodated with minimal conformational change in the remainder of the lactone rings.[4]

Epoxidation of 10,11-anhydroerythromycin B (**1b**) with either *m*-chloroperbenzoic acid or alkaline hydrogen peroxide, followed by catalytic reduction of the resulting *N*-oxide to the free amine, gave, as shown below, 10,11-anhydro-10(*R*),-11(*S*)-epoxyerythromycin B (**2**). The stereochemistry of epoxidation of **1b** is thus the same as that reported by Corey, Nicolaou, and Melvin for the alkaline hydrogen peroxide oxidation of the 3,5-acetonide of 10,11-anhydroerythronolide B (**5**) to the 10(*R*),11(*S*)-epoxy ketone (**6**).[3] The structure of **6** was determined[3] by catalytic hydrogenation of **6** to the 10-*epi*-erythronolide derivative **7**, followed by C_{10} epimerization of the latter with potassium carbonate in methanol, and hydrolysis of the 3,5-acetonide of the resulting product to give erythronolide B (**8**).



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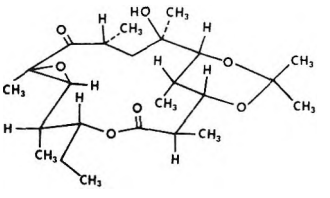

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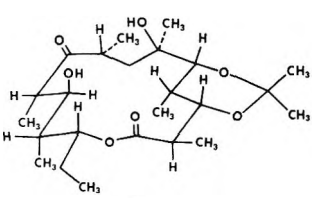

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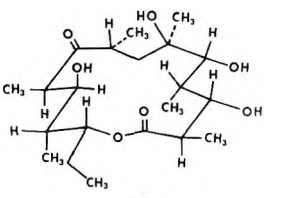

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Catalytic hydrogenation of epoxide ring of 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) was favored when the reaction was carried out with the *N*-oxide of **2** rather than the free amine. For the hydrogenation, the *N*-oxide was prepared from pure **2** with hydrogen peroxide in methanol–water

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solution. Hydrogenation of the resulting *N*-oxide under 3 atm of hydrogen in methanol for 22 h in the presence of 5% Pd–C and sodium bicarbonate gave, in 22% yield, a 4:1 mixture of 10-*epi*-erythromycin B (**3**) and erythromycin B (**4d**), based on recovered epoxy ketone **2**. Since catalytic hydrogenation of the epoxy ketone **2** to the hydroxy ketones **3** and **4d** must occur with retention at C_{11}, isolation of erythromycin B (**4d**) established the configuration at C_{11} for both the epoxy ketone **2** and 10-*epi*-erythromycin B (**3**). In addition, since *m*-chloroperbenzoic acid epoxidations of olefins, in contrast to alkaline hydrogen peroxide epoxidations, are known to occur with stereospecific cis addition of oxygen to the double bond,[7] the configuration of the epoxy ketone **2** could be assigned.

Examination of Prentiss–Hall molecular models showed that 10-*epi*-erythromycin B (**3**) would have a 1,3-diaxial interaction between the C_{10} and C_{12} methyl groups if the conformation of its lactone ring were identical with that of erythromycin B (**4d**).[4] This interaction may be readily relieved by rotations about the C_{10}–C_{11} and C_{11}–C_{12} bonds, which place the C_{10} and C_{12} methyl groups in a 1,3-gauche relationship with the C_{12} methyl group in an equatorial orientation and the C_{10} methyl group in an axial orientation. In the resulting conformation, the conformation of the C_2–C_8 segment of the lactone ring remains the same as that of erythromycin B. The change in conformation of the C_{10}–C_{13} segment should also be favored, since the C_{11} hydroxyl group is closer to the C_6 hydroxyl group than is the case for erythromycin B and should thus result in a stronger intramolecular hydrogen bond. The dihedral angles between the H_{10} and H_{11} protons and the H_{11} and H_{12} protons of 10-*epi*-erythromycin B appear to be about 140–150°. The observed coupling constants of 10-*epi*-erythromycin B ($J_{10,11} = J_{11,12} = 6$ Hz) are compatible with the values ($J^{140} = 5.3$ and $J^{150} = 6.8$ Hz) calculated from the original Karplus equation.[8] The contrast between the above values and the corresponding coupling constants ($J_{10,11} = 1$ and $J_{11,12} = 9.8$ Hz)[2a] of erythromycin B, which has dihedral angles of about 90 and 180°, respectively, is consistent with the structure and conformation of 10-*epi*-erythromycin B.

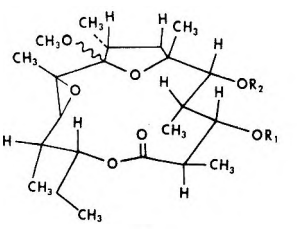
In our hands, attempted C_{10} epimerization of **3** with potassium carbonate in methanol gave only 10,11-anhydroerythromycin B (**1b**). Presumably the difference between the nature of the reactions of **3** and the 3,5-acetonide derivative (**7**) of 10-*epi*-erythronolide B described by Corey et. al.[3] is a consequence of the difference in lactone ring strain imposed by the different C_3 and C_5 substituents of **3** and **7**.

An attempt to convert the epoxy ketone **2** to 10-*epi*-erythromycin B (**3**) with chromous acetate gave only 10,11-anhydroerythromycin B (**1b**).

When the catalytic hydrogenation of the *N*-oxide of **2** was attempted with a sample which had not been rigorously freed of chloroform introduced during its isolation, the product obtained was the 6,9ξ-methyl acetal **9**. Formation of **9** from **2** is believed to be a consequence of the generation of hydrogen chloride under the hydrogenation conditions[9] from the chloroform present in the *N*-oxide. The 6,9ξ-methyl acetal **9** was readily converted to the epoxy ketone **2** on treatment with 1:1 (v/v) acetic acid–water solution.

Sodium borohydride reduction of **2** gave a mixture of the C_9 epimeric alcohols **10** and **11**, which were separated by chromatography, but were not distinguished structurally.

Sodium borohydride reduction of 10,11-anhydroerythromycin B (**1b**) gave the allylic alcohol **12**. Epoxidation of **12** with *m*-chloroperbenzoic acid in a sodium bicarbonate buffered chloroform–water system, followed by catalytic reduction of the *N*-oxide product to the free amine, gave a 10:1 mixture of the 10,11-epoxy alcohol **13** and the 6,10-epoxy alcohol **14**, which were separated chromatographically. The epoxy alcohol **13** was assigned the 10(*R*),11(*R*) stereochemistry, since it



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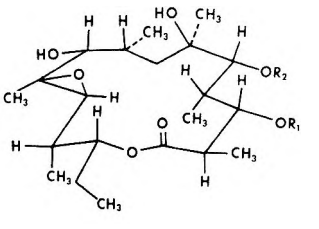

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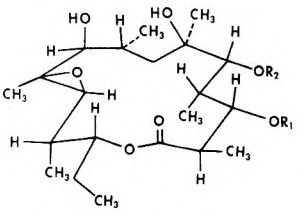

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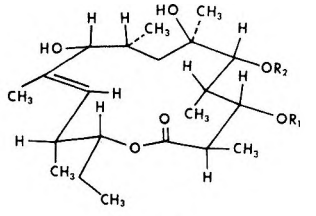
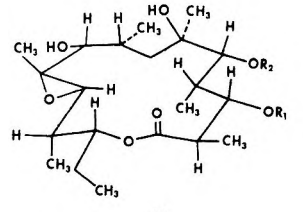


12

differed from the C_9 epimeric 10(*S*),11(*S*)-epoxy alcohols **10** and **11**.

The contrast in the stereochemistry of the epoxidations of the allylic alcohol **12** and the α,β-unsaturated ketone **1b** suggests a directing effect of the C_9 hydroxyl group of **12**, which results in epoxidation cis to the C_9 hydroxyl.[10] This consideration together with the 10(*R*),11(*R*) stereochemistry of the epoxy alcohol **13** led to the assignments of the 9(*R*) configurations to the allylic alcohol **12** and to both of the derived epoxy alcohols **13** and **14**.



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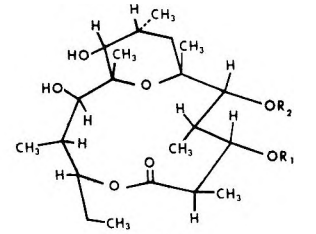

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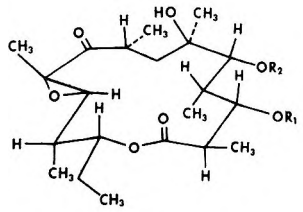

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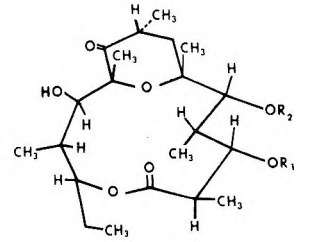


16a

An attempt to open the 10,11-epoxide ring of **13** with sodium azide in dimethylformamide in the presence of boric acid[11] led instead to quantitative rearrangement to the 6,10-epoxide **14**. The same product, **14**, was formed on treatment of the 10,11-epoxy alcohol **13** with 1:1 (v/v) acetic acid–water at room temperature. The latter rearrangement was shown by thin-layer chromatography to be complete within 0.5 h. In contrast, the diastereomeric epoxy alcohols **10** and **11** appeared to be stable for 24 h in 1:1 (v/v) acetic acid–water solution.

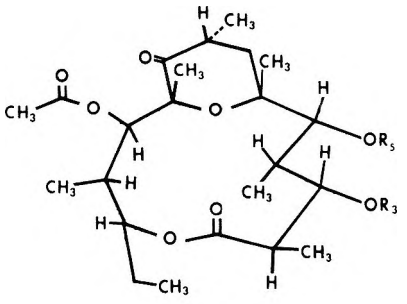
The facile acid-catalyzed rearrangement of the 10,11-epoxy alcohol **13** to the 6,10-epoxide **14** is compatible with backside attack of the C_6 hydroxyl group of **13** at C_{10} of the 10,11-epoxide ring. This rearrangement thus confirms the stereochemical assignment of the epoxide ring of **13**, and thus the stereochemical assignment of the diastereomeric epoxy alcohols **10** and **11** and the epoxy ketone **6** from which the latter two alcohols are derived.

An attempt to oxidize the 10(*R*),11(*R*)-epoxy alcohol **13** to the 10(*S*),11(*R*)-epoxy ketone **15** with Jones reagent gave instead 6,10(*S*)-epoxy-11-*epi*-erythromycin B (**16a**). The same

product was formed by Jones oxidation of the 6,10-epoxide **14**, and it seems likely that formation of **15** from the 10,11-epoxy alcohol **13** occurs via initial acid-catalyzed rearrangement of **13** to **14** under the acidic Jones conditions. In contrast to the behavior of **13**, Jones oxidation of both the diastereomeric epoxy alcohols **10** and **11** regenerated the epoxy ketone **2**.

Our assignment of structure to the oxidation product **16a** as the C_9 rather than the C_{11} ketone is based on our assumption that the internally directed axial C_{11} proton of **14** would be hindered to attack by base in an intermediate 11-*O*-chromate ester. Preferential oxidation of axial over equatorial steroid alcohols has been similarly attributed to steric hindrance of axial protons, since the rate-determining step for chromic acid oxidation of alcohols is normally attack by base on the geminal proton of intermediate chromate esters.[12]

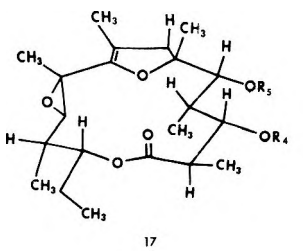
The ketone **16a** was converted into the 11,2′,4″-tri-*O*-acetyl derivative **16b** with acetic anhydride in pyridine. The latter,



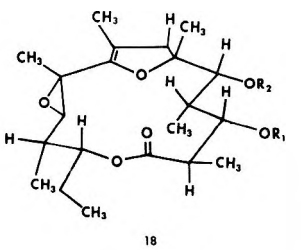
16b

16b, showed the absence of hydroxyl absorption in the infrared. Comparison of the NMR absorptions of the C_{11} protons of **16a** and **16b** (δ 4.03 and 5.20, respectively) showed that the expected paramagnetic shift on acetylation of the C_{11} hydroxyl group occurred. In addition, the C_{11} proton absorptions of both **16a** and **16b** appeared as slightly broadened singlets ($W_{1/2}$ = 3 and 2 Hz, respectively) which were compatible with the coupling constants $J_{11,12} \simeq 0$, which was expected since models indicated the dihedral angles between the C_{11} and C_{12} protons of **16a** and **16b** to be ~90°.

An attempt to convert the epoxy alcohol **13** to the epoxy ketone **15** by the Albright–Goldman modification of the Moffatt oxidation gave the 2′-*O*-acetyl-4″-oxoepoxy enol ether **17**, which was converted to the epoxy enol ether **18** by methanolysis of the 2′-*O*-acetyl group and sodium borohydride reduction[13] of the 4″-oxo group of **17**. The epoxy enol



17



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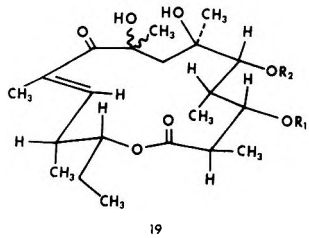

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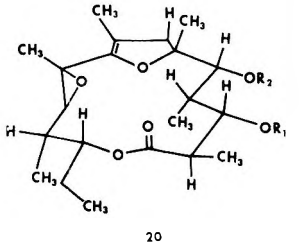

20

ether is most likely formed from the desired epoxy ketone **15** under the Albright–Goldman conditions. Enol ether formation from **15** contrasts with the behavior of erythromycin B (**4d**) under the Albright–Goldman conditions, which yields 2′-*O*-acetyl-4″-oxo-11-*O*-methylthiomethylerythromycin B[14] rather than the corresponding 8,9-anhydro 6,9-hemiacetal.

An attempt to convert the epoxy enol ether **18** to the epoxy ketone **15** by hydration of the enol ether double bond in 1:1 (v/v) acetic acid–water gave a mixture from which the major product was isolated with difficulty by chromatography. Spectral properties (IR, NMR) suggested that this material was one of the C_8 epimeric 8-hydorxy-10,11-anhydroerythromycins (**19**). Formation of the latter (**19**) from **18** may be formulated as shown in Scheme I.

An attempt to form the enol ether **20** from the epoxy ketone **2** under conditions which readily convert both erythromycin A and erythromycin B to their corresponding enol ethers (glacial acetic acid, 4 h, room temperature)[15] gave predominantly recovered starting material (~75%), while after 24 h extensive decomposition had occurred, leading to a multicomponent mixture. Under Albright–Goldman conditions **2** gave an intractable mixture. An examination of molecular models showed that the enol ether **20** would have a severe steric interaction between the C_8 and C_{10} methyl groups. No such interaction is present either in the diastereomeric enol ether **18** formed by Albright–Goldman oxidation of the epoxy alcohol **13**, or in either of the two possible C_9 epimers of the 9 ξ-methyl acetal **9** formed from the epoxy ketone **2** under the hydrochloric acid generating hydrogenation conditions.

The in vitro antibacterial activities of compounds **4c**, **4b**, **1b**, **2**, **3**, **10–14**, **16a**, **18**, and **19** are shown in Table I together with those of erythromycin A (**4c**), erythromycin B (**4d**), and the 9-dihydroerythromycins A and B (**21** and **22**). Although none of the derivatives reported have activities approaching those of the naturally occurring antibiotics **4c** and **4d**, it is of interest that both of the C_9 epimeric 9-dihydro-10(*S*),-11(*S*)-epoxy ketones **10** and **11** are much more active than the 10(*S*),11(*S*)-epoxy ketone **2** from which they were prepared. This contrasts with the greatly reduced activities of the 9-dihydroerythromycins A and B (**21** and **22**) compared with the parent antibiotics **4c** and **4d**. In addition, it may be noted that both of the C_9 epimeric 9-dihydro-10(*S*),11(*S*)-epoxyerythromycins (**10** and **11**) are much more active than the diastereomeric 9(*R*)-dihydro-10(*R*),11(*R*)- epoxyerythromycin (**13**). The importance of the stereochemistry of the erythromycin lactone rings is dramatically illustrated by the observation that 10-*epi*-erythromycin B (**3**), like 8-*epi*-erythromycin B reported previously,[2a] has greatly reduced antibacterial activity.

Experimental Section

The purity of all compounds was established spectroscopically and by TLC.[16] All compounds reported were characterized by M^+ peaks in their mass spectra. Optical rotations were determined with a Hilger and Watts polarimeter. IR spectra were obtained on deuteriochloroform solutions using a Perkin-Elmer Model 521 grating spectrometer. NMR spectra were determined at 100 MHz with a Varian HA-100 spectrometer with deuteriochloroform solutions. Chemicals shifts are reported in parts per million from internal tetramethylsilane (δ 0) and coupling constants are reported in hertz. Partition column chromatographies were carried out by the method of Oleinick and Corcoran[17] using silica gel (Merck, Darmstadt).

10,11-Anhydro-10(*R*),11(*S*)-epoxyerythromycin B (2). A. To a magnetically stirred solution of 8.0 g of 10,11-anhydroerythromycin B (**1b**) in 160 mL of CH_2Cl_2 was added, portionwise, 8.0 g of *m*-chloroperbenzoic acid. After the addition was complete, stirring was continued at room temperature for 25 h. The product was isolated by CH_2Cl_2 extraction. The CH_2Cl_2 was evaporated under reduced pressure and residual CH_2Cl_2 was removed by codistillation with CH_3OH under reduced pressure, leaving the *N*-oxide (8.4 g) of 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) as a light yellow foam.

Scheme I

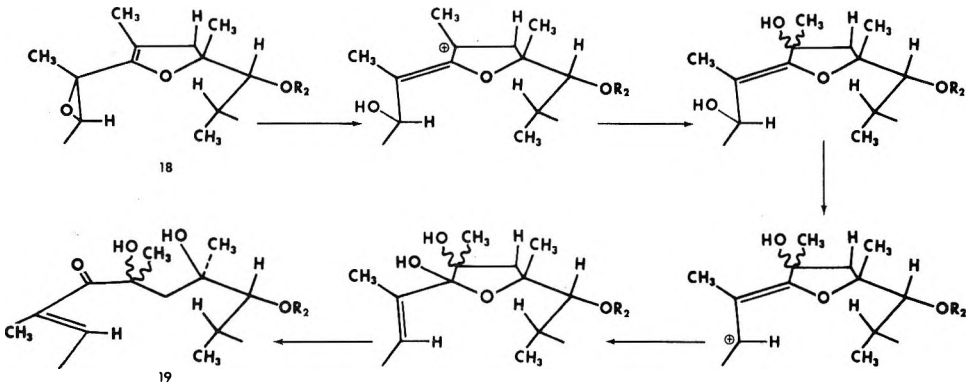

Table I. Antibacterial Activity of Selected Erythromycins

Structure	*Staphylococcus aureus* 9144	Minimum inhibitory concentration, mcg/mL[a]					
		Staphylococcus aureus Smith ER	*Streptococcus faecalis* 10541	*Klebsiella pneumoniae* 10031	*Shigella sonnei* 9290	*Haemophilus influenzae* 9334	*Mycoplasma pneumoniae* FH
4c	0.2	>100	0.05	3.1	12.5	1.56	0.05
4d	0.39	>100	0.05	6.2	25	3.1	0.1
1b	6.2	>100	1.56	25	>100		
2	6.2	>100	1.56	12.5	>100	50	0.25
3	3.1	>100	1.56	25	>100		
10	3.1	>100	0.39	3.1	50	12.5	0.5
11	1.56	>100	0.39	6.2	25	12.5	0.25
12	>100	>100	50	25	>100	>100	5.0
13	>100	>100	>100	>100	>100	>100	5.0
14	>100	>100	100	>100	>100	>100	5.0
16a	50	>100	50	>100	>100	>100	50.0
18	25	>100	1.56	100	>100	>100	10
19	6.2	>100	3.1	12.5	>100		
21	3.1	>100	0.2	12.5		25	0.5
22	3.1	>100	0.39	12.5		50	1.0

[a] Determined by an agar dilution method using brain heart infusion medium.

A portion (4.1 g) of the product thus obtained was hydrogenated under 3 atm of hydrogen for 2 h in 250 mL of C_2H_5OH in the presence of 1.25 g of 5% Pd–C to yield 3.6 g of the free amine **2**. Partition column chromatography of 2.6 g of the free amine gave 1.25 g of colorless glass. Crystallization from ethyl acetate–hexane gave 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) as prisms: mp 126.5–129 °C; $[\alpha]^{22}_D$ −36.4° (*c* 1.01, CH_3OH); IR 3610, 3510, 1727, and 1702 cm^{-1}; NMR δ 1.61 (C_6Me), 2.29 (NMe_2), 2.99 ($C_{11}H$, $J_{11,12}$ = 10.0 Hz), 3.30 (OMe), 4.50 ($C_1'H$), 4.96 ($C_1''H$), 5.18 ($C_{13}H$); M^+ 715.4512, calcd for $C_{37}H_{65}NO_{12}$ 715.4506.

Anal. Calcd for $C_{37}H_{65}NO_{12}$: C, 62.07; H, 9.15; N, 1.95. Found: C, 61.97; H, 9.36; N, 1.90.

B. To a solution prepared from 2.0 g of 10,11-anhydroerythromycin B (**1b**), 0.57 g of NaOH, and 80 mL of CH_3OH, cooled in an ice bath, was added 12 mL of 30% aqueous H_2O_2. The resulting solution was stirred at 4 °C for 1 h and then overnight at room temperature. The major portion of the CH_3OH was evaporated under reduced pressure and the product was isolated by $CHCl_3$ extraction. The $CHCl_3$ extract was dried ($MgSO_4$) and the $CHCl_3$ was evaporated under reduced pressure, leaving 1.55 g of *N*-oxide. The catalytic reduction of the *N*-oxide to the free amine was carried out in C_2H_5OH under 3 atm of hydrogen in the presence of 5% Pd–C to yield 1.26 g of free amine. Partition column chromatography of the product gave 0.50 g of 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) identical with that prepared as described above.

9(*R*)-Dihydro-10,11-anhydro-10(*S*),11(*S*)-epoxyerythromycin B (10) and 9(*S*)-Dihydro-10,11-anhydro-10(*S*),11(*S*)-epoxyerythromycin B (11). To a stirred solution of 6.2 g of 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) in 124 mL of CH_3OH, cooled to −10 °C in a salt–ice bath, was added a freshly prepared solution of 4.0 g of $NaBH_4$ in 11 mL of water over a period of 20 min. Stirring was then continued at −10 °C for 4 h. The product was isolated by $CHCl_3$ extraction. The $CHCl_3$ extract was dried ($MgSO_4$) and the $CHCl_3$ was evaporated under reduced pressure, leaving 6.5 g of product as a glass. Partition column chromatography gave the pure epoxy alcohols **10** and **11**. The minor product (0.81 g) was eluted first. Crystallization from methanol–water gave the analytical sample: mp 182.5–183.5 °C; $[\alpha]^{23}_D$ −53.2° (*c* 1.0, CH_3OH); IR 3380 and 1725 cm^{-1}; NMR δ 2.28 (NMe_2), 3.32 (OMe), 3.40 ($C_{11}H$, $J_{11,12}$ = 10.0 Hz), 3.70 (C_9H, $J_{8,9}$ = 3.0 Hz), 4.44 ($C_1'H$), 4.94 ($C_1''H$), 5.22 ($C_{13}H$); M^+ 717.4614, calcd for $C_{37}H_{67}NO_{12}$ 717.4663.

Anal. Calcd for $C_{37}H_{67}NO_{12}$: C, 61.90; H, 9.40; N, 1.95. Found: C, 61.08; H, 9.55; N, 2.04.

The major product (3.6 g) was eluted in subsequent fractions and isolated as a glass: $[\alpha]^{23}_D$ −53.7° (*c* 1.0, CH_3OH); IR 3603, 3500, and 1727 cm^{-1}; NMR δ 2.28 (NMe_2), 3.08 ($C_{11}H$, $J_{11,12}$ = 10.0 Hz), 3.32 (OMe), 3.66 (C_9H, $J_{8,9}$ = 3.0 Hz), 4.44 ($C_1'H$), 4.91 ($C_1''H$), 5.14 ($C_{13}H$); M^+ 717.4651, calcd for $C_{37}H_{67}NO_{12}$ 717.4663.

Anal. Calcd for $C_{37}H_{67}NO_{12}$: C, 61.90; H, 9.40; N, 1.95. Found: C, 61.56; H, 9.43; N, 1.70.

9(*R*)-Dihydro-10,11-anhydroerythromycin B (12). To a stirred solution of 5.0 g of 10,11-anhydroerythromycin B (**1b**) in 100 mL of CH_3OH, cooled to −8 °C in a salt–ice bath, was added a freshly prepared solution of 3.3 g of $NaBH_4$ in 10 mL of water over a period of 10 min. After the addition was complete, stirring was continued in the cold for 4 h, and 3 mL of acetone was then added. The product was isolated by $CHCl_3$ extraction. The $CHCl_3$ extract was dried ($MgSO_4$) and the $CHCl_3$ was evaporated under reduced pressure, leaving 5.37 g of colorless foam. Partition column chromatography of 2.37 g of the product thus obtained gave 1.8 g of pure 9(*R*)-dihydro-10,11-anhydroerythromycin B (**12**) as a colorless glass: $[\alpha]^{22}_D$ −53.8° (*c* 1.0, CH_3OH); IR 3605, 3430, and 1718 cm^{-1}; NMR δ 1.60 ($C_{10}Me$), 2.32 (NMe_2), 3.29 (OMe), 3.54 (C_9H, $J_{8,9}$ = 3.0 Hz), 4.50 ($C_1'H$), 4.74 ($C_1''H$), 4.82 ($C_{13}H$), 5.46 ($C_{11}H$, $J_{11,12}$ = 10.0 Hz); M^+ 701.4689, calcd for $C_{37}H_{67}NO_{11}$ 701.4714.

Anal. Calcd for $C_{37}H_{67}NO_{11}$: C, 63.31; H, 9.62; N, 1.99. Found: C, 61.78; H, 9.67; N, 1.83.

9(*R*)-Dihydro-10,11-anhydro-10(*R*),11(*R*)-epoxyerythromycin B (13). A. To a vigorously stirred mixture of 7.5 g of 9(*R*)-dihydro-10,11-anhydroerythromycin B (**12**) in 190 mL of $CHCl_3$ and 300 mL of 5% $NaHCO_3$ was added, dropwise, a freshly prepared solution of 7.7 g of *m*-chloroperbenzoic acid in 90 mL of $CHCl_3$ over a period

of 1 h. After the addition was complete, stirring was continued for 20 h. To the resulting stirred mixture was added dropwise a solution of 22 mL of cyclohexene in 75 mL of $CHCl_3$ over a period of 1.5 h. After the addition was complete stirring was continued at room temperature for 3 h. The product was isolated by $CHCl_3$ extraction. Evaporation of the $CHCl_3$ from the $CHCl_3$ extract under reduced pressure left 8.0 g of an *N*-oxide as a white glass.

Catalytic reduction of 4.09 g of the *N*-oxide in 250 mL of C_2H_5OH for 2 h under 3 atm of hydrogen in the presence of 1.4 g of 5% Pd–C yielded 3.91 g of free amine. This product (3.82 g) was chromatographed on a partition column. Early fractions contained 705 mg of a less polar product.

Further elution gave 2.16 g of a two-component mixture which upon chromatography on Sephadex LH20 in $CHCl_3$–hexane 1:1 (v/v) gave, in the initial fractions, 1.64 g of 9(*R*)-dihydro-10,11-anhydro-10(*R*),11(*R*)-epoxyerythromycin B (**13**): $[\alpha]^{23}_D$ −60.6° (*c* 1.0, CH_3OH); IR 3545, 3420, and 1721 cm^{-1}; NMR δ 2.36 (NMe_2), 3.36 (OMe), 3.53 ($C_{11}H$, $J_{11,12}$ = 2.0 Hz), 3.64 (C_9H, $J_{8,9}$ = 2.5 Hz), 4.41 ($C_{1'}H$), 4.70 ($C_{13}H$), 4.79 ($C_{1''}H$); M^+ 717.4644, calcd for $C_{37}H_{67}NO_{12}$ 717.4663.

Anal. Calcd for $C_{37}H_{67}NO_{12}$: C, 61.90; H, 9.40; N, 1.95. Found: C, 59.54; H, 9.37; N, 1.68.

Subsequent fractions contained 0.24 g of 9(*R*)-dihydro-6,10(*R*)-epoxy-11-*epi*-erythromycin B (**14**), identical with that prepared from 9(*R*)-dihydro-10,11-anhydro-10-(*R*),11(*R*)-epoxyerythromycin B (**13**) as described below.

9(*R*)-Dihydro-6,10(*R*)-epoxy-11-*epi*-erythromycin B (14). A. A solution prepared from 1.51 g of 9(*R*)-dihydro-10,11-anhydro-10(*R*),11(*R*)-epoxyerythromycin B (**13**), 25 mL of glacial acetic acid, and 25 mL of water was allowed to stand at room temperature for 1 h. The resulting solution was carefully added to a solution of 22.5 g of Na_2CO_3 in 225 mL of water with vigorous stirring. After the addition was complete, water (200 mL) was added followed by excess solid $NaHCO_3$. The product was isolated by $CHCl_3$ extraction. Evaporation of the $CHCl_3$ from the $CHCl_3$ extract under reduced pressure left 1.54 g of pale yellow glass. Partition column chromatography of the product gave 0.67 g of colorless foam. Crystallization from CH_3OH–water gave an analytical sample of 9(*R*)-dihydro-6,10(*R*)-epoxy-11-*epi*-erythromycin B (**14**): mp 266–268 °C; $[\alpha]^{24}_D$ −41.6° (*c* 1.0, CH_3OH); IR 3600, 3570, 3450, and 1722 cm^{-1}; NMR δ 1.46 (C_6Me), 2.29 (NMe_2), 3.33 (OMe), 3.39 (C_9H, $J_{8,9}$ = 2.0 Hz), 4.25 ($C_{11}H$, $J_{11,12}$ = 1.0 Hz), 4.51 ($C_{1'}H$), 4.72 ($C_{13}H$), 4.84 ($C_{1''}H$); M^+ 717.4644, calcd for $C_{37}H_{67}NO_{12}$ 717.4663.

Anal. Calcd for $C_{37}H_{67}NO_{12}$: C, 61.90; H, 9.41; C, 1.95. Found: C, 61.64; H, 9.79; N, 1.85.

B. A mixture prepared from 103 mg of **13**, 101 mg of NaN_3, 109 mg of H_3BO_3, and 2 mL of DMF was stirred at room temperature for 23 h. The product was isolated by $CHCl_3$ extraction, and residual DMF was removed by codistillation with benzene to yield 103 mg of **14** as a white glass, identical in all respects with that described above.

6,10(*S*)-Epoxy-11-*epi*-erythromycin B (16a). A. From 9(*R*)-Dihydro-10,11-anhydro-10(*R*),11(*R*)-epoxyerythromycin B (13). To a stirred solution of 2.0 g of **13** in 250 mL of acetone, cooled to −8 °C, was added 1.52 mL of Jones reagent. Stirring was continued at −8 °C for 3 min, after which time 5 mL of CH_3OH was added. The resulting solution was poured into 1.5 L of 5% aqueous $NaHCO_3$. The aqueous solution was extracted with $CHCl_3$ and the $CHCl_3$ extract was washed with water and dried ($MgSO_4$). Evaporation of the $CHCl_3$ under reduced pressure left 1.6 g of yellow foam. Partition column chromatography of this material gave 0.68 g of **16a**. An analytical sample was prepared by chromatography on Sephadex LH20 in $CHCl_3$–hexane 1:1 (v/v) followed by crystallization from ether: mp 169.5–170.5 °C; $[\alpha]^{23}_D$ −37.4° (*c* 1.0, CH_3OH); IR 3560, 3450, and 1726 cm^{-1}; NMR δ 1.67 (C_6Me), 2.29 (NMe_2), 3.33 (C_4H), 3.35 (OMe), 4.01 ($C_{11}H$, $W_{1/2}$ = 3 Hz, $J_{11,12}$ = 0 Hz), 4.56 ($C_{1'}H$), 4.69 ($C_{13}H$), 4.80 ($C_{1''}H$). M^+ 715.4488, calcd for $C_{37}H_{65}NO_{12}$ 715.4507.

Anal. Calcd for $C_{37}H_{65}NO_{12}$: C, 62.07; H, 9.15; N, 1.96. Found: C, 61.71; H, 9.28; N, 1.79.

B. From 9(*R*)-Dihydro-6,10(*R*)-epoxy-11-*epi*-erythromycin B (14). To a stirred solution of 1.45 g of **14** in 230 mL of acetone, cooled to −8 °C, was added 1.05 mL of Jones reagent. Stirring was continued at −8 °C for 6 min and then 10 mL of CH_3OH was added. The product (1.14 g) was isolated as described in part A above. Partition column chromatography of this material gave 0.85 g of **16a** in about 80% purity (TLC). Chromatography of 0.34 g of this material on Sephadex LH20 in $CHCl_3$–hexane 1:1 (v/v) gave 0.27 g of pure **16a**, identical with that described above.

11,2′,4″-Tri-*O*-Acetyl-6,10(*S*)-epoxy-11-*epi*-erythromycin B (16b). A solution prepared from 235 mg of 6,10(*S*)-epoxy-11-*epi*-erythromycin B (**16a**), 6 mL of pyridine, and 1 mL of acetic anhydride was kept at room temperature for 15 days. The product (256 mg of orange glass) was isolated by $CHCl_3$ extraction, but TLC and NMR showed the acetylation was incomplete. The recovered material was treated with 1 mL of acetic anhydride in 6 mL of pyridine at 50 °C for 43 h. Isolation of the product by $CHCl_3$ extraction gave 241 mg of 11,2′,4″-tri-*O*-acetyl-6,10(*S*)-epoxy-11-*epi*-erythromycin B (**16b**) as an orange glass: IR 1722 cm^{-1}; NMR δ 2.29 (NMe_2), 3.36 (OCH_3), 2.06, 1.96 (CH_3CO), 5.20 ($C_{11}H$, $W_{1/2}$ = 2 Hz, $J_{11,12}$ = 0 Hz); M^+ 841.4829, calcd for $C_{43}H_{71}NO_{15}$ 841.4824.

8,9:10,11-Dianhydro-10(*S*),11(*R*)-epoxyerythromycin B 6,9-Hemiacetal (18). A solution prepared from 2.31 g of 9(*R*)-dihydro-10,11-anhydro-10(*R*),11(*R*)-epoxyerythromycin B (**13**), 16 mL of acetic anhydride, and 23 mL of dimethyl sulfoxide was allowed to stand at room temperature for 20.5 h. The resulting solution was added dropwise, by pipet, to a suspension of 8 g of Na_2CO_3 in 80 mL of water. After the addition was complete, 80 mL of water was added, followed by careful addition of excess solid $NaHCO_3$. The product was isolated by $CHCl_3$ extraction. The $CHCl_3$ was evaporated from the $CHCl_3$ extract under reduced pressure. Residual dimethyl sulfoxide was removed by codistillation with benzene under reduced pressure. The residue [2′-*O*-acetyl-4″-oxo-8,9:10,11-dianhydro-10(*S*),11(*R*)-epoxyerythromycin B 6,9-hemiacetal (**17**)] was allowed to stand for 23 h in a solution prepared from 70 mL of CH_3OH and 7 mL of 5% aqueous $NaHCO_3$. The product, 2.23 g of 4″-oxo-8,9:10,11-dianhydro-10(*S*),11(*R*)-epoxyerythromycin B 6,9-hemiacetal, was isolated by $CHCl_3$ extraction in the usual manner.

To a solution of 2.18 g of the product thus obtained in 46 mL of CH_3OH, cooled in an ice bath, was added a freshly prepared solution of 1.4 g of $NaBH_4$ in 5 mL of water. Stirring was continued at 0 °C for 4 h. The product was isolated by $CHCl_3$ extraction in the usual manner. Evaporation of the $CHCl_3$ from the $CHCl_3$ extract gave 2.29 g of white foam. A sample (2.0 g) of product prepared in this manner was chromatographed on a silica gel column prepared by benzene and eluted with increasing amounts of acetone in benzene to yield 0.985 g of 8,9:10,11-dianhydro-10(*S*),11(*R*)-epoxyerythromycin B 6,9-hemiacetal (**18**): $[\alpha]^{25}_D$ −78.4° (*c* 0.94, CH_3OH); IR 3550, 3450, and 1726 cm^{-1}; NMR δ 1.68 (C_6Me), 2.49 (NMe_2), 3.01 ($C_{4''}H$, $J_{4,5}$ = 9.0 Hz), 3.32 (OMe), 4.42 ($C_{1'}H$), 4.82 ($C_{13}H$), 5.29 ($C_{1''}H$); M^+ 697.4394, calcd for $C_{37}H_{63}NO_{11}$ 697.4401.

Anal. Calcd for $C_{37}H_{63}NO_{11}$: C, 63.68; H, 9.10; N, 2.01. Found: C, 63.61; H, 9.39; N, 1.87.

Treatment of 8,9:10,11-Dianhydro-10(*S*),11(*R*)-epoxyerythromycin B (18) with 1:1 (v/v) Acetic Acid–Water. A solution prepared from 2.2 g of **18**, 36 mL of glacial acetic acid, and 36 mL of water was allowed to stand at room temperature for 0.5 h. The resulting solution was added dropwise to a stirred solution of 36 g of Na_2CO_3 in 360 mL of water. Water (60 mL) was added, and the product was isolated by $CHCl_3$ extraction. Evaporation of the $CHCl_3$ from the $CHCl_3$ extract under reduced pressure left 2.2 g of white glass. Partition column chromatography of 0.97 g of this material gave 0.45 g of a two-component mixture in a ratio of about 3:1 as estimated from TLC. A purified sample of the major component, **19**, taken from the earlier fractions, had the following spectral characteristics: $[\alpha]^{25}_D$ −54.2° (*c* 1.05, CH_3OH); IR 3420, 1719, and 1648 cm^{-1}; NMR δ 1.60 (C_6Me), 1.86 ($C_{10}Me$), 2.29 (NMe_2), 3.27 (OMe), 4.37 ($C_{1'}H$), 4.77 ($C_{1''}H$), 4.85 ($C_{13}H$), 6.16 ($C_{11}H$, $J_{11,12}$ = 10.0 Hz); M^+ 715.4513, calcd for $C_{37}H_{65}NO_{12}$ 715.4507.

Anal. Calcd for $C_{37}H_{65}NO_{12}$: C, 62.07; h, 9.15; N, 1.96. Found: C, 61.27; H, 9.30; N. 1.89.

Chromous Acetate Reduction of 10,11 Anhydro-10(*R*),-11(*S*)-epoxyerythromycin B (2). A mixture of 0.79 g of **2**, 2.4 g of freshly prepared chromous acetate, and 60 mL of ethanol was stirred under nitrogen for 42 h. Insoluble material was removed by filtration through a Celite mat. Evaporation of the C_2H_5OH from the filtrate under reduced pressure left a deep blue glass. The product was shaken with a mixture of 5% aqueous $NaHCO_3$ and $CHCl_3$ (severe emulsions developed which were broken with difficulty). The $CHCl_3$ extract was washed with water and the $CHCl_3$ was evaporated under reduced pressure.

Partition column chromatography of the product gave in the early fractions 0.36 g of 10,11-anhydroerythromycin B (**16**). Subsequent fractions yielded 0.24 g of 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**).

The *N*-Oxide of 10,11-Anhydro-10(*R*),11(*S*)-epoxyerythromycin B (2). To a magnetically stirred solution of 324 mg of pure **2**, 7.64 mL of CH_3OH, and 6.18 mL of water was added 1.85 mL of 30% H_2O_2. Stirring was continued for 22 h at room temperature. The resulting solution was shaken with a mixture of 50 mL of 5% aqueous $NaHCO_3$ and 30 mL of $CHCl_3$. The $CHCl_3$ solution was separated, washed with water, and dried ($MgSO_4$). Evaporation of the $CHCl_3$

left 319 mg of the *N*-oxide of **2**: NMR δ 1.42 (C_6Me), 3.20 ($NMe_2 \rightarrow O$), 3.35 (OMe), 4.96 ($C_{1'}H$), 5.18 ($C_{13}H$).

Conversion of 10-*epi*-Erythromycin B (3) to 10,11-Anhydroerythromycin B (1b). A solution of 86 mg of 10-*epi*-erythromycin B (**3**) in 17 mL of a saturated methanolic K_2CO_3 solution was heated at 43 °C for 1.25 h. The product, 58 mg of 10,11-anhydroerythromycin B (**1b**), was isolated by $CHCl_3$ extraction and identified by NMR and TLC comparisons with an authentic sample of **1b**.

10-*epi*-Erythromycin B (3). Chloroform was removed from a sample (1.8 g) of the *N*-oxide of 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) by repeated codistillation under reduced pressure with CH_3OH. The product thus obtained was hydrogenated in 250 mL of CH_3OH for 22 h under 3 atm of hydrogen in the presence of 110 mg of $NaHCO_3$ and 2.7 g of 5% Pd–C. After removal of the catalyst by filtration, the major portion of the CH_3OH was evaporated under reduced pressure. The residue was shaken with a mixture of 250 mL of 5% $NaHCO_3$ and 200 mL of $CHCl_3$. The $CHCl_3$ solution was washed with three 125-mL portions of water. The aqueous solutions were washed in series with two 100-mL portions of $CHCl_3$. The $CHCl_3$ solutions were combined and dried ($MgSO_4$). Evaporation of the $CHCl_3$ under reduced pressure left 1.35 g of product. Partition column chromatography of this material gave 306 mg (17%) of 10,11 anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) and 328 mg (22% based on recovered **2**) of a 4:1 mixture of 10-*epi*-erythromycin B (**3**) and erythromycin B (**4d**) as estimated by TLC. Repeated chromatography of the latter mixture of **3** and **4d** on a Sephadex LH20 column in $CHCl_3$–hexane 1:1 (v/v) led to isolation of 16 mg of pure erythromycin B (**4d**), identified by comparison of its NMR spectrum and TLC behavior with an authentic sample, and 91 mg of pure 10-*epi*-erythromycin B (**3**): $[\alpha]^{25}_D$ −68.2° (c 1.0, CH_3OH); IR 3610, 3450, and 1713 cm^{-1}; λ_{max} 280 (ε 56); NMR δ 2.32 (NMe_2), 3.32 (OMe), 3.79 (C_5H, $J_{4,5}$ = 5.0 Hz), 3.86 ($C_{11}H$, $J_{10,11}$ = ~6 Hz, $J_{11,12}$ = ~6 Hz), 4.16 (C_3H) 4.57 ($C_{1'}H$, $J_{1',2'}$ = 7.2 Hz), 4.86 ($C_{1''}H$, $J_{1'',2a''}$ = 4.5 Hz, $J_{1'',2e''}$ = ~1 Hz), 5.09 ($C_{13}H$, $J_{12,13}$ = ~1 Hz); M^+ 717.4673, calcd for $C_{37}H_{67}NO_{12}$ 717.4663.

Anal. Calcd for $C_{37}H_{67}NO_{12}$: C, 61.90; H, 9.41; N, 1.95. Found: C, 61.09; H, 9.19; N, 1.93.

6,9ξ-Methyl Acetal (9) of 10,11-Anhydro-10(*R*),11(*S*)-epoxyerythromycin B (2). The $CHCl_3$ of a $CHCl_3$ solution of the *N*-oxide of 10,11-anhydro-10(*R*),11(*S*)-epoxyerythromycin B (**2**) was evaporated under reduced pressure and the residue was dried overnight at room temperature under high vacuum. A 0.293-g sample of the *N*-oxide thus obtained in 40 mL of CH_3OH was hydrogenated for 45 h under 3 atm of hydrogen in the presence of 441 mg of 5% Pd–C and 18.1 mg of $NaHCO_3$. After removal of the catalyst by filtration, the major portion of the CH_3OH was evaporated under reduced pressure. The residue was shaken with a mixture of 50 mL of 5% $NaHCO_3$ solution and 30 mL of $CHCl_3$. The $CHCl_3$ solution was separated and washed with three 35-mL portions of water. The aqueous solutions were washed in series with 30 mL of $CHCl_3$. The $CHCl_3$ solutions were combined and dried ($MgSO_4$). Evaporation of the $CHCl_3$ left 235 mg of the 6,9ξ-methyl acetal **9**: $[\alpha]^{24}_D$ −83° (c 1.0, CH_3OH); IR 3560 and 1726 cm^{-1}; NMR δ 1.57 (C_6Me), 2.29 (NMe_2), 3.30, 3.36 (OMe), 4.46 ($C_{1'}H$), 5.11 ($C_{13}H$), 5.25 ($C_{1''}H$); M^+ 729.4637, calcd for $C_{38}H_{67}NO_{12}$ 729.4663.

Anal. Calcd for $C_{38}H_{67}NO_{12}$: C, 62.53; H, 9.25; N, 1.92. Found: C, 61.92; H, 9.41; N, 1.91.

Conversion of the 6,9ξ-Methyl Acetal (9) to 10,11-Anhydro-10(*R*),11(*S*)-epoxyerythromycin B (2). A solution of 50 mg of **9** in 1.66 mL of 1:1 acetic acid–water solution was allowed to stand at room temperature for 3 h. The resulting solution was slowly added to a suspension of excess Na_2CO_3 in water. The resulting aqueous suspension was extracted with several portions of $CHCl_3$. The $CHCl_3$ solutions were washed with water, combined, and dried ($MgSO_4$). Evaporation of the $CHCl_3$ under reduced pressure left 51 mg of **2**, which was identified by comparison of its IR and NMR spectra and TLC behavior with those of an authentic sample.

Acknowledgments. The authors are indebted to Ms. R. Stanaszek and Mr. M. Cirovic for determining the NMR spectra and to Ms. S. Mueller for measuring the mass spectra. We wish to thank Dr. R. Girolami and Ms. C. Vojtko for determining antibacterial activities, Mr. W. Washburn for IR spectra, Mr. J. Leonard for many thin-layer chromatographies, Ms. J. Hood for microanalyses, and Dr. R. Egan for helpful discussions of NMR spectra and erythromycin lactone ring conformations. We wish to express our appreciation to Ms. Ginny Giovenco and Ms. Judy Fritz for typing the manuscript.

Registry No.—**1b**, 66101-01-7; **2**, 66027-58-5; **2** *N*-oxide, 66027-59-6; **3**, 66101-02-8; **4c**, 114-07-8; **4d**, 527-75-3; **9**, 66027-60-9; **10**, 66027-57-4; **11**, 66068-82-4; **12**, 66027-65-4; **13**, 66068-83-5; **13** *N*-oxide, 66027-61-0; **14**, 66027-62-1; **16a**, 66027-63-2; **16b**, 66027-55-2; **17**, 66027-54-1; **18**, 66027-56-3; **19**, 66027-64-3; **21**, 13200-64-1; **22**, 33442-49-8.

References and Notes

(1) The stereochemical relationships among the compounds reported are best illustrated with the conformational representations used here rather than with plane projections we have employed previously.[2] Such conformational representations have been used by Corey et al.[3] in the case of some related erythronolide B derivatives. However, a referee suggested that desirability of pointing out that, unless otherwise stated, the conformational representations of the new products reported here are based on the conformation of erythromycin B[4] and have not been determined experimentally. Since it has been shown[5] that the 14-membered lactone rings of a variety of 14-membered macrolides have approximately the same conformations, these conformational representations are probably reasonable approximations.

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Product Stereospecificity in the Microbial Reductions of Hydroaromatic Ketones

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A series of benzo-α-tetralone derivatives and related phenyl conjugated ketones were reduced by *Sporobolomycetes pararoseus*. The absolute stereochemistries of the alcohols obtained were determined as *S* by degradation to dimethyl (−)-α-acetoxyadipate and dimethyl (−)-α-acetoxyglutarate. Additional studies of the effects of substituents on the carbon atom α to the carbonyl and of ring size on the stereochemistries of the products are described. These results are discussed with reference to Prelog's suggestion that some enzymes exhibit "product stereospecificity".

Although considerable progress has been made in increasing the enantiomeric excesses obtained in the asymmetric reductions of ketones,[1] and in developing resolving agents that simplify the resolution of a series of alcohols, comparatively little work has been devoted to the use of microorganisms as reducing agents for the preparation of alcohols with a predictable absolute stereochemistry. If one could prepare optically active hydroaromatic alcohols of a predictable configuration, then studies similar to ones we have carried out on the absolute stereochemistry of a series of metabolites[2] (cis and trans dihydrodiols) would be greatly simplified. Our interest in metabolites of aromatic substrates prompted us to examine first the reduction of a series of α-tetralone derivatives. We wish to report on: (1) the absolute stereochemistry of the tetralols obtained in these microbiological reductions; (2) the effect on the reduction due to substituents on the methylene groups adjacent to the carbonyl in α-tetralone; (3) a solution to the problem of preparing the enantiomer of the alcohol formed in these reductions.

Prelog and his co-workers[3] have determined the stereochemistry of a series of aliphatic alcohols obtained by reduction of the corresponding ketones using a purified oxidoreductase isolated from *Curvularia falcata*. From these studies, Prelog formulated the rule shown in Figure 1 to account for the observed stereochemistry: if the ketone is placed with the larger group on the observer's left, the hydroxyl group formed is closer to the observer.

In addition, Prelog et al.[3a,b] investigated the effect of a variety of substituents on the cyclohexanone ring on the rate of reduction. Their analysis described the topological surface of the ternary complex formed by the enzyme, substrate, and coenzyme, in which the chair conformation of cyclohexanol formed the center of a polycyclohexane diamond-like arrangement (lattice) of carbon atoms. The hydrogen delivered during the reduction is that resulting from an equatorial approach.[3b] Prelog et al. and other groups noted that the effect of substituents at several positions varies from slightly decreasing the rate of reduction to completely stopping it. In the latter, substituents occupied what were called "forbidden positions".

The microbiological reductions of several hydroaromatic ketones have been previously reported. Cervinka and Hub[4] have described the reduction of α-tetralone in low yield (1.4%), to (+)-(1*S*)-tetralol (**1**), using *Saccharomyces cerevesiae*. Siewinski[5] reported in the reduction of several polycyclic aromatic ketones (precursors of **2** and **3**) using *Rhodotorula mucilaginosa*. However, while **2** was assigned a *S* configuration, consistent with Prelog's rule shown in Figure 1, Siewinski assigned **3** an *R* configuration, thus greatly complicating the projected use of these microbial reductions to prepare alcohols of a predictable stereochemistry. It is possible to rationalize the *R* configuration for **3** by assuming in this case that for steric considerations the enzyme treats the methylene adjacent to the carbonyl as relatively larger than the aromatic group. However, estimates of the relative sizes of groups flanking the carbonyl must then be made on the basis of empirical observations. A second explanation of Siewinski's results postulates the existence of more than one oxidoreductase and assumes that different enzymes are responsible for the formation of **2** and **3**. A third explanation challenges the assigned absolute stereochemistry of **3**. The reported assignment was made by the method of Horeau and Kagan[7] in which *dl*-α-phenylbutyric anhydride is reacted with an optically active alcohol. The absolute stereochemistry of the alcohol is assigned empirically from the sign of $[\alpha]_D$ of the α-phenylbutyric acid formed. Although the method has been successful in numerous cases, Horeau et al.[8] also have reported several examples where the absolute stereochemistry assigned by this procedure differed from that determined by chemical degradation. Therefore, before embarking on a lengthy study defining the relative size of a substituent or attempting to isolate and purify a single enzyme from a microorganism, we reinvestigated the absolute stereochemistry of (−)-**3**.

Results and Discussion

Although we were unable to obtain a culture of *R. mucilaginosa* (used by Siewinski), a related organism, *Sporobolomycetes pararoseus* (ATCC No. 11386), was found to reduce the ketone precursors of **1**, **2**, and **3**, yielding optically active alcohols of the same sign as reported by Siewinski. The specific rotation observed for microbiologically produced **1** was 26.8°, reported 26.5°;[6] thus it is optically pure within experimental error. The rotations and yields for **2** and **3** obtained by reduction of the ketones are listed in Table I.

To verify the configurations assigned to **2** and **3** we have developed a general procedure to determine the configuration of hydroxyhydroaromatic compounds. The procedure is shown for (1*S*)-tetralol (see Scheme I) and involves acetylating the alcohol, followed by exhaustive ozonolysis to produce a mixture of α-acetoxyadipic and α-acetoxyglutaric acids. The dimethyl esters (**4** and **5**) were prepared, using diazomethane, and separated by preparative GLC. Dimethyl α-acetoxyadipate (**4**) was identified by a comparison of its NMR spectrum, mass spectrum, and GLC retention time with that of authentic **4** prepared from ozonolysis of 3-acetoxycyclohexene. The structure of dimethyl α-acetoxyglutarate (**5**) was assigned

Scheme I

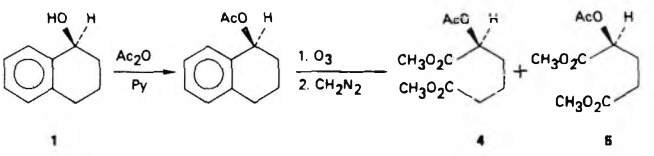


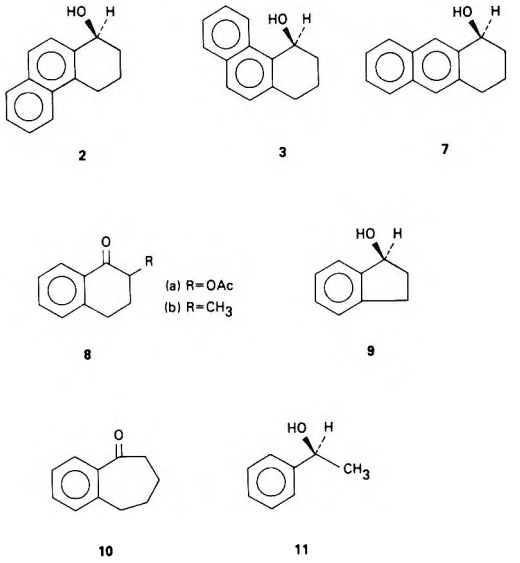
Table I. Microbiological Reductions

Alcohol or ketone precursor	Registry no.	Yield of alcohol, %	Registry no. of alcohol	Recovered ketone, %	Absolute stereochemistry	Alcohol $[\alpha]^{25}_D$ Obsd	Alcohol $[\alpha]^{25}_D$ Reported [ref]
1[b]	529-34-0	15	53732-47-1	80	1*S*	+26.8° ($CHCl_3$)	+26.5° ($CHCl_3$) [6]
2[a]	573-22-8	6	27544-17-8	77	1*S*	−59° (acetone)	−72° (acetone) [5]
3[a]	778-48-3	41	27549-85-5	59	4*S*	−19.5° (acetone)	−5° (acetone) [5]
7[a]	54784-07-5	13	65915-71-1	36	1*S*	+138° ($CHCl_3$)	
8a[a]	65915-70-0	23	65915-61-9		1*R*,2*R* (trans)	+87.9° ($CHCl_3$)	−110° [9]
		23	65915-62-0		1*R*,2*S* (cis)	−43° ($CHCl_3$)	−38° [9]
8b[a]	65941-82-4	2	65941-81-3	79	1*S*,2*S* (cis)	−61° (C_6H_{12})	+33° (benzene) [11]
		5	38157-10-7		1*S*,2*R* (trans)	+79° (C_6H_{12})	+65° (benzene) [11]
9[a]	83-33-0	9	25501-32-0	90	1*S*	+22.6°	+17° [3]
10[b]	826-73-3	27	65915-63-1	73	1*S*	−26.6° (*c* 4, $CHCl_3$)	
11[b]	98-86-2	90	1445-91-6		1*S*	−57° ($CHCl_3$)	+54° [14]

[a] These reductions were carried out using *Sporobolomycetes pararoseus* ATCC No. 11386. [b] These reductions were carried out using *Cryptococcus macerans* obtained from Dr. D. Perlman of the University of Wisconsin.

Table II. Ozonolysis of Hydrocarbon Acetates

Alcohol	Acetate $[\alpha]^{25}_D$ (*c* 2.95, $CHCl_3$)	Registry no. of acetate	Wt ozonized, mg	Wt of crude ester mixture, mg	$[\alpha]^{25}_{320}$ ($CHCl_3$) 4	$[\alpha]^{25}_{320}$ ($CHCl_3$) 5
(1*S*)-Tetralol	−97°	65915-64-2	390	135	−52°	−72°
2	−178° (c 3.3)	65915-65-3	250	61	−62°	−46°
3	−128° (*c* 1.0)	65915-66-4	250	73	−69°	−74°
7	−74° (*c* 4.1)	65915-67-5	200	90	−62°	−63°



from its NMR spectrum, mass spectrum, and a comparison of the mass spectrum's fragmentation pattern with that of one obtained from **4**. The relation between $[\alpha]^{20}_{320}$ and the absolute stereochemistry of **4** (and **5**) was thus established.[9] The tricyclic alcohols **2** and **3** were then acetylated and ozonized as described for **1**. The rotations of **4** and **5** obtained from **2** and **3** are listed in Table II. The results clearly show that the *configuration of both* **2** *and* **3** *are S*, and that the previously assigned configuration of **3** was incorrect. Both esters (**4** and **5**) were used to assign absolute stereochemistries because the quantities of each acid formed in the ozonolysis depend upon the structure of the starting acetate, i.e., one of the acids was not consistently the major ozonolysis product. In addition, **4** contained some dimethyl phthalate, which although optically inactive does affect the magnitude of the specific rotation.

For completeness and as a test of the "product stereospecificity" concept, we prepared the remaining tricyclic α-tetralone derivative, **6**, as shown in Scheme II. Microbiological reduction of this precursor by *S. pararoseus* produced the (+)-alcohol **7** which was converted to the (−)-acetate. On ozonolysis and purification (as described for **1**) the esters **4** and **5** were each found to be levorotatory (Table II), again demonstrating that the *S* alcohol was formed in the reduction. The evidence now strongly suggests that the reduction exhibits "product stereospecificity".[3]

The above experiments establish that microbiological reduction of benzo-α-tetralone derivatives yield the *S* alcohols. Since the enzyme appears to distinguish between substituents on either side of the carbonyl on the basis of size, the effect of introducing a substituent on the methylene group was uncertain. The presence of a substituent also permitted us to reduce α-tetralone derivatives which yield diols closely related to the metabolites from the mammalian[2c] and microbial oxidation[2a,b] of aromatic hydrocarbons. We chose to study the reduction of 2-acetoxytetral-1-one (**8a**) because the configurations of the *cis*- and *trans*-1,2-tetrahydrodiols are known.[10] As reduction of the carbonyl now can yield two geometric (cis and trans) isomers, we were therefore interested in determining whether one or both stereoisomers were formed and in establishing the absolute stereochemistry of the products. The configuration of the diols produced should eliminate the possibility that reduction occurred by another oxidoreductase with a different "product specificity". Microbiological reduction of **8a** yielded a mixture which was separated into three fractions: recovered starting material, a mixture of hydroxy acetates, and trace quantities of the cis and trans diols. The

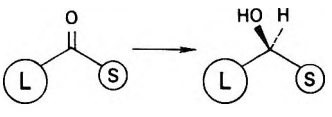
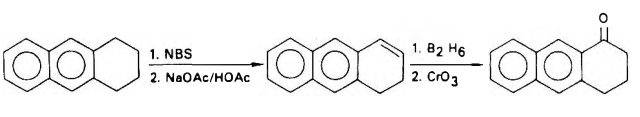


Figure 1.

Scheme II



6

fraction containing the mixture of hydroxy acetates was reductively ($LiAlH_4$) hydrolyzed, and the resulting mixture of cis and trans diols separated by thick-layer chromatography. The absolute stereochemistry of diols obtained is given in Table I. As the configuration at C-1 in each of the diols is *R*,[11] the presence of a substituent does *not* alter the course of the reduction, and the aromatic ring is always the "large group". These reductions can thus be employed to prepare optically active cis and trans diols. Furthermore, as the conversion of cis diols to epoxides has been established,[12] these diols can be used to prepare amino alcohols, mercapto alcohols, and a host of other products. These results, therefore, dramatically increase the potential value of these microbiological reductions.

As our confidence in applying Prelog's principle of "product stereospecificity" increased, we examined the reduction of 2-methyltetral-1-one (**8b**). At the time this work started, the configuration of the cis alcohol was unknown while that of the trans alcohol had been reported by Kagan et al.[13a] Microbiological reduction of 2-methyltetral-1-one yielded a mixture of alcohols which were separated by column chromatography to yield the (+)-trans and (−)-cis alcohols identified from their NMR spectra. From geometric considerations the (+)-trans alcohol was either (1*R*,2*S*) or (1*S*,2*R*), while the principle of "product stereospecificity" requires the *S* configuration at C-1. The absolute stereochemistry deduced for the trans alcohol is then (1*S*,2*R*), the opposite of that assigned by Kagan et al.[13a] This discrepancy has now been removed by Horeau et al.[13b] in a recent publication where they related the *cis*- and *trans*-2-methyltetralols to 2-aminotetralin of unequivocal stereochemistry. This group also established the absolute stereochemistry of the (−)-cis alcohol as (1*S*,2*S*), in agreement with that required using the product stereospecificity argument.

In attempted microbiological reductions of 2,2-dimethyltetral-1-one and 2,2-dimethylindan-1-one, we were unable to isolate any alcohol. Prelog and co-workers[3] have observed similar examples in their studies and suggested that substituents in "forbidden positions" interfered (steric effects) with the formation of a substrate coenzyme complex on the enzyme surface, which is necessary for reduction to occur.

Finally, the effect of varying the size of the cycloalkanone ring on the course of the reduction was examined. When 1-indanone was reduced under the usual conditions, (+)-(1*S*)-indanol (**9**) formed,[3] reduction occurring with the usual stereospecificity.

Although the high optical yields and defined configurations are important assets, the yields of alcohol in these reductions was lower than desired. We therefore devoted time searching for other microorganisms that exhibit stereospecificity while increasing the yields of alcohol produced. We found that *Cryptococcus macerans* increased the yield of α-tetralol two- to threefold and showed the same stereospecificity. This organism was then used to reduce the next higher homologue of α-tetralone, 1-benzsuberone (**10**) to yield the levorotatory alcohol ($[\alpha]^{25}_D$ −26.6°) whose stereochemistry was not otherwise examined, but is presumed to be *S* on the basis of the "product stereospecificity" concept. The same microorganism was used to reduce acetophenone, which produced the (−)-alcohol **11** known to be *S*.[15]

While these reductions allow one to prepare one enantiomer, in many studies in pharmacology and molecular biology it is important to have both enantiomers. We were therefore interested in determining if the stereochemistry of these benzylic alcohols could be inverted without extensive racemization. One attractive procedure employing triphenylphosphine, benzoic acid, and diethyl azodicarboxylate has been used to epimerize and esterify a variety of secondary alcohols.[16] When (−)-(1*S*)-phenylethanol was esterified in this manner, the (−)-(1*R*)-benzoate formed with an enantiomeric excess of approximately 95%. While some racemization has occurred, the optical purity is sufficiently high for many studies. It is also possible that additional work on reaction conditions could reduce the amount of racemization.

Conclusion

We have shown that microbiological reductions may be employed to prepare optically active hydroaromatic alcohols with a predictable configuration. Furthermore, it is not necessary to search for an organism to prepare the desired enantiomer, but in concert with standard chemical transformations either or both antipodes can be prepared. Substituents near the carbonyl group do not alter the configuration of the alcohols produced, but sometimes hinder reduction.

Experimental Section

Microbiological Reductions. A. α-Tetralone. A 1-L Erlenmeyer flask containing 600 mL of a solution of 6% glucose, 4% peptone, 4% yeast extract, and 4% malt extract was innoculated with a culture of *S. pararoseus*,[17] and the flask was shaken at 30 °C for 2 days. To the optically dense culture was then added 0.7 mL of α-tetralone and 600 mg of sodium desoxycholate, and shaking was continued for 5–7 days. The suspension was then extracted three times with 250-mL portions of ethyl acetate, the organic phase was concentrated in vacuo, and the dark residue was extracted into warm hexane. The hexane solution was again concentrated in vacuo and the desired alcohol separated by column chromatography on silica gel to yield 90 mg of (1*S*)-tetralol, $[\alpha]^{25}_D$ +26.8 (c 2.3, $CHCl_3$), and recovered α-tetralone (500 mg). The alcohol was acetylated with acetic anhydride in pyridine in the usual manner, and the resulting acetate was purified by thick-layer chromatography on silica gel.

B. 1-Oxo-1,2,3,4-Tetrahydrophenanthrene. A solution of 1-oxo-1,2,3,4-tetrahydrophenanthrene (200 mg) in acetone was mixed with 600 mg of Celite and the acetone was allowed to evaporate. This powder was used in the reduction which was otherwise done as described for α-tetralone. The alcohol (22 mg) purified by thick-layer chromatography was crystallized from hexane–acetone to yield 9.8 mg, $[\alpha]^{25}_D$ −59° (c 4.9, acetone). The NMR spectrum of the alcohol **2** was identical with that of racemic material prepared from hydride reduction of the starting ketone. The acetate was prepared as described for α-tetralol, $[\alpha]^{25}_D$ −178° (c 3.3, $CHCl_3$).

C. 4-Oxo-1,2,3,4-tetrahydrophenanthrene. A solution of 4-oxo-1,2,3,4-tetrahydrophenanthrene (300 mg) in acetone was mixed with 1.0 g of Celite and the solvent was allowed to evaporate. The solid was then divided into three equal parts and added to three 1-L Erlenmeyer flasks as described for α-tetralone. The alcohol [162 mg, $[\alpha]^{25}_D$ −19.5° (c 2.17, acetone)] was separated by thick-layer chromatography and its NMR spectrum was identical with racemic material obtained by hydride reduction of the starting ketone. The acetate was prepared as described for α-tetralol, $[\alpha]^{25}_D$ −128° (c 1.0, $CHCl_3$).

D. 1-Oxo-1,2,3,4-tetrahydroanthracene. Synthesis of this ketone is described below in the Experimental Section. A solution of the ketone (101 mg) in acetone was mixed with 460 mg of Celite, and the acetone was allowed to evaporate. The powder was added to the culture as described for α-tetralone. The alcohol **7** [26 mg, $[\alpha]^{25}_D$ +138° (c 0.8, $CHCl_3$)] was obtained by thick-layer chromatography and its NMR spectrum was identical with that of racemic material prepared by hydride reduction of the ketone. The acetate was prepared as described for α-tetralol, $[\alpha]^{25}_D$ −74° (c 4.1, $CHCl_3$).

E. 2-Methyl-1-tetralone. To each of four 1-L cultures of *S. pararoseus* was added 0.5 mL of 2-methyl-1-tetralone but *no* sodium desoxycholate. The reduction was worked up as usual and the resulting mixture (2 g) was purified by column chromatography on silica gel. The NMR spectrum of the cis alcohol was identical with that of racemic material prepared by hydride reduction of the ketone and purified by column chromatography. The cis stereochemistry was assigned on the basis of the coupling constant at δ 4.52 with $J_{1,2}$ = 2 Hz and $[\alpha]^{25}_D$ −44° (c 1.1, $CHCl_3$). The trans isomer showed a doublet at δ 4.27 with $J_{1,2}$ = 10 Hz and $[\alpha]^{25}_D$ +24° (c 2.46, $CHCl_3$).

F. 2-Acetoxy-1-tetralone. 2-Acetoxy-1-tetralone was prepared as described by Gardner[18] from α-tetralone by oxidation (*m*-chloroperbenzoic acid) of the intermediate α-tetralone enol acetate. A solution of **8a** (507 mg) in acetone was mixed with 1.0 g of Celite and the solvent was evaporated. The solid was then divided into two and

added to two Erlenmeyer flasks as usual. The mixture of acetoxy alcohols obtained from thick-layer chromatography on silica gel was reduced with lithium aluminum hydride in ether, and the resulting diols were separated by thick-layer chromatography on silica gel. The cis alcohol, $[\alpha]^{25}_D$ −43° (c 3.35, methanol), reported[10b] −38°. The trans alcohol, $[\alpha]^{25}_D$ +87.9° (c 2.39, $CHCl_3$), had an optical purity of 80%.

G. Indan-1-one. A solution of indan-1-one (500 mg) was mixed with 1.0 g of Celite and the solvent was evaporated. The solid was added to one flask and continued as above. The alcohol (42 mg), $[\alpha]^{25}_D$ +22.6° (c 4.2, $CHCl_3$), was then isolated by thick-layer chromatography and vacuum distillation.

H. Benzsuber-1-one. Benzsuber-1-one was reduced with a different microorganism, *Cryptococcus macerans*, obtained from Professor D. Perlman at the University of Wisconsin. The same culture medium, etc., were used *except* each 1-L Erlenmeyer flask contained only 250 mL of medium and sodium desoxycholate was omitted. To each of two 1-L Erlenmeyer flask was added 0.15 mL of benzsuber-1-one, and the flasks were shaken for 5 days and worked up as usual. The alcohol (81 mg) was separated by thick-layer chromatography: $[\alpha]^{25}_D$ −26.6° (c 4.0, $CHCl_3$); mp 73–4 °C.

I. Acetophenone. To four 1-L Erlenmeyers containing growing *Cryptococcus macerans* was added 0.25 mL of acetophenone. The workup was simplified since no starting ketone remained. The alcohol was distilled at 115 °C (3.5 Torr) and had an $[\alpha]^{25}_D$ −57° (c 5.12, $CHCl_3$). The NMR spectrum was identical with that of racemic material perpared by hydride reduction of the starting ketone.

Ozonolysis of (1*S*)-Acetoxy-1,2,3-4-tetrahydronaphthalene. A stream of ozone (2–4%) from an Ozonator, Model O3V2, was passed through a solution of 1-acetoxy-1,2,3-4-tetrahydronaphthalene (390 mg, $[\alpha]^{25}_D$ −97°) in 4 mL of acetic acid. The volume of the acetic acid solution was maintained during the ozonolysis by addition of acetic acid as required. After 8 h on completion of the ozonolysis 1 mL of 30% hydrogen peroxide was added and the reaction mixture was allowed to stand overnight at room temperature. The solution was then warmed to 50 °C for 30 min and sodium sulfite was added to decompose any remaining hydrogen peroxide. The solvent was removed in vacuo, excess saturated aqueous sodium bicarbonate was added, and the solution was extracted with hexane. The aqueous layer was then acidified with hydrochloric acid, saturated with sodium chloride and extracted several times with ethyl acetate. The ethyl acetate extract was washed with saturated sodium chloride, dried over sodium sulfate and concentrated in vacuo. The residue was treated with a solution of diazomethane in ether. The solvent was then removed and distillation of the residue (bath temperature 100–120 °C/0.2 Torr) yielded a colorless oil (135 mg) from which pure samples of **4** and **5** were obtained by preparative GLC using a temperature programmed Bendix 2200. The column was a 10 ft 5% FFAP on 100–120 mesh ABS. The yields of **4** and **5** obtained in these ozonolyses varied from 2–10%. A portion of the crude mixture of dimethyl esters was purified by preparative GLC to yield 2–5 mg of **4** and **5**. The specific rotations at 320 nm of **4** and **5** obtained from each of the acetates is given in Table II and the NMR ($CDCl_3$, 220 MHz) spectrum of **4** showed resonances at δ 2.16 (s), 3.68 (s), 3.75 (s), and 5.02 (t) while the spectrum of **5** showed resonances at δ 2.14 (s), 3.68 (s), 3.75 (s), and 5.07 (q).

The mass spectrum (LKB) for **4** showed peaks at *m/e* values of: 233 (weak), 201 (weak), 190 (moderate), 173 (strong), 159 (strong), 141 and 140 (weak), 131 (strong), and 99 (strong). The mass spectrum for **5** showed peaks at: 219 (weak), 187 (moderate), 176 (strong), 159 (moderate), 145 (strong), 126 and 127 (weak), 117 (strong), and 85 (strong). For each strong peak in **4** there is in **5** a corresponding strong peak shifted by 14 mass units.

An authentic sample of **4** was prepared by ozonolysis of 3-acetoxycyclohexene, followed by esterification of the acid with diazomethane. The dimethyl ester was then distilled in vacuo.

Preparation of 1-Oxo-1,2-3,4-tetrahydroanthracene (6). To a solution of 5.01 g of 1,2,3,4-tetrahydroanthracene in carbon tetrachloride (125 mL) was added *N*-bromosuccinimide (4.06 g) and benzoyl peroxide (20 mg). The solution was refluxed for 2 h and the solvent was removed in vacuo. The residue was treated with acetic acid (50 mL) and potassium acetate (5 g), heated for 1 h on a steam bath, and poured into water. The mixture was extracted with dichloromethane, and the organic phase was washed with saturated aqueous sodium bicarbonate, dried, and concentrated. The residue was dissolved in dry tetrahydrofuran, cooled in ice–water, and treated with excess diborane. The solution was slowly allowed to warm to room temperature and the borane was oxidized with 10% sodium hydroxide (10 mL) and 30% hydrogen peroxide (5 mL) at room temperature. Unreacted hydrogen peroxide was decomposed by stirring with Pt/charcoal and the tetrahydrofuran was removed in vacuo. Water was added and the mixture was extracted with chloroform. The chloroform solution was concentrated and the residue was chromatographed over silica gel to yield 1.465 g (27%) of 1-hydroxy-1,2,3,4-tetrahydroanthracene, mp 83–4 °C. Anal. Calcd for $C_{14}H_{14}O$: C, 84.79; H, 7.12. Found: C, 84.51; H, 7.07.

The NMR spectrum (220 MHz, $CDCl_3$) showed a broad singlet at δ 4.91 (1 H), 2.95 (m, 2 H), and 1.7–2.4 (complex, 4 H).

The alcohol was oxidized with Jones reagent to yield the ketone, mp 90–91 °C, in essentially quantitative yield. Anal. Calcd for $C_{14}H_{12}O$: C, 85.66; H, 6.17. Found: C, 85.75; H, 6.22.

The NMR spectrum of the ketone showed aromatic absorption and triplets at δ 3.11 and 2.73 and a multiplet at δ 2.18.

Epimerization of (−)-(1*S*)-Phenylethanol. A solution of (−)-(1*S*)-phenylethanol (122 mg, 1 mmol), triphenylphosphine (524 mg, 2 mmol), and benzoic acid (244 mg, 2 mmol) in dry THF (10 mL) was stirred under N_2 at room temperature. To this solution was added dropwise a solution of diethyl azodicarboxylate (348 mg, 2 mmol) in dry THF (5 mL). After stirring overnight the residue was dissolved in chloroform (20 mL), washed with 10% aqueous sodium bicarbonate and water, dried over sodium sulfate, filtered, and concentrated. Analysis of the crude reaction mixture by NMR indicated that 95% of the starting alcohol had been converted into the corresponding benzoate. The benzoate was purified by thick-layer chromatography (silica gel, ethyl acetate/hexane, 7:93) to yield 178 mg (91% yield) of (−)-(1*R*)-phenylethanol benzoate as a viscous oil, $[\alpha]^{25}_D$ −20.7° (c 2.28, EtOH). The NMR spectrum of this benzoate was identical with that of racemic material: δ 1.66 (3 H, d, J = 6.4 Hz), 6.13 (1 H, q, J = 6.4 Hz), ~7.27–7.55 (6 H, m), 7.33 (2 H, d, J = 7.1 Hz), 8.08 (2 H, d, J = 7.1 Hz).

The optical purity was 95% based on the rotation of (+)-(1*S*)-phenylethanol benzoate, $[\alpha]^{25}_D$ +21.9° (c 2.78, EtOH), prepared by reaction of (−)-(1*S*)-phenylethanol and benzoyl chloride in pyridine.

The (−)-(1*R*)-benzoate was then hydrolyzed to (+)-(1*R*)-phenylethanol. A solution of 178 mg (0.91 mmol) of (−)-(1*R*)-benzoate in 5 mL of methanol containing 1 mL of water and 200 mg of KOH was refluxed for 2 h. The solvent was removed in vacuo, the residue was extracted with ethyl acetate, washed with water, dried over sodium sulfate, and concentrated to yield an oil which was purified by thick-layer chromatography (silica gel, ethyl acetate/hexane, 3:7). The (+)-(1*R*)-phenylethanol (92 mg, 83% yield) was isolated, $[\alpha]^{25}_D$ +53.2° (c 5.41, $CHCl_3$), optical purity 98% based on the absolute rotation reported in the literature.[15] The NMR spectrum of this sample was identical with that of racemic material.

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Registry No.—**4**, 65915-68-6; **5**, 55095-00-6; 1,2,3,4-tetrahydroanthracene, 2141-42-6; (−)-(1*R*)-phenylethanol benzoate, 65915-69-7; (+)-(1*S*)-phenylethanol benzoate, 57473-79-7; (+)-(1*R*)-phenylethanol, 1517-69-7.

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Douglas Fir Tussock Moth Pheromone: Identification of a Diene Analogue of the Principal Attractant and Synthesis of Stereochemically Defined 1,6-, 2,6-, and 3,6-Heneicosadien-11-ones

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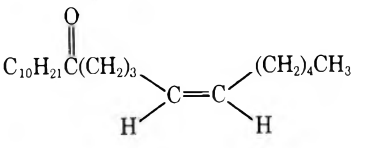
A diene analogue of the principal Douglas fir tussock moth sex pheromone (*Z*)-6-heneicosen-11-one has been isolated and identified as a 1,6-heneicosadien-11-one using mass spectrometry, microozonolysis, and gas chromatography. Five geometric and positional heneicosadien-11-one isomers were synthesized for chromatographic and spectroscopic comparison and for biological testing. Unambiguous structural assignments of the five isomers were established by capillary column gas chromatography, carbon magnetic resonance spectroscopy, infrared and laser Raman spectroscopy, and mass spectrometry.

The principal attractant of the sex pheromone system of the Douglas fir tussock moth (DFTM), *Orgyia pseudotsugata* (McDunnough), was identified as (*Z*)-6-heneicosen-11-one (**1**),[1] synthesized,[2-4] and successfully tested in laboratory and field bioassays.[5] We have now detected a closely related compound in attractive extracts of DFTM female abdominal tips and identified it as a 1,6-heneicosadien-11-one **2** or **3**. Both isomers (*Z*)-1,6-heneicosadien-11-one (**2**) and (*E*)-1,6-heneicosadien-11-one (**3**) have been synthesized for comparison with the natural material and for biological evaluation. In addition, the isomers (*E,Z*)-2,6-heneicosadien-11-one (**4**), (*Z,Z*)-3,6-heneicosadien-11-one (**5**), and (*E,Z*)-3,6-heneicosadien-11-one (**6**) were also synthesized, characterized, and evaluated for attractiveness to DFTM males.

Isolation and Structure Elucidation

The dienone was first observed by gas chromatography–mass spectrometry (GC/MS) studies of partially purified fractions obtained by dry column chromatography[1] of active DFTM extracts. Its mass spectrum is very similar to that of the principal attractant (**1**, Figure 1a) and corresponds to a diene analogue of **1**. Thus the molecular ion (*m/e* 306) established the probable empirical composition as $C_{21}H_{38}O$ and a cleavage ion at *m/e* 169 established the presence of a carbonyl at C-11 and a ten-carbon saturated alkyl chain. The other carbonyl α cleavage ion at *m/e* 165 confirmed assignment of both sites of unsaturation to the remaining ten-carbon alkyl chain. Furthermore, the appearance of an ion at *m/e* 122 (corresponding to the ion at *m/e* 124 in the spectrum of **1**, see Figure 1a), derived via a McLafferty rearrangement with charge retention on the hydrocarbon fragment, strongly suggested that one double bond was at position six[1] and the second double bond was contained in the five-carbon terminus of the alkyl chain (i.e., at positions 1, 2, or 3, see the spectra in Figures 1b, 1c, and 1d).

Isolation of the diene was undertaken from the dichloromethane extract of 1000 crushed DFTM female abdominal



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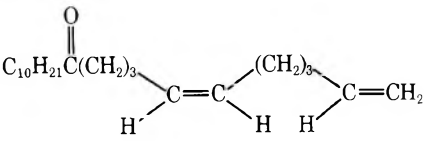

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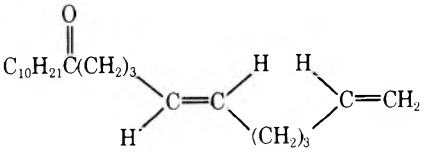

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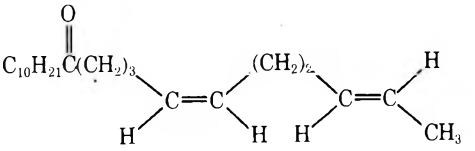

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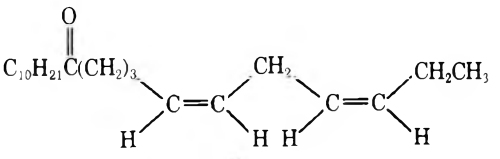

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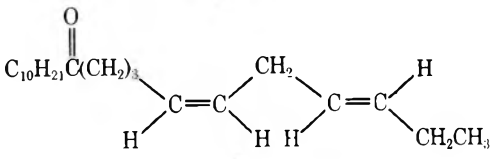

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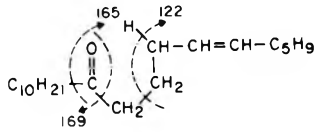


tips. Dry column chromatography on neutral alumina followed by preparative gas liquid chromatography produced a sample (<2 μg) which was subjected to chemical and chromatographic examination. Reductive ozonolysis of the isolated dienone followed by GC/MS analysis (OV-17 column) showed essentially one component which exhibited a retention time and mass spectrum establishing its structure as 5-ketopentadecanal, a sample of the latter being obtained for comparative analysis by ozonolysis of 1.[1] A second GC/MS analysis of an ozonolysis product mixture (Porapak PS column) again revealed a single, but different, compound. This compound was identified as glutaric dialdehyde, establishing that the two sites of unsaturation in the diene are separated by three methylene units. These results established all features of the dienone structure (a 1,6-heneicosadien-11-one) except the stereochemistry about the C-6,7 double bond, i.e., the diene is either **2** or **3**. Unfortunately, definitive determination of the double bond stereochemistry must await isolation of an additional, adequately pure sample for chromatographic comparison with synthetic dienones **2** and **3**; despite a number of attempts we have not succeeded in obtaining an adequate sample.

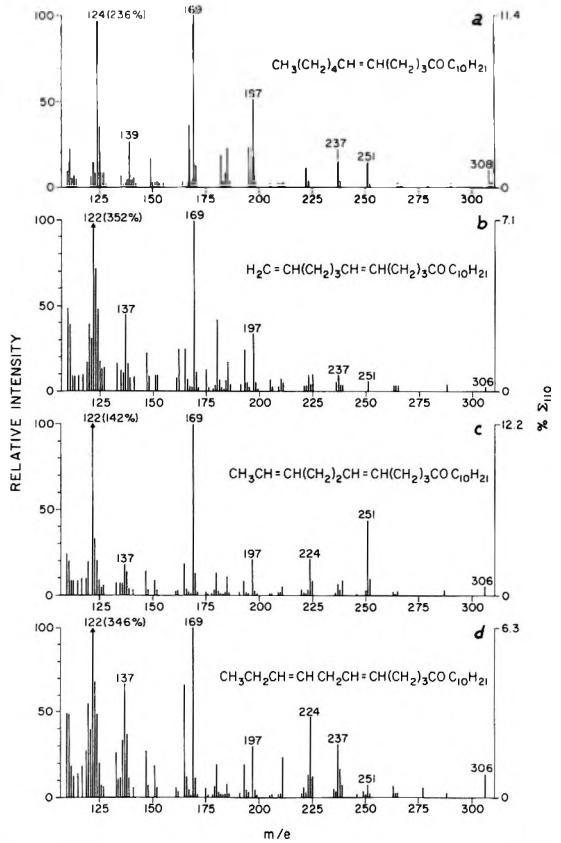
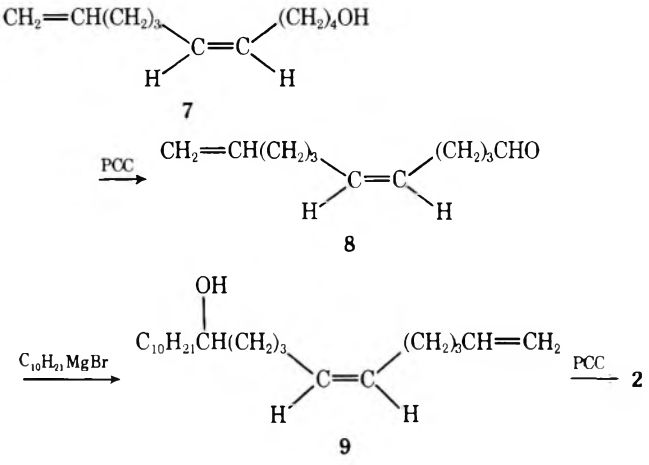


Figure 1. Mass spectra of 6-heneicosen-11-one, and of 1,6-, 2,6-, and 3,6-heneicosadien-11-ones.

Synthesis

Determination of the double bond stereochemistry of the DFTM dienone requires the availability of the two alternative stereoisomers **2** and **3**. Furthermore, the limited supply of material isolated from the insect extract prompted the syntheses of double bond position isomers **4**–**6** of the dienone for comparative chromatographic, spectrometric, and bioassay studies.

The key synthetic intermediate in each sequence was an 11-carbon dienol possessing the desired double-bond placement and stereochemistry. Thus, oxidation of (*Z*)-1,6-undecadien-11-ol (**7**) with pyridinium chlorochromate (PCC)[6] to the corresponding aldehyde (**8**) followed by reaction with *n*-decylmagnesium bromide yielded the 21-carbon dienol **9**



which was again oxidized to produce (*Z*)-1,6-heneicosadien-11-one (**2**).

The preparation of **7** was accomplished in good yield by coupling 5-bromo-1-pentene with the dilithium derivative of 1-hexyn-5-ol (or the corresponding *O*-tetrahydropyranyl derivative[7]) followed by syn hydrogenation of the acetylenic bond over modified P-2 nickel catalyst.[8] A similar sequence employing anti hydrogenation with $Na/NH_3/Et_2O$[9] yielded (*E*)-1,6-undecadien-11-ol, which was subsequently converted to **3**. Synthesis of (*E,Z*)-2,6-heneicosadien-11-one (**4**) was carried out in a sequence analogous to that for **2** and **3**. Somewhat more difficult were the syntheses of (*Z,Z*) and (*E,Z*)-3,6-undecadien-11-ols, precursors to **5** and **6**, respectively. For these syntheses, (*Z*)- and (*E*)-1-bromo-2-pentenes (**10**) were prepared and coupled with copper acetylide **11** in dimethylformamide solution containing sodium cyanide.[10] The coupling reaction yielded a mixture of undecenynols **12** and **13** in which the desired product (**12**) predominated in a ratio of 4:1 over the product of allylic rearrangement (**13**). This represents the first application of this newly developed coupling procedure in pheromone synthesis and, although the specificity of the reagent toward allylic halides is attractive, the production of an unwanted structural isomer (**13**) to such

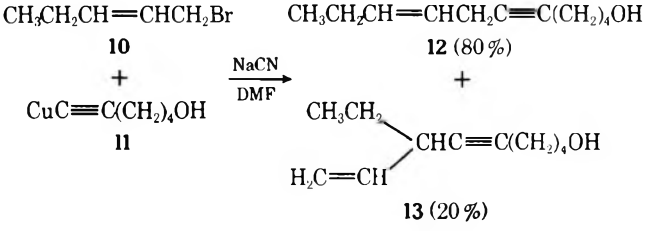


Table I. Gas Chromatographic Selectivities toward Heneicosenones and Heneicosadienones[d]

Column	Relative adjusted retention volumes[d]						
	(*E*)-6[2]	(*Z*)-6- (1)	(*E*)-1,6- (3)	(*Z*)-1,6- (2)	(*E,Z*)-2,6- (4)	(*E,Z*)-3,6- (6)	(*Z,Z*)-3,6- (5)
Support-bonded PEG 20M[a]	1.03	1.00	1.16	1.11	1.15	1.14	1.15
Cyanosilicone (packed)[b]	1.00	1.00	1.25	1.25	1.23	1.20	1.30
Cyanosilicone (capillary)[c]							
Column 1		1.00	1.29		1.23	1.27	1.32
Column 2	0.98	1.00	1.23	1.25			

[a] 80/100 Chromosorb W, 6 ft × 2 mm i.d. stainless steel, 160 °C. [b] 10% on 100/120 Gas Chromosorb Q, 10 ft × mm i.d. stainless steel, 200 °C. [c] Glass capillary columns, 60 m × 0.25 mm i.d., 170 °C. [d] Registry No.—**1**, 54844-65-4; **2**, 65956-73-2; **3**, 65956-72-1; **4**, 65956-74-3; **5**, 65956-76-5; **6**, 65956-75-4.

an extent leads us to conclude that syntheses of skipped methylene enynes may be accomplished more efficiently using the acetylene Grignard/CuCl system.[11,12]

Gas Chromatographic Analyses

Partial resolution of synthetic (*E*)- and (*Z*)-1,6-dienones (**2** and **3**) was possible using a glass capillary column coated with a cyanopropyl silicone polymer and using a packed column of annealed, support-bonded polyethylene glycol 20M. The best resolution of the (*E*)- and (*Z*)-1,6-dienones (**2** and **3**) and of the dienone positional and geometric isomers (**4–6**) was observed on the capillary column due to the much greater efficiency relative to the packed columns. Only the (*Z*)-1,6 dienone (**2**) was adequately resolved from the other four dienones on the support-bonded 20M column, and only the (*Z,Z*)-3,6 dienone (**5**) was resolved from the other dienones on a packed column of a cyanopropylsilicone phase. Table I records the selectivities of these columns toward the monoenones and dienones (**1–6**).

Spectrometric Studies

Synthetic dienones **2–6** were examined by a variety of spectrometric methods which served to unambiguously establish their structures.

Mass Spectra. Mass spectra of the three double bond position isomers are shown in Figure 1. Although mass spectrometry is not a reliable method for determining the positions of carbon–carbon double bonds[13] unless the double bond is specifically modified,[14] comparison of the spectra of the dienone positional isomers **1b–d** with that of the DFTM dienone permits the latter to be assigned correctly as a 1,6-dienone. Although the spectra of the three positional isomers show the same *m/e* values for nearly all their fragmentation and rearrangement products, significant differences are apparent in relative ion abundances.

Carbon Magnetic Resonance Spectra. Carbon magnetic resonance spectra were obtained for isomeric dienones **2, 3, 4,** and **6.** The chemical shifts and assignments are listed in Table II. The assignments were made by comparison with literature values[15–20] and are not rigorously established. Comparison of the ^{13}C NMR spectra of the (*Z*)-1,6 and (*E*)-1,6-dienones (**2** and **3,** respectively) shows differences which are characteristic of opposite geometries at the six position double bond. The olefinic carbons of the *E* double bond are deshielded by 0.5 ppm or more with respect to those of the *Z* isomer.[15–20] The observed line shift (from 26.6 ppm for the *Z* isomer to 31.9 ppm for the *E* isomer) for carbons 5 and 8 is characteristic of these allylic carbons.[15–17,19]

In the spectrum of (*E,Z*)-2,6-heneicosadien-11-one (**4**), the chemical shifts of carbon one (17.96 ppm), of carbon two (124.9 ppm), and of carbon four (32.56 ppm) are characteristic of an *E* olefin at position two.[16,18,19] The chemical shifts of carbons six and seven are essentially the same as those for the (*Z*)-1,6-dienone and thus consistent with a *Z* double bond at position six. Likewise, the assigned shifts of allylic carbons five (27.29 ppm) and eight (26.59 ppm) further support the *Z* geometry.

The spectrum of (*E,Z*)-3,6-heneicosadien-11-one (**6**) is similarly characteristic. The chemical shift of carbon two (25.59 ppm) as well as the absence of a line at about 20 ppm (expected for a (*Z*)-3 double bond) and the chemical shift of carbon three (132.2 ppm) are consistent with an *E* geometry at position three.[16,17] The apparent shielding of carbon 6 (relative to similar carbons of the 1,6- and 2,6-dienones **2, 3,**

Table II. ^{13}C Nuclear Magnetic Resonance Chemical Shifts for Isomeric Heneicosadien-11-ones

Carbon type[a]	^{13}C NMR resonances, δ_{Me_4Si} (C position no.)			
	(*Z*)-1,6(**2**)	(*E*)-1,6(**3**)	(*E,Z*)-2,6(**4**)	(*E,Z*)-3,6(**6**)
Olefinic C	138.5 (2)	138.6 (2)	130.5 (3)	132.2 (3)
	130.2, 128.9 (6, 7)	130.7, 129.5 (6, 7)	130.0, 128.8 (6, 7)	129.0, 128.6 (4, 7)
	114.3 (1)	114.2 (1)	124.9 (2)	127.0 (6)
Allylic CH_2	33.28 (3)	33.13 (3)	32.56 (4)	30.36 (5)
	26.58 (5, 8)	31.92 (5, 8)	27.29 (5)	26.49 (8)
			26.59 (8)	25.59 (2)
α-Carbonyl CH_2	42.83, 41.96 (10, 12)	42.86, 41.87 (10, 12)	42.76, 41.96 (10, 12)	42.85, 41.96 (10, 12)
Other CH_2	31.85 (19)	31.92 (19)	31.84 (19)	31.94 (19)
	29.45, 29.29, 28.87 (≤, 9, 15–18)	29.45, 29.29, 28.67 (4, 9, 15–18)	29.45, 29.28 (9, 15–18)	29.41 (9, 15–18)
	23.80, 23.65, 22.63 (13, 14, 20)	23.82, 23.52, 22.65 (13, 14, 20)	23.81, 23.62 (13, 14)	23.90, 23.61, 22.71 (13, 14, 20)
Methyl	14.21 (21)	14.09 (21)	17.96 (1)	14.19 (21)
			14.09 (21)	13.89 (1)

[a] Carbonyl carbon chemical shifts were not determined.

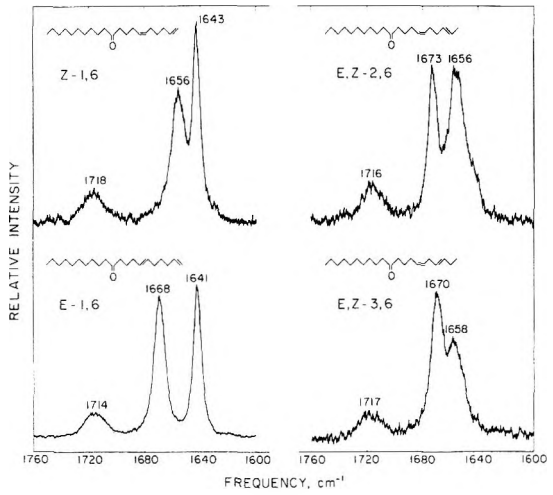


Figure 2. Laser Raman spectra of heneicosadien-11-ones (**2, 3, 4,** and **6**) in the carbonyl and olefinic double bond stretching region.

and **4**) is consistent with the skipped methylene structure.[16,17] In the spectrum of **6**, the double allylic carbon five has a chemical shift of 30.36 ppm which is expected for an *E,Z* skipped methylene;[16,18] no absorption in this region is observed in the other three spectra. The shift of carbon eight (26.49 ppm) agrees with a *Z* geometry of the double bond at position six.

Vibrational Spectra. The laser Raman spectra of the heneicosadien-11-ones (Figure 2) provide unambiguous characterization of their olefinic bond geometries. The structurally sensitive C=C stretching vibrations lie in the 1640–1675-cm^{-1} region,[21] while the carbonyl vibrations for all isomers were observed at 1716 ± 2 cm^{-1}. For the terminal double bonds of the (*Z*)-1,6 and (*E*)-1,6 isomers (**2** and **3**, respectively), strong and symmetrical peaks were recorded at 1642 ± 1 cm^{-1}. The (*Z*)-6 C=C absorptions appear to be somewhat less intense and lie at ~1656 cm^{-1}. (The reference compounds (*E*)- and (*Z*)-6-heneicosen-11-ones[2] exhibit single, symmetrical peaks at 1668 and 1654 cm^{-1} due to the *E* and *Z* double bonds, respectively, and peaks at ~1715 cm^{-1} due to the carbonyl vibrations.) Slightly greater variation in peak position was observed for the *E* double bonds, giving rise to peaks between 1668 and 1673 cm^{-1}. These vibrational bands are similar in intensity and shape to the terminal bond vibrations. All Raman frequencies in this spectral region were strongly polarized, as expected.

Infrared spectra of these compounds were studied in the structurally sensitive in-phase, out-of-plane CH wagging region near 970 cm^{-1} for trans-disubstituted hydrocarbon olefins.[22] The (*E*)-1,6(**2**), (*E,Z*)-2,6(**4**), and (*E,Z*)-3,6(**6**) isomers showed moderately strong absorptions at 968, 959, and 965 cm^{-1}, respectively; however, no such band could be observed in this region for the (*Z*)-1,6 isomer (**2**), further confirming the structural identities of these compounds.

Biological Activity. Laboratory bioassays[1,5] of the isolated DFTM dienone and laboratory and field bioassays of the synthetic (*Z*)-1,6-dienone (**2**) and (*E,Z*)-3,6-dienone (**6**) showed these compounds to be attractive to DFTM males; dienones **3–5** exhibited little or no attractiveness. A more detailed study of the biological activities of the synthetic dienones will be the subject of a separate report.

Experimental Section

Partial purification of insect extracts[1] was carried out by chromatography (dry column or TLC) with benzene on alumina (activity III), R_f 0.8. Further purification was accomplished by trapping of components during elution from gas chromatography (GC) (Apolar 10C column) using glass capillaries along which a thermal gradient was established.[23] Collected material was washed from the capillaries with CH_2Cl_2 into conical vials and was ozonized at −70 °C.[24] Efforts were unsuccessful to develop a procedure for the GC analysis of low molecular weight aldehydes (at levels less than 100 ng from ozonolysis) as their 2,4-dinitrophenylhydrazones.[25] GC analyses were made on OV-101, OV-17, and Carbowax 20M columns (1.5 to 3% on 80/100 Chromosorb W, AW-DMCS, 6 ft × 2 mm i.d., glass and stainless steel), on an Apolar 10C column (10% on 100/120 Gas-Chromosorb Q, 10 ft × 2 mm i.d., stainless steel), on a Porapak PS column (80/100, 6 ft × 2 mm i.d., glass), and on glass capillary columns (0.25 mm i.d., 60 m SP 2340, 30 m FFAP, and 10 m SE30, J&W Scientific, Inc.) using flame ionization detection. Analytical high pressure liquid chromatography (HPLC) with $AgNO_3$-impregnated silica gel was carried out on a 20 × 0.6 cm column packed with 5% $AgNO_3$/silica gel + LiEF54 using benzene,[26] and preparative HPLC utilized a 25 × 2.45 cm column packed with 20% $AgNO_3$/silica gel.[26] ^1H NMR spectra were obtained with a Varian HA-100 spectrometer usually with a lock on benzene in 10% C_6H_6/CCl_4 solutions. ^{13}C NMR spectra were obtained using a Varian XL-100 spectrometer, and IR Spectra using a Perkin-Elmer 621 spectrometer. Mass spectra were obtained using a DuPont 21-491B GC/MS system, and the mass spectra of the positional isomers of the dienones shown in Figure 1 were all recorded within a 30 min period under identical operating conditions. Raman spectra were recorded on a Jarrell-Ash 25–300 spectrophotometer equipped with an RKB, Inc. digital grating drive. Excitation at 514.5 nm was obtained from a Coherent Radiation Model 52 MG Ar/Kr laser. Throughout the syntheses described below, analyses by GC/MS were made and were consistent with the indicated conversions.

Preparations of Pentenols. 2-Pentyn-1-ol was prepared by the coupling of propargyl alcohol with bromoethane using $LiNH_2/NH_3$.[27] (*Z*)-2-Penten-1-ol was synthesized by syn hydrogenation of 2-pentyn-1-ol using P-2 nickel modified with ethylenediamine (P-2 Ni/EDA) at 30 to 40 psi H_2 in methanol for 7 to 10 h[28] (mole ratio catalyst/acetylenic compound-1/20).[8] GC analyses (OV-101 and Apolar 10C columns) showed no acetylenic compound remaining and 1 to 3% *n*-pentanol; resolution of the *E* and *Z* isomers of 2-penten-1-ol was not attained on these columns. Anti hydrogenations of 2-pentyn-1-ol and of commercial 2-pentyn-5-o1 (Chem Samples Co.) were carried out with $Na/NH_3/Et_2O$ over 4 to 6 h.[9] GC analyses (OV-101, Apolar 10C, and Porapak PS columns) showed no pentanol or acetylenic starting materials and, in the case of the (*E*)-2-penten-5-ol, no *Z* isomer.

Preparations of Bromopentenes. The pentenols were converted to the corresponding bromopentenes with either of two reagents: PBr_3/pyridine (catalytic amount)/Et_2O[29,30] or Ph_3PBr_2/pyridine/CH_2Cl_2.[31] Conversions with the latter reagent involved 1 equiv of the alcohol, 1.1 equiv of Ph_3PBr_2, and 1.1 equiv of pyridine in CH_2Cl_2, initially at 0 °C followed by gradual warming to 25 °C. The crude product was distilled from the reaction mixture under reduced pressure and purified by fractional distillation. In each of the reactions of Ph_3PBr_2 with (*Z*)-2-penten-1-ol and 1-penten-5-ol, one product only was detected by GC analyses in each case, the isolated yield in the latter reaction being 89%. Using the reagent PBr_3/pyridine/Et_2O, the isolated yields were usually about 50%, and the conversions were often accompanied by side reactions. Significant amounts of HBr addition products were observed using PBr_3 in the syntheses of the 5-bromo-2-pentenes (up to 15%) and of 5-bromo-1-pentene (20 to 40%). *Z* to *E* isomerization of the double bond was observed in the conversion of (*Z*)-2-penten-1-ol to the bromopentene with PBr_3 (~50% isomerization). Another side reaction observed in the latter conversion was S_N2' displacement which produced 3-bromo-1-pentene (10%). These side reactions were not observed when Ph_3PBr_2 was used. Partial resolution of 3-bromo-1-pentene, 1-bromo-(*E*)-2-pentene, and 1-bromo-(*Z*)-2-pentene was possible using a packed OV-17 column (6 ft. × 2 mm i.d., glass), and complete resolution was attained on a glass capillary column coated with SE-30 column (10 m × 0.25 mm i.d.).

5-Bromo-1-pentene: bp ~70 °C (140 mm); NMR (10% C_6H_6/CCl_4) δ 5.87–5.48 (m, 1), 5.12–4.90 (m, 2), 3.23 (t, 2), 2.08 (m, 2), 1.85 (m, 2). **5-Bromo-(*Z*)-2-pentene:** NMR (CCl_4) δ 5.78–5.18 (m, 2), 3.28 (t, 2), 2.62 (g, 2), 1.66 (d, 3); IR (film, KBr) 3024, 2970, 2924, 2865, 1654, 1435, 1268, 1255, 1207, 1030, 966, 702 cm^{-1}; laser Raman (neat) 1655 cm^{-1} (intense, symm). **5-Bromo-(*E*)-2-pentene:** NMR (CCl_4) δ 5.56–5.32 (m, 2), 3.28 (t, 2), 2.51 (t, 2), 1.67 (d, 3); IR (film, KBr) 3030, 2967, 2940, 2910, 2858, 1735, 1438, 1374, 1255, 1204, 1054, 964 cm^{-1}; laser Raman (neat) 1669 cm^{-1} (intense, symm). **1-Bromo-(*Z*)-2-pentene:** bp 75 °C (135 mm); NMR (10% C_6H_6/CCl_4) δ 5.74–5.36 (m, 2), 3.85 (d, 2), 2.10 (m, 2), 0.98 (t, 3). **1-Bromo-(*E*)-2-pentene:** bp 80 °C (144 mm); NMR (10% C_6H_6/CCl_4) δ 5.76–5.58 (m, 2), 3.84 (d, 2), 2.24–1.88 (m, 2), 0.94 (t, 3).

Preparations of Undecenynols. (*E*)-2-Undecen-6-yn-11-o1 (as

the THP derivative) was synthesized by the coupling of 5-(2′-tetrahydropyranyloxy)-1-hexyne[28] with 5-bromo-(*E*)-2-pentene using *n*-butyllithium in THF/hexane/hexamethylphosphoramide (HMPA).[7] 2-Undecen-6-yn-11-ol was synthesized by the coupling of 5-bromo-1-pentene with the dilithium adduct of 1-hexyn-6-ol in THF/hexane/HMPA. The tetrahydropyranyl derivative of 1-hexyn-6-ol was initially employed in the coupling reaction (75% yield); in later syntheses the dilithium adduct was used without complication. Two molar equivalents of *n*-BuLi (2.5 M in hexane) were added slowly to a 0.25 M solution of 1-hexyn-6-ol in dry THF at about −30 °C under dry nitrogen. Precipitation of a colorless solid at times required the addition of more THF to maintain efficient stirring. After 5 min, a volume of HMPA was added equal to one-fourth that of the reaction, and the resulting mixture was cooled to about −70 °C. One molar equivalent of 5-bromo-1-pentene (in a volume of HMPA equal to that added initially) was added and the cold bath was removed. Gradual warming of the stirred mixture to 25 °C produced a colorless solution. GC analysis (6 ft OV-101) of a quenched aliquot showed no starting materials and one product. The reaction solution was reduced in volume by ⅔, quenched with two volumes of H_2O, and extracted with hexane. After drying, fractional distillation (bp 90 °C (0.4 mm)) yielded the pure product, (*E*)-2-undecen-6-yn-11-ol (67%).

(*Z*)- and (*E*)-3-undecen-6-yn-11-ols were synthesized by the coupling of 1-bromo-(*Z*)-2-pentene and of 1-bromo-(*E*)-2-pentene with the copper acetylide of 1-hexyn-6-ol (11) in DMF/NaCN.[10] The method of in situ generation of the copper acetylide[33] was ineffective in our hands. Instead, the reagent (11) was synthesized separately,[34] dried, and then coupled with the allylic bromides. GC/MS analyses (OV-101 and Apolar 10C columns) of the hexane extracts of the reaction mixture showed no allylic bromide and two higher boiling products, the undecenynol (12) and 3-ethyl-1-nonen-4-yn-9-ol (13), 80 and 20%, respectively. Fractional distillation (85 °C (5 μm)) using a 30-cm Dufton column with a spiral of Nichrome wire gave a pure sample of 13 and a sample of 90% pure 3-undecen-6-yn-11-ol (12). Attempts to separate the two compounds by preferential reaction with bis(3-methyl-2-butyl)borane (disiamylborane)[35] or by preferential complexation with $CaCl_2$[36] were unsuccessful; in both procedures, the two compounds exhibited essentially equal reactivities.

1-Undecen-6-yn-11-ol: bp ~90 °C (0.4 mm); NMR (10% C_6H_6/CCl_4) δ 5.96–5.52 (m, 2), 4.10–3.86 (m, 2), 3.52 (br t, 2), 3.36 (br s, 1), 2.26–1.98 (m, 6), 1.70–1.42 (m, 6). **11-(2′-Tetrahydropyranyloxy)-1-undecen-6-yne:** bp 100 °C (5 μm); NMR (10% C_6H_6/CCl_4) δ 5.96–5.52 (m, 1), 5.12–4.84 (m, 2), 4.50 (m, 1), 3.88–3.54 (m, 2), 3.52–3.16 (m, 2), 2.26–1.98 (m, 6), 1.80–1.36 (m, 12). **11-(2′-Tetrahydropyranyloxy)-(*E*)-2-undecen-6-yne:** bp ~100 °C (10 μm); NMR (CCl_4) δ 5.50–5.32 (m, 2), 4.50 (m, 1), 3.82–3.54 (m, 2), 3.52–3.20 (m, 2), 2.13 (s, 6), 1.76–1.42 (m, 12). **(*E*)-3-Undecen-6-yn-11-ol:** bp ~80 °C (5 μm); NMR (10% C_6H_6/CCl_4) δ 5.84–5.16 (m, 2), 3.52 (t, 2), 3.26 (br s, 1), 2.88–2.74 (m, 2), 2.26–2.06 (m, 2), 2.06–1.90 (m, 2), 1.68–1.46 (m, 4), 0.96 (t, 3). **3-Ethyl-1-nonen-4-yn-9-ol:** NMR (10% C_6H_6/CCl_4) δ 5.88–5.50 (m, 1), 5.34–4.90 (m, 2), 3.52 (br t, 2), 3.14 (br s, 1), 3.04–2.78 (m, 1), 2.32–2.10 (m, 2), 1.74–1.38 (m, 6), 0.96 (t, 3).

Preparations of Heneicosadien-11-ones. The conversions of the hendecenyn-1-ols to the heneicosadien-11-ones were all carried out in essentially identical reaction sequences. The former compounds were syn hydrogenated with P-2 Ni/EDA[8] and anti reduced with $Na/NH_3/Et_2O$.[9] The resulting undecadien-1-ols were oxidized to the corresponding aldehydes with pyridinium chlorochromate (PCC).[6] Subsequent reaction with *n*-decylmagnesium bromide (iodide was less effective) in ether followed by oxidation of the resulting alcohol (heneicosadien-11-ol) with PCC yielded the crude heneicosadien-11-one. The product was purified by column chromatography on neutral silica gel using 15% CH_2Cl_2 in hexane. Throughout these conversions, GC/MS analyses confirmed the nearly quantitative conversions (1.5% OV-101, 6 ft. × 2 mm id, glass).

The catalytic hydrogenation of the acetylenic bond of 10-undecen-5-yn-1-ol with P-2 Ni/EDA required more carefully controlled conditions; the terminal olefinic bond apparently exhibited a significant degree of reactivity. The reduction was carried out at atmospheric pressure and was discontinued after 95 to 100% of 1 equiv of H_2 had been consumed. GC/MS analysis showed 5% starting material, 5% of a monounsaturated alcohol ($C_{11}H_{22}O$), and 90% (*Z*)-2,6-undecadien-11-ol. Under increased pressure (30–40 psi), considerably more monounsaturated alcohol was produced. Distillation of the reaction mixture (20 cm Vigreaux column, 70 °C (3 μm)) did not appreciably improve the purity of the dienol. The oxidations with PCC were carried out at 25 °C in CH_2Cl_2. The resulting black sludge was washed with CH_2Cl_2; the CH_2Cl_2 solution was reduced to a small volume and diluted with five times its volume of hexane and passed through Celite, to give a nearly colorless solution. The preparation of (*Z,Z*)-3,6-heneicosadien-11-one (5) produced a large amount of *E,Z* isomer (6) due to the *Z* to *E* isomerization during the preparation of the bromopentene. High-pressure liquid chromatography of the mixture on $AgNO_3$/silica gel produced a purified sample of the *Z,Z* isomer (5). Unfortunately, during the final workup step, microflash distillation, the sample underwent appreciable pyrolysis so that milligram quantities of this isomer were not available for NMR or IR. **(*Z*)-1,6-Heneicosadien-11-one (2):** liquid; NMR (10% C_6H_6/CCl_4) δ 6.05–5.60 (m, 1), 5.37 (m, 2), 5.10–4.90 (m, 2), 2.38 (t, 4), 2.20–1.90 (m, 6), 1.75–1.40 (m, 6), 1.26 (s, 14), 0.88 (t, 3); IR (film, KBr) 3080, 3003, 2930, 2856, 1712, 1637, 1455, 1408, 1365, 987, 907 cm^{-1}; laser Raman (neat) 1718, 1656, 1643 cm^{-1}. **(*E*)-1,6-Heneicosadien-11-one (3):** mp 30 °C; NMR (10% C_6H_6/CCl_4) δ 6.05–5.60 (m, 1), 5.37 (m, 2), 5.10–4.90 (m, 2), 2.38 (t, 4), 2.20–1.90 (m, 6), 1.75–1.40 (m, 6), 1.26 (s, 14), 0.88 (t, 3); IR (film, KBr) 3080, 2930, 2860, 1712, 1639, 1455, 1438, 1410, 1367, 990, 968, 909 cm^{-1}; laser Raman (neat) 1714, 1668, 1641 cm^{-1}. **(*E,Z*)-2,6-Heneicosadien-11-one (4):** liquid; NMR (10% C_6H_6/CCl_4) δ 5.54–5.30 (m, 4), 2.39 (t, 4), 2.05 (br s, 6), 1.76–1.50 (m, 6), 1.26 (s, 14), 0.88 (t, 3); IR (film, KBr) 3004, 2850, 2754, 1710, 1650, 1454, 1365, 959 cm^{-1}; laser Raman (neat) 1716, 1673, 1656 cm^{-1}. **(*E,Z*)-3,6-Heneicosadien-11-one (6):** liquid; NMR (10% C_6H_6/CCl_4) δ 5.46–5.24 (m, 4), 2.68 (br t, 2), 2.25 (t, 4), 2.10–1.88 (m, 4), 1.72–1.40 (m, 4), 1.26 (s, 14), 0.96 (t, 6); IR (film KBr) 3007, 2960, 2858, 1715, 1458, 1409, 1370, 965 cm^{-1}; laser Raman (neat) 1717, 1670, 1658 cm^{-1}.

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Registry No.—(*E*)-**2**, 65956-72-1; **7**, 65956-77-6; **8**, 65956-78-7; **9**, 65956-79-8; (*Z*)-**10**, 7348-78-9; (*E*)-**10**, 7348-71-2; **11**, 65956-80-1; (E)-**12**, 65956-81-2; (*Z*)-**12**, 65956-82-3; **13**, 65956-83-4; 2-pentyn-1-ol, 6261-22-9; (*Z*)-2-penten-ol, 1576-95-0; 2-pentyn-5-ol, 10229-10-4; 1-penten-5-ol, 821-09-0; 3-bromo-1-pentene, 53045-71-9; 5-bromo-1-pentene, 1119-51-3; 5-bromo-(*Z*)-2-pentene, 50273-84-2; 5-bromo-(*E*)-2-pentene, 7515-62-0; (*E*)-2-undecen-6-yn-11-ol THP derivative, 65956-84-5; 1-hexyn-6-ol 2Li salt, 65956-85-6; 1-hexyn-6-ol THP derivative, 1720-37-2; 1-hexyn-6-ol, 928-90-5; (*E*)-2-undecen-6-yn-11-ol, 65956-86-7; (*E*)-2-penten-5-ol, 764-37-4; 1-undecen-6-yn-11-ol, 65956-87-8; 11-(2′-tetrahydropyranyloxy)-1-undecen-6-yn, 65956-88-9; (*E*)-1,6-undecadien-11-ol, 65956-89-0; decyl bromide, 112-29-8.

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Chemiluminescence of 2-(6′-Hydroxy-2′-benzothiazolyl)-4-isopropylidene-Δ^2-thiazolin-5-one, a Byproduct Formed in the Chemiluminescence of a Firefly Luciferin Analogue

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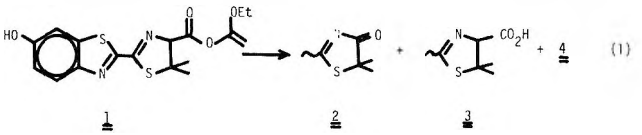
The structure of 2-(6′-hydroxy-2′-benzothiazolyl)-4-isopropylidene-Δ^2-thiazolin-5-one (**4**) is assigned to a byproduct formed in the chemiluminescence of esters of the dimethyl derivative of firefly luciferin (**3**). Compound **4** also proved to be chemiluminescent on reaction with potassium phenoxide and oxygen. Thiazolinecarboxylic acids and thiazolinones are apparently brought into equilibrium by base, and they share a common intermediate in the chemiluminescence reaction.

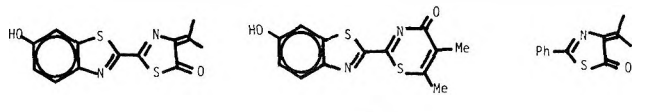
In studies dealing with the chemi- and bioluminescence of firefly luciferin we reported that the ethoxyvinyl ester of the 5,5-dimethyl derivative of luciferin (**1**) was chemilumi-



(1)

1 **2** **3**

nescent on treatment with base and oxygen and that three products were formed: 5,5-dimethyloxyluciferin (**2**) (formed in the excited state), 5,5-dimethylluciferin (**3**) (a hydrolysis product), and a compound analyzing for $C_{13}H_{10}N_2O_2S_2$ (**4**).[1-3] We had earlier proposed, on the basis of preliminary data, that the C_{13} compound was a thiazinone (structure **5**).[1] We now

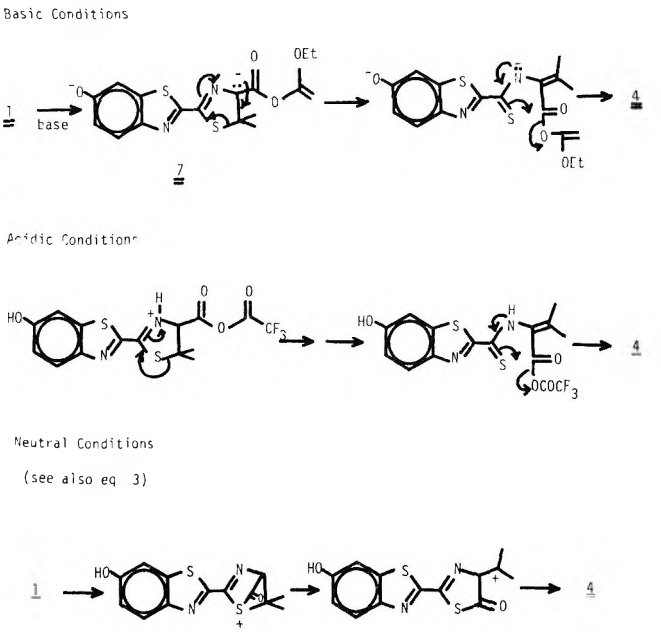


4 **5** **6**

report, with additional evidence, that the C_{13} compound is the isomer 2-(6′-hydroxy-2′-benzothiazolyl)-4-isopropylidene-Δ^2-thiazolin-5-one (**4**).

The proof of structure rests largely on the elemental analysis ($C_{13}H_{10}N_2O_2S_2$) and the formation of acetone on ozonolysis. The mass spectrum showed a parent ion at *m/e* 290, the molecular weight corresponding to the formula given above. The methyl signals in the NMR spectrum, δ 2.45 and 2.51, were similar to the values reported for analogue **6** (δ 2.38 and 2.44).[4] The ultraviolet absorption at 373 nm (in Me_2SO) was consistent with structure **4** in that dimethylluciferin (**3**) absorbs at 330 nm and oxyluciferin **2** absorbs at 390 nm. The infrared absorption at 1660 cm^{-1} (KBr) is consistent with structure **4** (λ_{max} for compound **6** is 1686 cm^{-1} in $CHCl_3$).[4]

Scheme I



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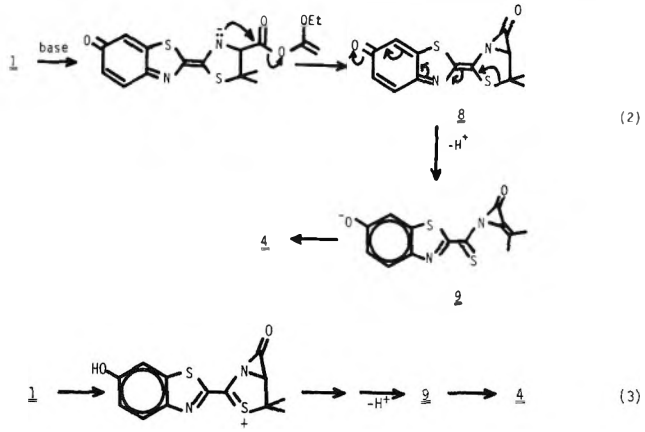
The isopropylidene compound (**4**) was formed under the basic conditions utilized in the chemiluminescence experiments (eq 1). It was also formed under acidic conditions in an attempted synthesis of the phenyl ester of dimethylluciferin (**3**) with a mixture of phenol and trifluoroacetic anhydride, and also under neutral conditions during attempted recrystallizations of compound **1**. Suggested mechanisms for these transformations are given in Scheme I.

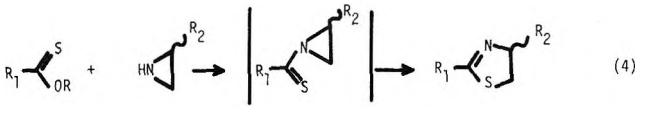
Other conceivable mechanisms involve ionic versions of vinylcyclopropane rearrangements (eq 2 and 3). The versions



(2)

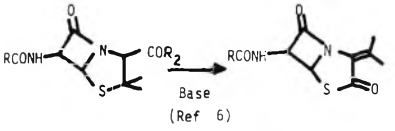
(3)

in eq 2 and 3 or the "neutral" rearrangement in Scheme I may account for the observations that the yield of **4** relative to that of **2** is somewhat greater at low base concentrations and the quantum yield of light emission is lower (the dinegatively charged anion **7** is required for chemiluminescence). Analogies for such rearrangements in heterocyclic compounds exist (eq 4).[5] Several analogies can be cited for the formation of compound **4**.



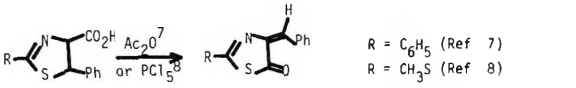
(4)

R_1, R_2 = alkyl or aryl

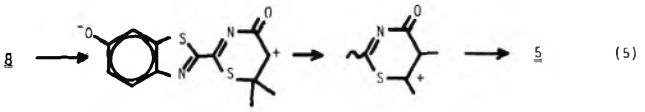


(Ref 6)

R_2 = Cl, OTs, etc.

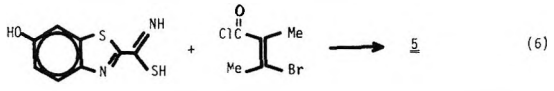


Thiazinones. In the early stages of this work, the C_{13} compound formed in the chemiluminescence of compound **1** was thought to be thiazinone **5** (eq 5). This compound, 2-(6′-



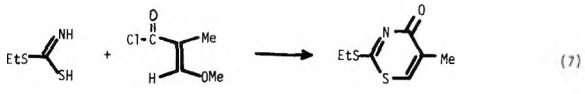
(5)

hydroxy-2′-benzothiazolyl)-5,6-dimethyl-4*H*-1,3-thiazin-4-one (**5**), was synthesized as shown in eq 6. The synthesis is



(6)

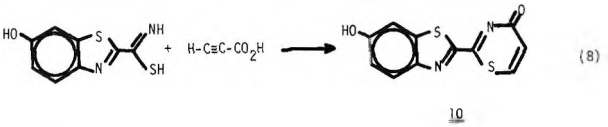
patterned after the preparation of the following thiazinone by Shaw and Warrener (eq 7).[9] The properties of isomers **4**



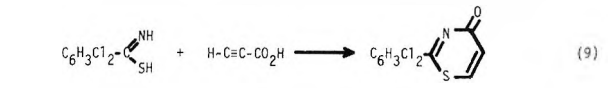
(7)

and **5** are similar, but the formation of acetone in the ozonolysis of **4** establishes its structure.

The parent thiazinone (**10**) was also synthesized (eq 8) since we wished to look for rearrangement products of firefly luciferin itself. The synthesis was patterned after the method of Daams[10] (eq 9) and also of Mushkalo and Yangol.[11] An

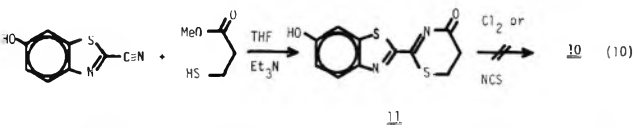


(8)



(9)

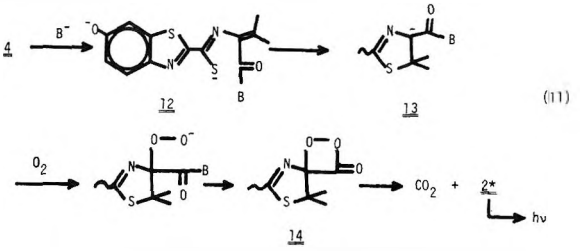
approach to the synthesis of thiazinone **10** via dihydrothiazinone **11** (eq 10) was unsuccessful because of the failure of the



(10)

oxidation step,[12] probably because of the oxidizability of the phenol ring and the heterocyclic functions.

Chemiluminescence. The Isopropylidene compound, **4**, proved to be chemiluminescent on treatment with bases in the presence of oxygen. These conditions are the same as those used in the chemiluminescence of the luciferin ester (**1**) that produces **4**,[1,3] but the isopropylidene compound reacts more slowly ($T_{1/2} \sim 1100$ s) than the luciferin ester ($T_{1/2} \sim 9$ s), permitting its accumulation in the reaction mixture. The only fluorescent compound formed in the chemiluminescence of compound **4** is oxyluciferin **2**. A reaction mechanism for this conversion based on an analogous proposal for the chemiluminescence of firefly luciferin[1] is given in eq 11.

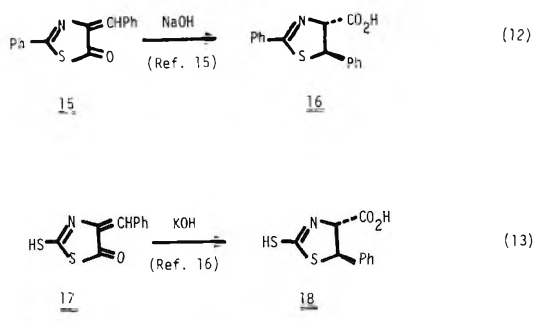


(11)

The quantum yield for the chemiluminescence of **4** is dependent on the nature of the base B. For B = phenoxide ion, QY $\sim 2.5 \times 10^{-2}$ and for B = hydroxide ion, QY $\sim 1.2 \times 10^{-4}$. The lower value for B = hydroxide ion presumably is a result of ionization of the carboxyl group in **12**; the charged carboxylate group would slow the formation of intermediate **13** and effectively block dioxetanone formation (i.e., **14**). An intermediate similar to **13** (B = adenosine monophosphate (AMP)) has been proposed for the bioluminescence of firefly luciferin.[13]

In dilute solutions (1.2×10^{-6} M), the chemiluminescence λ_{max} of **4** is 626 nm, a value close to that of the fluorescence of oxyluciferin (**2**) (631 nm)[1,3,14] and the chemiluminescence emission of the phenyl and AMP esters of **3**.[1,3] The chemiluminescence of ester **1** occurs at 630 nm. In more concentrated solutions ($>2 \times 10^{-5}$ M) the wavelength of chemiluminescence of **4** shifts to 584 nm. An exiplex emission (from **2** + **4**) may be involved since the addition of **4** (10^{-4} M) to a fluorescing solution of **2** (10^{-5} M) shifts the emission from 630 to 585 nm. Also, the addition of **4** to a chemiluminescing solution of ester **1** leads to a shift of the emission wavelength from 630 to 584 nm.

The conversion of compound **4** to **13** is in effect the reverse of the conversion of compound **1** to **4**, implying that the thiazoline carboxylic acid ring system of **1** and **13** and the thiazolinone ring system of **4** can be brought into equilibrium with



base. The conversions of **15** to **16** and **17** to **18**, cited from the literature, are analogies for the conversion of **4** to **13** (eq 11).

Experimental Section

Instrumentation. Melting points were taken with a Thomas-Hoover capillary melting point apparatus or a microscope hot stage and are uncorrected. Elemental analyses were performed by Galbraith Laboratories (Knoxville, Tenn.). Proton magnetic resonance spectra were measured on a JEOL MH-100 or a Varian HA-100 instrument and values are reported relative to tetramethylsilane (Me_4Si). Photometric determinations were made by measuring the output of EMI 9558B or 1P21 photomultiplier-photometers exposed to the reacting solution. The values obtained were corrected for phototube spectral response. Quantum yields are relative to luminol[17] and are ±0.5%. Thin-layer chromatography was performed using 20 × 20 cm Eastman plates coated with cellulose or silica gel.

Materials. Potassium phenoxide solutions were made immediately before use by dissolving freshly sublimed potassium *tert*-butoxide and a half-molar excess of phenol in dry Me_2SO. Phosphoric acid (100%) was prepared by a literature method.[18] Tetrahydrofuran was freshly distilled from $LiAlH_4$ prior to use. The following compounds were synthesized according to literature procedures: 2-cyano-6-hydroxybenzothiazole,[2] ethoxyacetylene,[19] 2-(6′-hydroxy-2′-benzothiazolyl)-5,5-dimethyl-Δ^2-thiazoline-4-carboxylic acid (5,5-dimethylluciferin),[20] 6-hydroxybenzothiazole-2-thiocarboxamide,[21] *trans*-2-methyl-3-bromo-2-butenoic acid (β-bromoangelic acid).[22]

Ethoxyvinyl 2-(6′-Hydroxy-2′-benzothiazolyl)-5,5-dimethyl-Δ^2-thiazoline-4-carboxylate (1) (5,5-Dimethylluciferin Ethoxyvinyl Ester). 5,5-Dimethylluciferin (308 mg, 1 mmol) was dissolved in dry freshly distilled THF (20 mL) under dry nitrogen. Ethoxyacetylene (1.0 mL, 793 mg, 11 mmol) was added via a syringe. Mercuric acetate (6 mg, 0.02 mmol) was added and the solution was stirred at room temperature and monitored by TLC (1:1 ethyl acetate–benzene on silica gel). After 32 h the reaction mixture was poured into ether (50 mL) and the mixture was extracted three times with 5% sodium bicarbonate and once with water. The ether layer was dried (sodium sulfate), filtered, and evaporated to give 354 mg (94%) of 5,5-dimethylluciferin ethoxyvinyl ester: mp 255–256 °C dec; IR (nujol) 3150 (broad), 1785, 1680, 1375, and 1220 cm^{-1}; UV λ_{max} (95% EtOH) 335 (16 200), 267 nm (7900); NMR (Me_2SO-d_6) δ 10.18 (s, 1), 7.96 (d, 1, J = 8.5 Hz), 7.46 (d, 1, J = 2.5 Hz), 7.08 (d of doublets, 1, J = 8.5, 2.5 Hz), 5.24 (s, 1), 3.95 (t, 2, J = 8.0 Hz), 3.95 (m, 2), 1.76 (s, 3), 1.48 (s, 3), 1.26 (t, 3, J = 8.0 Hz). Anal. Calcd for $C_{17}H_{18}N_2S_2O_4$: C, 53.97; H, 4.76; N, 7.41; S, 16.93. Found: C, 53.76; H, 4.61; N, 7.31; S, 16.85.

An attempted recrystallization of this ester from acetone/hexane resulted in the production ~10% of the isopropylidene compound, **4**.

2-(6′-Hydroxy-2′-benzothiazolyl)-4-isopropylidene-Δ^2-thiazolin-5-one (4) from 5,5-Dimethylluciferin, Phenol, and Trifluoroacetic Anhydride. Trifluoroacetic anhydride (4.5 g, 21 mmol) was added dropwise to 5,5-dimethylluciferin (**3**) (77 mg, 0.25 mmol) and phenol (240 mg, 2.5 mmol) with stirring under N_2 at 0 °C. The mixture was then stirred at room temperature for 1 h. The reaction mixture was evaporated to dryness to remove excess anhydride, trifluoroacetic acid, and phenol to give a quantitative yield of 2-(6′-trifluoroacetyl-2′-benzothiazolyl)-4-isopropylidene-Δ^2-thiazolin-5-one (trifluoroacetyl derivative of **4**): NMR ($CDCl_3$) δ 8.17 (d, 1, J = 8 Hz), 7.86 (d, 1, J = 2 Hz), 7.37 (d of d, 1, J = 8, 2 Hz), 2.55 (s, 3), 2.48 (s, 3); IR ($CHCl_3$) 1805, 1690 cm^{-1}. This product was dissolved in ethyl acetate (50 mL) and the solution was washed twice with water. The organic layer was dried (Na_2SO_4) and evaporated to give 66 mg (92%) of compound **4**: mp 250 °C dec; IR (KBr) 3400 (broad), 1660, cm^{-1}; NMR (Me_2SO-d_6) δ 8.12 (d, 1, J = 8 Hz), 7.81 (d, 1, J = 2 Hz), 7.32 (d of d, 1, J = 8, 2 Hz), 2.51 (s, 3), 2.45 (s, 3); UV λ_{max} (95% EtOH) 373 (17 300), 315 (6500), 280 (sh) (7100), 265 (10 900), 257 nm (10 400); λ_{max} (95% EtOH + base) 442 (21 000), 310 (sh) (6600), 285 (8200), 250 nm (9400); λ_{max} (Me_2SO + KOH) 473 (35 200), 320 nm (9400); fluorescence λ_{max} (Me_2SO + potassium phenoxide) 510 nm (λ_{exc} 468 nm); mass spectrum, *m/e* 290 (30), 195 (43), 194 (46), 149 (100).

Anal. Calcd for $C_{13}H_{10}N_2O_2S_2$: C, 53.78; H, 3.47; N, 9.65. Found: C, 53.80; H, 3.37; N, 9.57.

Reaction of 5,5-Dimethylluciferin Ethoxyvinyl Ester (1) with Potassium Phenoxide and Oxygen. 5,5-Dimethylluciferin ethoxyvinyl ester (**1**) (20 mg, 5.3 × 10^{-2} mmol) was placed in a small sealed reaction vessel equipped with a stopcock, magnetic stirring bar, and a septum. Freshly distilled dry Me_2SO (2 mL) was added through the septum and the solution was stirred for 1 min and then degassed by two freeze–pump–thaw cycles. Oxygen (1 atm) was introduced into the reaction vessel and the solution was stirred at room temperature. A freshly prepared potassium phenoxide solution (10 molar excess) was then injected into the vessel through the septum to initiate the reaction and the resulting reaction mixture was stirred for 5 min. The reaction mixture was then frozen in liquid nitrogen for subsequent analysis.

The dark red reaction mixture was thawed and an aliquot (150 μL) was transferred to the bottom of a microsublimer. The solution was acidified with a microdrop of 1 N HCl, the sublimer was evacuated, and the condenser was cooled with dry ice–acetone to remove Me_2SO and excess phenol. The residue was dissolved in 95% EtOH and the solution was applied to a cellulose-coated TLC plate. The plate was eluted with 1:1 MeOH/H_2O. Products separated (followed by R_f and color of band under fluorescent light) were: 5,5-dimethylluciferin (**3**) (R_f 0.88, blue), 5,5-dimethyloxyluciferin (**2**) (0.73, yellow), unknown degradation product (0.54, blue-green), isopropylidene compound **4** (0.19, green). The yields were: **3**, 12%; **2**, 30%; and **4**, 44% (when a 1/1 ratio of phenoxide/**1** was used, the yields were 17, 13, and 53%, respectively). The identities of the products were verified and the yields were determined by scraping the appropriate bands, eluting with 95% EtOH, and analyzing the organic solutions by UV spectroscopy. A close comparison of the IR and mass spectra of the isolated materials with those of authentic samples verified the structure assignments. The blue-green fluorescent compound, produced in low yields, absorbs in the UV at 320 nm and is probably a thiazoline ring-opened material.

A similar run carried out in the absence of oxygen (vacuum) yielded principally the isopropylidene compound (**4**) (55%) along with dimethylluciferin (**3**) (11%) and dimethyloxyluciferin (**2**) (1%).

Ozonolysis of 2-(6′-Hydroxy-2′-benzothiazolyl)-4-isopropylidene-Δ^2-thiazolin-5-one (4). Compound **4** (12.4 mg, 4.27 × 10^{-2} mmol) was dissolved in 1 mL of absolute methanol. The solution was cooled to −30 °C by a methanol–dry ice bath and ozone was bubbled through the yellow solution. The solution became colorless and the bubbling was stopped when the solution turned blue (~10 min). Nitrogen was passed through the solution to displace the ozone and a few drops of a saturated potassium iodide solution in methanol/acetic acid were added. The color of the reaction mixture turned purple. A few drops of a sodium sulfite solution was added to discharge the purple color and 2,4-dinitrophenylhydrazine reagent was added. The precipitate which formed was collected by centrifugation (26 mg, 3.8 × 10^{-2} mmol, 89%). This crude material was analyzed by TLC and was found to contain mostly acetone 2,4-dinitrophenylhydrazone. The crude material was heated to 70 °C under vacuum (10 μm) in a sublimer. The yellow material which sublimed had an R_f on TLC identical to that of authentic acetone 2,4-dinitrophenylhydrazone. TLC: 8:2 ethyl acetate–benzene on silica gel; R_f 0.65 (R_f of authentic acetone DNP 0.65); 8:2 ethyl acetate–benzene on alumina; R_f 0.81 (R_f of authentic acetone DNP 0.81); 1:1 methanol–H_2O on cellulose, R_f 0.76 (R_f of authentic acetone DNP 0.76).

The melting point of the sublimed material on a microscope hot stage was 127–130 °C. Authentic acetone DNP gave a mp of 126–130 °C (lit.[23] mp 130 °C). A control run was made duplicating the above operations except that compound **4** was omitted. No acetone 2,4-dinitrophenylhydrazone was detected in the control run by TLC. In addition a control run was made duplicating the above conditions using 2,4,4-trimethyl-2-pentene (5.8 mg, 5.17 × 10^{-2} mmol) as the substrate to verify the susceptibility of an isopropylidene group to ozonolysis under the above conditions. Acetone 2,4-dinitrophenylhydrazone was verified as the product of the reaction by TLC.

***trans*-2-Methyl-3-bromo-2-butenoyl Chloride (β-Bromoangelic Acid Chloride).** β-Bromoangelic acid (4.7 g, 26 mmol) was added slowly to phosphorous trichloride (2 mL) at 50 °C and the mixture was heated at 60–65 °C for 2.5 h. The supernatant liquid was decanted from the syrupy layer of phosphoric acid. Distillation of the decanted layer under reduced pressure (50 °C (15 mm)) yielded 4.1 g (85%) of 3-bromoangelic acid chloride: bp 55 °C (20 mm); NMR

($CDCl_3$) δ 2.20 (s), 2.55 (s); IR ($CHCl_3$) 1740 and 1775 cm^{-1} (C=O).

2-(6′-Hydroxy-2′-benzothiazolyl)-5,6-dimethyl-4*H*-1,3-thiazin-4-one (5). 6-Hydroxybenzothiazole-2-thiocarboxamide[3] (100 mg, 0.476 mmol) and β-bromoangelic acid chloride (93.6 mg, 0.476 mmol) were dissolved in dry THF (1 mL) in a Pyrex tube. The tube was sealed under vacuum and it was heated to 85 °C for 24 h. The precipitate obtained was filtered and purified by fractional sublimation to give 20 mg (14%) of compound **5**: mp >250 °C; IR (KBr) 1610 cm^{-1}; mass spectrum, *m/e* 290 (59), 176 (20), 149 (58), 114 (91), 86 (100); UV (95% EtOH) λ_{max} 383, 273 nm and with base 490, 300, 250 nm. Anal. Calcd for $C_{13}H_{10}N_2O_2S_2$: C, 53.78; H, 3.47. Found: C, 53.80; H, 3.50.

2-(6′-Hydroxy-2′-benzothiazolyl)-4*H*-1,3-thiazin-4-one (10). 6-Hydroxybenzothiazole-2-thiocarboxamide (100 mg, 0.476 mmol) was added all at once to propiolic acid (~4 mL) under N_2 at room temperature. The mixture turned a red color and became homogeneous. After ca. 0.5 h a precipitate began to form. The reaction was monitored by UV spectroscopy, the λ_{max} shifting from 360 to 380 nm as the reaction progressed. After 6 h the reaction mixture was centrifuged. The precipitate was washed several times by stirring with small portions of ethanol, followed by centrifugation and pipetting off the supernatants. On sublimation of the solids at 170 °C and 10 μm of pressure a yellow material deposited on the cold finger. This material (λ_{max} 320, 255 nm) was discarded. Material was collected after the ratio of the 380 and 325 nm peaks became constant. The residue was 2-(6′-hydroxy-2′-benzothiazolyl)-4*H*-1,3-thiazin-4-one: 58 mg (47%); mp 250 °C; IR (KBr) 3100 (broad), 1615 cm^{-1}; UV λ_{max} (95% EtOH) 385, 275 nm and with base 490, 300, and 250 nm; NMR (Me_2SO-d_6) δ 8.35 (d, 1, J = 10.5 Hz), 8.05 (d, 1, J = 8.0 Hz), 7.64 (d, 1, J = 2.5 Hz), 7.26 (d of d, 1, J = 2.5, 8.0 Hz), 6.70 (d, 1, J = 10.5 Hz); mass spectrum, *m/e* 262 (56), 176 (100), 149 (54), 86 (72). Anal. Calcd for $C_{11}H_6N_2S_2O_2$: C, 50.36; H, 2.29; N, 10.68; S, 24.42. Found: C, 50.46; H, 2.40; N, 10.44; S, 24.63.

2-(6′-Hydroxy-2′-benzothiazolyl)-5,6-dihydro-4*H*-1,3-thiazin-4-one (11). 6-Hydroxy-2-cyanobenzothiazole[3] (100 mg, 0.568 mmol) was dissolved in ca. 0.5 mL of freshly distilled dry THF; methyl 3-mercaptopropionate (732 mg, 6.11 mmol) was added. The solution was then deaerated by bubbling dry nitrogen through the solution. A 4:1 triethylamine–acetic acid mixture (20 microdrops) was added. The solution was refluxed and the reaction was monitored by UV spectroscopy.

The reaction was stopped after 6 h when the 490-nm peak began to decrease relative to a peak at 300 nm. The reaction mixture was evaporated to give an orange oil which was dissolved in THF and applied to six preparative silica gel TLC plates. The plates were eluted with a 4:1 ethyl acetate–benzene mixture. The corresponding bands from each TLC plate were scraped off, combined, and eluted with 95% ethanol. The yellow fluorescent band (red when basic) at R_f ~0.40 yielded 2-(6′-hydroxy-2′-benzothiazolyl)-5,6-dihydro-4*H*-1,3-thiazine-4-one (62.5 mg, 42%). The material was purified by removing volatiles at 10 μm and 180 °C. The residue had the following properties: IR (KBr) 3270 (broad), 1655 cm^{-1}; UV λ_{max} (95% EtOH) 385, 278 and with base 490, 335, 295 nm; mass spectrum, *m/e* 264 (35), 236 (100), 194 (21), 176 (75), 149 (31).

Attempted Oxidation of 2-(6′-Hydroxy-2′-benzothiazolyl)-5,6-dihydro-4*H*-1,3-thiazin-4-one (11). *N*-Chlorosuccinimide Method. 2-(6′-Hydroxy-2′-benzothiazolyl)-5,6-dihydro-4*H*-1,3-thiazin-4-one (0.518 mg, 1.96×10^{-3} mmol) was dissolved in ca. 0.5 mL of freshly distilled glyme. A solution of *N*-chlorosuccinimide (0.400 mg, 3×10^{-3} mmol) in glyme was added at room temperature and the reaction mixture was stirred under N_2. The reaction was followed by TLC (4:1 ethyl acetate–benzene on silica gel) and by liquid chromatography (LC) (12 ft corasil II; 3:1 hexanes–glyme). No compound with a UV spectrum or retention time consistent with the desired product was obtained. **Cl_2 Method:** The reaction operations were similar to the above methods except a Cl_2–glyme solution was used as the source of chlorine. One equivalent of Cl_2 was added to the dihydrothiazine–glyme solution at −78 °C in the dark.[12] No compound with a UV spectrum or retention time consistent with the desired product was obtained.

Chemiluminescence of the Isopropylidene Compound 4. A solution of **4** in dimethyl sulfoxide (2 mL, $M = 2.6 \times 10^{-5}$) was saturated with oxygen. The addition of 0.1 mL of a 1.4×10^{-2} M solution of potassium phenolate at 25 °C led to red light emission, λ_{max} 585 ± 10 nm (fwhm 1480 cm^{-1}) with a half-life of ~1100 s. The addition of 3 molar equiv of oxyluciferin **2** (fluorescence λ_{max} ~630 mm) led to emission at 624 nm. The quantum yield for **4** determined with the luminol standard[17] was 0.025 einstein/mol. At 55 °C the half-life was ~120 s, and the initial emission at 585 nm shifted to 603 nm as the light intensity dropped to the point that spectra could no longer be measured. For 1.2×10^{-6} M solutions at 55 °C, the emission occurred at 626 ± 20 nm; shortly after the first half-life, the intensity had dropped to a point where spectra could no longer be measured. The fluorescence spectrum for the 25 °C run showed λ_{max} at 508 nm initially (λ_{exc} 468 nm) (4 fluoresces at 510 nm) which shifted to 633 nm after standing overnight. The spent reaction mixture showed one spot on silica gel TLC (R_f 0.86; 1:1 benzene–ethyl acetate) corresponding to oxyluciferin **2**.

Chemiluminescence of Ester 1. A solution of **1** in oxygen saturated dimethyl sulfoxide (3.5×10^{-5} M; 3 mL) glowed very weakly; strong red light emission at λ_{max} 633 nm occurred when 0.1 mL of a solution of 1.4×10^{-2} M potassium phenolate in dimethyl sulfoxide was added at 25 °C (half-life = ~9 s). The spent reaction mixture showed two spots on TLC carried out as described above; they were identified as oxyluciferin **2** and isopropylidene compound **4** on the basis of the R_f's (0.86 and 0.54, respectively; the R_f for ester **1** is 0.68).

Chemiluminescence of Ester 1 in the Presence of Isopropylidene Compound 4. Dimethyl sulfoxide solutions of **1** ($M = 3.51 \times 10^{-5}$) and **4** ($M = 2.72 \times 10^{-5}$) were mixed in volume ratios of 3:1, 1:1, and 1:3, corresponding to mol ratios of 3.9, 1.3, and 0.43. To 4 mL of these solutions was added 0.1 mL of 1.4×10^{-2} M potassium phenolate solutions in the same solvent. The λ_{max} of the chemiluminescent emissions were 605, 599, and 584 nm, respectively.

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Registry No.—**1**, 54495-41-9; **3**, 66069-71-4; **4**, 66069-72-5; **4** trifluoroacetyl derivative, 66069-73-6; **5**, 66069-74-7; **10**, 66069-75-8; **11**, 66069-76-9; ethoxyacetylene, 927-80-0; *trans*-2-methyl-3-bromo-2-butenoyl chloride, 66069-77-0; β-bromoangelic acid, 35057-99-9; 6-hydroxybenzothiazole-2-thiocarboxamide, 36727-08-9; propiolic acid, 471-25-0; 6-hydroxy-2-cyanobenzothiazole, 939-69-5; methyl 3-mercaptopropionate, 2935-90-2.

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Mechanism of Photoacetylation of Substituted Adamantanes

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Mechanism of photoacetylation of adamantanes with biacetyl is discussed. The reaction proceeded via triplet biacetyl and had a large ρ^* value (−0.71). Thermolysis of *tert*-butyl 1-adamantaneperoxycarboxylate in biacetyl gave 1-acetyladamantane while *tert*-butyl 2-adamantaneperoxycarboxylate gave both 1- and 2-acetyladamantanes. The exclusive bridgehead substitution in the present photoacetylation is not determined by the radical transfer step, but mostly by the regiospecific abstraction of the bridgehead hydrogen by triplet biacetyl, probably due to the large nonbonded repulsion in a transition state of secondary hydrogen abstraction.

In our current studies on free-radical reactions[1-4] from mechanistic and preparative viewpoints, the authors have drawn a conclusion that adamantane is one of the most appropriate "probes" for radical reactions of saturated hydrocarbons because of its degeneracy (i.e., only two kinds of reaction sites are possible) and of the finding that neither (or least) cleavage nor intramolecular rearrangements take place.

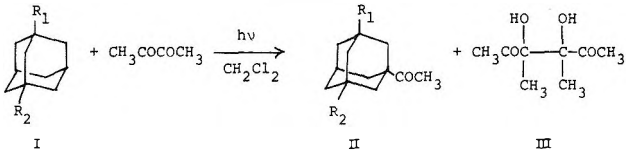
Although many direct functionalizations of adamantane have been successfully carried out via ionic[5-8] as well as free-radical[9-15] routes, no appropriate procedure is known for direct acetylation. Recently the authors have found that the photoacetylation is one of the most excellent procedures for the preparation of bridgehead acetyladamantanes[4,14] regiospecifically. The regiospecific bridgehead substitution is interesting and noteworthy because the photoacetylation proceeds via hydrogen abstraction from adamantanes by excited triplet state of biacetyl,[14] which leads to the simple expectation of nonregiospecific (bridgehead and bridge) product distribution. In this article, mechanistic study is made on the photoacetylation and a possible origin of the unusual regiospecificity, a plausible mechanism, or relative reactivities of substituted adamantanes are discussed.

Results

Products. Irradiation of a methylene chloride solution of adamantane (Ia) and excess biacetyl in a Pyrex vessel with a high-pressure 100-W mercury lamp gave 1-acetyladamantane (IIa) regiospecifically, in 92% preparative yield based on the consumed adamantane, and the coupling product of acetoin radical (III) was also formed in approximately equimolar amount to IIa.[14] The structure of IIa was determined on the basis of melting point and spectral data as well as the chemical conversions to the known compounds. Thus, IIa was converted to 1-adamantanol by the Baeyer–Villiger reaction followed by hydrolysis[5] or to 1-adamantanecarboxylic acid by the bromoform reaction. Any trace of 2-acetyladamantane, or its plausible derivative, was not detected. Substituted adamantanes (I) also gave bridgehead acetyladamantanes (II) regiospecifically and in excellent to good yields as shown in Scheme I. In the case of 1-methoxyadamantane (Ic), expected 1-acetyl-3-methoxyadamantane (IIc) was accompanied by adamantyloxyacetone (**IV**) in the ratio of 10/1.

Relative Reactivities. Sets of competitive reactions between two bridgehead-substituted adamantanes appropriately selected gave a series of relative reactivities of the three positions of 1-substituted adamantanes as shown in Table I. From a plot of the relative rates against σ^*[2] values, −0.71 was

Scheme I



I: (a) $R_1 = R_2 = H$.
(b) $R_1 = CH_3$, $R_2 = H$.
(c) $R_1 = OCH_3$, $R_2 = H$.
(d) $R_1 = CO_2CH_3$, $R_2 = H$.
(e) $R_1 = Br$, $R_2 = H$.
(f) $R_1 = R_2 = CH_3$

obtained as a ρ^* value of the present reaction. Adamantane was photoacetylated more than 100 times as fast as cyclohexane, so the latter was chosen as a relevant standard compound of secondary C–H, since the formation of bridge-substituted adamantanes is negligibly small.

Quenching and Quantum Yield. As shown in Table II, pyrene or oxygen showed a large influence on the reaction, the former quenched the photoacetylation completely and the latter, interestingly, accelerated the product formation in comparison with the run carefully deoxygenated and irradiated under nitrogen. Under oxygen, 1-acetyladamantane, 2-acetyladamantane, and 1-adamantanol[1] were obtained in the ratio of 3.4:1.5:1.

Quantum yields of the formation of 1-acetyladamantane and disappearance of biacetyl was found to be ca. 0.03 and 1.0, respectively, according to the standard method[15] utilizing

Scheme II

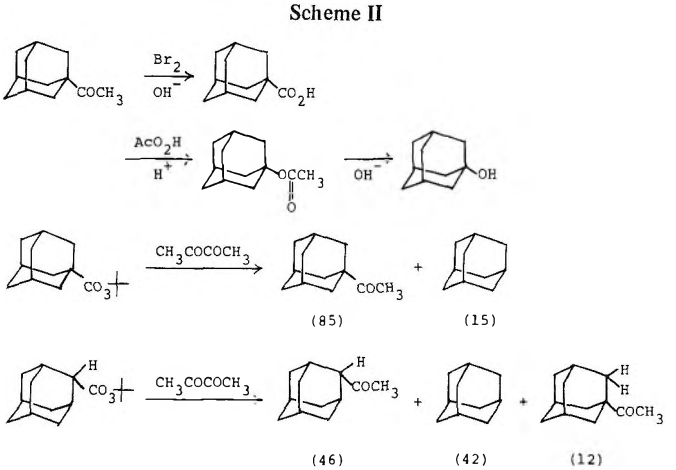


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Table I. Relative Rates of Bridgehead Hydrogen Abstraction from Ad(1)X by the Photoexcited Biacetyl

X	Registry no.	σ^{*a}	k_X/k_H
CH_3, CH_3	702-79-4	−0.20	1.016 ± 0.012
CH_3	768-91-2	−0.10	0.879 ± 0.008
H	281-23-2	0.00	1.00 ± 0.028
OCH_3	6221-74-5	0.52	0.403[b]
CO_2CH_3	711-01-3	0.71	0.220 ± 0.0036
Br	768-90-1	1.00	0.0528 ± 0.0004[c]

[a] Inductive effects estimated from Taft's σ^* values for a series of CH_2X were adopted in ref 2. [b] Taken as a standard, k was statistically corrected. [c] This value was not considered in the calculation of ρ^* because of low yield.

Scheme III

biacetyl ⟶ $(\text{biacetyl})^S$ ⟿ $(\text{biacetyl})^T$ (1)

$(\text{biacetyl})^T$ + AdH ⟶ Ad· + acetoin radical (2)

2 acetoin radical ⟶ III (3)

Ad· + biacetyl ⟶ $AdCOCH_3$ + $\cdot COCH_3$ (4a)

Ad· + Solv-H[a] ⟶ AdH + Solv· (4b)

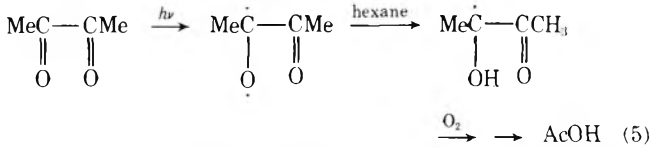
potassium ferrioxalate actinometer.[16] The concentrations employed were 8.4×10^{-2} mol/L of adamantane and 1.66 mol/L of biacetyl.

Decomposition of *tert*-Butyl Adamantaneperoxycarboxylates in Biacetyl. In similar procedure to the general perester preparation,[17] *tert*-butyl 1- and 2-peroxyadamantanecarboxylates were prepared and these peresters were decomposed in biacetyl. Results were shown in Scheme II. 1-Adamantyl perester gave adamantane and 1-acetyladamantane in a ratio of 15:85 and the combined yield was 56% based on *tert*-butyl 1-peroxyadamantanecarboxylate used. 2-Adamantyl perester gave adamantane and 1- and 2-acetyladamantane in a ratio of 42:12:46 and the combined yield was 60% again based on the perester used. No other product was detected.

Discussion

Nature of Hydrogen Abstracting Species. The present photoacetylation (product formation) was completely quenched by the addition of pyrene in an irradiating solution as shown in Table II. This finding indicates that the reaction proceeds via the triplet state of biacetyl since pyrene was reported to quench biacetyl phosphorescence in a nearly diffusion controlled rate through triplet energy transfer.[18] Thus, the mechanism shown in Scheme III was proposed.

In an interesting contrast to the pyrene quenching, oxygen *accelerated* the product formation of the present photoacetylation as shown in Table II. Oxygen is known to quench biacetyl phosphorescence again in a nearly diffusion-controlled rate[19] to give acetic acid.[20] A presented mechanism for acetic acid formation (eq 5) alone, however, does not interpret

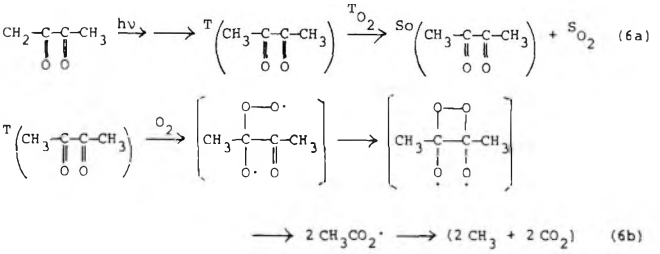


the observation of the efficient phosphorescence quenching. To interpret both of the reported facts, either the direct energy transfer from biacetyl triplet to ground oxygen leading to the formation of ground biacetyl and singlet oxygen, or some interaction between these in such a way as shown in Scheme IV (eq 6b), should be operative. The present finding of somewhat unusual acceleration of the product formation can be understood by accepting the above mechanism (eq 6b), where con-

Table II. Effect of Pyrene or Oxygen on the Photoacetylation of Adamantane (2.0 g of Adamantane, 10.0 g of Biacetyl in 70 mL of Methylene Chloride)

Condition	1-Acetyladamantane, %	2-Acetyladamantane, %	1-Adamantanol, %
N_2, 2.0 h	13.8		
N_2, 235 mg of pyrene added, 2.0 h	0.0		
O_2, 1.5 h	28.6	12.3	8.3

Scheme IV



centration of acetoxyl and/or methyl radical increases, resulting in the observed acceleration of the photoacetylation as well as induced autoxidation. The formation of a considerable amount of 2-acetyladamantane is consistent with the expected low regioselectivity of acetoxyl and/or methyl radicals. Generation of adamantanol under oxygen also supports the mechanism.

Hydrogen Abstraction and Acetyl Transfer. The second step of the reaction is the hydrogen abstraction from adamantane by triplet biacetyl (reaction 2 in Scheme III), which abstracts hydrogen from 2-propanol or ethanol.[21-23] Another product obtained was III (in approximately equimolar amount to acetyladamantane) as expected from the coupling of considerably stable acetoin radicals thus formed (reaction 3 in Scheme III). III was often produced in the solution photochemistry of biacetyl.[21-23] Adamantyl radical thus formed seems to give acetyladamantane by the transfer reaction with ground biacetyl not via the coupling with acetyl radical. The facile formation of 1-acetyladamantane (85% of total products) from 1-adamantyl radical generated by the thermolysis of the corresponding perester in biacetyl as shown in Scheme II supports the acetyl transfer mechanism (eq 4a) as the major path of the acetylation. A considerable amount (15% of total products) of adamantane was also detected, indicating the concurrent hydrogen abstraction (eq 4b). Similarly, 2-adamantyl radical gave 2-acetyladamantane (46%) as one of the major products, but 1-acetyladamantane (12%) was also formed together with adamantane (42%). Formation of the latter two compounds from 2-adamantyl radical is best interpreted by the mechanism of eq 9–12 via formation of adamantane. A ratio of transfer rate constant to abstraction rate constant was thus estimated for 1- or 2-adamantyl radical from the corresponding product ratio (see Scheme V). Relatively low value of k_{tr}/k_{ab} for 2-adamantyl radical may arise from larger steric hindrance in a transition state of 2-adamantyl transfer step (eq 9), since the steric effect is known to be a controlling factor in the atom transfer step of 2-adamantyl radical[1] (vide infra).

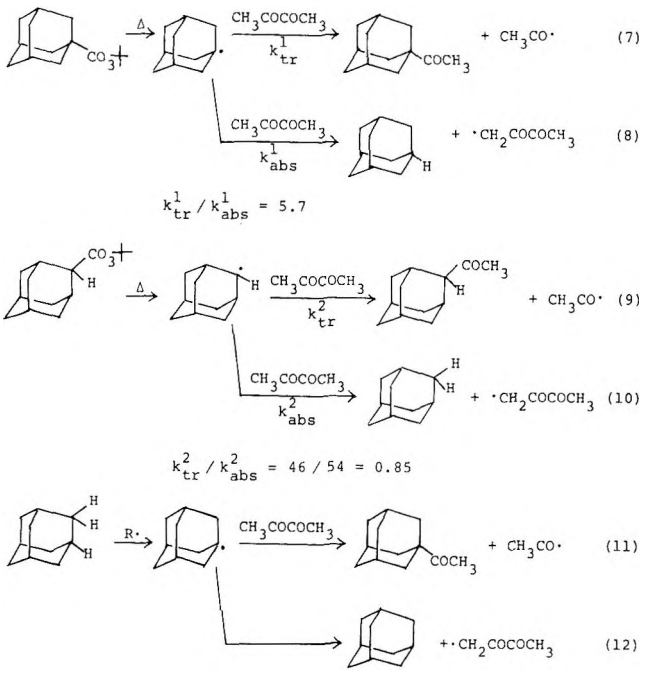
The quantum yield of the formation of acetyladamantane was ca. 0.03 and that of the disappearance of biacetyl was ca. 1. These values indicate that the major reaction for biacetyl[24] was its photodecomposition investigated earlier.[25] Acetyl radical from reaction 4 or methyl radical from the decarbonylation of acetyl may be a chain carrier of the decomposition of biacetyl. The low yield of acetylated compound in the case

Table III. BH/BR Reactivity Ratios

Attacking radical	BH/BR	Ref	ρ^*
·Cl	1.9–6.3	32	
·Br	9.0	1	−0.59[a]
·CH_2Br	9.0	1	
·CCl_3	24.3	1	−0.40[b]
T (biacetyl)	∞	This work	−0.71

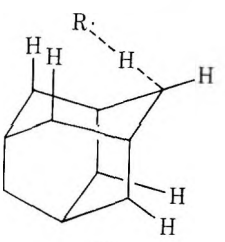
[a] Reference 27. [b] Reference 2.

Scheme V



of radical reaction utilizing initiator[26] may also be explained on the same grounds.

Exclusive Bridgehead Substitution. Although a radical in nature, biacetyl triplet in the present photoacetylation has a characteristic of exclusive bridgehead substitution. Reasonable assumptions to interpret this characteristic are: (i) Nearly exclusive hydrogen abstraction at bridgehead by triplet biacetyl, or (ii) much less facile acetyl transfer to adamantyl bridge than bridgehead radical from biacetyl. Among these, assumption (ii) is not the major product determining factor because adamantyl-2 radical, once formed, should give 2-acetyladamantane in ca. 30% yield (loc. cit.) in the presence of biacetyl (see Scheme V). Thus the conclusion may be drawn that the bridge hydrogen is not appreciably abstracted by triplet biacetyl. This very low reactivity of the bridge hydrogen toward radical abstraction may be due to the significant nonbonded repulsion between the attacking radical and β-axial hydrogens in the transition state IV. In Table III,



IV

bridgehead/bridge reactivity ratios were listed for a series of radical species. Comparing with other abstracting species, biacetyl should be very bulky in a sense that remote nonbonded repulsion is important. As is apparent from the table, *polar* effect (magnitude of ρ^*) is not reflected by the observed reactivity ratio (vide infra).

Large ρ^* Value. From a series of competitive experiments on substituted adamantanes, the ρ^* value of the photoacetylation was estimated to be −0.71. For comparison, several ρ values are shown in Table IV. Reported ρ^+ values for the benzylic hydrogen abstraction from substituted toluenes are multiplied by 0.4/1.46 in order to draw direct comparison with ρ^* for adamantanes, taking trichloromethyl radical as a standard. The present photoacetylation gives the largest ρ^* value among the radical substitutions investigated and it is considerably larger than that for benzophenone which is estimated to be −0.32 or −0.49. It is suggested[2] that the ρ^* value was a direct indicator of positive charge developed in the transition state of hydrogen abstraction. Oxygen atom in the ($n\pi^*$) state is formally half electron deficient and thought to be highly electrophilic.[28] The highly electrophilic character of the oxygen of triplet biacetyl (much stronger than triplet benzophenone on the basis of ρ^* values observed) may be due to electron withdrawal of the neighboring acetyl group.

Experimental Section

Materials. Commercially available adamantane and biacetyl were used with purification. 1-Bromoadamantane,[5] 1-adamantanecarboxylic acid,[6] 1-carbomethoxyadamantane,[6] and 1-methoxyadamantane[2] were prepared according to the literature.

***tert*-Butyl 1-Peroxyadamantanecarboxylate.** A dry pentane solution (5 mL) of 1-adamantanecarbonyl chloride, prepared from 1-adamantanecarboxylic acid (900 mg; 5 mmol) and thionyl chloride (6 mL), was kept at −6 to −7 °C. Into the solution was added a pentane solution (20 mL) of *tert*-butyl hydroperoxide (460 mg; 5.1 mmol) and pyridine (410 mg) dropwise and with stirring for 30 min. After the addition was over, the solution was further stirred below 0 °C for a few hours and allowed to warm up to room temperature and then kept overnight. The white precipitate was filtered and the filtrate was washed with dilute aqueous $NaHCO_3$ and then with water. The pentane solution was dried over $MgSO_4$ and evaporated. The residual oil was purified on a silica gel column using benzene as an eluent. Thus 420 mg (33%) of the perester was obtained. Spectral data were consistent with the literature.[29]

***tert*-Butyl 2-Peroxyadamantanecarboxylate.** 2-Adamantanecarboxylic acid was prepared by the free-radical chlorocarbonylation[12] of adamantane followed by esterification, fractional distillation, and hydrolysis.[12] *tert*-Butyl 2-peroxyadamantanecarboxylate was prepared in 49% yield from 2-adamantanecarboxylic acid by a similar procedure used for *tert*-butyl 1-peroxyadamantanecarboxylate: mp 61.0–62.0 °C; IR (neat) 2930, 1770, 1190, and 1165 cm^{-1}; NMR ($CDCl_3$) δ 1.37 (9 H, *tert*-butyl, singlet), 1.7–2.1 (12 H, multiplet), 2.1–2.5 (2 H, multiplet), 2.73 (1 H, α-H of the perester, multiplet).

Thermolysis of *tert*-Butyl 1-Peroxyadamantanecarboxylate. A solution of *tert*-butyl 1-adamantaneperoxycarboxylate (540 mg, 2.14 mmol) and biacetyl (7.544 g, 87.5 mmol) was kept at 80 °C for 2 h in a sealed tube. Products obtained were adamantane and acetyladamantane and any other product was not detected. Yields of adamantane and 1-acetyladamantane were found to be 8.5 and 48%, respectively. 2-Acetyladamantane was not detected at all by GLC or NMR which was investigated for acetyladamantane collected by preparative GLC.

Thermolysis of *tert*-Butyl 2-Adamantaneperoxycarboxylate. A solution of *tert*-butyl 2-adamantaneperoxycarboxylate (540 mg, 2.14 mmol) and biacetyl (7.544 g, 87.5 mmol) was kept at 80 °C for 70 h[30] in a sealed tube. Yields of adamantane and acetyladamantanes were found to be 25 and 35%, respectively, from the GLC analysis. Separation of 1- and 2-acetyladamantane by GLC was very poor. For the determination of the ratio of 1- to 2-acetyladamantane, a mixture of acetyladamantanes collected by preparative GLC was analyzed by NMR spectrum on the methyl protons of 1- and 2-acetyl groups which appeared as sharp singlets at δ 2.04 and 2.09, respectively. The NMR methyl signal was further ascertained by acetyladamantanes in relevant syntheses (vide infra). Thus, the ratio of 1- to 2-acetyladamantane in the photoacetylation was determined as 21/79.

Preparation of 2-Acetyladamantane. 2-Acetyladamantane was prepared from 2-adamantanecarboxylic acid by a similar procedure as that reported for the preparation of 1-acetyladamantane[31] in 48% yield: bp 103–105 °C (15 mmHg); $\mu_{C=O}$ 1710 cm^{-1}; NMR (CCl_4) δ 2.09 (singlet, $COCH_3$) and 2.0–1.6 (multiplet, 15 H).

Table IV

Substrate	Abstracting species	Kind of σ employed	ρ	Ref
p-X-C_6H_4-CH_3	·CCl_3	σ^+	−1.46	*e*
p-X-C_6H_4-CH_3	·Br	σ^+	−1.39	*f*
p-X-C_6H_4-CH_3	$(C_6H_5)_2\dot{C}$–Ȯ	σ^+	−1.16	*g*
p-X-C_6H_4-CH_3	·Cl	σ^+	−0.66	*h*
p-X-C_6H_4-CH_3	$(CH_3)_3C$–O·	σ and σ^+	−0.599[a], −0.35[b]	
1-X-$C_{10}H_{14}$-3-H[c]	·Br	σ^*	−0.59	27
1-X-$C_{10}H_{14}$-3-H	·CCl_3	σ^*	−0.40	2
1-X-$C_{10}H_{14}$-3-H	$CH_3(CH_3CO)\dot{C}$–Ȯ	σ^*	−0.71	This work
1-X-$C_{10}H_{14}$-3-H	$(C_6H_5)_2\dot{C}$–Ȯ	σ^*	−0.32, −0.49[d]	

[a] In benzene (footnote *i*). [b] In 1,1,2-trichlorotrifluorethane (footnote *j*). [c] 1-Substituted adamantanes. [d] Extrapolated from ρ values for trichloromethyl radical-substituted toluene reactions by use of k_X/k_H and σ^* in Table I. [e] E. S. Huyser, *J. Am. Chem. Soc.*, **82**, 394 (1960). [f] R. E. Pearson and J. C. Martin. *ibid.*, **85**, 354 (1963). [g] C. Walling and M. J. Gibian, *ibid.*, **87**, 3361 (1965). [h] G. A. Russell and R. C. Williamson, Jr., *ibid.*, **86**, 2357 (1964). [i] R. D. Gillion and B. F. Ward, Jr., *J. Am. Chem. Soc.*, **87**, 3944 (1965). [j] H. Sakurai and A. Hosomi, *ibid.*, **89**, 458 (1967).

Table V. NMR Spectra of Acetyladamantanes (CCl_4 or $CDCl_3$*, Me_4Si, δ)

Compd	Registry no.	NMR Spectra[a]
IIb*	42825-01-4	2.5–1.84 (m, 5 H) [2.09 (s, 3 H)], 1.80–1.30 (m, 12 H), 0.84 (s, 3 H)
IIc	42825-02-5	3.17 (s, 3 H), 2.40–2.10 (m, 2 H), 2.03 (s, 3 H), 1.77–1.47 (m, 12 H)
IV	42824-40-8	3.80 (s, 2 H), 2.16 (s, 3 H)
IId	42825-03-6	3.64 (s, 3 H), 2.25–2.10 (m, 2 H), 2.05 (s, 3 H), 1.95–1.65 (m, 12 H)
IIe	39917-43-6	2.40–2.20 (m, 6 H), 2.2–2.06 (m, 2 H), 2.04 (s, 3 H), 1.83–1.47 (m, 6 H)
IIf	40430-57-7	2.14 (m, 1 H), 2.00 (s, 3 H), 1.77–1.53 (m, 2 H), 1.53–1.27 (m, 8 H), 1.27–1.10 (m, 2 H), 0.87 (s, 6 H)

[a] m, multiplet; s, singlet.

Determination of Quantum Yield. Quantum yields of the formation of acetyladamantane and disappearance of biacetyl were determined by the standard method[15] with a potassium ferroxalate actinometer.[16] A three-compartment quarz cell of optical paths of 5, 5, and 10 cm was used. In the front cell $CoSO_4$ solution (8.4 g/100 cm^3),[15] in the central cell methylene chloride solution (35 mL) of adamantane (400 mg) and biacetyl (5 g), and in the rear cell $K_3Fe(C_2O_4)_3$ solutions (0.006 M)[15] were placed. The amounts of acetyladamantane that formed and biacetyl that disappeared were determined by GPC. Thus quantum yield was estimated to be ca. 0.03 for the formation of 1-acetyladamantane and ca. 1.0 for the disappearance of biacetyl.

Competitive Reactions. 1-Methoxyadamantane was used as a reference compound to investigate the relative reactivity of a 1-substituted adamantane. Thus, 2 g of 1-methoxyadamantane and an appropriate amount of a 1-substituted adamantane (the amount of the latter was calculated on the basis of the preliminary results of the competitive reaction so as to give roughly the equimolar amount of acetylated products from 1-methoxy and from the other adamantane in order to maximize the precision on GPC analyses) were irradiated in a Pyrex vessel with a 100-W high-pressure mercury lamp in methylene chloride solution (90 mL) of biacetyl (20 mL) under nitrogen. The relative rate of the formation of 1-bridgehead-substituted 3-acetyladamantane was followed by GPC. Based on the observed product ratio, k_X/k_{OCH_3} (methoxyadamantane is taken as a standard) was calculated in a similar way as in the literature,[2] where K_X is rate constant for 1-X-substituted adamantane (see Table I) and k_X/k_{OCH_3} was converted into k_X/k_H. The mean value from several runs was shown in Table I.

Preparative Photoacetylation. As a typical example, photoacetylation of adamantane is described. The procedure is practically the same for any other substituted adamantane. A solution of adamantane (5.0 g) and biacetyl (30 mL) in methylene chloride (80 mL) was irradiated in a Pyrex vessel by a high-pressure 100-W mercury lamp with water cooling under nitrogen for 8.5 h. Methylene chloride was distilled off and the adamantane that precipitated was collected and washed with methanol. The filtrate was further condensed to gain an additional crop of unreacted adamantane which was washed with methanol. Thus, from the precipitate was recovered 3.9 g of practically pure adamantane. The filtrate was distilled and the distillate at 72–82 °C (5 mmHg) was collected, dissolved in methylene chloride, and washed with 0.1 N NaOH solution. The organic layer was dried over $CaCl_2$ and methylene chloride was distilled off. From the residue practically pure 1-acetyladamantane was obtained (1.33 g, 92%) through a silica gel column eluted with petroleum ether, mp 53–54 °C (MeOH–H_2O) (lit.[31] mp 53–54 °C). Yields of isolated acetyladamantanes based on adamantanes consumed are described below in parentheses. NMR spectra are shown in Table V.

1-Acetyl-3,5-dimethyladamantane (IIf): 89%; $n^{25}D$ 1.4900; IR (neat) 1700 (C=O), 1230, 1170 cm^{-1}; mass spectrum *m/e* (fragment assigned, rel intensity) 206 (M^+ 3.66), 165, 164, and 163 ($Ad(Me)_2)^+$, 21.5, 93.2, 98.5), 107 (100).

1-Acetyl-3-carbomethoxyadamantane (IId): 75%; $n^{25}D$ 1.4967; IR (neat) 1730 and 1700 (C=O), 1260, 1210, 1090 cm^{-1}; mass spectrum *m/e* (fragment assigned, rel intensity) 236 (M^+, 8.1), 194 and 193 ($AdCO_2CH_3^+$, 20.8, 100), 177 ($AdCOCH_3^+$, 13.6), 161 (35.0), 137, 136 and 135 (Ad^+, 11.0, 16.2, 79.2).

1-Acetyl-3-bromoadamantane (IIe): 22%; $n^{25}D$ 1.5395; IR (neat 1700 (C=O), 1220 cm^{-1}; mass spectrum *m/e* (fragment assigned, rel intensity) 258, 257, and 256 (M^+, 0.15, 0.075, 0.17), 213, 214, 215, and 216 ($AdBr^+$, 3.84, 37.0, 4.34, 37.8).

1-Acetyl-3-methoxyadamantane (IIc): 58%; $n^{25}D$ 1.4971; IR (neat) 1700 (C=O), 1120, 1100, 1060 cm^{-1}; mass spectrum *m/e* (fragment assigned, rel intensity) 209 and 208 (M^+, 1 9, 15.5), 177 ($AdCOCH_3^+$, 2.07), 166 and 165 ($AdOMe^+$, 26.8, 100).

1-Adamantyloxyacetone (IV): 5.2%; IR (neat) 1720 (C=O), 1360, 1120, 1100 cm^{-1}; mass spectrum (fragment assigned, rel intensity) 208 (M^+, 0.9), 198 (2.8), 178 (10.2), 166 and 165 ($AdOCH_2^+$, 1.33, 12.0), 136 and 135 (Ad^+, 33.0, 100).

1-Acetyl-3-methyladamantane (IIb): 86%; $n^{25}D$ 1.4901; IR (neat) 1700 (C=O), 1230, 1140 cm^{-1}; mass spectrum *m/e* (fragment assigned, rel intensity) 193 and 192 (M^+, 0.66, 4.25), 177 ($AdCOCH_3^+$, 0.72), 150 and 149 ($AdMe^+$, 13.5, 100).

Registry No.—IIa, 1660-04-4; *tert*-butyl 1-peroxyadamantanecarboxylate, 21245-43-2; 1-adamantanecarbonyl chloride, 2094-72-6; *tert*-butyl 2-peroxyadamantanecarboxylate, 53561-90-3; 2-adamantanecarboxylic acid, 15897-81-1; 2-acetyladamantane, 22635-58-1; biacetyl, 431-03-8.

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Correlation of Rate–Solvent Effects in Ionogenic Reactions

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There is ample evidence that a relation of log k with some commonly employed solvent parameter at a given temperature is not always a reliable index of the polarity of the activated complex. Through study of the temperature dependence of log k as a function of an empirical solvent property, viz. $\Delta G^{\ddagger}$ vs. (say) E_T, some perception of the ionogenic character of a reaction can be gained. The principal objective of this report is to show in some instances that the same rate data may be correlated with a universal and directly measurable property of matter, namely the dielectric, to permit a more quantitative and informative comparison of reaction transition states with respect to their polarities. For ionogenic reactions, where the activated complex possesses a significant dipole moment, a simple electrostatic argument based on the model developed by Kirkwood[9] is used to derive relationships between the activation parameters and readily accessible functions of the solvent dielectric (eq 9 → 13). These relationships have been tested by data gathered for two well known cases, the thermolysis of α-chlorobenzyl alkyl ethers[1] and the cycloaddition of TCNE to enol ethers,[8,10] both in aprotic solvents. In both cases the linear relationship involving activation free energy is found to be relatively insensitive to the occurrence of "chemical" interactions between the solvent and zwitterionic activated complex. However, though this treatment predicts an inverse linear correlation of negative activation entropy and solvent polarity, it is shown that "chemical" contributions of this nature can destroy the linearity and steeply invert the relationship so that the most polar solvents appear to be associated with the most negative entropies of activation. But, for a transition state of sufficiently high dipole moment, the "chemical" contribution term tends to predominate over the solvent dielectric term and to influence the $\Delta S^{\circ\ddagger}$ in such a way as to restore the appearance of linearity for all cases except those in which the solvent has nearly zero polarizability.

The use of empirical solvent parameters as a means of correlating solvent effects on rate has developed greatly since the introduction of the Winstein–Grunwald Y-value scale.[1a] Others such as the Kosower Z values[1b] and the Reichardt E_T values[1c] have gained widespread application in probing the polarity of the activated complex. Such applications rely on the occurrence of a simple linear plot of log k vs. (say) E_T at a given temperature, the steepness of the slope of the resulting line being accepted as a proportional measure of transition state polarity. But the information to be realized from this exercise is frequently of limited value; such factors in a polar transition state as charge separation and dipole moment do not emerge from the empirical solvent parameter relationship with rate.

Moreover, it is by no means unusual for an ionogenic reaction to display an inverse relationship between rate and an empirical measure of solvent polarity at a single temperature. Under circumstances where this is close to the isokinetic temperature,[2,3a] a frequently undetected occurrence, plots of log k vs.(say) E_T can be illusory. Two recent examples come to mind in which, at the given temperature, the observed inverse relationship of rate and solvent polarity suggested a non-ionogenic or a concerted process with an unpolarized transition state, namely, the thermolysis of trimethylsilylacetophenones to siloxyalkenes[2] and the corresponding rearrangement of aryl allyl sulfides[4] in aprotic solvents. Unequivocal evidence has subsequently been found to demonstrate the intervention of zwitterionic activated complexes in both of these cases.[3,4]

In a previous article[5] reporting on the thermolysis of α-chloro ethers in aprotic solvents, it was noted that the activation parameters E_a, $\Delta S^{\ddagger}$ and $\Delta G^{\ddagger}$ for the reaction in seven solvents showed a decreasing trend with increasing ionizing character of the solvent. These results in conjunction with

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other considerations have been construed to support the classical Ingold picture[6] of a reaction process with an ion pair intermediate. However, the observation in such cases that greater negative values of $\Delta S^{\ddagger}$ occur with more polar solvents is not without exception; in fact a fairly extensive body of data has accumulated which does not fulfill this expectation.[7,8]

In order to avoid some of these pitfalls and to gain a greater perception of the charged structure of the transition state through application of a rate–solvent effect criterion it becomes necessary to reconsider the use of empirical solvent parameters. A return to correlations of rate with a direct, physical measure of solvent polarity, namely, the dielectric property, seemed to be recommended. Some well-trodden ground has been chosen as the foundation for an approach to interpreting solvent–rate effects in ionogenic reactions; it is based on a well-established treatment[9,10] which has previously provided sound guidance in the understanding of electrostatic interactions in solution.

Discussion of Results

Before considering the specific problem associated with α-chloro ether thermolysis[5] it is useful to review in a qualitative way the molecular basis for the effect of solvent on reaction rates. Given the reaction expressed by the equation

$$A \rightleftharpoons \ddagger \xrightarrow{k} \text{products} \qquad (1)$$

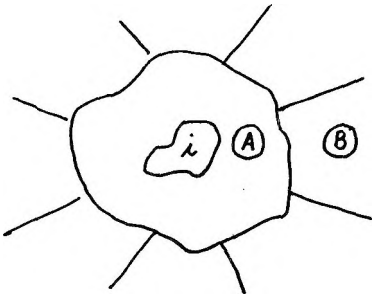
where A and $\ddagger$ denote reactant and activated complex, respectively, and applying the transition state theory of reaction rates,[11] the rate constant k for this process is obtainable from the equation

$$\ln k = \ln (KT/h) - \Delta G^{\circ\ddagger}/RT \qquad (2)$$

where h, K, and T have their usual meanings and $\Delta G^{\circ\ddagger}$ is the difference between the standard state chemical potentials of the activated complex and the reactants expressed by the equation

$$\Delta G^{\circ\ddagger} = \mu^{\circ\ddagger} - \mu^{\circ A} \qquad (3)$$

The standard state chemical potential refers to the species at infinite dilution in the particular solvent under consideration. It is constituted from contributions which depend upon the structure of the solute species (intrinsic effects) and contributions arising from species–solvent interactions (extrinsic effects). Although it is convenient to visualize the chemical potential as being composed of contributions from these two sources, strictly speaking they are not completely independent and separable. The molecular situation for a given solute species, i, can be represented diagrammatically[12,13] as follows.



The region A corresponds to solvent adjacent to solute species i and having properties which differ to a greater or lesser extent from the properties of bulk solvent represented by the region B. The difference in properties of these two solvent regions stem from the presence of the solute species perturbing the solvent in its immediate vicinity. Expectedly, also, the solvent should modify the solute molecule to some extent and cause a lack of additivity of intrinsic and extrinsic contributions to the solute chemical potential. However, in all probability this effect is small and can be neglected in most of the following considerations. We may, therefore, assume[14] that the standard state chemical potential of a species can be represented as the sum of two contributions as given by the equation

$$\mu^{\circ} = \mu^{\circ}_{\text{int}} + \mu^{\circ}_{\text{ext}} \qquad (4)$$

where μ°_{int} depends on the molecular nature of the species, and μ°_{ext} reflects the extrinsic interaction stemming from the specific interaction of the species with the solvent.

As a consequence, the standard free energy change (eq 2) for the reaction (eq 1) is given by the equation

$$\Delta G^{\circ\ddagger} = (\mu^{\circ}_{\ddagger,\text{int}} - \mu^{\circ}_{\text{A,int}}) + (\mu^{\circ}_{\ddagger,\text{ext}} - \mu^{\circ}_{\text{A,ext}}), \text{ or}$$

$$\Delta G^{\circ\ddagger} = \Delta G^{\circ\ddagger}_{\text{int}} + \Delta G^{\circ\ddagger}_{\text{ext}} \qquad (5)$$

It is apparent from this that a solvent effect on the rate of reaction should generally be expected since, although the first term on the right hand side of eq 5 would be essentially solvent independent, the second term should depend to a greater or lesser extent upon the solvent nature.

Applying the usual thermodynamic manipulations to eq 5 leads to the equations

$$\Delta G^{\circ\ddagger} = \Delta H^{\circ\ddagger} - T\Delta S^{\circ\ddagger}$$

$$\Delta G^{\circ\ddagger} = (h^{\circ}_{\ddagger,\text{int}} - h^{\circ}_{\text{A,int}}) + (h^{\circ}_{\ddagger,\text{ext}} - h^{\circ}_{\text{A,ext}}) - T[(s^{\circ}_{\ddagger,\text{int}} - s^{\circ}_{\text{A,int}}) + (s^{\circ}_{\ddagger,\text{ext}} - s^{\circ}_{\text{A,ext}})] \qquad (6)$$

As before, we would expect the changes in intrinsic enthalpy and entropy to be solvent independent, while the remaining terms would not be. Thus, the basic formulation of the effect of solvents on free-energy changes and reaction rate constants, within the context of transition state theory, is apparently quite straightforward. The problem, however, is to arrive at expressions for the extrinsic contributions based on the physical properties of the solvents considered.

There have been many discussions of this matter[2] all of which foster the conclusion that no single approach can be applied for all types of reactions. In certain situations, by making rather drastic assumptions, it is possible to derive expressions for rate dependence on solvent. For instance, in reactions involving the formation of ions from a covalency, a simple expression results by assuming that the solvent is a continuous dielectric. This relationship, the Born equation, describes the dependence of the extrinsic free-energy change on the dielectric constant. There is a considerable body of evidence,[15] however, which indicates that the Born equation[16] estimates the free-energy changes of real chemical processes only in a semiquantitative way at best. On the other hand, it is clearly preferable[14] to designate the extrinsic contribution to the chemical potential of a given ionic process as the sum of two terms, one arising from electrostatic effects and the other from what one might call "chemical" effects. The latter would include contributions from (say) solvent reorganization and packing effects and such specific interactions between solvent and solute as hydrogen bonding. It would seem eminently reasonable, therefore, to represent in an analogous way the contributions to the free-energy change which occur when completely isolated ionic charges are not formed, i.e., by transforming eq 5 into

$$\Delta G^{\circ\ddagger} = \Delta G^{\circ\ddagger}_{\text{int}} + \Delta G^{\circ\ddagger}_{\text{elec}} + \Delta G^{\circ\ddagger}_{\text{chem}} \qquad (7)$$

where the last two terms on the right hand side correspond to $\Delta G^{\circ\ddagger}_{\text{ext}}$. Though it cannot be stated categorically, it may be supposed that $\Delta G^{\circ\ddagger}_{\text{chem}}$ would be smaller the less structured and idiosyncratic the solvent species is. If, for example, the

Table I. Solvent Dielectrics and Dielectric Functions

Solvent	ϵ[a]	$-d\epsilon/dT$[a]	$(\epsilon-1)/(2\epsilon+1)$	$-(d\epsilon/dT)\cdot[1/(2\epsilon+1)^2]$
Acetonitrile	36.75	0.186	0.4799	3.35×10^{-5}
Sulfolane	43.32		0.4829	
Chloroform	4.72	0.0177	0.3563	1.62×10^{-4}
Chlorobenzene	5.62	0.0168	0.3775	1.12×10^{-4}
Toluene	2.38	0.00243	0.2396	7.32×10^{-5}
Carbon tetrachloride	2.23	0.00200	0.2253	6.71×10^{-5}
Nitrobenzene	34.82	0.1804	0.4788	3.62×10^{-5}
Cyclohexane	2.02	0.00160	0.2030	6.30×10^{-5}
Tetrahydrofuran	7.39		0.4050	
Ethyl acetate	6.02	0.0150	0.385	8.82×10^{-5}
Methylene chloride	9.08	0.0373	0.422	1.016×10^{-4}
Acetone	20.7	0.0977	0.465	5.43×10^{-5}
Benzonitrile	25.19		0.471	

[a] These data are taken or computed from data in ref 17 and 18.

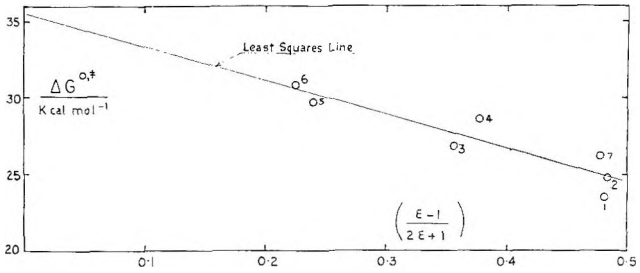


Figure 1. Activation free-energy change with solvent dielectric function in thermolysis of α-chlorobenzyl methyl ether. Least-squares computation: slope = −21.6; intercept = 35.4; correlation coefficient R = −0.92.

Solvent	Graph index	$\Delta G^{\circ\ddagger}$, kcal mol^{-1}[a]
CH_3CN	1	23.6
Sulfolane	2	24.8
$CHCl_3$	3	26.8
C_6H_5Cl	4	28.6
$C_6H_5CH_3$	5	29.7
CCl_4	6	30.8
$C_6H_5NO_2$	7	26.2

[a] Data from ref 5.

solvent was capable of hydrogen bonding with either the reactant or the activated complex, this interaction would presumably drive $\Delta G^{\circ\ddagger}_{chem}$ toward a large value.

Bearing in mind the above deductions, we may now turn to consideration of the specific problem of the thermolysis of α-chloro ethers in aprotic solvents shown[1] to take place via an ion-paired intermediate. This develops from an activated complex possessing a high dipole moment. For such circumstances it is plausible to use a simple electrostatic argument based upon a model developed some years ago by Kirkwood[9] to explain some of the thermodynamic properties of amino acids. The solvent dependence of the electrostatic contribution to the free energy of zwitterionic species has been considered in the Kirkwood treatment.[9] The model he used corresponded to a spherical solute species in the continuous dielectric solvent. For such a system the electrostatic contribution to the chemical potential is given by the equation

$$\mu^{\circ\ddagger}_{elec} = \frac{L\bar{\mu}^2}{b^3}\left(\frac{1-\epsilon}{2\epsilon+1}\right) \quad (8)$$

where L, μ, b, and ϵ are Avogadro's constant, the dipole moment, and the radius of the zwitterionic species, respectively, and the dielectric constant of the solvent. Equation 8 and modifications of it have been used successfully to explain the behavior of peptides in solution.[17]

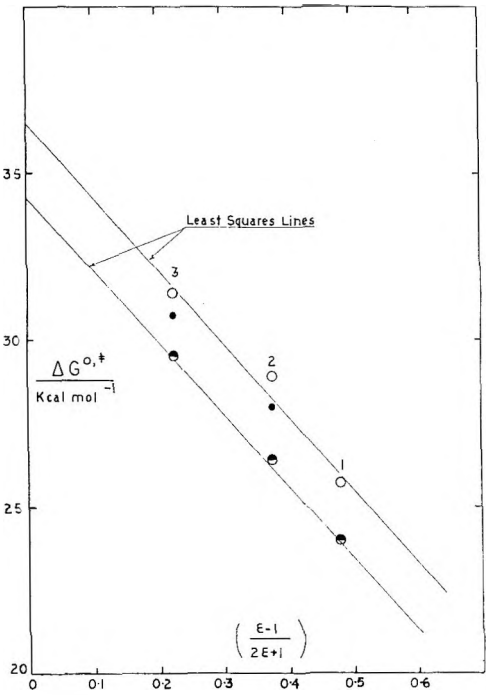


Figure 2. Activation free-energy change with solvent dielectric function in thermolysis of para-substituted α-chlorobenzyl methyl ethers.

Solvent	Graph index	$\Delta G^{\circ\ddagger}$, kcal mol^{-1}[a] p-Cl	p-F	p-CH_3
Sulfolane	1	25.7		24.0
C_6H_5Cl	2	28.9	28.0	26.4
CCl_4	3	31.4	30.7	29.5
Symbol		⊙	●	◒
Least Squares Computations				
R		−0.985		−0.998
Slope		−21.7		−21.4
Intercept		36.5		34.2

[a] Data from ref 5.

If we assume for the specific examples to be analyzed here that the reactant species has no significant dipole moment, the combination of eq 7 and 8 results in the equation

$$\Delta G^{\circ\ddagger} = \Delta G^{\circ\ddagger}_{int} + \left(\frac{L\bar{\mu}^2}{b^3}\right)\left(\frac{1-\epsilon}{2\epsilon+1}\right) + \Delta G^{\circ\ddagger}_{chem} \quad (9)$$

The simplest situation which could possibly arise is when the "chemical" term makes no contribution. We then obtain a direct link between the standard free-energy change and the solvent dielectric constant, viz. the equation

$$\Delta G^{\circ\ddagger} = \Delta G^{\circ\ddagger}_{int} - \frac{L\bar{\mu}^2}{b^3}\left(\frac{\epsilon-1}{2\epsilon+1}\right) \quad (10)$$

The solvent dielectric data[2,18] and the quantities computed therefrom are listed in Table I. The plot according to eq 10, delineating the solvent effect on activation free energy, $\Delta G^{\circ\ddagger}$, for the solvolytic rearrangement of α-chlorobenzyl methyl ether, is given in Figure 1. The plots in Figure 2 (along with the data from which they were constructed) are presented as a correlation of the effect of the para substituent on the parameters of eq 10. Clearly, all substituted cases in Figures 1 and 2 are correlated by lines of the same slope, i.e., $L\bar{\mu}^2/b^3$ = 21.6, because their activated complexes have about the same

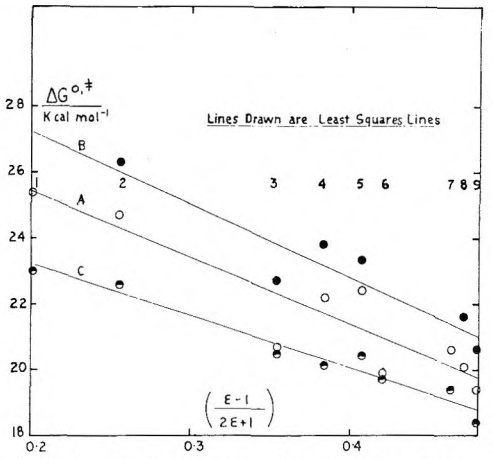
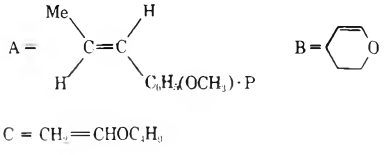


Figure 3. Activation free-energy change with solvent dielectric function in cycloaddition of TCNE with various vinylic ethers.

Solvent	Graph index	$\Delta G^{\circ\ddagger}$ kcal mol^{-1} [a] A	B	C
Cyclohexane	1	25.4		23.0
CCl_4	2	24.7	26.3	22.6
THF	3	22.4		20.4
EtOAc	4	22.2	23.3	20.1
$CHCl_3$	5	20.7	22.8	20.5
CH_2Cl_2	6	19.9	22.7	19.7
Acetone	7	20.6		19.4
C_6H_5CN	8	20.1	21.6	
CH_3CN	9	19.4	20.6	18.4
Symbol		⊙	●	◓
Least-Squares Computations				
R		−0.916	−0.956	−0.978
Slope		−20.2	−22.3	−15.7
Intercept		29.4	31.7	26.3

[a] Data from ref 8.



C = CH_2=$CHOC_4H_9$

degree of charge separation as suggested previously by the linearity of their Hammett free-energy plot.[1] The differences in intercept suggests that the substitutent effect is exerted only on the $\Delta G^{\circ\ddagger}_{int}$ term, varying with the polar nature of the substituent in an expected way. It is therefore apparent from these plots that the linear relation encompassed by eq 10 is obeyed to an acceptable approximation, implying that the "chemical" contributions to the standard free-energy change are relatively unimportant. Moreover, it can be shown that the slopes of the lines in Figures 1 and 2 are of the proper magnitude for reactions of the type under consideration (see Appendix).

Further confirmation of the correctness of this approach is to be found in studies reported by Steiner and Huisgen[8] on the solvent dependence of the rate of reaction of tetracyanoethylene (TCNE) with enol ethers, which is characterized by a zwitterionic transition state. The data obtained by these authors for the cycloaddition of TCNE to anethole, 2,3-dihydro-4*H*-pyran and butyl vinyl ether are listed in the table accompanying the plot in Figure 3, constructed in accordance with the variables of eq 10.

The general trend of these data is satisfactorily correlated with the terms of the electrostatic treatment outlined above, although the scatter of points about the linear relationships encompassed by eq 10 is such as to suggest that "chemical contributions" are not insignificant for some of the systems investigated. Nonetheless, it can be seen that these systems still show significant differences in slope which reflect the expected differences in transition-state charge separation, as well as differences in intercept indicative of differences in their $\Delta G^{\circ\ddagger}_{int}$ terms.

The general approach applied here for the change of standard activation free energy can be readily extended to other activation parameters. For example, the entropic analogues of eq 7, 9, and 10 are obtained by partial differentiation with respect to temperature at constant pressure.

$$\Delta S^{\circ\ddagger} = \Delta S^{\circ\ddagger}_{elec} + \Delta S^{\circ\ddagger}_{chem} \quad (11)$$

$$\Delta S^{\circ\ddagger} = \Delta S^{\circ\ddagger}_{int} + \frac{3L\bar{\mu}^2}{b^3}\frac{1}{(2\epsilon+1)^2}\left(\frac{d\epsilon}{dT}\right) + \Delta S^{\circ\ddagger}_{chem} \quad (12)$$

$$\Delta S^{\circ\ddagger} = \Delta S^{\circ\ddagger}_{int} + \frac{3L\bar{\mu}^2}{b^3}\frac{1}{(2\epsilon+1)^2}\left(\frac{d\epsilon}{dT}\right) \quad (13)$$

Since the $d\epsilon/dT$ terms are negative, the primary equation (eq 12) anticipates that the activation entropy becomes more negative with lower values of the solvent dielectric, providing the $\Delta S^{\circ\ddagger}_{chem}$ term is negligible, i.e., the circumstances under which the simplifying equation (eq 13) would prevail. Where the $\Delta S^{\circ\ddagger}_{chem}$ term is not negligible the entropic changes originating in "chemical contributions" would be greatest for the more polar and structured solvents and may even exceed in magnitude the second term involving the dielectric function. These contributions can be estimated in a qualitative way to be possibly more negative in value the greater the degree of chemical interaction between solute and solvent, since under these circumstances the reaction thermodynamics would include the process:

$$\left\{\begin{array}{l}\text{solvent interacting}\\ \text{chemically with other}\\ \text{solvent molecules}\end{array}\right\} \rightarrow \left\{\begin{array}{l}\text{Solvent interacting}\\ \text{"chemically" with the}\\ \text{zwitterionic complexes}\\ \text{even more strongly}\end{array}\right\}$$

Thus, the entropic change would be much more negative for the more polar solvents than is predicted by the simplified equation (eq 13) deduced from the electrostatic model.

Figure 4 has been plotted according to the variables of eq 13 from the data of Kwart and Silver[5] (which is listed in the accompanying table). Clearly the correlations are much less satifactory than those obtained for the corresponding activation free-energy changes. The slope to be expected (the "theoretical lines") has been drawn in the Figure 4 plot; it should have a value 3000 times greater (for $\Delta S^{\circ\ddagger}$ expressed in cal K^{-1} mol^{-1}) than the corresponding free-energy plot in Figure 1 based on eq 10.

It is obvious from the Figure 4 plot that the more structured solvents such as acetonitrile and nitrobenzene deviate most from the simple relationship of eq 13. Such deviation is to be expected where the zwitterionic activated complex has a moderate dipole moment. For low and average polarity solvents the slope tends to become more horizontal (than if eq 13 was applicable), since the normal direction of change of the dielectric function term is being opposed by a $\Delta S^{\circ\ddagger}_{chem}$ term arising from proportionately moderate chemical contributions. A sudden, large contribution to this term can therefore be correlated with a highly structured solvent, producing a degree of interaction which is extraordinary among the members of the solvent series. This seems to be the case for acetonitrile and nitrobenzene in Figure 4, where these higher dielectric solvents drive the reaction steeply toward more negative $\Delta S^{\circ\ddagger}$ values.

The converse might also be found for a zwitterionic transition state with a larger dipole moment. Here the $\Delta S^{\circ\ddagger}_{chem}$ may be very large and dominate the right-hand side of eq 12 for most members of the solvent series having more than a threshold degree of polarity. For such cases, in fact, the

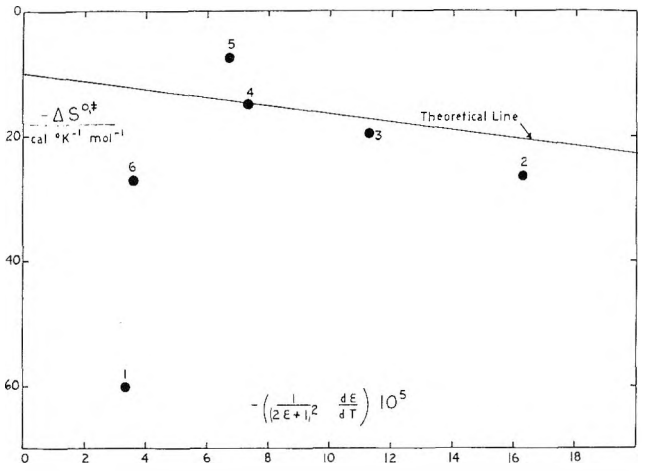


Figure 4. Activation entropy change with solvent dielectric function in thermolysis of α-chlorobenzyl methyl ether. Slope drawn is that calculated from the experimental value of Figure 1 in accordance with eq 13.

Solvent	Graph index	$-\Delta S^{\circ\ddagger}$, cal K^{-1} mol^{-1} [a]
CH_3CN	1	60.1
$CHCl_3$	2	26.1
C_6H_5Cl	3	19.5
$C_6H_5CH_3$	4	15.0
CCl_4	5	7.5
$C_6H_5NO_2$	6	26.9

[a] Data from ref 5.

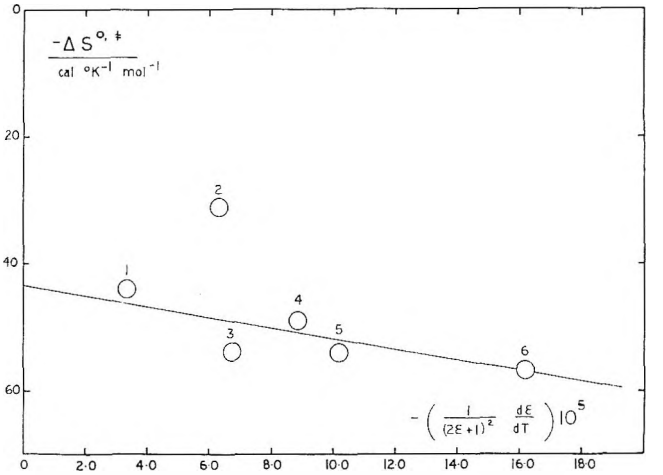


Figure 5. Activation entropy change with solvent dielectric function in cycloaddition of TCNE to anethole.

Solvent	Graph index [1]	$-\Delta S^{\circ\ddagger}$, cal K^{-1} mol^{-1} [a]
Acetonitrile	1	44
Cyclohexane	2	31
CCl_4	3	54
Ethyl acetate	4	49
CH_2Cl_2	5	54
$CHCl_3$	6	57

[a] Data from ref 8.

$\Delta S^{\circ\ddagger}_{chem}$ term would tend to parallel solvent properties such as polarizability,[19] which come into play most importantly when the solvent is introduced into a sufficiently strong field. That is to say, a $\Delta S^{\circ\ddagger}_{chem}$ term based largely on polarizability interactions will tend to eclipse the dielectric function term of eq 12 for transition states of higher dipole moment. However, for solvents which lack any structure and are nonpolarizable we could expect strong deviation from the line correlating the more polarizable members of the solvent series. This appears to be the case for the TCNE–enol ether cycloaddition reaction studied by Huisgen[8,10] where the transition state dipole moment (~14 D) is some 50% greater than that characterized for the α-chlorobenzyl methyl ether (~9 D). As is evident from Figure 5 and the accompanying table of data, only the very inert, nonpolarizable cyclohexane stands away from the correlation line of the five other solvents, ranging from acetonitrile to the highly polarizable carbon tetrachloride.

Since $\Delta G^{\circ\ddagger}$ has been assumed in this treatment to be linearly related to $\Delta S^{\circ\ddagger}$, it may be surprising to observe an acceptable linear correlation of $\Delta G^{\circ\ddagger}$ and the appropriate dielectric function from eq 10 in Figure 1, and a nearly complete lack of correlation of the $\Delta S^{\circ\ddagger}$ data accordirg to Figure 4. But this is not an unprecedented experience; rather it is another example of the operation of the "compensation law" wherein a reaction factor bringing about a significant change in the entropy is simultaneously effecting a compensatory change in enthalpy.[20] As a consequence, the $\Delta G^{\circ\ddagger}$ may respond to the influence of this reaction factor with no significant deviation from linear behavior.

An analogous treatment could be applied to the volumes of activation[19,20] ($\Delta V^{\circ\ddagger}$), but in terms of an electrostatic model the appropriate physical property, viz., $d\epsilon/dP$ (see eq 15), is generally not available for the sorts of solvents which might be expected to obey the predicted electrostatic relationships.

Regarding the Correlation of $\Delta S^{\circ\ddagger}$ and $\Delta G^{\circ\ddagger}$ with Solvent Polarity as an Index of Charge Separation in the Activated Complex. A basis for the expectation that reactions which give rise to zwitterionic intermediates should show more negative activation entropies in less polar solvents stems from many kinetic studies at high pressures,[21,22] which yield estimates of the activation volume $\Delta V^{\circ\ddagger}$. This conclusion apparently is deduced from two considerations: (a) $\Delta V^{\circ\ddagger}$ values for such ionogenic reactions as solvolysis are very much more negative in nonpolar solvents,[21] and (b) $\Delta S^{\circ\ddagger}$ tends to parallel $\Delta V^{\circ\ddagger}$ since both are derivative functions of $\Delta G^{\circ\ddagger}$. What is implicit in the latter assumption is that $\Delta S^{\circ\ddagger}$ is determined largely by solvent electrostriction. The $\Delta V^{\circ\ddagger}$ is taken as a *direct measure* of electrostriction on the basis of the Drude–Nernst equation (eq 15), which expresses the volume change resulting from immersion of a *discrete ion* into a continuous, structureless dielectric ε.[16] The Drude–Nernst equation, in turn, is a derivative of the classical Born equation.[16]

The Born equation (eq 15) is analogous to eq 10 which we derived above for zwitterions, but it applies *only* to species with a discrete charge, i.e., + rather than +−. Thus, if we consider a process where discrete charge rather than a zwitterion or ion pair is created (A → A^+ rather than A → $^-A^+$), in a solvent of dielectric ε, the free-energy change on forming a mole of charged species A^+ from *electrostatic sources only* is

$$\Delta G^{\circ\ddagger} = \frac{-LZ^2e^2}{2r}(1 - 1/\epsilon) \qquad (14)$$

where L is Avogadro's number, Z is the valence, e is the electron charge, and r is the charge radius. The volume change corresponding to this is given by

$$\Delta V^{\circ\ddagger} = \left(\frac{\partial \Delta G^{\circ\ddagger}}{\partial P}\right)_T = -\frac{LZ^2e^2}{2r\epsilon^2}\left(\frac{d\epsilon}{dP}\right) \qquad (15)$$

Comparison of eq 14, which expresses the free energy of activation involved with formation of a discrete charge within a dielectric ε, with eq 10, which expresses the analogous rela-

tionship in cases of zwitterion formation, conveys a measure of understanding as to why the Drude–Nernst equation and derivatives thereof cannot ordinarily be applied as criteria for ionogenic reaction processes.

Finally, the results discussed here suggest that correlation of $\Delta G^{\circ\ddagger}$ and solvent dielectric expressed in eq 10 provides a reasonably reliable index of a zwitterionic or ion pair structured transition state. Evidently, the effects of "chemical"contributions arising from the solute zwitterions interacting with the solvent are generally cancelled out and appear to be insignificant compared to their influence on the entropy of activation. Thus, it would appear that any given attempt to establish a relation between entropy of activation and some solvent polarity parameters, depending on the range of solvents employed, may lead to results which are contrary to expectation.[3] This is particularly so where a large degree of charge separation is developed in the activated state and a high extent of solvent polarization and other kinds of interaction with solvent can occur as a consequence.

Acknowledgment. This work is dedicated to Professor Egbert Havinga of the Gorlaeus Laboratorium of the University of Leiden, The Netherlands, on the occasion of his retirement celebration in June 1979.

Appendix: Estimation of Charge Separation in the Transition State

Equation 10 can be rewritten as:

$$\Delta G^{\circ\ddagger} = \Delta G^{\circ\ddagger}_{\text{int}} + 14.40 \left(\frac{\bar{\mu}^2}{b^3}\right)\left(\frac{1-\epsilon}{2\epsilon+1}\right) \qquad (16)$$

$$(\text{kcal mol}^{-1}) = (\text{kcal mol}^{-1})$$

if the dipole moment of the zwitterion is expressed in debye units and the radius is in angstrom units. Similarly, eq 13 may be written as

$$\Delta S^{\circ\ddagger} = \Delta S^{\circ\ddagger} + 0.0432 \left(\frac{\bar{\mu}^2}{b^3}\right)\left(\frac{1}{(2\epsilon+1)^2}\right)\left(\frac{d\epsilon}{dT}\right) \qquad (17)$$

$$(\text{cal deg}^{-1}\text{ mol}^{-1}) = (\text{cal deg}^{-1}\text{ mol}^{-1})$$

Sample Calculation. To consider the effective radius of α-chlorobenzyl methyl ether we may assume to a fair approximation that the densities of inert substances in the liquid phase are nearly unity. That is to say, assuming the density of the ether to be 1.0 ± 0.1, this structure of mol wt 157, having a packing density[23] = 0.9, is deduced to have a molar volume of $(157 \times 0.9) = 141$ cm^3 mol^{-1}. Therefore, the molecular volume (of 141/Avogadro's number) is calculated to be 253 Å^3 per molecule. Consequently, the cube of the molecular radius, equal to b^3 in eq 10, becomes 56.1 Å^3. Since the slope of the Figure 1 graph gives us 21.6 kcal mol^{-1}, then

$$21.6 = 14.4\,\bar{\mu}^2/56.1$$

and

$$\bar{\mu}^2 = 84.2\text{ D}^2$$

$$\bar{\mu} = 9.2\text{ D}$$

and since $\bar{\mu} = e{\cdot}d$, the electron charge times the separation, the charge separation in the transition state is

$$d = 9.2/4.8 = 1.9\text{ Å}$$

Bearing in mind the approximations[23] which have been made throughout, the error is not significant.

Registry No.—α-Chlorobenzyl methyl ether, 35364-99-9; α-p-dichlorobenzyl methyl ether, 56377-71-0; α-chloro-p-fluorobenzyl methyl ether, 56377-73-2; α-chloro-p-methylbenzyl methyl ether, 56377-70-9; anethole, 104-46-1; 3,4,-dihydro-2H-pyran, 110-87-2; butyl ethenyl ether, 111-34-2; TCNE, 670-55-2.

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(23) In a condensed phase only a fraction of the space is taken up by molecules, there being some dead space arising from packing effects. It is difficult to estimate what this dead space contribution would be for other than hard spherical molecules. Under those conditions we can estimate that the fraction of the total volume taken up by the molecules is 0.637 (this corresponds to dense, randomly packed spheres: see, e.g., K. Gotoh and J. L. Finney, *Nature (London)*, **252**, 202 (1974)). This must be very much a lower limit and as soon as one has mixtures of spheres of different sizes (corresponding more closely to our experimental situation) the number rises. For unlike-sized spheres W. M. Vischeer and M. Bolsterli [*Nature (London)*, **239**, 504 (1972)] found that it could rise to a value of 0.868. Not withstanding these points it would seem that with the molecules we consider, which are much "flatter" than spheres, the packing fraction would be considerably higher than results with the hard spheres. A value of 0.9 would thus seem not unreasonable.

MINDO/3 Calculations on the Acid-Catalyzed Ring Opening of Oxaziridine

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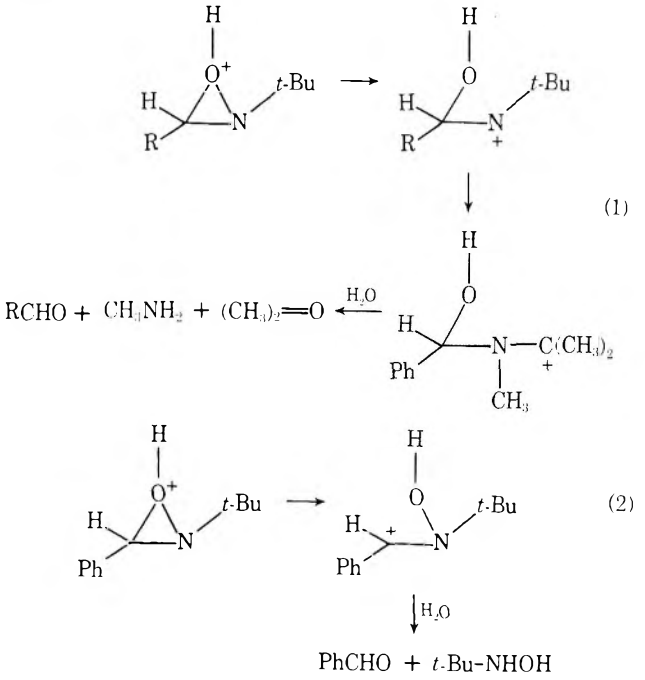
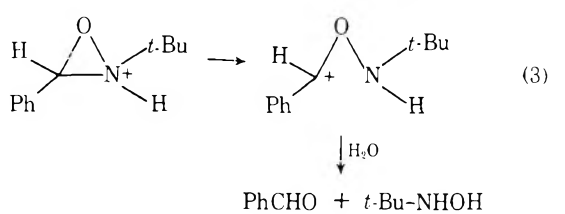
MINDO/3 semiempirical molecular orbital calculations were performed on oxaziridine and four protonated derivatives (N-protonated, O-protonated cis, O-protonated trans, and edge protonated). For the first three of these, further calculations were done along reaction coordinates, leading to ring cleavage at each of the three possible bonds. The results are interpreted to favor a mechanism for the ring opening of *N*-alkyloxaziridines which goes through the O-protonated intermediate, while in a *C*-phenyl derivative a mechanism with an N-protonated intermediate is favored. Reaction coordinates for the intramolecular interconversion of the four protonated derivatives were also calculated.

Oxaziridines (derivatives of **1**) decompose rapidly in acid medium to form acyclic products. This reaction is interesing because oxaziridine is a small molecule with several possible protonation sites (N, O, and the ring edge). The two mechanisms proposed for this reaction[1,2] have as their initial step protonation at the oxygen. Substitution of a carbonium ion stabilizing group, such as phenyl, at the ring carbon changes the products from those of eq 1 to those of eq 2.



Ab initio molecular orbital calculations on this system indicate nitrogen as the favored site for protonation,[3] and a recent study of the $AgBF_4$ complex of an oxaziridine derivative indicates nitrogen as the preferred site for Ag^+ complexation.[4] A third mechanism (eq 3), with initial N-protonation, can also explain the products which would be given by eq 2.



In an attempt to provide further evidence to help clarify the mechanism of this reaction, we have performed extensive MINDO/3 calculations[5] on the potential energy surface of protonated oxaziridine.

Calculations. MINDO/3 calculations were performed on oxaziridine (**1**), N-protonated oxaziridine **2**, cis and trans O-protonated oxaziridines (**3** and **4**), and oxaziridine protonated on the N–O bond (**5**).

CN and CO edge-protonated species were not calculated because they were expected to be significantly less stable than **5**, which itself has only a very shallow potential well. The calculated energies and charge densities of each of these species are presented in Table I, and their structures, found by minimization of the MINDO/3 energy of each species with respect to all geometry parameters (bond lengths, angles, and twist angles), are presented in Figure 1.

For species **2**–**4** calculations were then carried out on the species with each of the three ring bonds separately stretched. For each constant distance of the single ring bond which was stretched, all other geometry parameters were optimized to give a point on the reaction coordinate leading to ring opening by cleavage of one bond. This procedure was repeated with successive small increments until a transition state was found. Once each transition state was passed, all geometry parameters were again optimized to obtain product geometries. In all, nine reaction coordinates of this type were followed, involving several thousand MINDO/3 calculations.

In addition to the nine reaction coordinates described above, reaction coordinates for cis–trans isomerization of the O-protonated species, and for the intramolecular O–N proton transfer reaction, starting with either cis or trans O-protonated oxaziridine were calculated.

Results

The nine reaction paths were labeled as

NHCN: N-protonated, C–N bond cleavage
NHON: N-protonated, O–N bond cleavage
NHCO: N-protonated, C–O bond cleavage
COHCN: cis O-protonated, C–N bond cleavage
COHON: cis-O-protonated, O–N bond cleavage
COHCO: cis O-protonated, C–O bond cleavage
TOHCN: trans O-protonated, C–N bond cleavage
TOHON: trans O-protonated, O–N bond cleavage
TOHCO: trans O-protonated, C–O bond cleavage

The geometries of the transition states and the products of eight of these ring cleavage steps are summarized in Figures 2–4. Path NHCO was followed to a C–O bond length of 2.8 Å (289.6 kcal/mol). At longer C–O distances the SCF procedure did not converge.

The transition states for cis–trans isomerization of the O-protonated species and for the O to N proton transfer reactions are given in Figure 5. Energies and charge densities for each species in the figures are presented in Table I. Complete geometry data for each of the 21 intermediates and transition states are presented in the supplementary material.

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Table I. Calculated Energies and Charge Densities

Compd	ΔE_f, kcal/mol	q_C	q_N	q_O	q_{H_1}	q_{H_2}	q_{H_3}	q_{H_4}
1	0.4	+0.38	+0.07	−0.35	−0.06	−0.06	+0.02	
2	173.7	+0.36	+0.35	−0.20	+0.08	+0.08	+0.16	+0.16
3	181.6	+0.34	+0.22	−0.16	+0.10	+0.06	+0.12	+0.33
4	182.7	+0.36	+0.18	−0.17	+0.08	+0.04	+0.14	+0.34
5	200.9	+0.38	+0.15	−0.20	+0.09	+0.08	+0.15	+0.35
6	208.4	+0.77	+0.18	−0.30	+0.03	+0.03	+0.15	+0.15
7	253.6	+0.38	+0.29	−0.09	+0.05	+0.05	+0.16	+0.16
8	186.1	+0.66	+0.32	−0.28	+0.05	+0.05	+0.10	+0.10
9	133.0	+0.91	−0.14	−0.14	+0.23	+0.23	0.00	+0.00
10	263.3	+0.51	−0.01	−0.08	+0.11	+0.07	+0.08	+0.33
11	212.3	+0.35	+0.34	−0.27	+0.02	+0.10	+0.14	+0.32
12	211.2	+0.42	+0.22	−0.23	+0.06	+0.11	+0.12	+0.30
13	261.1	+0.46	−0.05	−0.02	+0.13	+0.08	+0.07	+0.33
14	106.1	+0.62	−0.04	−0.35	+0.05	+0.18	+0.19	+0.34
15	167.8	+0.09	+0.50	−0.32	+0.16	+0.14	+0.10	+0.33
16	264.4	+0.51	−0.03	−0.10	+0.11	+0.07	+0.10	+0.35
17	205.6	+0.37	+0.29	−0.28	+0.08	+0.07	+0.15	+0.21
18	216.0	+0.48	+0.14	−0.23	+0.07	+0.08	+0.15	+0.32
19	194.9	+0.42	+0.24	−0.31	+0.06	+0.07	+0.11	+0.40
20	202.6	+0.36	+0.17	−0.16	+0.06	+0.12	+0.11	+0.34
21	204.5	+0.47	+0.17	−0.19	+0.08	+0.09	+0.15	+0.33

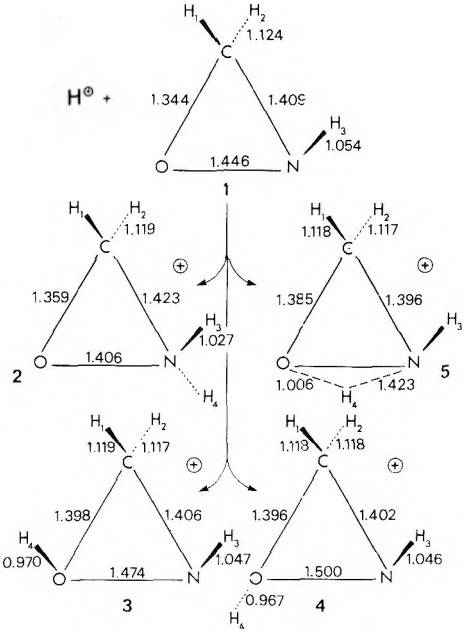

Figure 1. Calculated structures of oxaziridine (1) and four protonated oxaziridines (2–5).

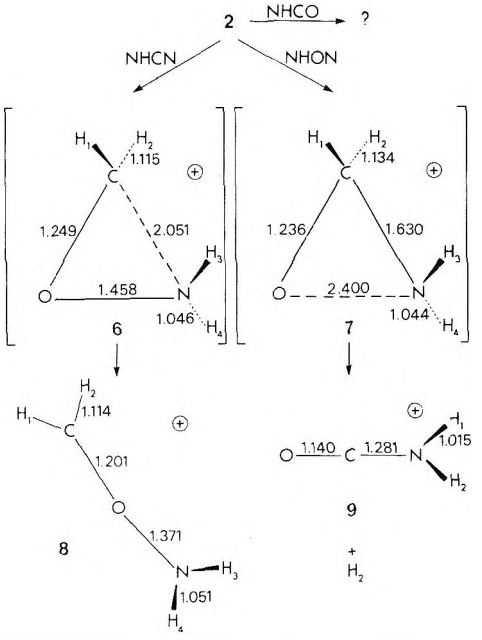

Figure 2. Calculated structures of the transition states and products for the ring openings of N-protonated oxaziridine (2).

Several important points should be noted. (1) Nitrogen is predicted to be the preferred site of protonation, as shown in Table I with the energies of N-protonated species **2** at 173.7 kcal/mol, cis O-protonated **3** at 181.6 kcal/mol, trans O-protonated **4** at 182.7 kcal/mol, and N–O edge-protonated **5** at 200.9 kcal/mol.

(2) The preferred reaction path is through the O-protonated species, but the energy differences between O-protonated and N-protonated transition states are probably too small to be significant. These path preferences are obtained by comparison of the energies of transition states: **6**, 208.4 kcal/mol; **11**, 212.3 kcal/mol; **12**, 211.2 kcal/mol; **17**, 205.6 kcal/mol; and **18**, 216.0 kcal/mol.

(3) Transition states for intramolecular proton transfer reactions (including the cis–trans isomerization) are of lower energy than those of the ring cleavage reactions: **19**, 194.9 kcal/mol; **20**, 202.6 kcal/mol; and **21**, 204.5 kcal/mol. Intermolecular proton transfer probably requires less activaion energy.

(4) The COHON and TOHON paths produced products in which a proton has moved from the ring carbon to the nitrogen.

(5) Path NHON (which has a high energy transition state) results in products formed by loss of a molecule of hydrogen from the organic compound. Loss of H_2 as well as the proton transfer described in point 4 were results of the calculations. They were not assumed paths.

(6) The products of path COHCN differ from those of TOHCN by rotations around single bonds; the energies are essentially identical. The same relation holds between the products of paths COHCO and TOHCO, and the products of paths COHON and TOHON are identical.

(7) The O to N proton transfer reaction goes through a transition state to a shallow minimum when starting from the

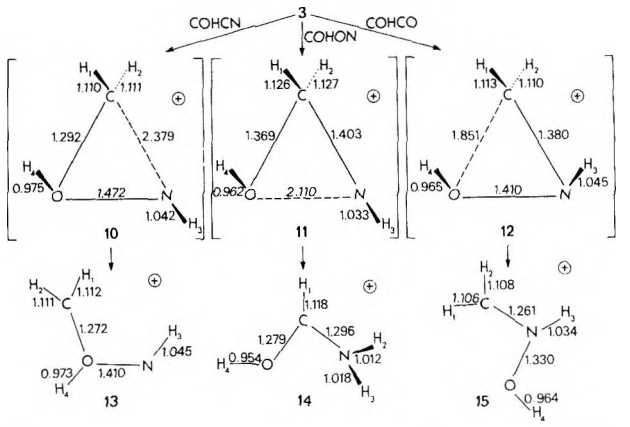

Figure 3. Calculated structures of the transition states and products for the ring openings of cis O-protonated oxaziridine (**3**).

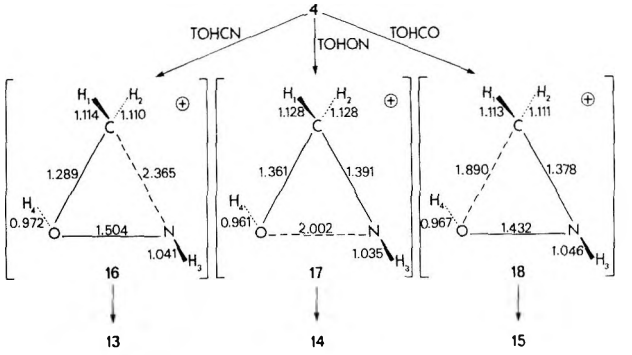

Figure 4. Calculated structures of the transitions states and products for the ring openings of trans O-protonated oxaziridine (**4**).

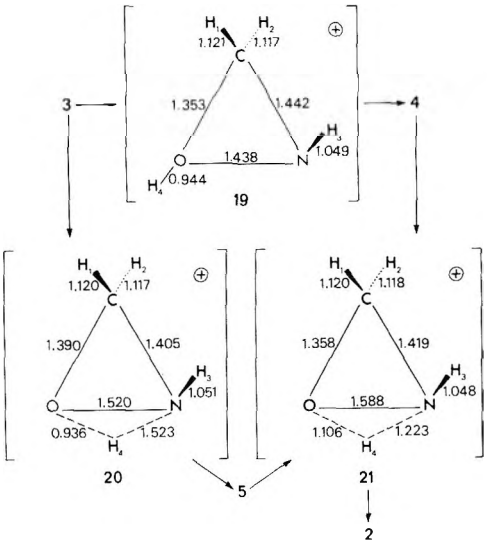

Figure 5. Calculated structures of the transition states for intramolecular proton transfer of protonated oxaziridines.

trans O-protonated species. This minimum is the edge-protonated species **5**. Further progress along this reaction path leads to a second transition state which is identical with that for the cis O-protonated to N proton transfer reaction which has no minimum along the reaction coordinate.

Discussion

Care must be used in using molecular orbital calculations to interpret reactions in solution. To make this type of interpretation, one must assume that solvent effects cancel. In the present case it would be futile, from the calculations, to try to predict the energy changes of the protonation reaction, but the energies of the four protonated intermediates (**2**–**5**) may reasonably be compared using the assumption that each is similarly solvated. This assumption is perhaps more valid in the case of charged species, such as studied here, because the major solvation interaction is a charge–dipole interaction, which would be similar for species with similar net charges and similar geometries in the vicinity of the charge.

Errors due to the inability of the MINDO/3 method to account for strain energy preclude the comparison of cyclic with acyclic species, but the three-membered ring intermediates may be compared with each other. Comparison may also be made between ring opening transition states if the transition state is about equally far from the starting material in each case.

The results show that the N-protonated species is somewhat more stable than any other protonated species, in agreement with the experimental and computational conclusions referred to above. Paths NHON, NHCO, COHCN, and TOHCN are clearly of too high an energy to be important in the actual reactions. The remaining five paths are of similar enough energy to allow minor changes in structure and substitution to alter the preferred path among them. Proton transfer among the protonated oxaziridines appears to be somewhat faster than the ring opening reactions.

In two of the paths (COHON and TOHON) proton transfer from the ring carbon to the nitrogen occurs in the course of the reaction. For the reaction with a *tert*-butyl group on the nitrogen, CH_3^+ is transferred (as in reaction 1). Both types of transfer are possible in the *N*-*tert*-butyl system, so the observation of products resulting exclusively from methyl transfer indicates that the transition state including this process is at a lower energy than that with proton transfer. Therefore, for *N*-alkyloxaziridines eq 1 is predicted to be the favored mechanism.

The transition state for path NHCN (**6**) shows a considerable increase of positive charge compared to its precursor **2**. This charge localization, the difference between q_C for **6** (+0.77) and q_C for **2** (+0.36), is +0.41. An aryl substitutent on the carbon will stabilize the positive charge of **6** more than the smaller positive charge on **2**. The activation energy for path NHCN will therefore be lowered by aryl substitution. A similar but smaller effect is seen in paths COHCO (q_C: **12**, 0.42; **3**, 0.34; $\Delta q_C = 0.08$) and TOHCO (q_C: **18**, 0.48; **4**, 0.36; $\Delta q_C = 0.12$), which indicates less decrease in the activation energy for these paths.

The resonance stabilization of a positive charge by a phenyl group can be obtained by comparing the experimental enthalpies of the reactions shown in eq 4–10. Assuming that the transition state stabilization is proportional to the increment of positive charge at the carbon atom, a phenyl group would lower the activation energy of path COHCO by 5.6 kcal/mol, of path TOHCO by 8.4 kcal/mol, and of path NHCN by 28.7 kcal/mol. For the phenyl derivative this last path seems most probable.

$$CH_4 \rightarrow CH_3\cdot + H\cdot \quad 103 \text{ kcal/mol}^6 \quad (4)$$

$$CH_3\cdot \rightarrow CH_3^+ + e^- \quad 226 \text{ kcal/mol}^7 \quad (5)$$

$$CH_4 \rightarrow CH_3^+ H\cdot + e^- \quad 329 \text{ kcal/mol} \quad (6)$$

$$PhCH_3 \rightarrow PhCH_2\cdot + H\cdot \quad 83 \text{ kcal/mol}^8 \quad (7)$$

$$PhCH_2\cdot \rightarrow PhCH_2^+ + e^- \quad 176 \text{ kcal/mol}^9 \quad (8)$$

$$PhCH_3 \rightarrow PhCH_2^+ + H\cdot + e^- \quad 259 \text{ kcal/mol} \quad (9)$$

$$\text{Net: } CH_3^+ + PhCH_3 \rightarrow CH_4 + PhCH_2^+ \quad -70 \text{ kcal/mol} \quad (10)$$

Conclusions

Within the uncertainties stated above, it appears probable that N-protonation of oxaziridine is somewhat favored over

O-protonation and considerably favored over edge protonation. The various protonated species are in equilibrium with each other, and this intramolecular equilibrium is probably somewhat faster than the ring opening. Intermolecular equilibrium among the protonated species may well be faster still. The three postulated mechanisms are similar in transition state energies for oxaziridine itself, but N-alkylation can be expected to favor eq 1 (O-protonation followed by O–N bond cleavage) over the others. Since it is observed that substitution of an aryl group at the carbon changes the products from those expected for eq 1 to those which would be expected for eq 2 or 3 and since aryl substitution is predicted to favor eq 3 far more than it does eq 2, it seems probable that the observed products result from eq 3 rather than 2. The previously accepted mechanism involving O-protonation followed by C–O bond cleavage is less supported by the calculations than is the mechanism involving N-protonation followed by C–N bond cleavage.

Acknowledgment. We wish to thank Dr. DeLanson R. Crist for many helpful discussions and the Georgetown University Central Computer Facility for providing access to its IBM 370/145 computer on which this work was done.

Registry No.—1, 32201-41-5.

Supplementary Material Available: A complete listing of the optimized geometry parameters of species **1–21** (8 pages). Ordering information is given on any current masthead page.

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Steric Effects. 12. Substituents at Phosphorus

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Ionization constants of four sets of alkyl-substituted phosphorus oxy acids, rate constants for hydrolysis of four sets of alkyl-substituted phosphorus oxy acid esters, rate constants for the reaction of 22 sets of XZ(PO)Cl with water, and rate constants for the reaction of a set of trialkylphosphines with ethyl iodide have been correlated with both the υ and the υ' steric parameters by means of the modified Taft equation. The pK_as gave best results with the υ parameters, in accord with the tetrahedral geometry of the acids. The rate constants for the reaction of XZ(PO)Cl with water are best correlated by the υ' constants, the results in agreement with a transition state exhibiting trigonal-bipyramidal geometry with the nucleophile and leaving group at opposite positions. The success of the correlations with the υ or υ' steric parameters shows that significant steric effects occur in the acidity of phosphonic and phosphinic acids, the reaction of derivatives of these acids with nucleophiles, and the reaction of trialkylphosphines with ethyl iodide. Furthermore, steric parameters evaluated from reactions of carbon compounds may be successfully applied to the reactivity of compounds of phosphorus. The $\sigma\phi$ constants proposed by Kabachnik for use with substituents at phosphorus were correlated with $\sigma\phi_X = L\sigma_{IX} + D\sigma_{RX} + S\upsilon_X + c$ with excellent results. The steric term was significant at the 99.9% confidence level. The results show clearly that substituents exert the same types of electrical effects at phosphorus that they do when bonded to carbon. They also provide verification for the conclusion that υ values for alkoxy, alkylthio, and dialkylamino groups are on the same scale as the υ values for other substituents.

We have hitherto studied the steric effect of alkyl substituents attached to oxygen[1] and to nitrogen[2] in carbonyl compounds and alkyl groups attached to sulfur[3] in a variety of compounds. In this work we turn our attention to steric effects of alkyl groups attached to phosphorus. We have examined the correlation with the modified Taft equation[1-3]

$$Q_X = S\upsilon_X + h \quad (1)$$

with the pK_as for four sets of alkyl-substituted phosphorus oxy acids; four sets of rate constants for the hydrolysis of esters of alkyl-substituted phosphorus oxy acids; 22 sets of rate constants for reactions of alkyl-substituted acyl chlorides of phosphorus oxy and thio acids with water; and one set of rate constants for the reaction of trialkyl phosphines with ethyl iodide. The data used in the correlations are reported in Table I. We have considered only steric effects on the reactions studied because the magnitude of the localized (field and/or inductive) electrical effect as measured by reliable σ_I values[4] for nine alkyl groups (Me, Et, Pr, *i*-Pr, Bu, *i*-Bu, *s*-Bu, and *t*-Bu) is -0.01 ± 0.02. The magnitude of the delocalized (resonance) electrical effect as determined by reliable σ_R values[4] for four alkyl groups is -0.16 ± 0.02. These values lead to the inexorable conclusion that the electrical effects of alkyl groups are constant and independent of alkyl group structure. This view is supported by our previous work.[5,6]

There are two different sets of υ parameters for alkyl groups available: the υ values derived from rate constants for esterification of carboxylic acids[7,8] and the υ' values derived from the reaction of alkyl carbinyl bromides with bromide ion.[9] These constants differ in their sensitivity to branching in the alkyl group.[10] The υ parameters reflect steric effects in a tetrahedral species while the υ' parameters represent steric effects in the S_N2 transition state which may be considered as a trigonal bipyramid. We have examined the correlation of all the data with both types of steric parameter and some results of the correlations for those sets with five or more points. [For complete statistics for all the sets studied, see the paragraph at the end of this paper about the supplementary material.] Sets designated A were correlated with υ and sets designated B were correlated with υ' values. We found it necessary to estimate a value of υ' for the *s*-Bu group for use with several of the sets studied. To accomplish this, we have assumed addi-

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Table I. Data Used in the Correlations

1,2. pK_{a_1}, pK_{a_2} of $XPO(OH)_2$ in H_2O at 25 °C[a]
Me, 2.38, 7.74; Et, 2.43, 8.05; Pr, 2.49, 8.18; *i*-Pr, 2.66, 8.44; Bu, 2.59, 8.19; *s*-Bu, 2.74, 8.48; *i*-Bu, 2.70, 8.43; *t*-Bu, 2.79, 8.88; *t*-$BuCH_2$, 2.84, 8.65

3. pK_a, X(PO)H(OH) in H_2O at 25 °C[a]
Me, 3.08; Et, 3.29; Pr, 3.46; *i*-Pr, 3.56; Bu, 3.41; *t*-Bu, 4.24

4. pK_a, $X_2PO(OH)$ in 75% EtOH–H_2O[b]
Me, 4.72; Bu, 5.24; *i*-Bu, 5.60; *s*-Bu, 5.75; *t*-Bu, 6.26

5. k_{rel}, $XPO(O\text{-}i\text{-}Pr)_2 + OH^-$ in H_2O[c]
Me, 1; Et, 0.16; Pr, 0.062; Bu, 0.039; *t*-Bu, 0.002

6. k_{rel}, $XPO(O\text{-}i\text{-}Pr)_2 + H_3O^+$ in H_2O[c]
Me, 1.0; Et, 0.5; Pr, 0.5; Bu, 0.33; *t*-Bu, 0.33

7. 10^3k_r, $X_2PO(OMe)$ in 60% dimethoxyethane–H_2O at 75 °C[d]
Me, 500; Et, 10.9; Bu, 3.08; *i*-Pr, 0.3

8. 10^2k_r, XMe(PO)Cl + H_2O in 95% v/v MeAc–H_2O at 0 °C[e]
Et, 5560; Pr, 3093; *i*-Pr, 83.7; Bu, 2968; i-Bu, 1360

9. 10^2k_r, XEt(PO)Cl + H_2O in 95% v/v MeAc–H_2O at 0 °[e]
Me, 5560: Et, 551; Pr, 445

10. 10^2k_r, XPr(PO)Cl + H_2O in 95% v/v MeAc–H_2O at 0 °C[e]
Me, 3093; Et, 445; Pr, 371

11. 10^2k_r, $X(PO)Cl_2$ + H_2O in 95% v/v MeAc–H_2O at 0 °C[e]
Me, 3847; Et, 793; Pr, 671; *i*-Pr, 30.4; *s*-Bu, 28.1

12. 10^3k_r, X(EtS)(PO)Cl + H_2O in 95% v/v MeAc–H_2O at 0 °C[f]
Me, 202; Et, 74.2; *i*-Pr, 2.84; *s*-Bu, 2.51

13. 10^3k_r, $X(ClCH_2CH_2S)(PO)Cl$ + H_2O in 95% v/v MeAc–H_2O at 0 °C[f]
Me, 814; Et, 258; *i*-Pr, 8.47; *s*-Bu, 6.48

14. 10^3k_r, X(MeO)(PO)Cl + H_2O in 95% v/v MeAc–H_2O at 0 °C[g]
Me, 135.6; Et, 60.6; Pr, 51.47; *i*-Pr, 2.48; Bu, 36.1

15. 10^3k_r, X(MeO)(PO)Cl + H_2O in 95% v/v MeAc–H_2O at 10 °C[g]
Me, 200.6; Et, 82.3; Pr, 82.15; *i*-Pr, 4.19; Bu, 58.1

16. 10^3k_r, X(MeO)(PO)Cl + H_2O in 95% v/v MeAc–H_2O at 20 °C[g]
Me, 319.6; Et, 134.5; Pr, 134.2; *i*-Pr, 6.55; Bu, 99.0

17. 10^3k_r, X(MeO)(PO)Cl + H_2O in 95% v/v MeAc–H_2O at 30 °C[g]
Me, 469.5; Et, 193.5; Pr, 185.3; *i*-Pr, 9.69; Bu, 147.6

18. 10^3k_r, X(EtO)(PO)Cl + H_2O in 95% v/v MeAc–H_2O at 0 °C[g]
Me, 82.1; Et, 30.07; Pr, 25.58; *i*-Bu, 17.4

19. 10^3k_r, X(EtO)(PO)Cl + H_2O in 95% v/v MeAc–H_2O at 10 °C[g]
Me, 137.3; Et, 52.50; Pr, 42.08; *i*-Pr. 1.77

20. 10^3k_r, X(EtO)(PO)Cl + H_2O in 95% v/v MeAc–H_2O at 20 °C[g]
Me, 235.0; Et, 76.5; Pr, 68.33; *i*-Pr, 3.15; *i*-Bu, 39.2

21. 10^3k_r, X(EtO)(PO)Cl + H_2O in 95% v/v MeAc–H_2O at 30 °C[g]
Me, 337.8; Et, 114.9; Pr, 101; *i*-Pr, 6.05; *i*-Bu, 62.3

22. 10^3k_r, $X(ClCH_2CH_2O)(PO)Cl$ + H_2O in 95% v/v MeAc–H_2O at 0 °C[g]
Me, 187.2; Et, 68.3; *i*-Pr, 2.58; *s*-Bu, 2.47

23. 10^3k_r, $X(ClCH_2CH_2O)(PO)Cl$ + H_2O in 95% v/v MeAc–H_2O at 10 °C[g]
Me, 331; Et, 104.0; *i*-Pr, 4.24; *s*-Bu, 4.31

24. 10^3k_r, $X(ClCH_2CH_2O)(PO)Cl$ + H_2O in 95% v/v MeAc–H_2O at 20 °C[g]
Et, 169.7; *i*-Pr, 7.03; *s*-Bu, 7.07

25. 10^3k_r, $X(ClCH_2CH_2O)(PO)Cl$ + H_2O in 95% v/v MeAc–H_2O at 30 °C[g]
Et, 233.0; *i*-Pr, 11.67; *s*-Bu, 11.03

26. 10^3k_r, X(*i*-PrO)(PO)Cl + H_2O in 95% v/v MeAc–H_2O at 0 °C[g]
Me, 41.5; Et, 16.76; Pr, 14.65

27. 10^3k_r, X(*i*-PrO)(PO)Cl + H_2O in 95% v/v MeAc–H_2O at 10 °C[g]
Me, 74.7; Et. 26.15; Pr, 23.63

28. 10^3k_r, X(*i*-PrO)(PO)Cl + H_2O in 95% v/v MeAc–H_2O at 20 °C[g]
Me, 120.1; Et, 42.58; Pr, 41.55

29. 10^3k_r, X(*i*-PrO)(PO)Cl + H_2O in 95% v/v MeAc–H_2O at 30 °C[g]
Me, 196.0; Et, 67.5; Pr, 56.52; *i*-Pr, 3.81

30. 10^3k_r, X_3P + EtI in MeAc at 34.97 °C[h]
Me, 2.24; Et, 1.54; Pr, 1.36; Bu, 1.62; *i*-Bu, 0.138; $BuCH_2$, 1.58

31. 10^4k_r, $X(PO)(OEt)(OC_6H_4NO_2{}^{4-})$ + OH^- in H_2O (pH 8.3) at 37.5 °C[i]
Me, 24.2; Et, 5.06; Pr, 4.17; Bu, 4.23; $BuCH_2$, 3.62; $BuCH_2CH_2$, 3.56; *i*-Pr, 1.07; *i*-Bu, 2.34; *i*-$PrCH_2CH_2$, 2.45; *i*-$Pr(CH_2)_3$, 3.62; *t*-Bu, 0.032;[j] *t*-$Bu(CH_2)_3$, 3.41;[k] cC_6H_{11}, 0.307

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tivity of the effects of branching. Five different estimates were made in the following manner:

1. $\upsilon'_{Pr} - \upsilon'_{Et} = \beta_{CH_2} = 0.04$
   $\upsilon'_{i\text{-}Pr} + \beta_{CH_2} = \upsilon'_{s\text{-}Bu} = 0.62 + 0.04 = 0.66$
2. $\upsilon'_{i\text{-}Pr} - \upsilon'_{Et} = \alpha_{CH_2} = 0.62 - 0.38 = 0.24$
   $\upsilon'_{Pr} + \alpha_{CH_2} = \upsilon's\text{-}Bu = 0.42 + 0.24 = 0.66$
3. $\upsilon'_{i\text{-}Bu} - \upsilon'_{Et} = 0.55 - 0.38 = 0.17 = 2\beta_{CH_2}$, $\beta_{CH_2} = 0.09$
   $\upsilon'_{i\text{-}Pr} + \beta_{CH_2} = \upsilon'_{s\text{-}Bu} = 0.62 + 0.09 = 0.71$
4. $\upsilon'_{t\text{-}Bu} - \upsilon'_{Et} = 2\alpha_{CH_2} = 1.23 - 0.62 = 0.61$, $\alpha_{CH_2} = 0.31$.
   $\upsilon'_{Pr} + \alpha_{CH_2} = \upsilon'_{s\text{-}Bu} = 0.42 + 0.31 = 0.73$
5. $\upsilon'_{Et} - \upsilon'_{Me} = \alpha_{CH_2} = 0.03$, $\upsilon'_{Pr} - \upsilon'_{Me} = \alpha_{CH_2CH_2} = 0.07$
   $\upsilon'_{Me} + \alpha_{CH_2} + \alpha_{CH_2CH_2} = \upsilon'_{s\text{-}Bu} = 0.45$

An average value of 0.64 is obtained from the five approximations. We have used the value of 0.66 obtained with approximations 1 and 2 as a reasonable estimate of $\upsilon'_{s\text{-}Bu}$.

Five of the sets studied have tetrahedral (sets 1–4) or close to tetrahedral (set 30) geometry throughout the course of the reaction being studied. For sets 1–4, best results were obtained on correlation with the υ values. This is in agreement with the fact that υ is defined from a reaction involving a tetrahedral intermediate. Excellent correlations were obtained for all four sets (sets 1A–4A). It must be noted that the $X_2PO(OH)$ acids of set 4 are disubstituted, thus the equation

$$Q_{X^1X^2} = S\Sigma\upsilon + h \tag{2}$$

would presumably be required, where

$$\Sigma\upsilon = \upsilon_{X^1} + \upsilon_{X^2} \tag{3}$$

As in this set $X^1 = X^2$,

$$\Sigma\upsilon = 2\upsilon_{X^1} \tag{4}$$

and

$$Q_{X^1X^2} = S\upsilon_X + H \tag{5}$$

$$= S'\upsilon_X + h \tag{6}$$

Thus, the correlations were carried out with eq 6. Set 30 gave somewhat better results with υ' than with υ, although the two correlations were significant at the same confidence level. We are unable to account for this at the present time. Inspection

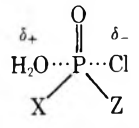
Table II. Results of Correlations with Equation 1

Set	S	h^A	$100r^2$	S	h^B	$100r^{2a}$	n^b
1	0.521	2.17	89.5	0.413	2.36	61.9	9/8
2	1.04	7.44	82.3	1.06	7.69	79.7	9/8
3	1.50	2.39	98.0	1.13	2.86	93.3	6
4	1.98	3.75	97.2	1.49	4.56	81.7	5
5	−3.18	1.12	87.6	−2.30	0.0659	76.7	5
6	−0.432	0.0047	40.6	−0.283	−0.154	28.9	5
8	−1.80	4.47	15.2	−6.53	6.27	85.4	5
11	−4.13	5.37	75.5	−6.45	5.58	95.8	5
14	−5.74	5.19	72.3	−6.20	4.23	98.6	5
15	−5.41	5.17	69.2	−5.94	4.31	97.8	5
16	−5.42	4.38	68.2	−6.01	4.55	98.0	5
17	−5.41	5.54	68.9	−5.97	4.69	98.2	5
20	−1.87	2.94	24.2	−5.48	4.18	83.4	5
21	−1.74	3.05	24.4	−5.09	4.19	83.2	5
30	−2.60	1.81	88.4	−6.17	2.62	92.5	6
31	−3.29	2.80	79.7	−2.84	1.93	94.3	12/7

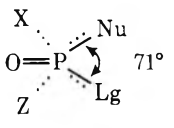
[a] Percent of data accounted for by the correlation equation. [b] Number of points in A/B set. When only one number is given, it applies to both A and B sets.

of the S values obtained for sets 1–4 and comparison with the υ values of the constant substituents attached to the phosphorus atom suggests that the magnitude of S is more dependent on the electrical effect of the constant substituent than upon its steric effect.

Sets 8–29 involve the reaction of water with compounds of the type XZ(PO)Cl where Z is a constant substituent. Of the 22 sets studied, seven gave significant correlation with the υ parameters and 15 did not. Furthermore, five of the seven significant correlations were poor. By contrast, 16 of the sets gave significant correlation (five excellent, three very good, four good, two fair, and two poor) with the υ' constants whereas six sets did not give significant correlation (of which three sets had only three points). Clearly then, much better results are obtained with υ' than with υ. These results are in agreement with a transition state such as I for the reaction of XZ(PO)Cl with water.



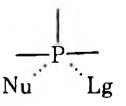
I



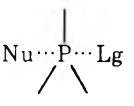
II

Transition state I has trigonal-bipyramidal geometry. The argument upon which this statement is based is that the steric effect of an unsymmetrical substituent, a category into which most alkyl groups fall, upon a rate constant is dependent upon the geometry of the transition state for reaction which is occurring. When transition states have similar geometry (that is, are of the same geometric type, although bond lengths may differ) the rate constants for the corresponding reactions should be correlated by the same type of substituent constant. Differences in bond lengths would then be reflected in differences in the coefficient, S.

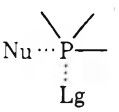
There does not seem to be a consensus in the literature as to the mechanism of nucleophilic attack on XZ(PO)Lg where X and Z are substituents and Lg is a leaving group. Kirby and Warren[11] state that three structures have been suggested for the transition state in nucleophilic attack on tetrahedral pentacovalent phosphorus: (1) a square pyramide with $d_{x^2-y^2}$, p_s, p_y, and p_zs hybrid bonds; (2) the structure II with three sp^3 bonds and two long ($\frac{1}{4}sp^3$–d_{xy}) bonds to the entering and leaving groups, Nu and Lg; and (3) trigonal bipyramids in which the entering and leaving groups may occupy either opposite or adjacent positions. Three such transition states can be written, III, IV, and V. I is of course equivalent to IV.



III



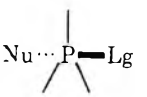
IV



V

Osterheld[12] is of the opinion that the most probably bimolecular mechanism for this type of reaction involves a pentacovalent *intermediate* of the trigonal bipyramid type, VI. The

VI



VII

location of the groups in VI is not shown since by appropriate pseudorotation any two groups may occupy either opposite or adjacent positions. Emsley and Hall[13] feel that the bimolecular mechanism is probably of the S_N2 type. The mechanism of these reactions has also been discussed by Benkovic[14].

Although a better correlation with υ' is suggestive of a rate-determining step involving either I or the transition state VII which leads to the intermediate VI, it cannot be regarded as conclusive at the present. Steric effects can however distinguish between associative mechanisms such as the $S_N2(P)$ and dissociative mechanisms such as the $S_N1(P)$. The former will have more repulsions between the substituent and the rest of the molecule in the transition state than are present in the substrate. The result is steric hindrance, which is indicated by a negative value for S. In the latter type of mechanism there are more repulsions in the substrate than the transition state, and therefore the result is steric acceleration, indicated by a positive value of S.

The last group of sets studied represents the reaction of esters of alkyl-substituted phosphorus oxy acids with hydronium ion, water, or hydroxide ion (sets 5–7, 31). The reaction of the diisopropyl phosphonates with hydronium ion (set 6) did not give a significant correlation with either the υ or the υ' constants and their reaction with hydroxide ion (set 5) was best correlated by the υ constants giving good results. The reaction of the ethyl *p*-nitrophenyl phosphonates with hydroxide ion (set 31) was best correlated by the υ' constants, however. Although correlations with both υ and υ' were significant at the 99.9% confidence level, CL, the former accounted for 79.6% of the data while the latter accounted for 94.4% of the data. The difference in behavior between the two

types of ester may possibly be due to the differences in leaving group character between the *p*-nitrophenoxy group and the isopropoxy group, the former being a much better leaving group. Further work is required before we can make use of the steric effect of alkyl groups to indicate the geometry of the transition state in the reaction of esters of phosphorus oxy acids with nucleophiles. The dialkyl methyl phosphinates (set 7) give somewhat better correlation with υ (poor results) than with υ' (results not significant).

Our successful correlation of the pK_as of phosphonic and phosphinic acids with steric parameters suggested to us that it might be useful to reexamine the $\sigma\phi$ constants of Kabachnik.[15] These constants were defined from the pK_as of phosphorus oxy acids and are intended to represent the effect of substituents at a phosphorus atom. It had previously been shown by one of us that[16] $\sigma\phi$ is a function of σ_I and σ_R; thus for 20 substituents,

$$\sigma\phi = L\sigma_I + D\sigma_R + c \quad (7)$$

Mastryukova and Kabachnik[17] reinvestigated the correlation of values with eq 1 and reported a value of r of 0.931. Thus the correlation accounted for only 86.7% of the data although it was significant at the 99.9% CL. They ascribed this failure to account for more of the data to a difference in resonance effects between a substituent bonded to phosphorus and a substituent bonded to carbon. We have examined the correlation of $\sigma\phi$ values with the equation

$$\sigma\phi_X = L\sigma_{IX} + D\sigma_{RX} + S\upsilon_X + c \quad (8)$$

The σ_I and σ_R values were taken from our compilation;[4] the υ_X values were from our previous work[10] whenever possible. The σ_I value for *i*-PrCH_2CH_2 was assumed equal to the average value of −0.01 found for nine alkyl groups (only reliable values were considered). The σ_R values for *i*-Bu, *s*-Bu, c-C_6H_{11}, *i*-PrCH_2CH_2, and *t*-BuCH_2 were assumed equal to the average value of −0.16 found for nine alkyl groups. Again, only reliable values were considered. The σ_I values for $CHCl_2$ and $CHPh_2$ were calculated from the equation

$$\sigma_{I,CHX^1X^2} = 0.318\Sigma\sigma_{IX} + 0.005 \quad (9)$$

The σ_{R,CH_2Cl_2} value was estimated graphically from a plot of σ_R vs. the number of chlorine atoms for CCl_nH_{3-n} groups. The σ_R value for *i*-PrO, BuO, *i*-PrCH_2CH_2O, and c-$C_6H_{11}O$ was assumed equal to the average σ_R value of −0.57 for OR groups. The σ_I values for BuCH_2O, *i*-PrCH_2CH_2O, and c-$C_6H_{11}O$ were assumed equal to the average σ_I value of 0.28 for OR groups. The σ_I value of *i*-PrS and the σ_R value of PrS were assumed to be equal to the average values for SR groups of 0.26 and −0.27, respectively. The σ_R value for the Ph_2CH group was obtained from the equation

$$\sigma_R = \sigma_p - \sigma_I \quad (10)$$

using a σ_p value reported by Little et al.[18] The υ value for the PhO group was estimated from the equation

$$\upsilon_{OX} = 0.959\upsilon_{CH_2X} - 0.100 \quad (11)$$

to be 0.57. The $\sigma\phi$ values are taken from Mastryukova and Kabachnik. Of the 41 values of $\sigma\phi$ reported by these workers, we have used 38, excluding the values for the phenyl, vinyl, and Me_3SiCH_2 groups. These groups were not included in the correlation due to either uncertainty in or lack of the appropriate υ parameters. The results of the correlation with eq 8 are L, 4.09; D, 1.34; S, −0.551, c, −0.428; correlation coefficient, 0.959; F, test for significance of regression; 131.5 (99.9% CL); partial correlation coefficients of σ_I on σ_R, σ_I on υ, σ_R on υ, 0.381 (95.0% CL), 0.167 (<90.0% CL), 0.405 (98.0% CL); standard errors of the estimate, L, D, S, and c, 0.191, 0.213 (99.9% CL), 0.155 (99.9% CL), 0.113 (99.9% CL), 0.112 (99.9% CL), 38 points. The correlation obtained is excellent and accounts for 92.1% of the data. This represents a significant improvement over the results of Mastryukova and Kabachnik and indicates that *most* of the effect of a substituent attached to phosphorus can be accounted for in terms of the *same electrical effects and steric effects which the substituent exerts when attached to carbon*. The 7.9% of the data which remains unaccounted for may be due in part at least to errors in determining $\sigma\phi$ constants for strong acceptor groups such as F, Cl, DFa, and CCl_3. We find it particularly significant and rewarding that values for such a wide range of substituent effects give a correlation with significant at the 99.9% confidence level as this substantiates the argument that υ values for alkoxy, alkylthio, and dialkylamino groups are indeed on the same scale as the other υ values.

Supplementary Material Available: Complete statistics for all of the sets studied (2 pages). Ordering information is given on any current masthead.

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Evaluation of Through-Space Interaction in 9-Substituted Pentacyclononane Derivatives

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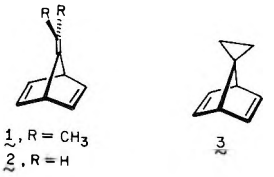
The pentacyclic hydrocarbons **4–7** have been prepared from homocuneone (**9**) and their photoelectron spectra have been recorded. In each instance, it has proved possible to assign the first five bands, reliance being placed upon a ZDO model and comparison with related compounds. The matrix elements for the through-space interaction between the dicyclopropyl fragment and the structural unit at the 9 position were determined to be the same as in the corresponding norbornadiene compounds. A comparison between experiment and computational results derived from the all-valence-electron methods EH, CNDO/2, MINDO/3, and SPINDO/1 indicates that the first three drastically underestimate through-space interaction.

Recent photoelectron (PE) spectroscopic measurements on 7-isopropylidenenorbornadiene (**1**)[3] and 7-methylenenorbornadiene (**2**)[4] have shown that considerable through-space interaction exists between the exocyclic π orbital and $b_2(\pi)$ orbital of the norbornadiene moiety. A similar interaction has been detected in **3**.[5] In this connection, it was of interest to supplant the double bonds in **1–3** by cyclopropane



rings as in **4–7** and to investigate the magnitude of the through-space interaction in such structurally rigid molecules. Accordingly, these hydrocarbons were synthesized and their PE spectra were recorded. The first measured vertical ionization potentials, $I_{V,J}$, are listed in Table I together with our assignments. The relevant spectra are illustrated in Figure 1 and appropriate correlation of the first bands is made in

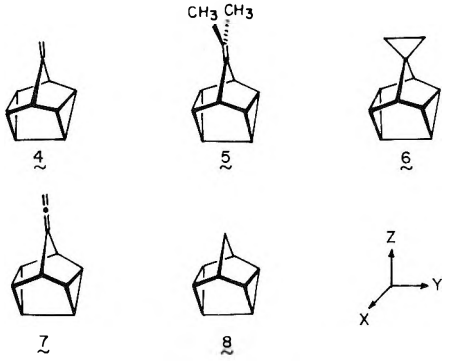
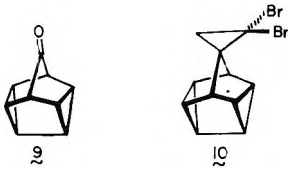


Figure 2. In this work, the validity of Koopmans' theorem ($-\epsilon_J = I_{V,J}$) is assumed.[6] The individual orbital energies (ϵ_J) have been derived by a zero differential overlap (ZDO) treatment as discussed below. A comparison of the ZDO results with those of semiempirical calculations is subsequently provided.

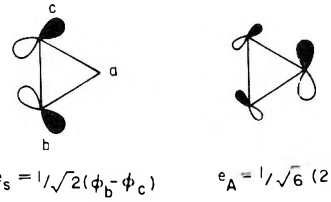
Synthesis. The pentacyclononane derivatives **4** and **5** were available by direct condensation of homocuneone (**9**)[7] with



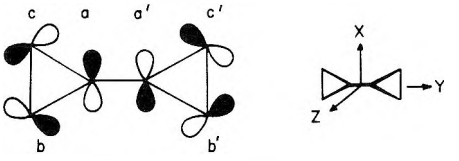
methylene- and isopropylidenetriphenylphosphorane, respectively, in tetrahydrofuran solution. Treatment of **4** with bromoform and potassium *tert*-butoxide in pentane afforded the dibromocarbene adduct **10**. This intermediate gave the spirocyclopropane derivative **6** when reduced with lithium in a combined *tert*-butyl alcohol–tetrahydrofuran solvent system. Allene **7** was obtained when **10** was exposed to the action of methyllithium.

ZDO Model for 4, 5, and 6. To derive the orbital energies for **4–6** within a ZDO model, it is necessary to define the wave functions, basis orbital energies, and interaction parameters.

(a) Wave Functions. Wave functions for the highest occupied MO's of **4–6** are constructed from the two basis orbitals e_S and e_A of the cyclopropane ring shown below:



The relative phases of the tangential p orbitals, ϕ_μ, of dicyclopropyl are defined as follows:



Assuming C_{2v} symmetry for the dicyclopropyl unit, one obtains the following four linear combinations:

	C_{2v}
$\psi_4 = 0.5(\phi_a + \phi_{a'}) - 0.354(\phi_b + \phi_c + \phi_{c'} + \phi_{b'})$	a_2
$\psi_3 = 0.5(\phi_b - \phi_c + \phi_{c'} - \phi_{b'})$	a_1
$\psi_2 = 0.5(\phi_b - \phi_c - \phi_{c'} + \phi_{b'})$	b_2
$\psi_1 = 0.628(\phi_a - \phi_{a'}) - 0.230(\phi_b + \phi_c - \phi_{c'} - \phi_{b'})$	b_1

The irreducible representations according to which these wave functions transform in the point group C_{2v} are listed following the equations. The wave functions are sketched below.

(b) Basis Orbital Energies. The basis orbital energies for the wave functions of the dicyclopropyl unit in **4–6** are derived from **8**.[8] As concerns **4** and **6**, an inductive effect of −0.15 eV is assumed for the double bond and the three-membered ring. This assumption is consistent with the results of earlier investigations.[5] In the case of **5**, the inductive effect of the iso-

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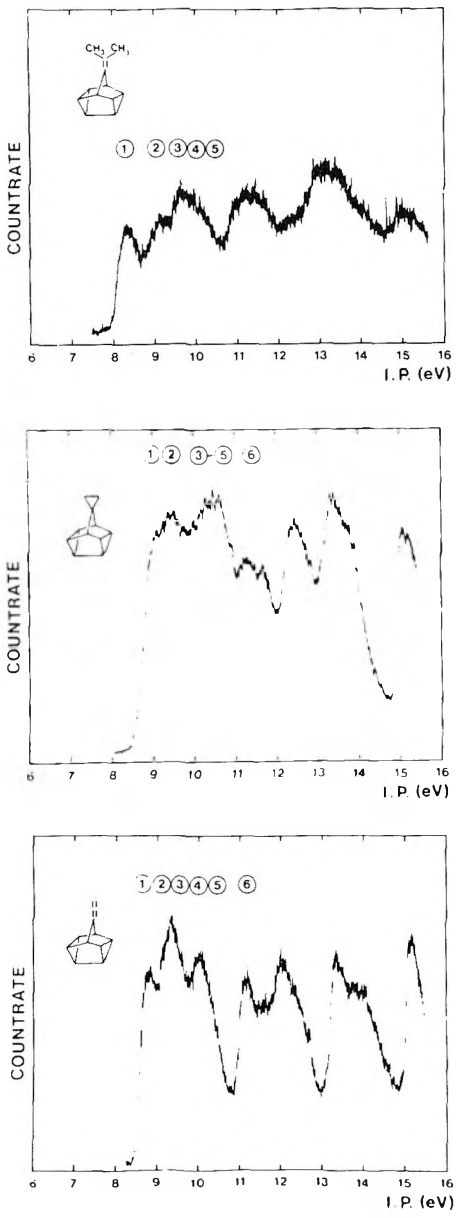
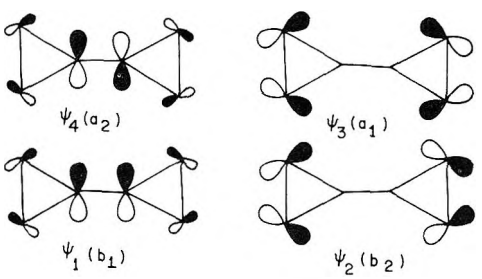


Figure 1. PE spectra of 5–7.

propylidene group is taken to be +0.1 eV.[3]

In these terms, the basis orbital energy for the ethylene moiety in **4** is expected to reside at −9.6 eV. This value is derived from the ionization potential of 7-methylenenorbornane (9.4 eV)[4,5] reduced by the inductive effect (−0.2 eV) of the two



cyclopropane rings. In a similar manner, the basis orbital energy of the π orbital in **5** (−8.7 eV) is derived from the ionization potential of 7-isopropylidenenorbornane (8.5 eV).[5] Since the ionization potentials assigned to the two Walsh orbitals of the three-membered ring in 7-spirocyclopropylnorbornane are 9.6 eV for $b_2(e_A)$ and 10.9 eV for $a_1(e_S)$, the corresponding basis orbitals in **6** are anticipated to be −9.8 and −11.1 eV.

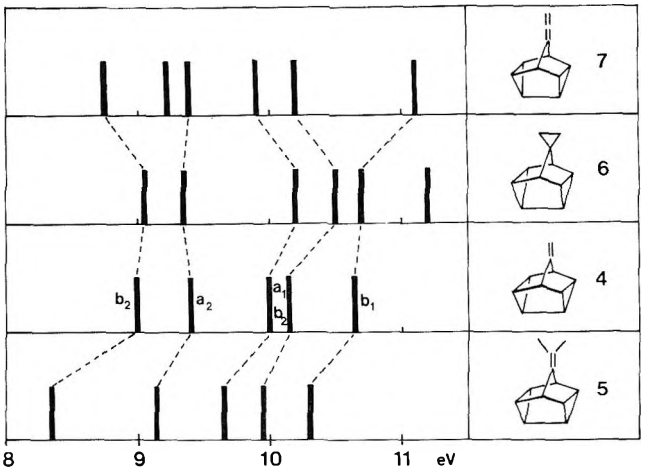


Figure 2. Correlation between the first bands in the PE spectra of 4–7.

(c) Interaction Parameters. The calculated orbital energies for **1** and **2** agree well with experiment[3] by assuming the matrix element

$$\langle \pi_- | H | \pi \rangle = -0.64 \text{ eV}$$

In this expression, π_- represents the antisymmetric linear combination of the π orbitals in the norbornadiene unit and π the ethylene moiety at the 7 position. For **3**, the corresponding matrix element has been found[5] to be

$$\langle \pi_- | H | e_A \rangle = -0.66 \text{ eV}$$

If the same matrix element values are adopted for **4** and **5** (H_{ij} = −0.64 eV) as well as for **6** (H_{ij} = −0.66 eV), the following secular determinants and solutions for the eigenvalues corresponding to the orbitals of B_2 symmetry are obtained:

$$\mathbf{4}\quad \begin{vmatrix} -9.6-\epsilon & -0.64 \\ -0.64 & -9.8-\epsilon \end{vmatrix} = 0 \qquad \epsilon_1 = -9.05 \text{ eV},\ \epsilon_2 = -10.34 \text{ eV}$$

$$\mathbf{5}\quad \begin{vmatrix} -8.7-\epsilon & -0.64 \\ -0.64 & -9.5-\epsilon \end{vmatrix} = 0 \qquad \epsilon_1 = -8.42 \text{ eV},\ \epsilon_2 = -9.87 \text{ eV}$$

$$\mathbf{6}\quad \begin{vmatrix} -9.8-\epsilon & -0.66 \\ -0.66 & -9.8-\epsilon \end{vmatrix} = 0 \qquad \epsilon_1 = -9.15 \text{ eV},\ \epsilon_2 = -10.48 \text{ eV}$$

We have not carried out a comparable ZDO based calculation on **7** since PE data on 7-allenylidenenorbornane or 1,1′-diisopropylallene are missing. However, an alternate model for 7-vinylidenenorbornane is 1,1-di-*tert*-butylallene. For this compound, the first two ionization potentials are seen to be located at 8.55 and 9.30 eV.[9] These values lie close to the first two bands of **7**. The values for the ionization potentials of bands ③–⑤ of **7** compare closely to the ones observed for **4**, as anticipated. The agreement between the calculated orbital energies and the measured band positions for **4–6** is very good.

Semiempirical Calculations. To check the assignments made above, semiempirical calculations of the EH,[10] CNDO/2,[11] MINDO/3,[12] and SPINDO/1 types[13] have been performed for **4–7**. Since the detailed structures of these compounds are not known, their geometries were optimized using the MINDO/3 method under the assumption of C_{2v} symmetry. The predicted heats of formation, H_f, together with the orbital sequences are listed in Table II. The MINDO/3, CNDO/2, and EH calculations predict in all cases a much smaller split between the b_2 orbitals than the values provided by the ZDO and SPINDO/1 models. This implies a relatively minute through-space interaction between ψ_2 and the π sys-

Table I. Comparison between Measured Vertical Ionization Potentials ($I_{V,J}$) and ZDO Orbital Energies for 4–7 (all values in eV)

Compd.	Registry no.	Band	$I_{J,V}$	Assignment	ZDO
4	64630-96-2	1	9.00	7 b_2 ($\pi - \psi_2$)	8.05
		2	9.40	3 a_2 (ψ_4)	9.30
		3	10.00	10 a_1 (ψ_3)	10.05
		4	10.15	6 b_2 ($\psi_2 + \pi$)	10.34
		5	10.65	6 b_1 (ψ_1)	10.75
5	65915-87-9	1	8.35	7 b_2 ($\pi - \psi_2$)	8.42
		2	9.14	4 a_2 (ψ_4)	9.05
		3	9.65	12 a_1 (ψ_3)	9.80
		4	9.95	6 b_2 ($\psi_2 + \pi$)	9.87
		5	10.3	7 b_1 (SA)	10.55
6	65915-88-0	1	9.05	6 b_2 ($e_A - \psi_2$)	9.15
		2	9.35	4 a_2 (ψ_4)	9.30
		3	10.2	10 a_1 (ψ_3)	10.05
		4	10.5	5 b_2 ($\psi_2 + e_A$)	10.48
		5	10.7	6 b_1 (ψ_1)	10.8
		6	11.2	9 a_1 (e_S)	11.1
7	65915-89-1	1	8.75	7 b_2 ($\pi - \psi_2$)	
		2	9.22	6 b_1 (π)	
		3	9.38	3 a_2 (ψ_4)	
		4	9.9	11 a_1 (ψ_3)	
		5	10.2	6 b_2 ($\psi_2 + \pi$)	
		6	11.1	5 b_1 (ψ_1)	

tem positioned at C_9. As a consequence, the highest occupied orbitals of **4–6** are predicted to belong to the irreducible representations A_2 and A_1 (see Table II). A similar discrepancy has been encountered in the case of spiroconjugated molecules.[14] A detailed analysis of the shortcomings of the CNDO and MINDO methods in reproducing long-range through-space interaction has been given by Heilbronner and Schmelzer.[15] According to their results, the SPINDO/1 model seems at present the most appropriate model for interpreting the PE spectra of hydrocarbons.

The SPINDO/1 results we have obtained on structures derived from MINDO/3 optimization compare very closely to those obtained from ZDO calculations, especially as regards **4, 5,** and **7.** The only differences are the ordering between 10 a_1 and 6 b_2 in the case of **4** and the corresponding orbitals in **5** and **7.** The main discrepancy is associated with **6** (see Tables I and II). Such differences have previously been observed in other hydrocarbons endowed uniquely with small ring fragments.[16]

Concluding Remarks. The ZDO model predicts the HOMO for **4–7** to be $b_2(\pi-\psi_2)$ or $b_2(e_A-\psi_2)$. This prediction is corroborated by the following observations: (i) The first ionization potentials of 7-methylenenorbornane (9.4 eV),[4] 7-isopropylidenenorbornane (8.5 eV),[5] and 7-spirocyclopropylnorbornane (9.6 eV)[5] are close to, but slightly higher than, the corresponding first ionization potentials of **4–6.** The lower values for **4–6** are due to the larger carbon skeleton and the through-space interaction discussed. (ii) Methyl substitution on a double bond is known to substantially lower the ionization potential of the π orbital. A comparison between the spectra of **4** and **5** shows that an appropriate shift is observed only for the first band.

One of the purposes underlying publication of our semiempirical results at this time is to point out the difficulties and pitfalls encountered with such methods when applied to strained hydrocarbons.

Experimental Section

Proton magnetic resonance spectra were obtained on a Varian A-60A spectrometer; apparent splittings are given in all cases. Carbon spectra were recorded with a Bruker HX-90 instrument. Infrared spectra were obtained with a Perkin-Elmer Model 467 spectrometer, while mass spectra were measured with an AEI-MS9 spectrometer at an ionization potential of 70 eV. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

9-Methylenepentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonane (4). To a stirred suspension of methyltriphenylphosphonium bromide (4.20 g, 11.76 mmol) in 30 mL of dry tetrahydrofuran was added under nitrogen at 25 °C 5.0 mL of a 2.35 M solution of *n*-butyllithium in hexane (11.75 mmol). After 2 h, a solution of **9**[7] (1.50 g, 11.35 mmol) in 20 mL of dry tetrahydrofuran was introduced dropwise via syringe. The reaction mixture was stirred for an additional 2 h at 25 °C, heated to a gentle reflux for 30 min, cooled, poured into ice water (300 mL), and filtered. The precipitate was washed with 75 mL of pentane which was used to extract the aqueous filtrate. The pentane layer was washed with water (3 × 100 mL), dried, filtered, and distilled at ambient pressure through a 1 × 13 cm Vigreux column to remove solvent. The residual oil was vacuum transferred at 50 °C (0.2 mm) into an

Table II. Calculated Heats of Formation and Orbital Energies for 4–7 According to EH, CNDO/2, MINDO/3, and SPINDO/1 Methods (orbital energies are given in eV)

Compd	H_f, kcal/mol	EH	CNDO/2[a]	MINDO/3	SPINDO/1
4	121.74	−12.27 (a_2)	−11.80 (a_2)	−9.07 (a_2)	−10.14 (b_2)
		−12.35 (a_1)	−11.91 (a_1)	−9.31 (a_1)	−10.45 (a_2)
		−12.56 (b_2)	−13.77 (b_2)	−9.35 (b_2)	−10.58 (b_2)
		−12.70 (b_2)	−14.00 (b_2)	−9.51 (b_2)	−10.76 (a_1)
		−12.96 (b_1)	−15.34 (b_1)	−9.76 (b_1)	−10.87 (b_1)
5	109.34	−12.18 (b_2)	−11.59 (b_2)	−8.87 (b_2)	−9.71 (b_2)
		−12.28 (a_2)	−11.73 (a_2)	−9.09 (a_2)	−10.52 (a_2)
		−12.33 (a_1)	−11.89 (a_1)	−9.31 (a_1)	−10.66 (b_2)
		−12.59 (b_2)	−13.07 (b_2)	−9.49 (b_2)	−10.73 (a_1)
		−12.83 (b_1)	−15.13 (b_1)	−9.70 (b_1)	−11.07 (b_1)
6	122.76	−12.26 (a_2)	−11.65 (a_2)	−9.05 (a_2)	−10.48 (a_2)
		−12.30 (a_1)	−11.83 (a_1)	−9.15 (a_1)	−10.58 (b_2)
		−12.50 (b_2)	−12.49 (b_2)	−9.35 (b_2)	−10.61 (a_1)
		−12.62 (b_2)	−13.53 (b_2)	−9.49 (b_2)	−10.95 (b_2)
		−13.00 (b_1)	−14.61 (a_1)	−9.87 (b_1)	−11.07 (b_1)
		−12.15 (a_1)	−15.20 (b_1)	−10.23 (a_1)	−11.36 (a_1)
7	144.37	−12.27 (a_2)	−11.78 (b_2)	−8.85 (b_2)	−9.57 (b_2)
		−12.34 (b_2)	−11.82 (a_2)	−8.99 (b_1)	−9.90 (b_1)
		−12.36 (a_1)	−12.00 (a_1)	−9.09 (a_2)	−10.44 (a_2)
		−12.58 (b_1)	−13.02 (b_1)	−9.36 (a_1)	−10.56 (b_2)
		−12.59 (b_2)	−13.18 (b_2)	−9.47 (b_2)	−10.68 (a_1)
		−13.36 (b_1)	−15.38 (b_1)	−10.66 (b_1)	−11.42 (b_1)

[a] Several σ levels in the region between 12 and 15 eV have been omitted.

ice-cooled receiver to give 1.09 g (73.7%) of **4**: ν_{max} (neat) 3045, 2985, 1669, 1283, 810, 777, and 728 cm^{-1}; ^1H NMR (CCl_4) δ 4.03 (s, 2 H), 2.61 (m, 2 H), 2.18 (m, 2 H), and 1.94 (m, 4 H); ^{13}C NMR ($CDCl_3$) 172.54, 89.10, 44.13, 37.23, and 36.93 ppm; *m/e* calcd 130.0782, obsd 130.0785.

Anal. Calcd for $C_{10}H_{10}$: C, 92.26; H, 7.74. Found: C, 92.23; H, 7.83.

***9-Isopropylidenepentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonane* (5).** To a magnetically stirred suspension of anhydrous isopropyltriphenylphosphonium bromide (1.40 g, 3.63 mmol) in 6.0 mL of anhydrous tetrahydrofuran was added dropwise under nitrogen at 25 °C a solution of *n*-butyllithium (1.64 mL of 2.08 M) in hexane. After 1 h, a solution of 9[7] (0.450 g, 3.41 mmol) in 4.0 mL of tetrahydrofuran was introduced dropwise via syringe. After 2.5 h the reaction mixture was heated at gentle reflux for an additional 2.5 h, cooled to ambient temperature, and processed as above. Vacuum transfer at 70 °C (0.1 mm) of the residual oil after removal of solvent gave 0.435 g (80.7%) of **5**: ν_{max} (neat 3045, 3000, 2915, 1283, 788, and 715 cm^{-1}; ^1H NMR (CCl_4) δ 2.86 (m, 2 H), 2.13 (m, 2 H), 1.88 (m, 4 H), and 1.55 (m, 6 H); ^{13}C NMR ($CDCl_3$) 159.43, 105.59, 40.76, 37.74, 36.55, and 20.18 ppm; *m/e* calcd 158.1095, obsd 158.1098.

Anal. Calcd for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 91.09; H, 8.99.

Dibromocarbene Addition to 4. A solution of bromoform (1.30 g, 5.14 mmol) in 3.0 mL of pentane was added dropwise to a vigorously stirred suspension of potassium *tert*-butoxide (0.480 g, 4.28 mmol) and 4 (0.550 g, 4.22 mmol) in 10 mL of pentane under nitrogen at 15 °C. The reaction mixture was stirred at 25 °C for 12 h, poured into 15 mL of water, and extracted with 2 × 10-mL portions of ether. The combined extracts were washed with 3 × 20 mL of water, dried, filtered, and evaporated to leave a semisolid suspended in a small amount of oil. This material was taken up in 4 mL of 5% benzene in pentane and washed down a 1 × 5-cm column of neutral alumina (activity grade 1) using an additional 20 mL of solvent. Evaporation left 0.94 g of a white semisolid which was recrystallized from pentane to give 0.583 g (45.5%) of **10**: mp 98.5–99.5 °C; ν_{max} (KBr) 3050, 1185, 1032, 1017, 789, 764, and 684 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.44 (br s, 2 H), 2.32 (br s, 4 H), 2.11 (br s, 4 H), and 1.76 (s, 2 H); *m/e* calcd 299.9150, obsd 299.9157.

9-Spirocyclopropylpentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonane (6). To a magnetically stirred solution of **10** (0.298 g, 0.987 mmol) and anhydrous *tert*-butyl alcohol (0.50 g, 6.75 mmol) in 10 mL of dry tetrahydrofuran was added at 25 °C under nitrogen finely cut lithium wire (0.22 g, 31.7 mg). The reaction mixture was stirred for 10 h at ambient temperature and excess lithium was removed by filtration (with ether washing). Twenty milliliters of 10% ammonium chloride solution was added, the layers were separated, and the aqueous layer was extracted with pentane (2 × 10 mL). The combined organic layers were washed with three 20-mL portions of water, dried, filtered, and freed of solvent by distillation at ambient pressure. The residual oil was vacuum transferred at 80 °C (0.1 mm) into an ice-cooled receiver to give 0.1143 g (80.5%) of **6**: mp 28 °C; ν_{max} (neat) 3040, 2965, 1288, 781, and 760 cm^{-1}; ^1H NMR (CCl_4) δ 2.02 (br s with shoulder at 1.97, 8 H) and 0.46 (s, 4 H); *m/e* calcd 144.0939, obsd 144.0942.

Anal. Calcd for $C_{11}H_{12}$: C, 91.61; H, 8.39. Found: C, 91.62; H, 8.43.

9-Allenylidenepentacyclo[4.3.0.0^{2,4}.0^{3,8}.0^{5,7}]nonane (7). To a magnetically stirred solution of **10** (0.2319 g, 0.768 mmol) in 10 mL of anhydrous ether was added under nitrogen at −24 °C 0.6 mL of a 1.84 M solution of methyllithium in ether via syringe. After 40 min at −24 °C, 3.0 mL of water was introduced, the layers were separated, the aqueous layer was extracted with 2 mL of ether, and the combined ether layers were washed three times with 5-mL portions of water, dried, and freed of solvent by distillation at ambient pressure. The residual material was vacuum transferred at 0.3 mm into a receiver cooled to −24 °C to give 0.103 g (94.5%) of **7** as a crystalline solid; mp 27 °C; ν_{max} (neat) 3045, 1277, 846, 787, and 720 cm^{-1}; ^1H NMR (CCl_4 δ 4.64 (s, 2 H), 2.96 (m, 2 H), and 2.12 (m, 6 H); *m/e* calcd 142.0782, obsd 142.0785.

Anal. Calcd for $C_{11}H_{10}$: C, 92.91; H, 7.09. Found: C, 93.01; H, 7.14.

Photoelectron Spectroscopy. The PE spectra were recorded on a Perkin-Elmer PS 18 instrument (Beaconsfield, England) and calibrated with argon. A resolution of about 20 meV on the argon line was observed.

Calculations. The semiempirical calculations have been carried out with standard programs. All calculations were based upon the geometrical parameters obtained by the MINDO/3 method.

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Registry No.—**9**, 20682-66-0; **10**, 65915-90-4; methyltrisphenylphosphonium bromide, 1779-49-3; isopropyltriphenylphosphonium bromide, 1530-33-2.

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Electronic Structure of Tricyclo[4.1.0.0^{2,7}]hept-3-enes. Correlation with the Regioselectivity of Electrophilic Attack[1]

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Received February 10, 1978

The photoelectron spectra of tricyclo[4.1.0.0^{2,7}]hept-3-ene (**4**) and several methyl-substituted derivatives have been recorded in an effort to gain further detailed information relating electronic structure to various fixed conformations of bicyclobutane rings. In the case of **4** and its congeners, the experimental data reveal the Walsh-type bicyclobutane orbital to be the HOMO in each instance, the conclusions being supported by MINDO/3 calculations. This finding contrasts in a striking way with the orbital ordering previously established for benzvalene. The origins of this difference are discussed and the chemical manifestations of this ordering are demonstrated by rearrangement of these molecules with H^+, D^+, and Ag^+.

That the chemical reactivity of some molecules can be rationalized by frontier orbital considerations is now extensively documented.[4] As a consequence, orbital sequencing can play a key role in the predictive capability of modern theoretical organic chemistry and there exists a need to develop in full our understanding of varied electronic interactions. In the special case of small cyclic molecules such as cyclopropane,[5] cyclobutane,[6] and bicyclobutane,[7] simple ZDO models have been widely accepted as suitable descriptors of their electronic structure.

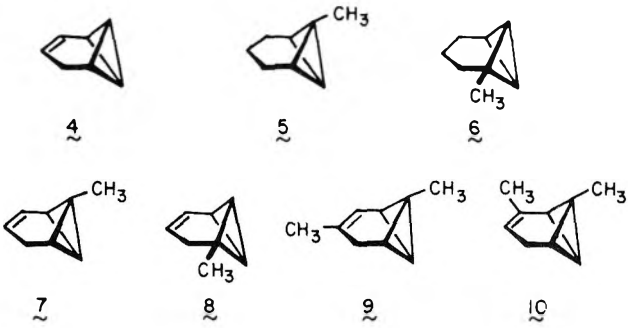
By assuming the validity of Koopmans' theorem,[8] one can experimentally check the calculated orbital sequencing of a molecule by means of photoelectron (PE) spectroscopy. The results of such investigations have recently increased our insight into, and improved our understanding of, cyclopropane and cyclobutane chemistry. We endeavor to establish that the somewhat more complicated bicyclobutane system can be treated analogously.

In this connection, we have previously investigated the electronic structure of benzvalene (**1**), tricyclo[3.1.0.0^{2,6}]-

1 **2** **3**

hexane ("dihydrobenzvalene", **2**), and tricyclo[4.1.0.0^{2,7}]-heptane (**3**) by PE spectroscopy. This series of molecules can be regarded as independent check points for the electronic structure of the bicyclobutane system at various fixed conformations. The experimental evidence fully corroborates the results of theoretical investigations and establishes that the postulated orbital sequence in **1** ($4b_2$, $10a_1$, $1a_2$, and $6b_1$) is due principally to two effects: (1) a strong interaction between the $b_2(\pi)$ orbital of the ethylene unit and the $b_2(\sigma)$ orbital of the adjacent bicyclobutane ring, and (2) a considerably smaller dihedral angle θ between the two fused cyclopropane rings in **1** (105°)[10] as compared to θ in the parent bicyclobutane (121.7°).[11]

The aim of the present study was to develop additional support for the conclusions arrived at earlier on the basis of rather limited information. To do so, the PE spectrum of tricyclo[4.1.0.0^{2,7}]hept-3-ene (**4**) was recorded, together with those of a series of methyl and dimethyl derivatives of both **3** and **4**. The structures of the hydrocarbons are illustrated. Whereas **4**, **7**, and **8** were available from a prior study,[12] **9** and **10** were prepared from dibromobicycloheptenes **11** and **13**, respectively (Chart I). Treatment of **11** with methyllithium in ether at 0 °C resulted in intramolecular C–H insertion to give **9** and **12** in a ratio of approximately 7:1, in compliance



4 **5** **6**

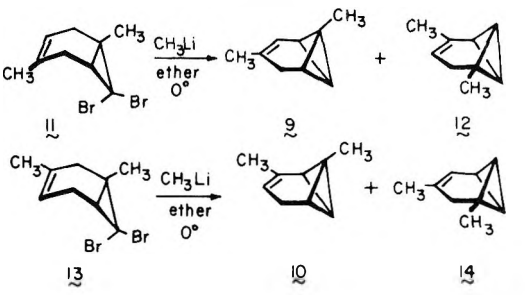
7 **8** **9** **10**

with the generalization that angular 1-methyl groups direct carbenoid capture preferentially to the more proximal α carbon.[12b] The regioselectivity observed upon similar cyclization of **13** proved to be entirely comparable. In this instance, **10** was found to dominate over **14** by a factor of 6. The identities of these dimethyltricycloheptenes were established by their characteristic ^1H NMR spectra as described in the Experimental Section. Interestingly, the preferred formation of **9** and **10** is also in line with MINDO/3 calculations according to which methyl substitution of the tricyclo[4.1.0.0^{2,7}]heptane or tricyclo[4.1.0.0^{2,7}]hept-3-ene skeleton in position 1 is predicted to be more stable than in position 6 (see Figure 2).

The PE spectra of **3**, **4**, and **7** which are considered representative for this class of compounds are shown in Figure 1. As regards **3**, and the saturated compounds **5** and **6** as well, the recorded spectra all exhibit one highly distinctive band at an ionization energy of about 8.5 eV. The lack of any marked vibrational fine structure indicates a considerable change of the equilibrium structure of the corresponding molecules during the ionization process. This has also been observed in the spectrum of the parent bicyclobutane molecule.[13] On the other hand, the spectra of the unsaturated compounds **4** and **7**–**10** show *two* close lying peaks below 9 eV (bands ① and ② of the corresponding spectra).

The measured vertical ionization potentials of all these

Chart I



11 **9** **12**

13 **10** **14**

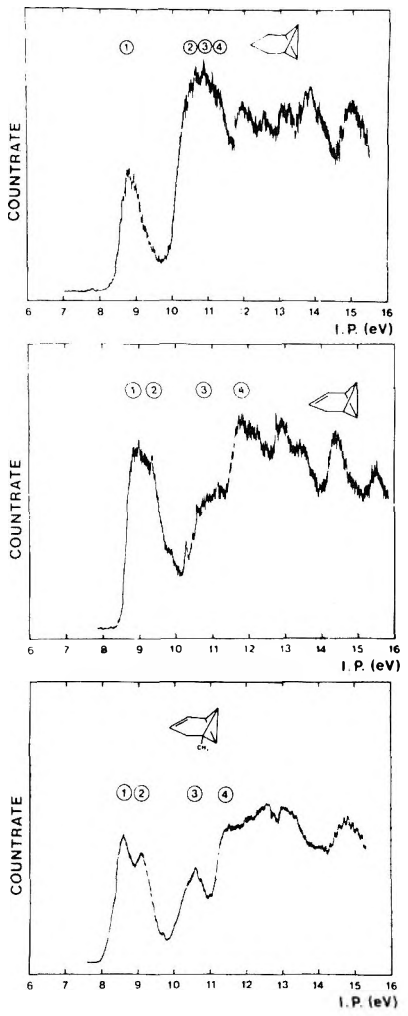


Figure 1. Photoelectron spectra of **3**, **4**, and **7**.

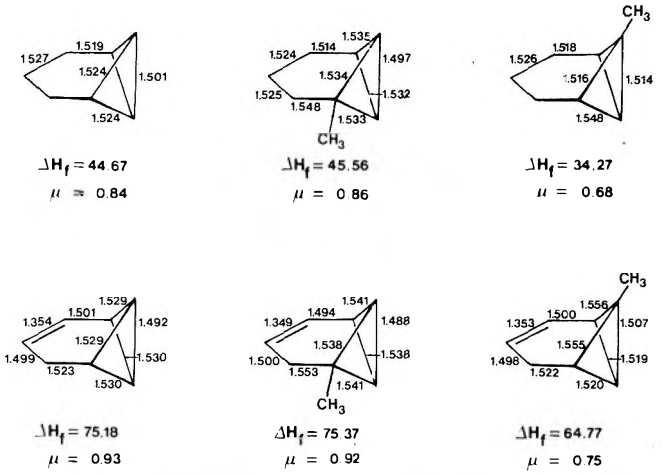


Figure 2. Calculated bond lengths, dipole moments (in Debye units), and heats of formation (kcal/mol) for **3**–**8** according to MINDO/3.

compounds are summarized in Table I where comparison is also made with calculated orbital energies resulting from MINDO/3 calculations.[14] Since the detailed three-dimensional structures of these molecules are not known, estimates were made by full geometry optimization of the individual molecules. The methyl substituents were assumed to have a local C_{3v} symmetry in order to avoid excessive calculations. The resulting structures for **3**–**8** are illustrated in Figure 2. The predicted structures of **1**[9] and parent bicyclobutane[11] have been noted to be in close agreement with experiment. The

Table I. Comparison between Measured First Vertical Ionization Potentials of **3** to **10** with Calculated Orbital Energies (All Values in eV)

Compd	Registry no.	Band	$I_{V,J}$	Assignment	ϵ_J(MINDO/3)
	287-13-8	①	8.72	$12a_1$	−8.66
		②	10.45	$2a_2$	−9.85
		③	10.8	$5b_2$	−10.03
		④	11.22	$7b_1$	−10.49
	35618-58-7	①	8.82	a_1*	−8.66
		②	9.20	π	−8.77
		③	10.80	a_2*	−10.05
		④	11.80	b_1*	−10.50
	32348-63-3	①	8.20	a_1*	−8.53
		②	9.90	a_2*	−9.64
		③	10.2	b_2*	−9.87
		④	10.8	b_1*	−10.45
	66036-90-6	①	8.42	a_1*	−8.63
		②	10.0	a_2*	−9.67
		③	10.35	b_2*	−9.96
		④	10.9	b_1*	−10.42
	61772-33-6	①	8.45	a_1*	−8.51
		②	8.95	π	−8.73
		③	10.60	a_2*	−9.87
		④	11.35	b_1*	−10.45
	61772-31-4	①	8.64	a_1*	−8.64
		②	9.16	π	−8.75
		③	10.67	a_2*	−9.81
		④	11.4	b_1*	−10.41
	66036-91-7	①	8.30	a_1*	−8.48
		②	8.70	π	−8.61
		③	10.40	a_2*	−9.84
		④	11.25	b_1*	−10.30
	66036-92-8	①	8.26	a_1*	−8.46
		②	8.66	π	−8.65
		③	10.36	a_2*	−9.87
		④	11.3	b_1*	−10.33

prediction that **3** should possess C_{2v} symmetry is in accord with the general trend of MINDO/3 to underestimate puckering amplitudes of saturated cyclic systems.[15] But this failure is not expected to affect the qualitative conclusions reached in this investigation. Figure 2 also includes the calculated heats of formation (ΔH_f) as well as the calculated dipole moments (μ) of the individual molecules.

In the ensuing interpretative discussion, reasonable use shall be made of local symmetry terms. This is because all molecules except **3** and **5** actually have no symmetry at all, thereby making it difficult to differentiate between the various orbitals or electronic state symmetries. To obviate this problem, we have utilized local symmetry terms which are indicated by an asterisk (*) in the corresponding symbols. Furthermore, the comparison between measured ionization potentials and calculated orbital energies at this level necessarily assumes the validity of Koopmans' theorem ($-\epsilon_J = I_{V,J}$).[8]

Discussion

In Figure 3, comparison is made of the measured band positions (left) and the calculated orbital energies for **3**–**8** (right). Clearly, the MINDO/3 calculations reproduce the general features very well except for the fact that the calculated gaps between bands ① and ② for the unsaturated species are too small in all cases. This tendency can be rationalized in terms of two effects: (1) Koopmans' defect in the sense that the excited state of the generated radical cation (i.e., corresponding to band ②) gains more electronic reorganization energy than its ground state (i.e., corresponding to band ①) and (2) a pseudo-Jahn-Teller effect acts to split nearly degenerate electronic states as witnessed in other context.[16] Both phe-

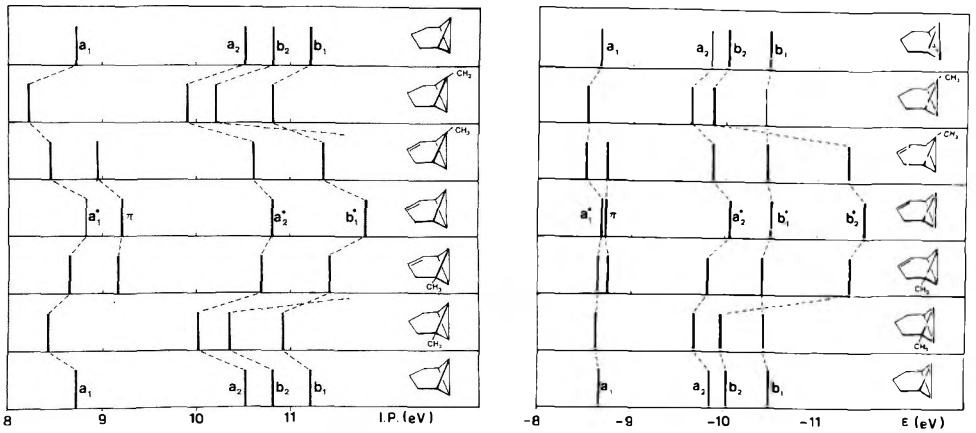


Figure 3. Comparison between the first bands in the PE spectra of **3**–**8** (left). Calculated orbital energies (MINDO/3) for **3**–**8** (right).

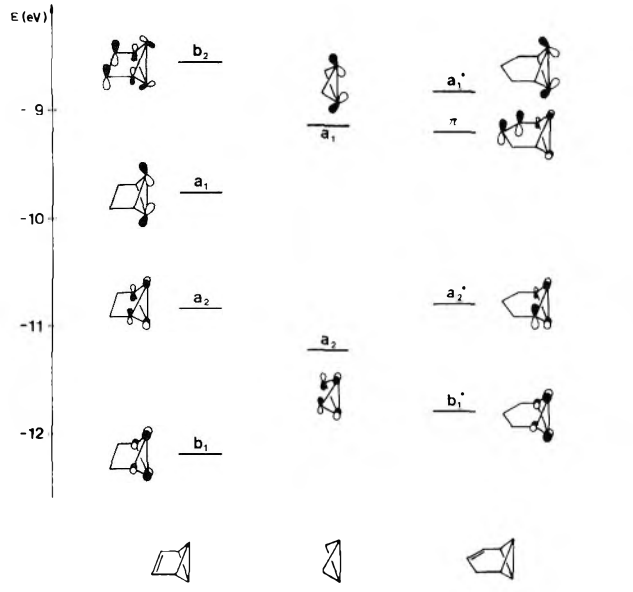


Figure 4. Comparison of the orbital sequences in benzvalene, bicyclobutane, and tricyclo[4.1.0.0^{2,7}]hept-3-ene.

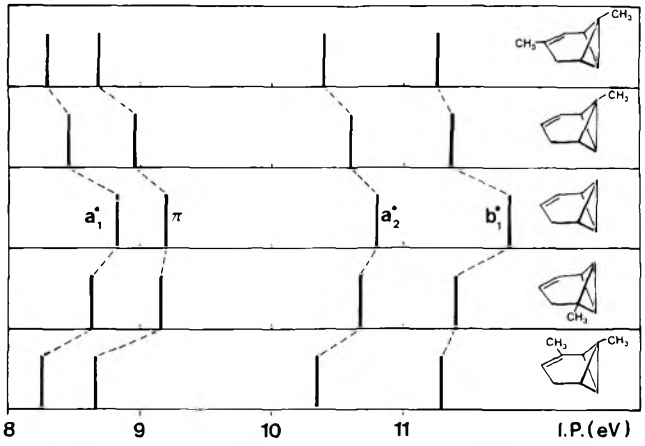


Figure 5. Comparison between the first bands in the PE spectra of **3** and **7**–**10**.

nomena parallel configuration interaction since the molecules have in fact no symmetry (see above), and both configurations therefore can mix to some extent to produce the observed energy levels.

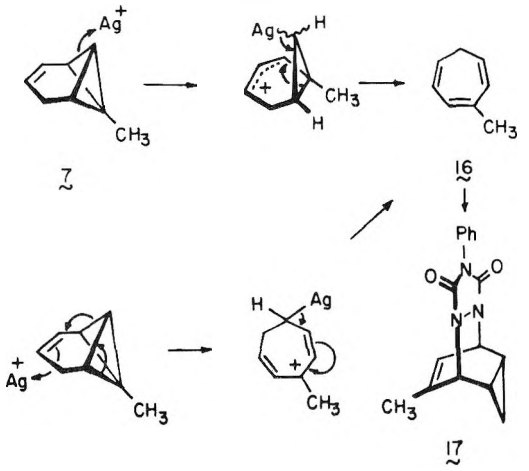
The calculations for **3** suggest that a_1 of the bicyclobutane unit is the HOMO of the molecule, well separated from the lower lying a_2, b_2, and b_1 orbitals. This interpretation has been confirmed by comparison with the corresponding levels in bicyclobutane and tricyclo[3.1.0.0^{2,6}]hexane (**2**).[9] Methyl substitution to provide **5** and **6** caused these levels to shift toward lower ionization energies. In general, this effect is assumed to be proportional to the corresponding orbital density at the substituted center. However, this crude approximation (based on the assumption that its cause is purely due to the electron-donating effect of the alkyl substituent) is only valid if the shifted orbital appears at very low ionization energy, i.e., well separated from the σ region of common hydrocarbons. If this is not the case, then resonance effects with the σ orbitals of the methyl group (IP(σ,Me) $\approx$ 12 eV) begin to contaminate the simple model and the net effect cannot be quantitatively predicted by such perturbation arguments. Notwithstanding, the MINDO/3 method appears to reproduce the observed shifts quite accurately (see Figure 3).

The orbital sequence suggested by our interpretation for **4** (Figure 3) is compared with the orbital sequence of **1** and bicyclobutane in Figure 4. Both sequences can be derived qualitatively from a bicyclobutane fragment and a double bond or a propenyl moiety, respectively. In the case of **1**, a strong interaction between the $b_2(\pi)$ orbital of the ethylene bridge and the b_2 orbital of the bicyclobutane part is encountered. As a result, the HOMO is a linear combination with large π character.[9] In contrast, the interaction between the double bond of the propenyl moiety and the orbitals of appropriate symmetry of the bicyclobutane part (a_2* and b_2*) in **4** should be approximately half as large as in benzvalene due to the fact there is only one link between the interacting systems. Since **4** possesses a maximum C_s symmetry, one should expect a further mixing of this linear combination with many other orbitals. However, these interactions should be too small to override the a_1* orbital as the HOMO of **4**. This expectation is nicely corroborated by comparison of the spectra given by **7**–**10** as illustrated in Figure 5. For **9** and **10**, the methyl group attached to the double bond shifts the band which is due to ionization out of the π orbital more strongly toward lower energy than the other bands, as expected.

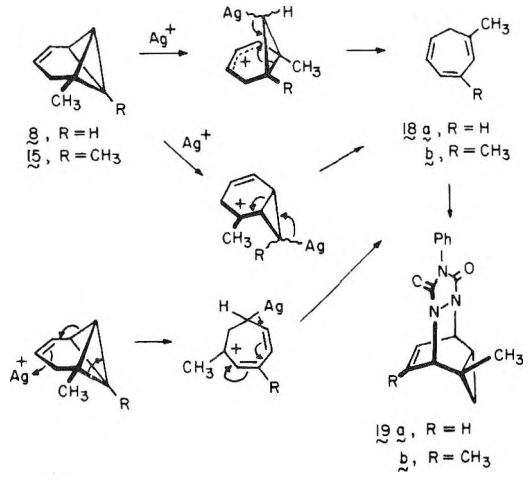
The observation that the a_1* level in tricyclo[4.1.0.0^{2,7}]-hept-3-ene and its various methyl substitution products lies above the π niveau leads, therefore, to the prediction that an electrophile should generally be directed to attack the bicyclobutane moiety. In **1**, however, electrophilic capture should occur at the double bond. The latter conclusions appear to be in line with available experiment. Thus, reaction of **1** with such reagents as bromine,[17] *N*-phenyltriazolinedione,[18] chlorosulfonyl isocyanate,[19] benzenesulfenyl chloride,[19] Ag^+,[20] and ozone[21] occurs by initial π-bond attack. In the ensuing section, the contrasting regioselectivity for electrophilic attack at a bicyclobutane edge bond is demonstrated.

Electrophilic Reactions of Tricyclo[4.1.0.0^{2,7}]hept-3-enes. Although **7**, **8**, and **15**[12] react exceedingly rapidly with

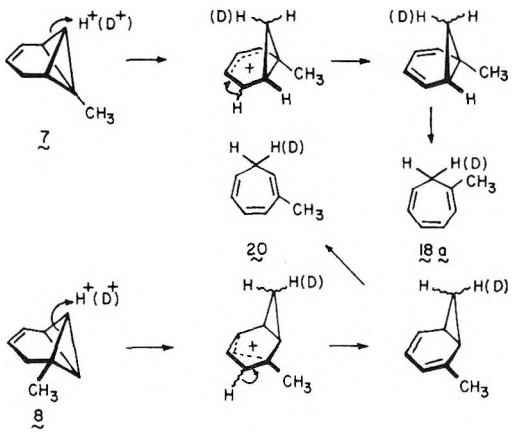
Scheme I



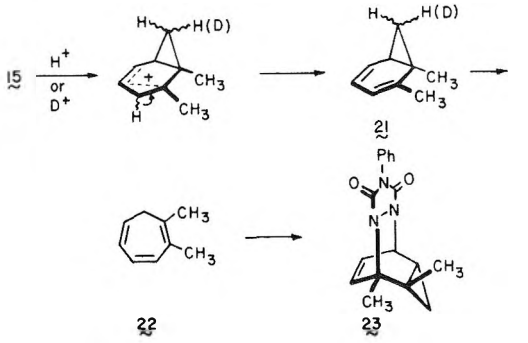
Scheme II



Scheme III



Scheme IV



catalytic quantities of Ag^+ and give rise quantitatively to methyl substituted cycloheptatrienes, the weight of evidence is insufficient to target specifically the site of electrophilic attack. The striking feature of these first experiments is the isomerically pure nature of the products, structural assignments to which follow from their ^1H NMR spectra[22] and adduct formation with *N*-phenyltriazolinedione. The outcome of these rearrangements can be rationalized in terms of several different hypothetical mechanisms. For example, the isomerization of **7** to 3-methylcycloheptatriene might be viewed as the result of electrophilic attack at the less substituted allylic bicyclobutane edge bond, followed by deargentation[23] (Scheme I). Alternatively, the conversion to **16** might easily be imagined to proceed by initial attack at the π bond as illustrated.

No comparable steric differentiation between the upper and lower faces of the tricycloheptene nucleus exists in **8**. However, the location of the methyl substituent can now be expected to cause the transient formation of allylic and tertiary carbocation intermediates to become more closely competitive. The same concession applies to **15** and this change in structure further complicates our analysis of the response of these molecules to Ag^+ catalysis (Scheme II).

It is now apparent that our mechanistic inquiry would be greatly facilitated if the electrophilic reagent were to remain covalently bonded in the product. Such experiments take on double- (for **7** and **8**) or triple-labeling characteristics (for **15**) and permit, in principle, a clearer analysis of the regioselectivity of tricycloheptene capture by electrophiles. Experimentally, D^+ is to be preferred in such circumstances and the susceptibility of these highly strained molecules to acid-catalyzed rearrangement was therefore examined.

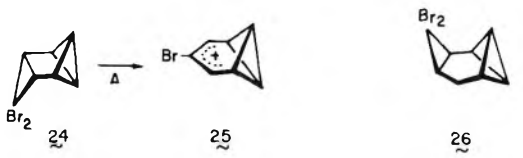
The addition of one drop of glacial acetic acid to an ethereal solution of **7** resulted in an immediate exothermic reaction and exclusive isomerization to **18a**. Similar treatment with acetic acid-d_4 led to deuterium incorporation only at C_7, as indicated by the sizable reduction in the intensity of the δ 2.25 doublet,[24] an apparent decrease in the multiplicity of the olefinic quartet at 5.3 due to H_6, and mass measurement of the parent ion as m/e 107 corresponding to C_8H_9D.

Under comparable conditions, **8** was quantitatively transformed to 2-methylcycloheptatriene (**20**).[22] The use of acetic acid-d_4 again resulted in incorporation of the isotopic label at C_7 (^1H NMR analysis). In purely phenomenological terms, these transformations serve to rule out attack of D^+ at the C=C bond present in **7** and **8**.[25] Rather, considerations of product structure lead us to conclude that H^+ and D^+ prefer to attack **7** at the less substituted bicyclobutane edge bond and **8** at one of its nonallylic edge bonds (Scheme III). Deprotonation to deliver norcaradiene intermediates apparently precedes valence isomerization and ultimate formation of **18a** and **20**.

1,6-Dimethyltricyclo[4.1.0.0^{2,7}]hept-3-ene (**15**) combines the structural features present in **7** and **8** and therefore holds especial interest as a substrate for acid-catalyzed isomerization. Its reaction with acetic acid resulted in rapid conversion to 1,2-dimethylcycloheptatriene (**22**), characterized both spectroscopically and by conversion to adduct **23** (Scheme IV). Addition of acetic acid-d_4 to a solution of **15** furnished 1,2-dimethylcycloheptatriene containing no detectable levels of isotopic label. However, as with the examples discussed earlier, deprotonation results in H^+ being available in competition with D^+. Thus, **15** was added directly to neat acetic acid-d_4, resulting now in incorporation of deuterium at C_7. These results suggest that **15** is attacked analogously to **8**, proceeding via norcaradiene **21** to **22**.

The mechanistic schemes proposed above concisely account for the product-forming transformations of the tricycloheptenes and, in particular, emphasize once again the interdependence of structural features and chemical reactivity in bicyclobutyl systems. A marked preference for electrophilic attack by D^+ at the edge bicyclobutane bonds in these molecules is apparent, in contradistinction to benzvalene which is π-olefinic reactive. These findings are in total agreement with the PE results. Whether other electrophiles (including Ag^+) share in this regioselectivity remains to be established.

Finally, the divergent electronic interactions in tricycloheptenes and benzvalenes may serve to explain why the thermolysis of **24** in carbon tetrachloride proceeds exclusively with dibromocyclopropane ring opening to generate cation **25**,[26] while heating of **26** and related molecules leads to thermal rearrangement in which the bicyclobutane moiety alone is ruptured.[27]



24 25 26

Experimental Section

7,7-Dibromo-1,4-dimethylbicyclo[4.1.0]hept-3-ene (11). 1,4-Dimethyl-1,4-cyclohexadiene was prepared by sodium in liquid ammonia reduction of *p*-xylene according to Birch.[28] VPC analysis of the recovered hydrocarbon showed substantial quantities (50–75%) of unreacted *p*-xylene to be present. Since the aromatic compound caused no difficulty in the subsequent dibromocarbene addition, this mixture was not resubjected to further reduction as recommended by Fehnel[29] but utilized directly; $\delta_{Me_4Si}^{CCl_4}$ 5.21 (m, 2), 2.48 (br s, 4), and 1.59 (br s, 6).

A stirred suspension of potassium *tert*-butoxide (12.96 g, 0.115 mol) and 1,4-dimethyl-1,4-cyclohexadiene (12.5 g, 0.115 mol, as 25% solution in *p*-xylene) in 250 mL of purified pentane cooled to 0 °C was treated dropwise during 1 h with 29.3 g (0.115 mol) of bromoform. Upon completion of the addition, the mixture was stirred at 0 °C for 1 h and then at room temperature for 2 h before being poured onto water (500 mL) and shaken. The layers were separated and the aqueous phase was extracted with pentane (100 mL). The combined organic solutions were washed with brine (100 mL), dried, and evaporated. The resulting oil was distilled to give 13.5 g (42%) of **11**: bp 79–80 °C (0.5 mm); ν_{max}^{neat} 2960, 2925, 2880, 2835, 1452, 1425, 1380, 1298, 1197, 1163, 1105, 1077, 1013, 988, 940, 796, and 755 cm^{-1}; $\delta_{Me_4Si}^{CDCl_3}$ 5.32–5.05 (m, 1), 2.42–1.90 (br m, 5), 163 (s, 3), and 1.48 (s, 3); calcd for $C_9H_{14}{}^{79}Br_2$ *m/e* 277.9307, found 277.9312.

Carbenoid Cyclization of 11. A stirred solution of **11** (5.60 g, 20 mmol) in ether (60 mL) maintained at 0 °C under a nitrogen atmosphere was treated dropwise during 1 h with a solution of ethereal methyllithium (10.9 mL of 1.84 M, 20 mmol). The resulting solution was stirred at 0 °C for 1 h and at room temperature for 2 h. Water (30 mL) was carefully introduced, the layers were separated, and the aqueous phase was extracted with ether (30 mL). The combined organic solutions were dried over anhydrous sodium sulfate and carefully concentrated by distillation of ether at atmospheric pressure. Flash vacuum distillation of the residue gave a colorless distillate which was subjected directly to preparative VPC purification (12 ft × 0.25 in. 10% QF-1 on 60/80 mesh Chromosorb G, 85 °C). There was isolated 520 mg (22%) of **9** and 80 mg (3%) of **12**.

For 1,4-dimethyltricyclo[4.1.0.0^{2,7}]hept-3-ene (**9**): ν_{max}^{neat} 3020, 2960, 2930, 2890, 2835, 1443, 1372, 1147, 934, 906, 838, 806, 790, 739, and 630 cm^{-1}; $\delta_{Me_4Si}^{CDCl_3}$ 5.55–5.33 (m, 1), 2.33–2.15 (m, 2), 2.07–1.75 (m, 3), 1.57 (s, 3), and 1.48 (s, 3); calcd *m/e* 120.0939, found 120.0941. Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 89.88; H, 10.17.

For 3,6-dimethyltricyclo[4.1.0.0^{2,7}]hept-3-ene (**12**): ν_{max}^{neat} 3020, 2970, 2930, 2890, 2835, 1454, 1440, 1382, 1134, 1038, 910, 848, 836, 822, 806, 788, and 736 cm^{-1}; $\delta_{Me_4Si}^{CDCl_3}$ 5.13–4.87 (m, 1), 2.33–2.13 (m, 1), 2.08–1.80 (m, 3), 1.70 (narrow m, 3), and 1.13 (s, 3); calcd *m/e* 120.0939, found 120.0941. Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 89.63; H, 10.10.

7,7-Dibromo-1,3-dimethylbicyclo[4.1.0]hept-3-ene (13). 2,4-Dimethyl-1,4-cyclohexadiene was prepared by sodium in liquid ammonia reduction of *m*-xylene according to Birch.[28] VPC analysis of the hydrocarbon so produced indicated 20–25% of unreacted aromatic to be present. This mixture was suitable for further use in this study. For pure diene: $\delta_{Me_4Si}^{CDCl_3}$ 5.40 (m, 2), 2.23 (br s, 4), and 1.63 (br s, 6).

2,4-Dimethyl-1,4-cyclohexadiene (16.6 g, 0.154 mol, as 83% solution in *m*-xylene) was allowed to react with potassium *tert*-butoxide (17.2 g, 0.154 mol) and bromoform (38.9 g, 0.154 mol) as described above. Distillation of the resulting oil gave 20.7 g (48%) of **13**: bp 91–92 °C (0.8 mm); ν_{max}^{neat} 2940, 2925, 2885, 2830, 1447, 1427, 1380, 1200, 1077, 1021, 979, 830, 793, and 748 cm^{-1}; $\delta_{Me_4Si}^{CDCl_3}$ 5.33–5.07 (m, 1), 2.57–2.03 (br m, 5), 1.60 (s, 3), and 1.48 (s, 3); calcd for $C_9H_{14}{}^{79}Br_2$ *m/e* 277.9307, found 277.9312.

Carbenoid Cyclization of 13. A solution of **13** (5.60 g, 20 mmol) in 60 mL of ether was treated with methyllithium in the predescribed fashion. Flash distillation of the residual oil was followed by direct VPC purification on the QF-1 column. There was isolated 490 mg (20%) of **10** and 85 mg (3.5%) of **14**.

For 1,3-dimethyltricyclo[4.1.0.0^{2,7}]hept-3-ene (**10**): ν_{max}^{neat} 3090, 3015, 2995, 2955, 2930, 2880, 2835, 1440, 1372, 1141, 1048, 922, 820, 782, and 734 cm^{-1}; $\delta_{Me_4Si}^{CDCl_3}$ 5.07–4.83 (m, 1), 2.37–2.20 (m, 2), 2.08–1.83 (m, 3), 1.75–1.63 (m, 3), and 1.60 (s, 3); calcd *m/e* 120.0939, found 120.0941. Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 89.47; H, 10.01.

For 4,6-dimethyltricyclo[4.1.0.0^{2,7}]hept-3-ene (**14**): ν_{max}^{neat} 3090, 3025, 2965, 2930, 2870, 2815, 1445, 1405, 1380, 1132, 1088, 1040, 1005, 950, 928, 848, 796, and 735 cm^{-1}; $\delta_{Me_4Si}^{CDCl_3}$ 5.68–5.47 (m, 1), 2.33–2.13 (m, 1), 1.98 (br s, 2), 1.87 (br s, 2), 1.68–1.52 (m, 3), and 1.15 (s, 3); calcd *m/e* 120.0939, found 120.0941. Anal. Calcd for C_9H_{12}: C, 89.94; H, 10.06. Found: C, 89.76; H, 10.22

General Procedure for Acid-Promoted Isomerizations. A solution of **15** (500 mg, 4.2 mmol) in ether (15 mL) was treated with acetic acid (0.5 mL). After standing for 30 min, the solution was washed with saturated sodium bicarbonate (5 mL) and sodium chloride solutions (5 mL). After drying, concentration affored 1,2-dimethylcycloheptatriene (**22**, 475 mg, 95%): ^{1}H NMR ($CDCl_3$) δ 6.35 (m, 2), 6.00 (m, 1), 5.40 (pseudo q, J = 8 Hz, 1), 2.25 (d, J = 6 Hz, 2), 1.93 (s, 3), and 1.83 (s, 3); for C_9H_{12} *m/e* calcd 120.0939, found 120.0941.

To a solution of 120 mg (1.0 mmol) of **22** in ethyl acetate (5 mL) cooled to −78 °C was added dropwise a solution of *N*-phenyltriazolinedione in ethyl acetate until the color persisted. Evaporation of solvent, chromatography on silica gel (elution with ether–chloroform 9:1), and recrystallization from ethyl acetate afforded pure **23**: mp 148–149 °C; ^{1}H NMR ($CDCl_3$) δ 7.40 (s, 5) 6.02 (m, 2), 5.21 (m, 1), 1.96 (s, 3), 1.47–1.28 (m, 1), 1.33 (s, 1), 0.54 (s, 1), 0.45 (d, 1). Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.13; H, 5.80; N, 14.23. Found: C, 68.82; H, 5.85; N, 14.23.

When **7** was similarly treated with acetic acid, the resulting lone hydrocarbon product (**18a**) was purified by preparative VPC (6 ft × 0.25 in. XF-1150 on 60/80 mesh Chromosorb G, 45 °C). Its ^{1}H NMR spectrum was identical to that illustrated in ref 22 for 1-methylcycloheptatriene.

Reaction of **18a** (28.8 mg) with *N*-phenyltriazolinedione (47.5 mg) in ethyl acetate at 0 °C afforded **19a**: mp 148–149 °C (from ethanol); ^{1}H NMR ($CDCl_3$) δ 7.42 (br s, 5), 6.17–5.85 (m, 2), 5.30–4.73 (m, 2), 1.40 (s, 3), 1.33–1.08 (m, 1), and 0.47–0.17 (m, 2). Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.10; H, 5.46; N, 15.01.

Treatment of **8** in the predescribed manner led exclusively to **20**, identified by direct spectral comparison with 2-methylcycloheptatriene.[22]

General Procedure for Ag(I)-Catalyzed Isomerizations. A solution of **7** (93 mg, 0.87 mmol) in anhydrous benzene (5 mL) was treated with 0.1 mL of 0.2 M silver perchlorate in benzene solution. After standing for 30 min, the mixture was washed with brine (3 × 10 mL), dried, and concentrated. Preparative VPC purification (XF-1150, 45 °C) afforded **16** as the sole product, identified by comparison of spectra.[22]

A solution of **16** (36 mg, 0.34 mmol) in ethyl acetate (2 mL) was treated at 0 °C with *N*-phenyltriazolinedione (59.5 mg, 0.34 mmol) in the same solvent (1 mL). The resulting solution was stirred for 1 h and evaporated. Recrystallization of the residue from ethanol gave **17** as colorless plates: mp 138.5–140 °C; ^{1}H NMR ($CDCl_3$) δ 7.42 (br s, 5), 5.76–5.50 (m, 1), 5.17–4.83 (m, 2), 1.85 (d, J = 2 Hz, 3), 1.67–1.33 (m, 2), 0.57 (q, J = 7 Hz, 1), and 0.31–0.03 (m, 1); *m/e* calcd 281.1164, found 281.1172. Anal. Calcd for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.28; H, 5.56; N, 14.99.

Analogous treatment of **8** (30 mg) with the silver perchlorate–

benzene reagent led exclusively to **18a**, identical to the sample obtained earlier.

From 500 mg (4.2 mmol) of **15**, **18b** was isolated in 97% yield: ^{1}H NMR ($CDCl_3$) δ 6.23 (d with fine splitting, J = 5 Hz, 1), 6.00 (dd, J = 9 and 5 Hz, 1), 5.82 (s, 1), 5.28 (m, 1), 2.30 (d, J = 7 Hz, 2), 2.00 (s, 3), and 1.97 (d, J = 1.5 Hz, 3); m/e calcd 120.0939, found 120.0941.

Cycloaddition of N-phenyltriazolinedione to **18b** in ethyl acetate solution at 0 °C gave **19b** as colorless needles: mp 118.5–120 °C (from ethyl acetate); ^{1}H NMR ($CDCl_3$) δ 7.37 (br s, 5), 5.70–5.42 (m, 1), 5.03 (t, J = 5.5 Hz, 1), 4.62 (d, J = 2 Hz, 1), 3.45 (s, 3), 1.33 (s, 3), 1.17 (m, 1), 0.43 (d, J = 2.5 Hz, 1), and 0.33 (s, 1); m/e calcd 295.1321, found 295.1320. Anal. Calcd for $C_{17}H_{17}N_3O_2$: C, 69.13; H, 5.80; N, 14.23. Found: C, 69.04; H. 6.04; N, 14.16.

Photoelectron Spectroscopy. The PE spectra have been recorded on a Perkin-Elmer Ltd PS 18 instrument (Beaconsfield, England). The spectra were calibrated with Ar and a resolution of about 20 meV on the Ar line was obtained.

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Registry No.—**11**, 66036-93-9; **12**, 66036-94-0; **13**, 66036-95-1; **14**, 66036-96-2; **15**, 61772-32-5; **16**, 3045-90-7; **17**, 66036-97-3; **18a**, 3045-88-3; **18b**, 61772-26-7; **19a**, 66036-98-4; **19b**, 66036-99-5; **22**, 66037-00-1; **23**, 66037-01-2; 1,4-dimethyl-1,4-cyclohexadiene, 4074-22-0; 2,4-dimethyl-1,4-cyclohexadiene, 4190-06-1; N-phenyltriazolinedione, 4233-33-4.

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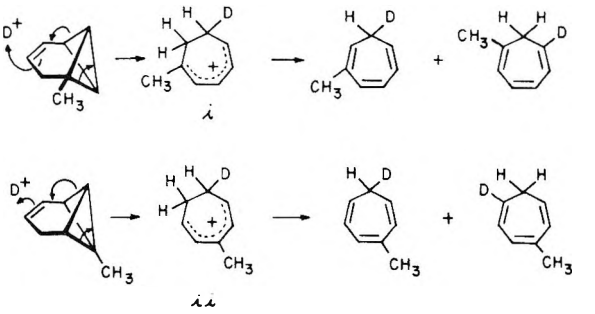
(24) Because of the relative amount of CD_3COOD added and the liberation of H^+ as the rearrangement proceeds, quantitative incorporation of 1 molar equiv of deuterium cannot be expected and is not seen.
(25) The following alternative mechanisms may be legitimately advanced for consideration:



However, they account neither for the exclusivety of product formation nor the absence of observable (^{1}H NMR) sp^2-bound deuterium (note particularly the latent symmetry of ii).
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Isocyanide Reductions. A Convenient Method for Deamination[1]

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Dissolving metal reductions of a number of isocyanides are reported. Dissolving metal reduction of a chiral acyclic isocyanide leads to formation of racemic product. Some stereoselectivity is observed in the reduction of a chiral cyclopropyl isocyanide. Due to the ease of conversion of primary amines to isocyanides and the excellent yields obtained in the dissolving metal reduction of isocyanides, this method is recommended for deamination of primary amines. The mechanism of dissolving metal reduction is discussed.

Ugi and Bodesheim[2] observed the nearly quantitative reduction of isocyanides to their corresponding hydrocarbons by solutions of metals (lithium, sodium, potassium, and calcium) in liquid ammonia. They conjectured that the isocyanide accepted two electrons, by either a one-step or a two-step process, followed by cleavage of the carbon–nitrogen bond.

$$RN{=}C + 2M \xrightarrow{NH_3} RH + MCN + MNH_2$$

Later, Büchner and Dufaux[3] observed that the reductive cleavage of isocyanides occurred in tetrahydrofuran as a solvent as well as in liquid ammonia. These workers postulated a two-step mechanism in which the addition of the first electron leads to formation of an anion radical intermediate which can accept a second electron leading to the formation of a carbanion intermediate and cyanide ions.

$$RN{=}C \xrightarrow{e^-} [RN{=}\dot{C}]^- \xrightarrow{e^-} R{:}^- + CN^-$$

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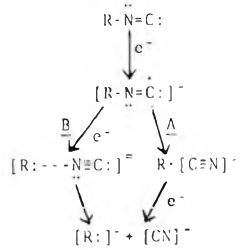
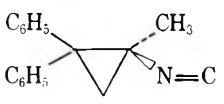


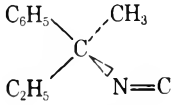
Figure 1. Scheme for the reduction of isocyanides

Our interest in the mechanism of interaction of organohalides with metals[4] prompted the investigation of the reductive cleavage of isocyanides since the results obtained by the early workers[2,3] fitted the reaction scheme proposed for halide reduction.[4,5] This scheme, when applied to the particular case of isocyanides, is depicted in Figure 1.

In order to gain some insight into the contribution of path A or path B to the overall reaction, the reduction of a chiral isocyanide whose chiral center is adjacent to the isocyanide moiety was selected for study. If path A were the sole process, the hydrocarbon formed from the free-radical intermediate should be essentially racemic. On the other hand, path B should lead to retention of configuration, if the carbanion intermediate is one whose configuration is stable. This has been shown to be the case for the 1-methyl-2,2-diphenylcyclopropyl anion[5,6] whose configuration is maintained whereas the 1-methyl-2,2-diphenylcyclopropyl radical intermediate, under homogeneous conditions, is unable to maintain its configuration and racemizes rapidly.[7] The stereochemistry of the reductive cleavage of chiral (+)-(*S*)-1-methyl-2,2-diphenylcyclopropyl isocyanide (**1**) and the acyclic (−)-(*S*)-2-phenyl-2-butyl isocyanide (**5**) is the subject of this paper.



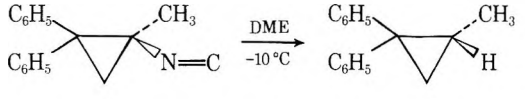
(+)-*S*-**1**



(−)-(*S*)-**5**

Results and Discussion

Dissolving Metal Reduction. The chiral isocyanides **1** and **5** have been synthesized previously[8] and their absolute configurations have also been established.[8] The reductive cleavage of **1** by lithium or sodium metal in 1,2-dimethoxyethane



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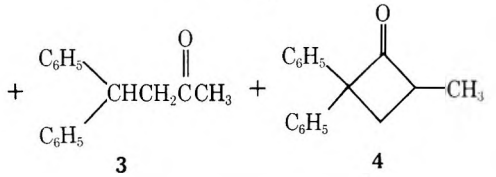
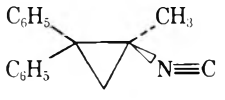


3 **4**

produced low yields of 1-methyl-2,2-diphenylcyclopropane,[9] the main products (82–86% of total) being the rearranged



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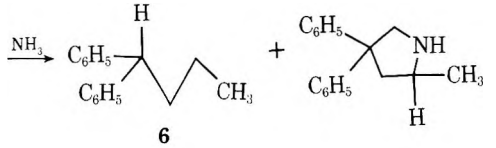


6 **7**

Table I. Sodium Napthalene Reduction of 1-Methyl-2,2-diphenylcyclopropyl Isocyanide in 1,2-Dimethoxyethane

	Yields, %[b]		
$[Na^+Naph^-]_{cor}$,[a] M	**2**	**3**	**4**
0.023	92	4	4
0.104	95	2.5	2.5
0.250	94	3	3
0.370	87	6.5	6.5

[a] Corrected according to eq 1. [b] Relative distribution based on peak areas of GLC.

4,4-diphenyl-2-butanone (**3**) and 2,2-diphenyl-4-methylcyclobutanone (**4**).[9] Sodium dissolved in liquid ammonia produced a different set of rearranged products, 1,1-diphenylbutane (**6**) and 3,3-diphenyl-5-methylpyrrolidine (**7**). The reduction of (−)-(*S*)-**5** by a blue solution of sodium (8%) in liquid ammonia or by a bronze solution of sodium (15%) in liquid ammonia yielded the hydrocarbon *sec*-butylbenzene in 92–98% yield but it was totally racemized.

It was found that the amount of rearranged product, obtained in the reduction of **1**, could be drastically diminished when sodium naphthalene in 1,2-dimethoxyethane was used as the reducing medium. Under these conditions **2** was obtained in 87–95% yield and the rearranged products **3** and **4** in 5–13% (Table I).

As was pointed out previously[9] the formation of **3** and **4** as the major products in the reduction of **1** with lithium or sodium dispersion in 1,2-dimethoxyethane was due to the formation of an intermediate 1-lithio- or 1-sodio-1-methyl-2,2-diphenylcyclopropane which then, by α addition, added to the unreacted isocyanide **1**. Since the reaction at a metal surface is necessarily much slower than with a homogeneous dissolved metal source, the α addition competes favorably under these conditions but unfavorably in the sodium naphthalene reduction.

Another apparent anomaly is in the reduction of **1** with sodium dissolved in liquid ammonia. Even under these homogeneous conditions the major products formed, 1,1-diphenylbutane (**6**) and 3,3-diphenyl-5-methylpyrrolidine (**7**), resulted from a rearrangement reaction. As has been discussed previously,[9] the initial electron transfer in liquid ammonia is not to the isocyanide moiety but to the benzene ring in **1** which leads to the reductive cleavage of the cyclopropyl ring. However, from the results obtained under aprotic conditions, sodium naphthalene in 1,2-dimethoxyethane, reduction seems to involve an electron transfer to the isocyanide. If our interpretation is correct, this is a unique solvent effect.

The reduction of **1** with sodium naphthalene in 1,2-dimethoxyethane proceeds with overall retention of configuration. The dependence of the retention of optical activity on the sodium naphthalene concentration is shown in Figure 2. The optically pure (+)-(*S*)-**1** was added to a 5 mol excess of sodium naphthalene in 1,2-dimethoxyethane at −10 °C. Although varying concentration of sodium naphthalene were used, the 5 mol excess was maintained.

The values for the concentrations used in plotting Figure 2 were corrected according to eq 1 since the measured retention of optical activity for the isolated reduction product was assumed to represent an average value from species generated throughout the course of reduction. The correction also takes into account the relative product distribution shown in Table I by which the α-addition products involve additional consumption of the cyclopropyl isocyanide and therefore a higher final sodium napthalene concentration than predicted from simple stoichiometry.[10]

$$[Na^+\ Naphth^-\cdot]_{cor} = [Na^+\ Naphth^-\cdot]_{init} - \tfrac{1}{2}([Na^+\ Naphth^-\cdot]_{init} - [Na^+\ Naphth^-\cdot]_{final}) \quad (1)$$

Table II. Experimental Data for the Reduction of (+)-(*S*)-1-Methyl-2,2-diphenylcyclopropyl Isocyanide

Run	$[Na^+Napth]^{-\cdot}{}_{init}$[a]	$[Na^+Naphth]^{-\cdot}{}_{corr}$[b]	$[\alpha]^{24}_{5461}$ 2[c]	Optical purity, %[d]
1	0.029 ± 0.005	0.023 ± 0.006	−0.9 ± 0.3	0.6 ± 0.2
2	0.128 ± 0.008	0.104 ± 0.010	−5.4 ± 0.2	3.6 ± 0.1
3	0.310 ± 0.008	0.250 ± 0.014	−13.0 ± 0.2	8.7 ± 0.1
4	0.461 ± 0.008	0.370 ± 0.017	−20 ± 1	13.3 ± 0.6

[a] Mol/L. [b] From eq 1. [c] Specific rotations (c 1, $CHCl_3$). [d] Authentic sample[11] of optically pure 2 has $[\alpha]^{24}_{5461}$ 150° (c 0.8, $CHCl_3$).

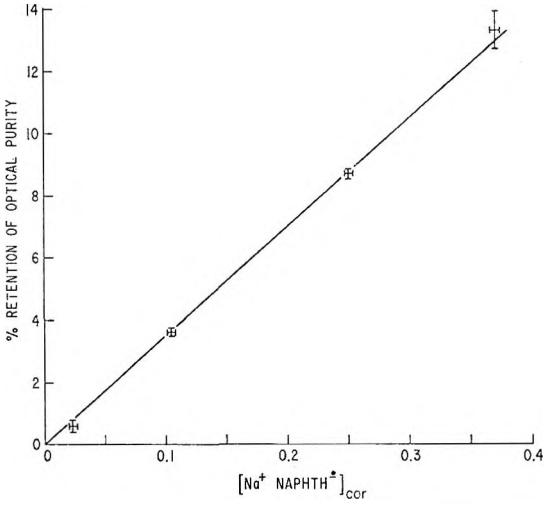
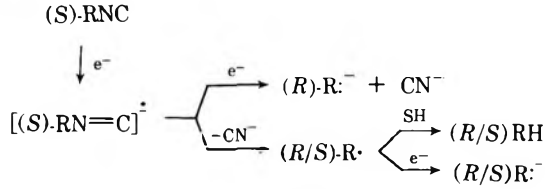


Figure 2. Retention of optical purity in the reduction of 2,2-diphenyl-1-methylcyclopropyl isocyanide to 1,1-diphenyl-2-methylcyclopropane with sodium naphthalene concentration (mol/L).

Qualitatively, two points become evident from the graph in Figure 2. First, there appears to be no residual retention mechanism such as hydrogen abstraction from solvent by a configurationally stable cyclopropyl radical since, if this were the case, extrapolation to zero concentration would have resulted in an intercept. This observation is consistent with previous evidence for the configurational instability of the 2,2-diphenyl-1-methylcyclopropyl radical.[7] Second, the linear relationship exhibited indicates that the overall reduction is probably a two-step process in which an optically active intermediate is short lived and therefore exists only in steady-state concentrations. These two observations lend support to a reduction mechanism similar to the one proposed earlier.[4,5,11]



The initially formed radical anion, of retained configuration, either dissociates to give the racemic radical or is reduced to a carbanion of retained configuration. The degree of retention of configuration in the final product will be dependent on the lifetime of the radical anion. In the metal dispersion reductions the radical anion would be in contact with the metal surface, its potential electron source. This may account for the higher degree of retention of optical purity (67% for sodium dispersion in DME). On the other hand, in the solvated electron systems, radical anion dissociation would be competing with the rate of molecular diffusion of its electron source, in this case sodium naphthalene. Thus, the degree of retention of configuration would be much lower and likewise should be dependent on the concentration of the electron source as was observed in Figure 2.

As one might expect, based on the relative configurational stabilities of the cyclopropyl anion and the acyclic 2-phenyl-2-butyl anion, the reduction of (−)-(*S*)-**5** with excess sodium naphthalene in tetrahydrofuran followed by quenching with carbon dioxide resulted in the formation of racemic 2-methyl-2-phenylbutanoic acid.

From a synthetic viewpoint, the use of sodium naphthalene as a reducing medium for the reduction of isocyanides should be the method of choice. Since both aromatic and alphatic primary amines can be converted to isocyanides conveniently and in high yield,[8,12] this may well turn out to be an excellent method for deamination, the only drawback being that the reduction is not stereospecific.

$$RNH_2 \rightarrow RN{=}C \rightarrow RH$$

Experimental Section[13]

Reduction of (−)-(*S*)-2-Phenyl-2-butyl Isocyanide.[8] The sodium–liquid ammonia reductions were carried out as previously described.[14] The product, sec-butylbenzene (bp 172–174 °C), was isolated in 96–98% yield and was racemic.

Reduction of (−)-(*S*)-2-Phenyl-2-butyl Isocyanide with Sodium Naphthalene. Under an argon atmosphere 0.65 g (0.03 g-atom) of sodium and 3.8 g (0.03 mol) of naphthalene in 50 mL of tetrahydrofuran freshly distilled from $LiAlH_4$ were stirred for 1.5 h. The solution was cooled to −5 °C and 0.29 g (0.002 mol) of (−)-(*S*)-2-phenyl-2-butyl isocyanide was added and stirring was continued for 10 min. The solution was cooled with a dry ice–acetone bath and anhydrous carbon dioxide gas was introduced rapidly over a 10-min period and then quenched with aqueous methanol. After ambient temperature was reached the solution was diluted with water. The aqueous layer was washed with methylene chloride and then acidified with hydrochloric acid. The acidified solution was extracted with methylene chloride and the extract was dried (magnesium sulfate). Removal of solvent followed by distillation yielded 0.12 g of 2-methyl-2-phenylbutanoic acid, mp 56–58 °C, whose IR and NMR spectra were identical with those of an authentic sample.[14] The acid was racemic.

Reductions of (+)-(*S*)-1-Methyl-2,2-diphenylcyclopropyl Isocyanide with Sodium Naphthalene. Spheres of sodium were prepared by melting the metal in hot xylene with gentle stirring. Prior to use the solidified spheres were cleaned to a bright metallic finish under argon by sequential washes of THF–methanol (anhydrous), THF, diethyl ether, and finally hexane. Under an argon atmosphere the sodium was reacted at −10 ± 1 °C with a predetermined amount of recrystallized naphthalene in a measured volume of freshly distilled (from $LiAlH_4$) 1,2-dimethoxyethane for 2 h with stirring. The sodium sphere was removed and an additional 5% of naphthalene was added and stirring was continued for 30 min. An aliquot of the solution was removed and titrated for total base content to determine the radical anion concentration and based on the volume of 1,2-dimethoxyethane the total moles of sodium naphthalene was determined. A quantity, equivalent to 20% of the above molar concentration of optically pure (+)-(*S*)-1-methyl-2,2-diphenyl isocyanide,[8] $[\alpha]^{24}_{5461}$ 167 ± 1° (*c*, 1.0, $CHCl_3$), was added and the mixture was stirred for 3.0 ± 0.2 min. The reaction mixture was extracted with ether, the ether extract was washed with water and dried over magnesium sulfate, and the solvent was evaporated. VPC analysis (15% SE-33 on 80/100 Chromosorb P, AW) was used to identify and estimate[9] the relative amounts of **2**, **3**, and **4**. The hydrocarbon **2** was isolated by preparative VPC and rotations measured. Table II lists the experimental results.

Registry No.—**1**, 53152-70-8; **2**, 10439-30-2; **3**, 5409-60-9; **4**, 65899-48-1; **5**, 65941-43-1; (±)-*sec*-butylbenzene, 36383-15-0; (±)-2-methyl-2-phenylbutanoic acid, 51018-80-5.

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(10) This correction appears to already assume a linear dependence of retention of optical purity on sodium naphthalene concentration. A nonlinear relationship could still have been detected by the graph of Figure 2 since sodium naphthalene is in a 5 mol excess.
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Synthesis and Deamination of 4-Aminospirohexane

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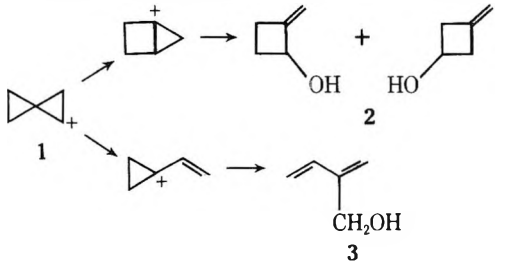
4-Aminospirohexane and 5-aminospirohexane were prepared by direct chlorocarbonylation of spirohexane followed by Curtius degradation. Deamination of 4-aminospirohexane with nitrous acid gave a mixture of spirohexan-4-ol, 2-methylenecyclopentanol, 3-methylenecyclopentanol, cyclohexanone, and several unidentified minor products. This mixture is compared with the products of the 4-spirohexyl cation as generated by solvolysis. 5-Aminospirohexane and nitrous acid gave only spirohexan-5-ol.

Rearrangements of the spiropentyl cation **1** show a remarkable dual behavior, depending upon the mode of generation.[1] When spiropentylamine is deaminated with nitrous acid, the cation rearranges like a cyclopropylcarbinyl cation, giving methylenecyclobutanols **2**. When chlorospiropentane



is allowed to hydrolyze, the cation undergoes electrocyclic ring opening like a cyclopropyl cation, leading to 2-hydroxymethylbutadiene (**3**). Although different ways of producing a carbonium ion generally lead to different compositions of the product mixture, the absence of any overlap in products in the above two cases is out of the ordinary, especially considering that both reactions were run in water.

In an effort to see if the same kind of duality of behavior could be found in a closely related system, it was decided to investigate the products from the 4-spirohexyl cation **4**. In this

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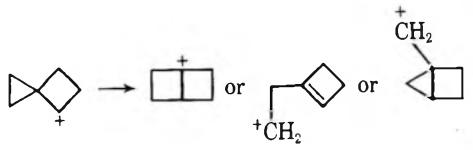
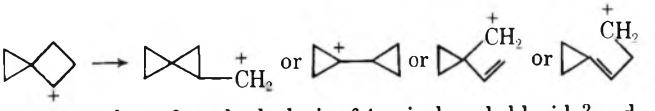
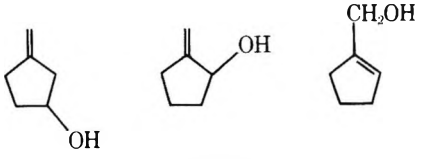
case the cation is again confronted with a competition between two favorable types of behavior. As a cyclopropylcarbinyl cation, it could give ring enlargement to a cyclobutyl cation, rearrangement to an isomeric cyclopropylcarbinyl cation, or



cleavage to an allylcarbinyl cation. As a cyclobutyl cation, it could give ring contraction or cleavage of the four-membered ring.

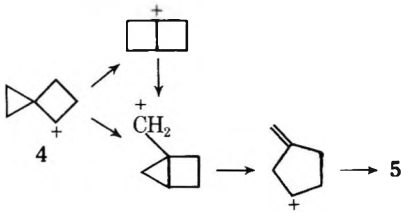


The products from hydrolysis of 4-spirohexyl chloride[2] and 3,5-dinitrobenzoate[3] have already been investigated. The rearranged products are alcohols **5**–**7**, with **5** making up more

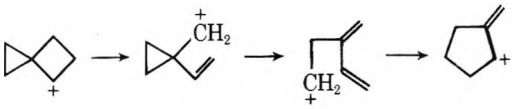


5; 52-64% **6**; 6-15% **7**; 0-5%

than half of the mixture. Product **5** seems most likely to have arisen from cyclopropylcarbinyl-type behavior of **4**. The origin



of **6** and **7** is more obscure; they could either come from a rearrangement of the 3-methylenecyclopentyl cation (from the above sequence) to the allylic 2-methylenecyclopentyl cation or from initial behavior of **4** in the other (cyclobutyl-type) mode.



We have prepared 4-aminospirohexane by a Curtius degradation procedure developed previously for aminospiro-

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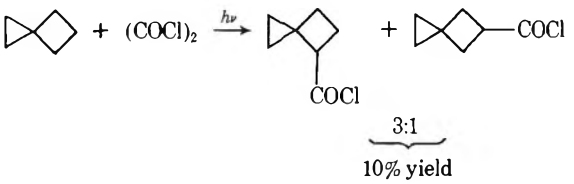
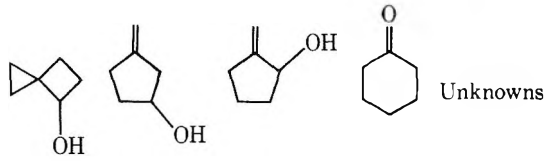
pentane.[4] The spirohexanecarboxylic acid required as starting material was prepared by the direct free-radical chlorocarbonylation of spirohexane with oxalyl chloride.[5] The two



isomers obtained were identified from the NMR spectra of the ethyl esters, which were separated by preparative VPC. In particular, the NMR spectrum of the 5 isomer, except for the signals due to the ethyl group, showed a pattern closely similar to the spectrum of the acid prepared by an independent, unambiguous route, namely, a Simmons–Smith reaction on 3-methylenecyclobutanecarbonitrile followed by hydrolysis.[6] The Curtius procedure was run on both the 4 and 5 isomers to produce the corresponding amines in the form of their β-naphthylurethane derivatives, which were hydrolyzed to the amines immediately prior to diazotization.

The 4-aminospirohexane was diazotized in water at pH 4.6 to give a mixture of volatile products with the following approximate composition.



The mixture is very similar to the previously described solvolysis mixtures, except for the unexpected appearance of cyclohexanone. A repetition of the hydrolysis of 4-chlorospirohexane[2] was therefore carried out, and a minor product previously found in 4% yield but not identified was found to be, in fact, cyclohexanone. Thus, the striking sensitivity to the leaving group of the rearrangement path of the spiropentyl cation is entirely absent in the 4-spirohexyl cation. No explanation can be offered here, but the cause of the effect in the spiropentyl case is under continuing investigation and will be the subject of a future report.

The mechanism of formation of cyclohexanone was not investigated, but an obvious possibility is that it is a secondary product from rearrangement of bicyclo[2.2.0]hexan-1-ol (8)

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under the reaction conditions. Compound 8 is apparently not known, so the hypothesis could not easily be tested.

The deamination of 5-aminospirohexane was carried out and found to give only unrearranged spirohexan-5-ol, exactly the same result as obtained in the hydrolysis of 5-chlorospirohexane.[2,6]

Experimental Section

Melting points and boiling points are uncorrected. Infrared spectra were recorded on Perkin-Elmer Model 521 or Model 237 grating spectrometers. NMR spectra were recorded on Varian A-60A, HA-100, and HR-220 instruments. We are indebted to Mr. Robert Thrift and associates for most of the spectra. Mass spectra were obtained with an Atlas CH-5 mass spectrometer. Preparative gas chromatography was done on an Aerograph Model A-700 Autoprep, and quantitative analysis was performed on an F&M Model 300 instrument. Elemental analyses were done by Mr. J. Nemeth and his associates.

Spirohexanecarboxylyl Chloride. The procedure followed was mainly that of Wiberg and Williams[7] in the bicyclo[1.1.1]pentane system. Spirohexane (11.366 g, 83.1% pure),[8] freshly distilled oxalyl chloride (16.774 g, 0.132 mol), and Freon 11 (20 mL) were placed in a double-walled tube equipped with a nitrogen inlet tube and a Drierite tube. The central part of the quartz tube was filled with an ice–brine mixture, and the outside area above the liquid level was covered with aluminum foil. Nitrogen was allowed to flow gently, and the reaction vessel was irradiated with a low-pressure mercury lamp (G8T5) in a Srinivasan–Griffin photochemical reactor for 25 h. The reaction mixture was transferred to a distillation flask and the solvent distilled off. After the unreacted starting materials had been recovered (15.0 g), the fraction with bp 38–48 °C (7 mm) [main fraction bp 47–48 °C (7 mm)] was collected (1.877 g). The pot residue amounted to 2.608 g.

Another run was carried out in a 200-mL round-bottom quartz flask equipped with a magnetic stirring system and a dry ice–pentane condenser. The flask was irradiated for 53 h. The result was almost the same as that of the previous run.

The yields of crude spirohexanecarboxylyl chlorides in the two runs were 11.3 and 10.4%, respectively, based on pure spirohexane. The main impurity in the starting hydrocarbon was methylenecyclobutane. The recovered unreacted starting materials were subjected to further irradiation. The IR spectrum of the crude spirohexanecarboxylyl chlorides (CS_2 solution) showed a strong carbonyl absorption at 1795 cm^{-1}, and the NMR spectrum ($CDCl_3$ solution) was similar to that of a mixture of 4- and 5-chlorospirohexanes: a multiplet at δ 3.45–4.00 (1 H, methine proton), 2.05–2.80 (4 H, cyclobutyl methylene protons), and 0.45–1.25 (4 H, cyclopropyl methylene protons).

Ethyl 4- and 5-Spirohexanecarboxylates. A mixture of the spirohexanecarboxylyl chlorides (1.67 g, 11.5 mmol) was allowed to react with 1.95 g (42 mmol) of ethanol and 1.7 g (14 mmol) of *N,N*-dimethylaniline. After the usual solvent extractions, the crude ester mixture was subjected to VPC on an 8 ft dodecyl phthalate column (3/8 in o.d.). Two peaks (other than solvents) were obtained with an uncorrected area ratio of 3.2:1.0. The major product with a shorter retention time was identified as ethyl 4-spirohexanecarboxylate and the minor product assigned to the 5 isomer based on comparison of their NMR spectra with those of 4-hydroxyspirohexane and 5-spirohexanecarboxylic acid, both reported by Bernett. The yield of the carboxylates collected by preparative GLC for several runs was 9.68% (3.768 g of the 4 isomer and 0.876 g of the 5 isomer) from spirohexane. The purities of the collected materials were checked by GLC. The 4-isomer fraction contained 3% of the 5 isomer, while the 4 isomer was not detected in the 5-isomer fraction. Elemental analysis of the 4 isomer gave satisfactory results, whereas the repeated elemental analyses of the 5 isomer did not.

The NMR spectrum of ethyl 4-spirohexanecarboxylate (CCl_4 solution) showed a multiplet at δ 0.23–0.70 (4 H, cyclopropyl methylene protons), a triplet at δ 1.25 (3 H, J = 7.2 Hz, methyl protons), a multiplet at δ 2.00–2.68 (4 H, cyclobutyl methylene protons) and 2.95–3.32 (1 H, methine proton), and a quartet at δ 4.13 (2 H, J = 7.2 Hz, methylene protons of the ethyl group).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.14; H, 9.08. Found: C, 69.88; H, 9.16.

The NMR spectrum of ethyl 5-spirohexanecarboxylate (CCl_4 solution) showed a singlet at δ 0.42 (4 H, cyclopropyl methylene protons), a triplet at δ 1.25 (3 H, J = 7.2 Hz, methyl protons), a multiplet at δ 1.98–2.70 (4 H, cyclobutyl protons) and 2.94–3.52 (1 H, methine proton), and a quartet at δ 4.15 (2 H, J = 7.2 Hz, methylene protons of the ethyl group).

Anal. Calcd for $C_9H_{14}O_2$: C, 70.14; H, 9.08. Found: C, 69.30; H, 8.95; C, 68.92; H, 9.03; C, 68.05; H, 8.88; C, 67.71; H, 8.83.

4-Spirohexanecarboxylic Acid Hydrazide. Ethyl 4-spirohexanecarboxylate (3.730 g, 24.2 mmol) in 10 mL of absolute ethanol was added dropwise to boiling 85% hydrazine hydrate (15 mL, ca. 256 mmol) over about a 70-min period. The reaction mixture was stirred for an additional 2 h at 105 °C and evaporated to dryness under reduced pressure. Recrystallization of the residue from cyclohexane gave 2.880 g (86.5%) of white fluffy crystals: mp 89.0–90.5 °C; NMR spectrum (D_2O solution), a multiplet centered at δ 0.46 (4 H, cyclopropyl methylene protons), 2.18 (4 H, cyclobutyl methylene protons), and 3.09 (1 H, methine proton); a Me_2SO-d_6 solution showed a broad NH peak at δ 3.75 (3 H).

Anal. Calcd for $C_7H_{12}ON_2$: C, 60.05; H, 8.57; N, 20.00. Found: C, 60.05; H, 8.46; N, 19.76.

β-Naphthyl 4-Spirohexylcarbamate. The procedure followed was that of Applequist and Fanta[4] for β-naphthyl spiropentylcarbamate. To a solution of 2.740 g (19.6 mmol) of 4-spirohexanecarboxylic acid hydrazide in 50 mL of water was added 12 mL of 6 N hydrochloric

acid and 60 mL of a mixture of 5 parts benzene and 3 parts *n*-heptane (by volume). After this mixture was cooled to −5 to −10 °C, a solution of 2.90 g (36.7 mmol) of sodium nitrite in 6 mL of water was added to the rapidly stirred mixture over a 20-min period. The reaction mixture was pink during the addition and became a slightly yellow heterogeneous solution at the end of the addition. The mixture was then stirred for 10 min at −5 to −10 °C, and the organic layer was separated. The aqueous solution was extracted with a benzene–heptane mixture (4 × 20 mL), and the combined organic extracts were washed with 5% sodium bicarbonate (3 × 30 mL) and water. The solution was then dried for 10 min in the cold over calcium chloride. The dried solution was heated under reflux for 5 h. A solution of 8.60 g (59.7 mmol) of β-naphthol (purified by sublimation) in 60 mL of hot benzene and 0.1 mL of a 10% solution of tributylamine in *n*-heptane (as a catalyst) were then added, and the resulting solution was heated under reflux for 39 h. Evaporation of the reaction mixture to dryness afforded 10.296 g of a tan crystalline solid. Excess β-naphthol was removed by sublimation (1 mm, 75 °C). The residue (3.115 g) was chromatographed on a Florisil column with a mixture of chloroform and cyclohexane (30:70 by volume) to afford 2.935 g (56.1% from 4-spirohexanecarboxylic acid hydrazide) of a white solid. The chromatographed product was recrystallized from benzene–hexane solution (fine needle crystals): mp 149.0–150.0 °C; NMR spectrum (Me_2SO-d_6 solution), a multiplet at δ 7.18–8.13 (7 H, β-naphthyl protons), a triplet at δ 4.23 (J = 7.5 Hz, 1 H, methine proton), and a multiplet at δ 1.70–2.44 (4 H, cyclobutyl methylene protons) and 0.30–0.88 (4 H, cyclopropyl methylene protons). The NH proton peak was not observed due to the presence of water (the NH proton appeared as a broad peak at δ 5.05 in a $CDCl_3$ solution). The infrared spectrum (KBr) showed peaks at 3280 (with a broad shoulder), 3580–3280 (NH stretch), 1690 (amide I), 1535 (amide II), 3060, 2990, 2945, 2860, 1510, 1465, 1352, 1275, 1240, 1210, 1165, 1148, 1135, 1123, 1005, 960, 888, 867, 827, and 757 cm^{-1}. A mass spectrum ($CHCl_3$ solution) showed a parent peak at *m/e* 267, with other characteristic peaks having *m/e* 145 and 144 at 70 eV.

Anal. Calcd for $C_{17}H_{17}O_2N$: C, 76.42; H, 6.36; N, 5.24. Found: C, 76.12; H, 6.46; N, 5.37.

5-Spirohexanecarboxylic acid hydrazide was prepared by essentially the same procedure as used for the 4 isomer. From 0.850 g (5.52 mmol) of ethyl 5-spirohexanecarboxylate and 3.5 mL of 85% aqueous hydrazine was obtained 700 mg (90.6%) of recrystallized (cyclohexane) product, mp 130–131 °C. The NMR spectrum (in Me_2SO-d_6) showed a singlet at δ 0.40 with subsidiary splitting (4 H, cyclopropyl methylene protons), a symmetrical multiplet at δ 1.77–2.55 (4 H, cyclobutyl methylene protons) and 2.82–3.43 (1 H, methine proton), and a broad singlet at δ 3.86 (3 H, the protons attached to nitrogen atoms).

Anal. Calcd for $C_7H_{12}ON_2$: C, 60.05; H, 8.57; N, 20.00. Found: C, 59.89; H, 8.64; N, 20.29.

β-Naphthyl 5-spirohexylcarbamate was prepared by the same procedure as used for the 4 isomer. From 0.631 g (4.5 mmol) of 5-spirohexanecarboxylic acid hydrazide, 0.610 g (8.84 mmol) of sodium nitrite, and 1.200 g (8.33 mmol) of β-naphthol was obtained 0.869 g of crude tan solid, and from that by chromatography (as described for the 4 isomer) and recrystallization from benzene–heptane was obtained 0.835 g (69.5%) of colorless needles, mp 167.0–169.0 °C. The NMR spectrum (Me_2SO-d_6) showed a singlet at δ 0.44 (cyclopropyl methylene protons), a doublet with subsidiary splitting at δ 2.31 (cyclobutyl methylene protons), and a multiplet at δ 4.30 (methine proton) and 7.16–8.03 (β-naphthyl protons). The infrared spectrum (KBr) had peaks at 3430 (broad), 3300, 3060, 2990, 2960, 2930, 1699, 1630, 1544, 1510, 1465, 1360, 1275, 1245, 1218, 1170, 1140, 1125, 993, 890, 869, 783, 758, and 484 cm^{-1}. A mass spectrum ($CHCl_3$ solution) showed a parent peak at *m/e* 267, with other characteristic peaks at *m/e* 145 and 144 at 70 eV.

Anal. Calcd for $C_{17}H_{17}O_2N$: C, 76.42; H, 6.36; N, 5.24. Found: C, 76.59; H, 6.28; N, 5.21.

Deamination of 4-Aminospirohexane. A mixture of β-naphthyl 4-spirohexylcarbamate (0.450 g, 1.68 mmol) and 1 N sodium hydroxide (40 mL) was stirred in a sealed flask for 32 h at 60 °C. (The flask had been previously purged with nitrogen and wrapped with aluminum foil.) Then the reaction mixture was cooled with ice–water and acidified with 14 mL of 3.17 N perchloric acid. The white precipitate (β-naphthol) was removed by extraction with three 35-mL portions of ether. Traces of the ether were removed by bubbling nitrogen through the aqueous solution. The acidic solution was diluted to 100 mL in a volumetric flask, and the pH was adjusted to 1.55. The acidic solution was poured into a stirred aqueous solution of sodium nitrite (15.30 g, 0.222 mol; in 25 mL of distilled water) in 15 s. The pH of the resulting solution was found to be 4.65. Then the solution was stirred at room temperature (24 °C) for 15 h in a flask (wrapped with aluminum foil) connected to a dry ice trap with a drying tube at the end. The pH of the reaction mixture was found to be 5.50 after the reaction. The reaction mixture was combined with a small amount of liquid in the cold trap, saturated with sodium chloride, and extracted with ether (5 × 80 mL). The ether extracts were combined, washed with 100 mL of 5% aqueous sodium carbonate and 50 mL of water, and then dried over magnesium sulfate. After filtration, most of the ether was removed by distillation through a 1 ft spiral wire column. The remaining solution was subjected to GLC on a Carbowax 20M column [9 ft, 20% Carbowax on Chromosorb P (base washed)] at 130 °C. Three discrete peaks were observed. The first peak had the same retention time as that of cyclohexanone. The retention times of the second and third peaks were identical with those of 4-hydroxyspirohexane and 3-methylenecyclopentanol, respectively. The peak area ratio was 2:37:61. Most of the ether-extractable product mixture was subjected to GLC to collect each fraction. The amounts collected were 2 (cyclohexanone), 14 (a mixture of 4-hydroxyspirohexane and 2-methylenecyclopentanol), and 16 mg (3-methylenecyclopentanol).

Confirmation that the first fraction was cyclohexanone was determined by a comparison of its infrared spectrum with that of an authentic sample.

The second largest peak was identified as a mixture of 4-hydroxyspirohexane, 2-methylenecyclopentanol, and at least one unknown compound (probably a carbonyl compound) based on a comparison of its NMR and IR spectra with those of authentic samples reported by Bernett.[2,6] The NMR spectrum (CCl_4 solution) showed a doublet at δ 4.99 (splitting of ca. 8 Hz (60 MHz), this splitting increased to 30 Hz (8 × 220/60) in the 220-MHz spectrum; exocyclic vinyl protons of 2-methylenecyclopentanol), a broad unsymmetrical triplet at δ 4.18 (this triplet was resolved into a broad singlet at δ 4.33 and a triplet at δ 4.16 in the 220-MHz NMR spectrum; the methine protons of 2-methylenecyclopentanol and 4-hydroxyspirohexane, respectively), complex multiplets at δ 2.50–1.50, a singlet at δ 2.09 (hydroxyl protons), and a complex multiplet at δ 1.00–0.20 (cyclopropyl methylene protons of 4-hydroxyspirohexane). The ratio of 2-methylenecyclopentanol and 4-hydroxyspirohexane was approximately 30:70 based on the NMR spectrum. The IR spectrum (CCl_4 solution) showed absorptions at 3600 (free OH stretch), 3430 (broad, associated OH stretch), 3070 (CH_2 stretch of C=CH_2 and cyclopropyl methylenes), 1655 (C=C stretch), and 900 (CH_2 out-of-plane deformation of C=CH_2) cm^{-1}. A weak carbonyl absorption was present at 1716 cm^{-1}.

The NMR spectrum (CCl_4 solution) of the largest fraction was identical with that of 3-methylenecyclopentanol reported by Bernett except for the position of the hydroxyl proton peak, which is concentration dependent: a quintet at δ 4.82 (2 H, splitting of 2.5 Hz, vinyl protons), a quintet centered at δ 4.23 (1 H, splitting of 4.5 Hz, methine proton), a singlet at δ 2.61 (1 H, hydroxyl proton), a complex multiplet at δ 2.16–2.55 (4 H), and an eight-peak multiplet at δ 1.50–2.10 (2 H). The IR spectrum (CCl_4 solution) of the largest fraction was identical with that of 3-methylenecyclopentanol reported by Bernett except for the presence of a strong absorption at 1135 cm^{-1}: 3620 (free OH stretch), 3330 (broad, associated OH stretch), 3075 (CH_2 stretch of C=CH_2), 1655 (C=C stretch), 1425 (CH_2 in-plane deformation of C=CH_2), and 881 (CH_2 out-of-plane deformation of C=CH_2) cm^{-1}.

Deamination of 5-aminospirohexane was done by the same procedure as described for the 4 isomer. When the product was analyzed on the VPC column, only one major product peak was observed in addition to the solvent peak, accompanied by a very small peak. The other detectable product peak had an intensity $^1/_{150}$th of that for the major product peak. The NMR spectrum (CCl_4 solution) of the crude product showed only the signals of diethyl ether and 5-hydroxyspirohexane. The mole ratio of the two compounds was determined based on the peak intensities of the methyl triplet of the ether and the cyclopropyl methylene singlet of the alcohol (diethyl ether/5-hydroxyspirohexane, 6:1). The amount of 5-hydroxyspirohexane determined by the mole ratio, the molecular weight ratio, and the total weight of the crude mixture was 0.226 g (92.5% based on the starting carbamate). The NMR spectrum (CCl_4 solution) of 5-hydroxyspirohexane collected by GLC showed a singlet at δ 0.38 (cyclopropyl methylene protons), a doublet at δ 2.20 (splitting of 7 Hz, cyclobutyl methylene protons), a quintet centered at δ 4.45 (splitting of 7 Hz, methine proton), and a singlet at δ 4.05 (hydroxyl proton). The IR spectrum (CCl_4 solution) showed absorptions at 3620 (sharp), 3310 (broad, strong), 3075, 3000, 2965, 2930, 2855, 1450 (w), 1425, 1328, 1220, 1115, 1055, 1010 (w), 903 (w), 840, and 694 cm^{-1}. These spectra were identical with those reported by Bernett.[6]

Control for Stability of 4-Hydroxyspirohexane. To test the possibility that any of the deamination products might be secondary rearrangement products from the 4-hydroxyspirohexane, the following experiment was done.

Perchloric acid (pH 1.55, 100 mL) was added to a stirred aqueous solution of sodium nitrite (15.35 g, 0.222 mol; plus 25 mL of water). The pH of the resulting solution was found to be 4.65. Then 4-hydroxyspirohexane (0.210 g, 2.14 mmol) was added. The mixture was stirred at room temperature (23 °C) for 40 h. The aqueous reaction mixture was saturated with sodium chloride and extracted with diethyl ether (3 × 100 mL and 1 × 50 mL). The combined ethereal solution was dried over magnesium sulfate. After filtration, the ether was distilled through a 1 ft spiral wire column. VPC on a Carbowax 20M column at 130 °C showed two product peaks in addition to those in the solvent peak region. Peaks corresponding to 3-methylenecyclopentanol and cyclohexanone were not observed. The major product peak had the same retention time as that of the starting alcohol. The retention time of the minor product peak was shorter than those of the major one and cyclohexanone. The two fractions corresponding to the two peaks were collected by VPC (13 mg and 85 mg, respectively). The NMR spectrum (CCl_4 solution) of the major product was identical with that of 4-hydroxyspirohexane. The NMR spectrum (CCl_4 solution) of the minor product showed two symmetrical pairs of multiplets centered at δ 0.96, 1.30, 2.19, and 3.00. The pattern was identical with that of 4-hydroxyspirohexane. However, some other unidentifiable peaks were present with much weaker intensities at δ 0.68 and 0.45 (a symmetrical pair of doublets), 1.56 (singlet), 1.70 (singlet), 4.26 (triplet), 5.20 (multiplet), and 7.86 (singlet). The IR spectrum (CCl_4 solution) of the minor product resembled that of spirohexan-4-one except for the presence of two additional absorptions at 1725 and 1550 cm^{-1}.

Acknowledgment. The authors wish to thank the National Science Foundation and the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

Registry No.—**5**, 21816-24-0; **6**, 20461-31-8; 4-spirohexanecarbonyl chloride, 66036-85-9; 5-spirohexanecarbonyl chloride, 66036-85-9; spirohexane, 157-45-9; oxalyl chloride, 79-37-8; ethyl 4-spirohexanecarboxylate, 66036-86-0; ethyl 5-spirohexanecarboxylate, 66036-86-0; 4-spirohexanecarboxylic acid hydrazide, 66036-87-1; β-naphthyl 4-spirohexanecarbamate, 66036-88-2; β-naphthol, 135-19-3; 5-spirohexanecarboxylic acid hydrazide, 66036-89-3; β-naphthyl 5-spirohexanecarbamate, 66036-88-2; 4-aminospirohexane, 38772-80-4; 4-hydroxyspirohexane, 21816-25-1; 5-aminospirohexane, 38772-81-5; 5-hydroxyspirohexane, 20054-19-7.

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(2) D. E. Applequist and W. A. Bernett, *Tetrahedron Lett.*, 3005 (1968).
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Synthesis of Chlorolium Ion Precursors: Solvolysis of Halobutadienes[1a]

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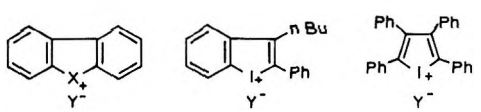
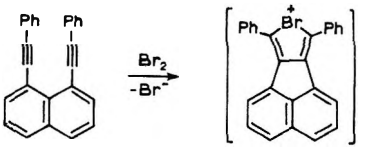
The *E,Z* and *Z,Z* isomers of 1-bromo-4-chloro-1,4-diphenyl-1,3-butadiene, 11*EZ* and 11*ZZ*, specifically deuterated in the 2 and 3 positions, were prepared. Silver-assisted solvolysis of 11*EZ* and 11*ZZ* in acetic acid and 11*EZ* in acetic anhydride gave a mixture of acetates 21*EZ* and 21*ZZ* and acetylene 9*Z*. The *E,E* isomer of 11 where chlorine participation is not possible and (*E*)-1-bromo-1-phenylpropene (29*E*) were solvolyzed in acetic acid with $AgBF_4$ to serve as model compounds. Using 29*E* deuterated in the 2 position, the isotope effect for acetylene formation from the vinyl cation was determined to be 2.0. Analysis of the deuterium distribution in the products from deuterated 11*EZ* led to the conclusion that 24 (in acetic acid) and 30% (in acetic anhydride) of the reaction proceeds through a chlorolium ion (13) intermediate. The isotope effect (k_H/k_D) for the deprotonation of 13 to give 9*Z* is 2.4 (in acetic acid) and 2.2 (in acetic anhydride). Similar results were obtained from the study of the solvolysis of 11*ZZ*. The vinyltriazenes 36*ZZ* from 11*ZZ* and its deuterated analogues were prepared and decomposed in situ with acetic acid. The deuterium content of the products showed that only 1% of the reaction involved a chlorolium ion. Even the vinyltriazene 37*ZZ* prepared from (*Z,Z*)-1-bromo-4-methylthio-1,4-diphenyl-1,3-butadiene showed little evidence (1%) of sulfur capture of the vinyl cation upon decomposition in acetic acid.

In contrast to the well studied group 7 heteroaromatic compounds furan, thiophene, selenophene, and even tellurophene, the chemistry of the analogous unsaturated halogen heterocycles, the halolium ions, has been little studied. Stable dibenzochlorolium, -bromolium, and -iodolium salts (1) were first prepared by Sandin and Hay.[2] More recently Beringer[3] has reported the synthesis of the benziodolium (2) and



1 X = I, Br, Cl 2 3

tetraphenyliodolium cations (3). A bromolium ion has been proposed by Bossenbroek and Shechter[4] as the intermediate in the bromination of 1,8-bis(phenylethynyl)naphthalene.



We report here the full details[1a] of our work on the ionization of halo- and triazenylbutadienes as a route to the 2,5-diphenylchlorolium ion (4) and related systems.

This approach to the halolium ion (4) involved the use of a halogen to trap a stabilized vinyl cation (5)[5] intramolecu-

4 X = Br, Cl 5

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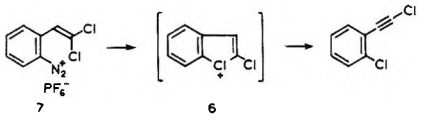
larly. Neighboring halogen is known to interact with carbonium ion centers in aliphatic systems[6] and participation of β-sulfur[7] and iodine[8] has been reported in the solvolysis of vinyl derivatives. The halolium ion (4), being isoelectronic with thiophene, might be aromatic and thus stable enough to be observed.

Olah and Yamada,[9] using a similar approach, have detected the intermediacy of 6 in the thermal decomposition of o-

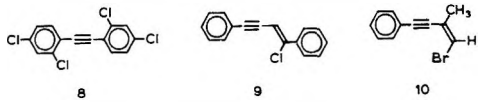


7 6

(β,β-dichloroethenyl)phenyldiazonium fluorophosphate (7).

Results

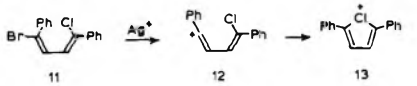
Our initial approach was to generate a vinyl cation by protonation of a suitably substituted phenylacetylene. The acetylenes 8, 9, and 10 were treated with HSO_3F or HSO_3F–



8 9 10

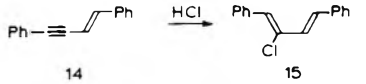
SbF_5. In each case highly colored solutions were formed, whose NMR spectra could not be reconciled with that of the expected halolium ion.

We then concentrated our efforts on the synthesis of 1,4-halobutadienes (11) which could be ionized to yield vinyl cations (12) suitably disposed for capture by neighboring halogen (13). A convenient approach to the desired 1,4-di-

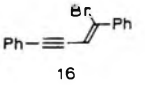


11 12 13

halo-1,4-diphenyl-1,3-butadienes (11), as well as the required deuterium labeled compounds, appeared to be the addition of hydrogen halides to 1,4-diphenyl-1,3-butadiyne or to 1,4-diphenyl-1,3-butenyne (14). In both cases, HCl or HBr addition led to the wrong regioisomer (i.e., 15). Attempted synthesis of 16 by bromination of 14 followed by dehydro-



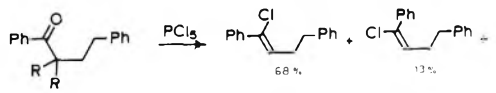
14 15



16

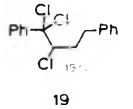
bromination was unsuccessful. Bromine addition to 14 yielded two crystalline products, each of which analyzed for addition of 2 mol of Br_2. Monoaddition products could not be detected. The ratio of the two tetrabromides depended on the brominating agent used.

Synthesis of 1-Bromo-4-chloro-1,4-diphenylbutadienes. The successful synthesis of 11*EZ* and -*ZZ* started with 1,4-diphenyl-1-butanone (17). Treatment with PCl_5 in refluxing benzene gave the *Z* vinyl chloride (18) in addition to 18*E* and 19 in the ratio indicated by GLC analysis. The crude



17a R = H
b R = D

18-Z 18E



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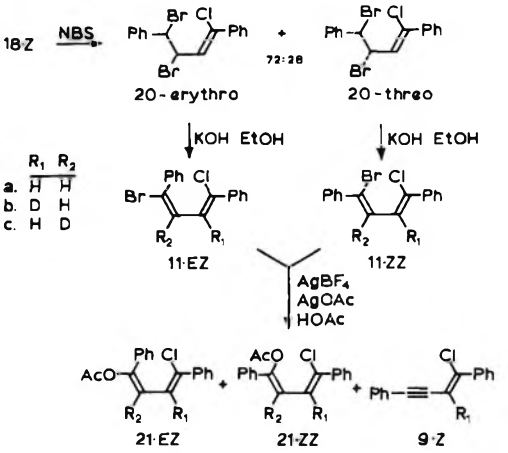
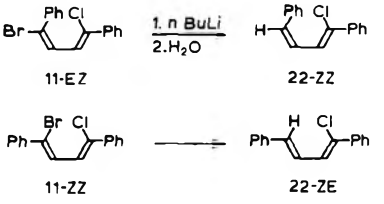
Scheme I



product mixture was treated with Zn in AcOH/Et_2O to reduce the trichloride 19 to 18*Z*. The deuterated vinyl chloride needed for mechanistic studies was formed from the deuterated ketone (17b) in an analoguous sequence. The vinyl chloride with the longer GLC retention time on SE-30 was assigned the *Z* configuration about the double bond since it was the major isomer formed (*Z*/*E* = 5) with the vinyl proton coming at δ 6.01 (δ 5.86 for the *E* isomer). This chemical shift difference, as well as the relative GLC retention times, is consistent with a number of related cis and trans isomers that have been observed.[10]

Treatment of 18*Z* with NBS in refluxing CCl_4 (Scheme I) gave sequentially the 3-bromo and 3,4-dibromo (20) compounds. The dibromide product 20 was a 72:28 mixture of erythro and threo diastereomers. The erythro isomer can be crystallized from the mixture in 48% yield and dehydrohalogenated to give 11*EZ*. Pure 11*ZZ* can be isolated by dehydrohalogenation of the crystallization mother liquor. Similar transformations using the deuterated vinyl chloride gave monodeuterated 11b*EZ* and 11b*ZZ* (98 ± 1%, d_1).[11] The stereochemistry of 11*EZ* and 11*ZZ* was proven by conversion to the monolithio compounds. Quenching of the vinyllithium from 11*EZ* with 1,2-dibromoethane gave back 93% isomerically pure 11*EZ* showing that the sequence proceeded with retention.[12,13] On quenching with water, 11*EZ* gave (*Z*,*Z*)-1-chloro-1,4-diphenyl-1,3-butadiene (22*ZZ*) with $J_{3,4}$ = 8 Hz, whereas 11*ZZ* gave the *Z*,*E* isomer (22*ZE*) with $J_{3,4}$ = 16 Hz.

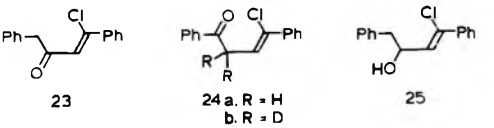


11-EZ 22-ZZ

11-ZZ 22-ZE

The deuterated bromo chlorides (11*b*,*c*) were carried through in an analogous manner. Quenching with hexachloroethane gave the isomeric 1,4-dichloro-1,4-diphenyl-1,3-butadienes. The stereochemical assignments here are unambiguous since the (*Z*,*Z*)-dichloride is symmetric, as shown by both ^1H and ^{13}C NMR, whereas the (*E*,*Z*)-dichloride is not.

The synthetic route of Scheme I was not suitable for the preparation of the deuterated compounds 11c*EZ* and 11c*ZZ*. Ketones 23 and 24 appeared to be potential precursors for these compounds. The alcohol precursor to 23 (25) could be



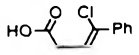
23 24a R = H
b R = D 25

Table I. Products of Silver Assisted Solvolyses of 1-Bromo-4-chloro-1,4-diphenyl-1,3-butadienes

Compd	% yield[a]	(% reaction)[b]	% 21*EZ*[c]	% 21*ZZ*[c]	% 9*Z*[c]	% *D* in 9*Z*
		In Acetic Acid at 118 °C				
11a*EZ*	97	(62)	21	52	27	
11b*EZ*	91	(72)	23	52	25	79
11c*EZ*	96	(63)	25	52	23	56
11a*ZZ*	78	(58)	24	52	24	
11b*ZZ*	75	(57)	22	51	27	83
11c*ZZ*	73	(64)	27	53	20	50
		In Acetic Anhydride at 80 °C				
11a*EZ*	93	(89)	19	53	28	
11b*EZ*	83	(67)	20	52	28	72
11c*EZ*	87	(61)	22	52	26	61

[a] Sum of products and recovered starting material. [b] Extent of reaction as determined by amount of recovered starting material. [c] Product ratios normalized to 100%.

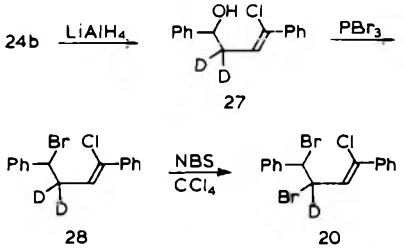
prepared by hydrolysis of the mono-NBS bromination product of 18*Z*, but oxidation of **25** could not be accomplished in acceptable yield using CrO_3, Collins or Jones conditions, or MnO_2. Attempts to prepare **24** from the readily available acid **26** by treatment with phenyllithium gave only low yields.



26

Reaction of the acid chloride of **26** with phenyllithium, $CdCl_2$ and phenyllithium, CuI and phenyllithium, phenylmagnesium bromide, and benzene under Friedel–Crafts conditions met with no better success.

Ketone **24** was prepared from the enol acetates **21**, obtained by silver-catalyzed ionization of **11** (Scheme I). These enol acetates were quite resistant toward both acid and base hydrolysis in refluxing THF–H_2O. Refluxing dioxane–H_2O–CF_3COOH did effect hydrolysis, but these conditions were strenuous enough to cause destruction of the product (**24**). Methyllithium cleaves the enol acetates cleanly to give **24** in 95% yield. This chloro ketone (**24**) was somewhat unstable and was deuterated directly by base-catalyzed exchange in D_2O. Reduction to **27**, conversion to the bromide **28** with PBr_3, and NBS bromination converted **24b** to a 75:25 mixture of erythro and threo dibromides **20**. These were separated and converted



to pure 11c*EZ* and 11c*ZZ* (97 ± 1%, d_1)[11] as described for the undeuterated compounds.

Solvolysis Results. Table I gives the yields of the solvolysis products from 11*EZ* and 11*ZZ* in AcOH and Ac_2O with $AgBF_4$ as catalyst. About 1 equiv of AgOAc was added to the solvolysis solution to remove fluoroboric acid generated by elimination. The stereochemistry of 21*EZ* and 21*ZZ* was assigned with the aid of $Eu(DPM)_3$ shift reagent.[14] The acetylene 9*Z* underwent facile dehydrohalogenation with ethanolic KOH to give 1,4-diphenyl-1,3-butadiyne. The stereochemistry was assigned on the basis of a 70-fold larger rate of elimination compared to 9*E* which was prepared by photochemical isomerization of 9*Z*. Both starting materials (**11**) and products (9*Z*, **21**) were shown to be stereochemically stable and not subject to deuterium exchange under the reaction conditions.

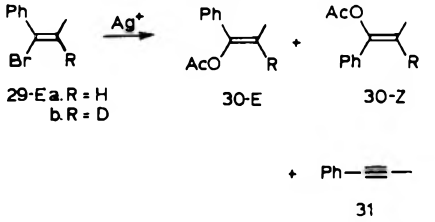
The deuterium content of the acetylene 9*Z* was determined mass spectrometrically and that of the acetates **21** was found by ^1H NMR with deuterium decoupling.

Solvolysis in AcOH or in Ac_2O shows no stereospecificity. The product ratios from 11*EZ* are the same, within experimental error, as those from 11*ZZ*. In AcOH 11*EZ* solvolyzes roughly five times as fast as 11*ZZ*.

The silver-assisted ionization of 11*EZ* and 11*ZZ* was also done in such aprotic solvents as toluene and nitrobenzene using $AgOCOCF_3$. In these cases the products were the acetylene 9*Z* and the *E,Z* and *Z,Z* trifluroacetates which were formed with partial retention of configuration.[10b] About twice as much acetylene was formed from 11*EZ* as from the *ZZ* isomer. The amount of deuterium isomerization observed in the products from 11b*EZ* in these solvents was roughly the same as what was observed in AcOH with $AgBF_4$. These results were not pursued since the absolute yield of products was quite low.

The intervention of a symmetrical intermediate, the chlorolium ion **13**, in the above solvolyses is evidenced by the observation of substantial deuterium isomerization in the acetylene 9*Z*. Since the deuterium content of 9*Z* is dependent on the position of deuterium in the starting material, some of the acetylene is arising from a nonsymmetrical species, either by deprotonation of the vinyl cation or E_2 elimination of the vinyl bromide. The acetates 21*EZ* and 21*ZZ*, on the other hand, must be derived almost entirely from the ion **12** since only small amounts (2–6%) of deuterium isomerization were detected. Unfortunately, the small amount of scrambling, together with our inability to accurately assess the deuterium distribution in 11c, makes conclusions drawn from this result somewhat tentative.

(*E*)-1-Bromo-1-phenylpropene (29*E*) was used as a model to determine the β-isotope effect on acetylene formation in the absence of participation. After 15 min in AcOH at 70 °C with $AgBF_4$, the solvolysis of 29*E* was essentially complete

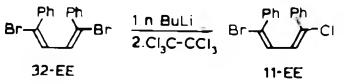


(>95%). A rough extrapolation gives about a factor of 10^4 for the rate acceleration of (*E*)-1-bromo-1-phenylpropene (29*E*) over (*E,Z*)-1-bromo-4-chloro-1,4-diphenyl-1,3-butadiene (11*EZ*). Thus the β-chlorovinyl group inductively retards vinyl cation formation. Product studies by GLC (Table II) indicated that k_H/k_D for acetylene formation is 2.0 ± 0.2 in AcOH with $AgBF_4$.

Table II. Silver Assisted Solvolysis of (*E*)-1-Bromo-1-phenylpropene in AcOH with $AgBF_4$ at 70 °C

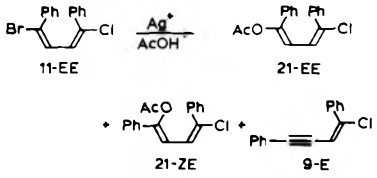
	% 30*E*	% 30*Z*	% 31	k_H/k_D
29a*E*	28	49	23	
29b*E*	34	53	13	2.0 ± 0.2

The solvolysis of 11*EE*, for which intramolecular capture by chlorine is not possible, was also examined. This compound was prepared from (*E*,*E*)-1,4-dibromo-1,4-diphenyl-1,3-butadiene (32*EE*).[13] In AcOH the products consisted of the



32-EE 11-EE

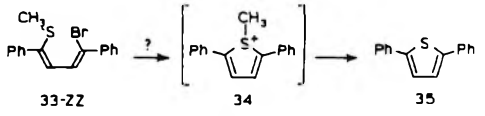
acetates 21*ZE* and 21*EE* and the acetylene 9*E* in a ratio of 72:18:10.



11-EE 21-EE 21-ZE 9-E

A Test for Sulfur Participation: Vinyl Triazene Decomposition. The low degree of participation by neighboring chlorine during silver-assisted solvolyses of 11*ZZ* and 11*EZ* made it desirable to examine a system in which the neighboring group has greater nucleophilicity.

A suitable substrate was (*Z*,*Z*)-1-bromo-4-methylthio-1,4-diphenyl-1,3-butadiene (33*ZZ*), prepared from 32*ZZ* via the monolithio compound.[13] A number of stable *S*-alkyl thiophenium salts (including 34) have been isolated. They



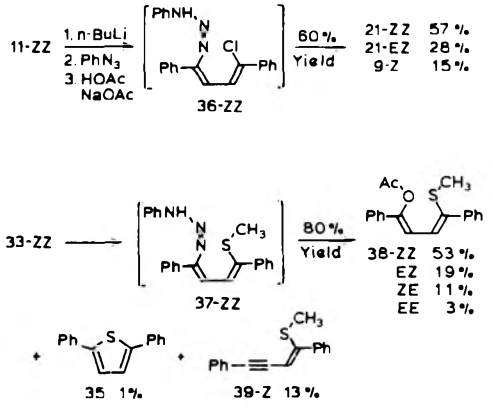
33-ZZ 34 35

undergo dealkylation under solvolytic conditions,[15] so the product of participation would be the stable 2,5-diphenylthiophene 35.

The usual conditions for silver-assisted solvolysis failed to ionize the bromide 33*ZZ* probably because of silver complexation with the sulfur. After 1 h in refluxing AcOH with $AgBF_4$, starting material was recovered along with 25% of 33*ZE*.

Acid treatment of vinyl triazenes has been reported as a route to vinyl cations.[16] They are prepared by treatment of organometallics with phenyl azide. For the present study the vinyl triazenes 36*ZZ* and 37*ZZ* were prepared as shown in Scheme II. They could not be isolated but were decomposed directly by addition of the reaction mixture to acetic acid.

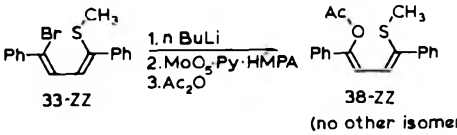
Scheme II



The equations above show the products isolated by preparative thin-layer chromatography. The triazene 36*ZZ* gave similar product distribution to that found for the solvolysis of 11a*ZZ*. However, when the deuterated dienes 11b*ZZ* and 11c*ZZ* were converted to triazenes and these treated with acetic acid the acetylenic product 9*Z* was not derived primarily from the chlorolium ion 13, as for the silver assisted solvolyses, since it was formed with little deuterium scrambling. Starting with 11b*ZZ* (97.5% d_1), the acetylene 9*Z* contained 96% deuterium, and from 11c*ZZ* (97% d_1), 11% deuterium (compare this with 83 and 50% for the silver-assisted solvolysis of 11*ZZ*, Table I). In contrast to the solvolysis, the enol acetate products showed no evidence for deuterium scrambling (<2%). There is clearly only a very small amount of chlorolium ion formed in this reaction.

The methylthio-substituted triazene 37*ZZ* gave an enol acetate 38*ZZ* as the major product, together with lesser quantities of 38*EZ*, 38*ZE*, and 38*EE*, the latter two having been formed by isomerization at the vinyl sulfide double bond. Only a trace amount of 2,5-diphenylthiophene was formed, identified by comparison with authentic material prepared according to the procedure of Böttcher and Bauer.[17]

The stereochemistry of 38*ZZ* was determined by comparison with material prepared by oxidation of the vinyllithium derivative with MoO_5·Py·HMPA.[18] The assignment of stereochemistry to the remaining acetates (38*EZ*, 38*ZE*, and 38*EE*) is tentative. First of all, 38*ZZ* is isomerized to 38*ZE* on



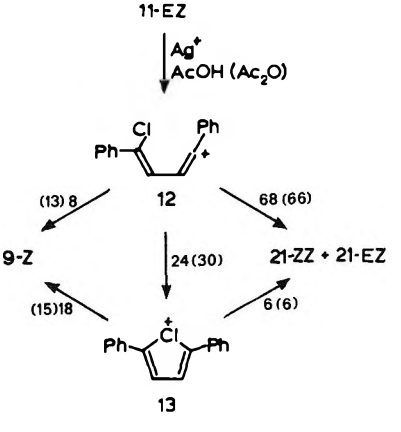
33-ZZ 38-ZZ (no other isomers isolated)

exposure to light. It has been our experience that all of the vinyl sulfides are readily isomerized even by ambient room lighting and that isomerization occurs at the vinyl sulfide double bond (for example, 33*ZZ* isomerizes to 33*ZE*; conversion of bromo to hydrogen with retention of configuration via the corresponding lithium reagents showed that the two compounds had the same configuration at the vinyl bromide double bond). Second, one of the vinyl proton chemical shifts usually moves upfield as a *Z* double bond is changed to an *E* double bond, with the *EE* isomer having both protons upfield compared to the *ZZ* isomer. For example, the dibromides 32*ZZ* and 32*EE* have chemical shifts at δ 7.30 and 6.63.[13] A number of other examples can be found among the chemical shifts reported in the Experimental Section.

Discussion

Our data have led us to propose the mechanistic Scheme III for the silver-assisted ionization of 11*EZ*. Yields refer to

Scheme III



100% of isolated products. Assuming that the isotope effect for the direct elimination (**12** → **9Z**) is 2.0 as determined in our model compound **29E**, we find[19] that in AcOH 24% of the solvolysis proceeds through the chlorolium ion (**13**) with k_H/k_D for **13** → **9Z** of 2.4 ± 0.2. In Ac_2O 30% of **13** is formed and k_H/k_D is 2.2.

The interpretation of these data is not crucially dependent on the assumption of isotope effects for the elimination **12** → **9Z**. If this isotope effect is 1.0, then the amount of chlorolium ion in AcOH only changes from 24 to 27%, and the isotope effect for **13** → **9Z** becomes 2.8. The observation of lower acetylene yields from **11c** in all cases is consistent with an isotope effect of about 2 for the deprotonation of **12**. The kinetic analysis of the two routes to **9Z** cannot simultaneously give values for both isotope effects unless the decrease in yield of **9Z** between **11a** (or **11b**) and **11c** is used. Unfortunately, the yields are not sufficiently accurate or reproducible to do this.

The solvolysis of **11ZZ** in AcOH gives essentially the same product distribution as does **11EZ**. In the case of **11ZZ**, however, slightly less of the acetylene is formed via the symmetrical intermediate. In order to obtain the same isotope effect for deprotonation of **12** during the solvolysis of **11ZZ** as was obtained from **11EZ**, it is necessary for the remainder of the elimination reaction to proceed with an isotope effect of 2.6 instead of 2.0 as used for **11EZ**. Since E_2 elimination is a commonly observed pathway for vinyl halide solvolysis when hydrogen is *trans* to the leaving group, we assume that a small contribution from this process is present. It is this contribution which results in the higher isotope effect and higher yield for the nonchlorolium ion portion of the elimination. Analyzing the yields and deuterium distribution for **11ZZ** according to the mechanistic scheme, we find that 20% of the reaction proceeds via the chlorolium ion **13**, of which 14% appears as acetylene, and, tentatively, 6% as acetate.

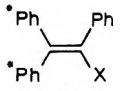
The solvolysis of **11EE**, for which participation of chlorine is not possible, gives products consistent with the above mechanism. In AcOH only 10% of acetylene **9E** is formed along with 90% of acetates. This is comparable to the amount of acetylene **9Z** that comes from direct elimination via the vinyl cation **12** in our mechanistic scheme. Although other products were not detected, a complication here is the possible intermediacy of a spirophenonium ion.

The results of the triazene decomposition give a rather different pattern. Analysis of the deuterium distribution in the acetylenes by the same procedure as used for the silver-assisted solvolyses[19] gave the following results, assuming an isotope effect (k_H/k_D) of 2.4 for deprotonation of the chlorolium ion: acetylene **9Z** from **11bZZ** was derived to the extent of only 5 ± 2% from chlorolium ion; from **11cZZ** 16 ± 2% came from chlorolium ion. The isotope effect for formation of acetylene from open ion could not be accurately determined (k_H/k_D = 1–5).

Since about 15% of the triazene decomposition leads to acetylene, the above results demonstrate that between 0.5 and 1.0% of the reaction goes via chlorolium ion, as compared with 20% during the silver-assisted solvolysis of **11ZZ**.

The main features of the reactions reported here are the following: the silver-assisted solvolysis of the *ZZ* and *ZE* isomers of the bromochlorodiene **11** in both acetic acid and acetic anhydride leads to 20–30% of chlorolium ion intermediate. The decomposition in acetic acid of the chloro- and methylthiotriazenes (**37**, **38**) leads to only about 1% of products derived from intramolecular capture of vinyl cation by the heteroatom.

The significantly different results obtained for the silver-assisted solvolyses and vinyltriazene decompositions would not appear to be explainable solely on the basis of different temperatures and somewhat different solvent for the two reactions. A direct comparison between vinyl cations generated by solvolyses or by triazene decomposition has been made by Lee and Ko.[20] The decomposition of radio-labeled triphenylvinyltriazene **39a** led to no detectable 1,2-phenyl rearrangement, whereas the silver-assisted acetolysis (**39b**) gave



(a) X = N=NNHPh
(b) X = Br

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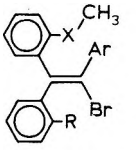
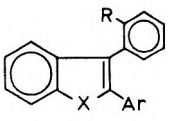
7% of rearranged material. This result would appear to parallel our observation. However, these workers also examined the tri-*p*-anisylvinyl system and found 38% rearrangement from the triazene and only 20% from AgOAc/HOAc solvolysis of the bromide. The vinyl cations in the anisyl series are enormously more stabilized than in the phenyl, and this could obviously contribute to the difference in behavior.

While participation (anchimeric assistance) by remote nucleophilic substituents has been rare for vinyl systems, intramolecular capture of vinyl cations has been observed frequently.[21,22] Particularly pertinent to the present study are the reactions reported by Taniguchi et al.[22] in which β-ortho-substituted aryl vinyl cations were generated either by solvolysis in ethanol or silver-assisted ionization of **40** (R = H, XCH_3) in acetic acid. These reactions gave exclusively the products (**41**) of intramolecular captures. The much higher



40 X = O, S, NCH_3



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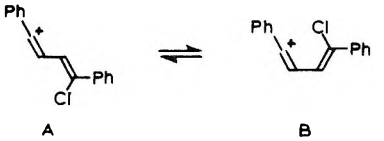
degree of cyclization here when compared with our system is somewhat surprising but can be rationalized on the basis that favorable conformations for the vinyl cation derived from **40** have the nucleophilic XCH_3 group in a suitable position to attack the carbonium ion center.

A satisfactory explanation for all features of the solvolytic reactions described in this paper has not been developed. In view of the probable high stability of the chlorolium and especially thiophenium ions, we had anticipated substantial or exclusive formation of cyclized intermediates. Instead, only minor amounts were observed even with the normally very strongly participating CH_3S group.

A possible explanation of these unexpected results may lie in the conformations of the 1,4-diphenyl-1,3-butadiene precursors and the vinyl cations derived from them. If the barrier to rotation interconverting cisoid and transoid conformations of the vinyl cation were higher than the activation barrier for solvent capture or deprotonation, then the amount of chlorolium or thiophenium ion formed would be a function of the fraction of cisoid ion (B) generated and not necessarily a reflection of the thermodynamic stability of the aromatic heterocycle or vinyl cation lifetime which must surely differ



A B

greatly between acetic acid and acetic anhydride as solvent. Furthermore, the ratio of A to B could well favor A much more strongly in the triazene reactions because of the lower temperature and different nature of the leaving group in this reaction. The difficulty encountered with an explanation of this type is that even if attack of solvent on the cation is diffusion

controlled, the barrier to rotation would still have to be significant ($\Delta G^{\ddagger} \approx 4$–6 kcal/mol)[23] to prevent rotational equilibrium. It is not, however, unreasonable to assume that the rotation barrier is higher in the vinyl cation than in the butadiene.

A possibility that cannot be completely ruled out is that the formation of chlorolium ion in the silver-assisted solvolysis is not a vinyl cation reaction at all but rather an addition–elimination pathway initiated by silver complexation of the olefin. Such a process has been observed by Sonoda, Kobayashi and Taniguchi[22c] for systems like **40** (X = S) but which lack the aryl substituent on the α carbon and hence cannot be proceeding through vinyl cations. A mechanism such as this should have resulted in especially facile silver-assisted solvolysis of the methylthio compound **33***ZZ* because such a mechanism involves nucleophilic participation. In actuality, **33***ZZ* was unaffected by the conditions which sufficed for ionization of the bromochlorodienes **11**.

Experimental Section

Nuclear magnetic resonance spectra were obtained on a Varian A-60A, Jeol MH-100, or Varian XL-100 spectrometer. Infrared spectra were obtained on a Beckman IR-8 or Perkin-Elmer IR-267 spectrophotometer and mass spectra were obtained on an AEI MS-902 spectrometer. Unless specified otherwise, NMR and IR spectra were measured in CCl_4 solution. A 5 ft × 0.125 in. column of 3% SE-30 on 100/120 Varaport 30 was used for analytical GLC. Preparative GLC was done on a 0.25 × 8 in. column of 20% SE-30 on 60/80 Chromosorb W, AW-DMCS.

2,2′,4,4′-Tetrachlorodiphenylacetylene (8) was prepared according to the procedure of Fieser[24] starting with 2,4-dichlorobenzaldehyde: mp 131–132 °C; NMR δ 7.14 (dd, J = 8.3, 2.4 Hz, 1 H), 7.40 (d, J = 2.4 Hz, 1 H), 7.41 (d, J = 8.3 Hz, 1 H). Anal. Calcd for $C_{14}H_6Cl_4$: C, 53.21; H, 1.91. Found: C, 53.19; H, 2.06.

(*Z*)- and (*E*)-1-Bromo-4-phenyl-2-methyl-1-buten-3-yne (10). A 10.9-g (25 mmol) portion of bromomethyltriphenylphosphonium bromide was stirred in 40 mL of anhydrous ether under N_2 while a mixture of 4 mL (3.4 g, 40 mmol) of dry piperidine and 16 mL of a 2.3 M solution of phenyllithium (37 mmol) in 70:30 benzene–ether was added dropwise. After being stirred for 20 min, a solution of 3.6 g (25 mmol) of 1-phenyl-1-butyn-3-one in an equal volume of anhydrous ether was added dropwise with cooling. The solution was stirred at room temperature 30 min and allowed to stand for 15 min. The solution containing the product was decanted from the precipitated phosphine oxide. The precipitate was washed with two 100-mL portions of ether. The combined washes and decanted solution were filtered and washed with two 100-mL portions of 2 N HCl, 100 mL of 5% Na_2CO_3, and two 100-mL portions of saturated NaCl. The solution was dried with Na_2SO_4 and the solvent was evaporated. The crude product was chromatographed on silica gel, eluting with pentane. Incomplete separation of the *Z* and *E* isomers was achieved. The more rapidly eluting isomer A (0.39 g) gave: NMR δ 2.02 (d, J = 1.6 Hz, 3 H), 6.60 (q, J = 1.6 Hz, 1 H), 7.2–7.5 (m, 5 H); IR 2210, 2185, 1590 cm^{-1}. Anal. Calcd for $C_{11}H_9Br$: m/e 219.9888. Found: m/e 219.9897. The slower moving isomer B gave: NMR δ 2.01 (d, J = 1.4 Hz, 3 H), 6.33 (q, J = 1.4 Hz, 1 H), 7.2–7.6 (m, 5 H); IR 2215, 2185, 1600 cm^{-1}. Anal. Calcd for $C_{11}H_9Br$: m/e 219.9888. Found: m/e 219.9890. In addition 1.24 g of a mixture of isomers was obtained. The total yield was 1.81 g (33%).

1,4-Diphenyl-1-butanone (17a). To the Grignard reagent prepared from 90.2 g (0.46 mol) of 3-bromo-1-phenylpropane, 11.2 g (0.46 mol) of magnesium, and 350 mL of ether was added 42.1 g (0.409 mol) of benzonitrile during 10 min. The reaction mixture was refluxed for 16 h, 150 mL of 5 N HCl was added slowly, and the mixture was steam distilled to remove unreacted benzonitrile. The product was taken up in ether and washed with 5% Na_2CO_3 solution and saturated NaCl solution. After drying (Na_2SO_4), solvent was removed and the product was crystallized from pentane, giving 77.6 g (85% yield), mp 55–56 °C (lit.[25] 56–57 °C).

(*Z*)-1-Chloro-1,4-diphenyl-1-butene (18*Z*). 1,4-Diphenyl-1-butanone (**17a**) (15.0 g, 67 mmol) was added to 42.5 g of PCl_5 (204 mmol) in 800 mL of benzene and the mixture was refluxed for 1 h. About 400 g of the ice was added to the solution and it was stirred vigorously until the ice melted. The benzene layer was then washed with 5% Na_2CO_3 and saturated NaCl solutions and chromatographed on 150 g of silica gel. The crude product is a mixture of three main components: 68% of (*Z*)-1-chloro-1,4-diphenyl-1-butene (18*Z*), NMR δ 2.5–3.0 (m, 4 H), 6.01 (t, J = 6.4 Hz, 1 H), 7.0–7.5 (m, 10 H); 13% of (*E*)-1-chloro-1,4-diphenyl-1-butene (18*E*), NMR δ 2.1–2.9 (m, 4 H), 5.86 (t, J = 7.6 Hz, 1 H), 6.9–7.3 (m, 10 H); and 19% of 1,1,2-trichloro-1,4-diphenylbutane (**19**), NMR δ 1.9–3.0 (m, 4 H), 4.28 (dd, J = 4.8, 1.1 Hz, 1 H), 6.9–7.7 (m, 10 H), mp 49–54 °C. Crystallization afforded pure 18*Z* and **19**. The two isomers of **18** can be separated preparatively by GLC at 175 °C. The retention times are for 18*E* 14.1 min and for 18*Z* 19.9 min.

The chromatographed crude product was dissolved in 100 mL of ether and 10 mL of acetic acid, and this solution was stirred with 4.4 g of zinc dust for 1 h to dehalogenate the 1,1,2-trichloro-1,4-diphenylbutane. Excess zinc was filtered; acetic acid was removed by extraction with $NaHCO_3$ solution. After drying (Na_2SO_4) and evaporation of the solvent, the residue was crystallized from 150 mL of pentane in dry ice, yielding 10.5 g (65%) of 18*Z*, mp 25–26 °C. Anal. Calcd for $C_{16}H_{15}Cl$: m/e 242.0862. Found: m/e 242.0866.

(*Z*)-1-Chloro-3,4-dibromo-1,4-diphenyl-1-butene (20). A suspension of 11.1 g (62 mmol) of *N*-bromosuccinimide in 125 mL of CCl_4 containing 6.9 g (28 mmol) of the vinyl chloride 18*Z* was refluxed for 22 h. If reaction was not complete, more *N*-bromosuccinimide and a small amount of benzoyl peroxide were added and reflux was continued. The succinimide was filtered and the solvent was evaporated. The residue was dissolved in ether and washed with ice cold 5% NaOH and saturated NaCl solution. The solution was dried and solvent was removed. NMR shows the presence of erythro and threo dibromides in a 72:28 ratio. Two crystallizations from dichloromethane–pentane yielded 5.48 g (48%) of the erythro isomer, mp 126–127 °C. The mother liquor had erythro/threo 18:82. Erythro dibromide: NMR δ 5.14 (d, J = 10 Hz, 1 H), 5.61 (t, J = 10 Hz, 1 H), 6.42 (d, J = 10 Hz, 1 H), 7.2–7.8 (m, 10 H). Anal. Calcd for $C_{16}H_{13}Br_2Cl$: C, 47.97; H, 3.27. Found: C, 48.03; H, 3.21. Threo dibromide: NMR δ 5.25 (d, J = 6, 1 H), 5.62 (dd, J = 6, 10 Hz, 1 H), 6.22 (d, J = 10 Hz, 1 H), 7.2–7.7 (m, 10 H).

(*E,Z*)-1-Bromo-4-chloro-1,4-diphenyl-1,3-butadiene (11*EZ*). Crystalline erythro dibromide (3.42 g) was heated with stirring at 55 °C for 0.5 h with 50 mL of absolute ethanol containing 7 mL of a 1.5 N ethanolic KOH solution. The reaction mixture was poured into ether and acidified (0.05 N HCl) water. The ether layer was washed with saturated NaCl solution and dried (Na_2SO_4). Removal of solvent gave an oil which was dissolved in pentane and allowed to crystallize, giving 2.22 g (81%) of 11*EZ*: mp 50–51 °C; NMR δ 6.64 (d, J = 11 Hz, H_3), 7.32 (d, J = 11 Hz, H_2), 7.1–7.6 (m, 11 H). Anal. Calcd for $C_{16}H_{12}BrCl$: C, 60.12; H, 3.79. Found: C, 60.11; H, 3.85.

(*Z,Z*)-1-Bromo-4-chloro-1,4-diphenyl-1,3-butadiene (11*ZZ*). The oily mother liquor from the dibromide crystallization (2.32 g of 18/82 erythro/threo) was stirred at room temperature for 3 h with 30 mL of ethanol containing 5.5 mL of 1.5 N ethanolic KOH solution. The reaction mixture was worked up as for 11*EZ*, and the product was crystallized from ether–pentane and from ethanol, giving 0.72 g (35%) of 11*ZZ*: mp 107.5–108.0 °C; NMR δ 7.24 (d, J = 11 Hz, H_3), 7.38 (d, J = 11 Hz, H_2), 7.1–7.8 (m, 12 H). Anal. Calcd for $C_{16}H_{12}BrCl$: C, 60.12; H, 3.79. Found: C, 60.22; H, 3.84.

(*Z,Z*)- and (*Z,E*)-1-Chloro-1,4-diphenyl-1,3-butadienes (22). To a solution of 50 mg (0.16 mmol) of 11*EZ* or 11*ZZ* dissolved in 1 mL of ether under nitrogen at 0 °C was added 0.10 mL (0.24 mmol) of 2.37 M *n*-butyllithium solution. After 10 min, 0.5 mL of methanol was added, and the solution was poured into ether and water. The ethereal layer was washed with saturated NaCl solution and solvent was removed. From 11*ZZ* the (*Z,E*)-chlorodiene is obtained: mp 111–112 °C (lit.[26] 114–5 °C); NMR δ 6.60 (d, J = 16 Hz, H_4), 6.91 (d, J = 11 Hz, H_2), 7.0–7.7 (m, 11 H). From 11*EZ*, the (*Z,Z*)-chlorodiene is obtained: NMR AB part of ABX pattern, δ 6.63 (J_{AB} = 11 Hz, J_{AX} = 0, H_A), 6.68 (J_{AB} = 11 Hz, J_{BX} = 8 Hz, H_B), 7.0–8.0 (m, 11 H). Anal. Calcd for $C_{16}H_{13}Cl$: m/e 240.0706. Found: m/e 240.0707.

To confirm that the metallation–protonation sequence proceeds with retention of configuration, a metallation as above was carried out using 11*EZ*, and the organolithium was treated with 1,2-dibromoethane. The product was 93% isomerically pure 11*EZ* by GLC analysis.

(*Z,Z*)- and (*E,Z*)-1,4-Dichloro-1,4-diphenyl-1,3-butadienes. To a solution of 80 mg (0.25 mmol) of 11*ZZ* in 2 mL of ether under nitrogen at 0 °C was added 0.20 mL (0.26 mmol) of 1.19 M *n*-butyllithium solution. After 10 min 71 mg (0.30 mmol) of solid hexachloroethane was added and stirring was continued for 10 min. The solution was poured into a separatory funnel containing ether and saturated aqueous $NaHCO_3$. After the $NaHCO_3$ wash the ethereal layer was washed with saturated NaCl and dried (Na_2SO_4). The solvent was removed yielding (*Z,Z*)-1,4-dichloro-1,4-diphenyl-1,3-butadiene identical to that prepared previously:[13] ^{13}C NMR δ_{Me_4Si} ($CDCl_3$) 137.60 (s, ipso), 136.25 (s, 1), 129.18 (d, para), 128.50 (d, meta), 126.58

(d, ortho), 129.6 (d, 2).

The *E,Z* isomer was prepared in an analogous manner from 11*EZ*: NMR δ 6.71, 7.05 (ABq, J = 11 Hz, 2 H), 7.1–7.6 (m, 10 H); ^{13}C NMR δ_{Me_4Si} ($CDCl_3$) 137.40 (s, ipso), 137.13 (s, ipso'), 136.87 (s, 1), 134.21 (s, 4), 129.30 (d, para'), 129.22 (d, ortho), 128.90 (d, para), 128.39 (d, meta, meta'), 126.39 (d, ortho'), 125.48 (d, 2), 121.23 (d, 3).

1,4-Diphenyl-1-butanone-2,2-*d* (17b). A solution of 15.0 g of 1,4-diphenyl-1-butanone and 0.3 g of $NaOCH_3$ in 70 mL of dry tetrahydrofuran and 15 mL of D_2O was refluxed for 4 h and poured into 200 mL of ether and 200 mL of water. The aqueous layer was extracted with 2 × 100 mL of ether, and the combined ethereal extracts were washed with saturated NaCl solution and dried (Na_2SO_4). The solvent was removed and the extent of deuteration was checked mass spectrometrically. Four deuterations as above, followed by crystallization from hexane, gave 14.5 g (97% yield) of ketone, 98.8% d_2.

(*E,Z*)- and (*Z,Z*)-1-Bromo-4-chloro-1,4-diphenyl-1,3-butadiene-3-*d* (11b*EZ* and 11b*ZZ*). 1,4-Diphenyl-1-butanone-2,2-d_2 was converted to the isomeric deuterated dienes as for the undeuterated compounds. In the first step (treatment with PCl_5) 30% of the 1,1-dichloro-1,4-diphenylbutane-2,2-d_2 is formed (less than 5% of this compound is formed in the undeuterated series). Treatment with zinc to remove 1,1,2-trichloro-1,4-diphenylbutane converted the dichloride to 1,4-diphenylbutane, and hence only 11% yield of the deuterated vinyl chloride was obtained.

Compounds 11b*EZ* and 11b*ZZ* were each 98 ± 1% d_1 (mass spectra). The NMR spectrum showed no detectable proton absorption at the chemical shift of H_3.

Preparative Silver-Assisted Solvolysis of 11*EZ*. A mixture of 5.6 g (17.5 mmol) of 11*EZ*, 3.0 g of AgOAc, 5.7 g of $AgBF_4$, 5 mL of acetic anhydride, and 100 mL of acetic acid was refluxed for 45 min. The bulk of the acetic acid was distilled under vacuum and 200 mL of 2:1 ether–pentane and 50 mL of saturated NaCl solution were added. The mixture was stirred for 10 min and filtered through celite. The organic layer was washed with 5% Na_2CO_3 (2×) and saturated NaCl solutions and dried (Na_2SO_4). Solvent was removed and the residue was adsorbed on 25 g of silica gel and chromatographed on 250 g of silica gel. The column was eluted first with pentane and then with increasing amounts of ether in pentane up to 7.5% ether. Unreacted 11*EZ* was eluted first followed by the acetylene 9*Z*. Pure acetylene fractions were combined and crystallized from pentane: mp 81–82 °C, NMR δ 6.41 (s, 1 H), 7.1–7.7 (m, 10 H); IR ($CHCl_3$) 2188 cm^{-1}. Anal. Calcd for $C_{16}H_{11}Cl$: C, 80.50; H, 4.65. Found: C, 80.57; H, 4.76.

Further elution gave 2.8 g (53%) of a mixture of enol acetates 21*EZ* and 21*ZZ*, with the early fractions being pure 21*EZ* and the last fractions pure 21*ZZ*. Each isomer was crystallized from pentane. 21*EZ*: mp 66–67 °C; NMR δ 2.17 (s, 3 H), 6.58, 6.84 (ABq, J = 11 Hz, H_2, H_3), 7.1–7.7 (m, 10 H); IR ($CHCl_3$) 1775 cm^{-1}. Anal. Calcd for $C_{18}H_{15}ClO_2$: C, 72.36; H, 5.06. Found: C, 72.35; H, 5.04. 21*ZZ*: mp 97–98 °C; NMR δ 2.26 (s, 3 H), 6.81, 6.91 (ABq, J = 11 Hz, H_3, H_2), 7.1–7.7 (m, 10 H); IR 1770 cm^{-1}. Anal. Calcd for $C_{18}H_{15}ClO_2$: C, 72.36; H, 5.06. Found: C, 72.42; H, 4.97.

The stereochemistry of 21*EZ* and 21*ZZ*, as well as the identity of the protons H_2 and H_3, was assigned with the aid of $Eu(DPM)_3$ using the method developed by Kelsey.[14] For 21*EZ* ΔOAc/ΔH_2 was 1.3 and ΔOAc/ΔH_3 was 2.0. For 21*ZZ* ΔOAc/ΔH_2 was 2.2 and ΔOAc/ΔH_3 was 1.6. These values were compared to those found for (*E*)- and (*Z*)-1-acetoxy-1-phenylpropene. For the *E* isomer ΔOAc/ΔH was 1.4 and for the *Z* isomer ΔOAc/ΔH was 2.2.

(*Z*)-4-Chloro-1,4-diphenyl-3-buten-1-one (24a*Z*). To a solution of 16 mL of 2.0 M methyllithium (32 mmol) in 100 mL of ether at 0 °C was added a solution of 2.6 g (8.7 mmol) of mixed enol acetates 21*EZ* and 21*ZZ* in 10 mL of ether. The solution was stirred for 10 min at 0 °C, 1.5 mL of ethyl acetate was added, and the reaction mixture was poured into ice water. The organic layer was washed with saturated NaCl solution and dried and solvent was evaporated. The crude solid is pure by NMR analysis but is somewhat unstable and was used without purification. Crystallization from ether–pentane gives a yellow solid: mp 74–75 °C, NMR δ 4.01 (d, J = 6 Hz, 2 H), 6.62 (t, J = 6 Hz, 1 H), 7.1–7.8 (m, 8 H), 7.93 (dd, J = 9, 2 Hz, 2 H); IR ($CHCl_3$) 1680 cm^{-1}.

Anal. Calcd for $C_{16}H_{13}ClO$: C, 74.85; H, 5.10. Found: C, 74.85; H, 5.09.

(*E,Z*)- and (*Z,Z*)-1-Bromo-4-chloro-1,4-diphenyl-1,3-butadiene-2-*d* (11a*EZ* and 11c*ZZ*). A solution of 2.3 g (9.0 mmol) of (*Z*)-4-chloro-1,4-diphenyl-3-buten-1-one in 10 mL of dichloromethane was stirred with 209 mg of Na_2CO_3 in 5 mL of D_2O for 20 h. The organic layer was separated and dried (Na_2SO_4) and solvent was evaporated. The extent of deuteration was checked by NMR. This procedure was repeated three more times, giving 2.2 g of dideuterated ketone, 95% deuterated at the 2 position.

A solution of 2.1 g (8.1 mmol) of (*Z*)-4-chloro-1,4-diphenyl-3-buten-1-one-2,2-d_2 in 20 mL of ether was added at 0 °C to 100 mL of ether containing 0.320 g (8 mmol) of $LiAlH_4$. The solution was stirred at 25 °C for 1 h and then transferred to a solution of 4 g of NH_4Cl in 100 mL of ice water. The ether portion was washed with saturated NaCl solution and dried (Na_2SO_4) and solvent was removed. The residue was chromatographed on 100 g of silica gel using 10–20% ether–pentane as eluant, giving 1.7 g of (*Z*)-4-chloro-1,4-diphenyl-3-buten-1-ol-2,2-d_2. The NMR spectrum of the undeuterated material, prepared as above, was δ 2.3 (bs, 1 H), 2.77 (t, J = 7 Hz, 2 H), 4.78 (t, J = 7 Hz, 1 H), 6.19 (t, J = 7 Hz, 1 H), 7.1–7.6 (m, 10 H). In the deuterated compound the multiplet at 3.1 was absent, and the triplets at δ 4.59 and 6.05 appeared as broad singlets.

The alcohol prepared above (1.6 g, 6.1 mmol) was converted to the bromide ((*Z*)-1-bromo-4-chloro-1,4-diphenyl-3-butene-2,2-d_2) by stirring for 13 h in 40 mL of ether containing 0.7 mL of PBr_3. Water was added, and the ethereal layer was washed with saturated $NaHCO_3$ and NaCl solutions and dried (Na_2SO_4). The solvent was removed and the residue was dissolved in 25 mL of CCl_4 and chromatographed rapidly on 8 g of silica gel, giving 1.6 g of bromide. The undeuterated compound, prepared as above, had NMR δ 3.2 (m, 2 H), 5.02 (t, J = 7.2 Hz, 1 H), 6.08 (t, J = 6.8 Hz, 1 H), 7.0–7.8 (m, 10 H). In the deuterated compound the multiplet at δ 3.2 was absent, and the triplets at δ 5.02 and 6.08 were broad singlets.

The deuterated bromide prepared above (1.6 g, 4.9 mmol) was refluxed in 50 mL of CCl_4 for 17 h with 2.6 g (15 mmol) of *N*-bromosuccinimide and 12 mg of benzoyl peroxide. NMR analysis showed 75% conversion to dibromides. The bromination was continued by refluxing for 11 h in CCl_4 with 1.0 g of *N*-bromosuccinimide and 11 mg of benzoyl peroxide. NMR analysis showed a 75:25 mixture of erythro–threo dibromides. These were separated and converted to pure (*E,Z*)- and (*Z,Z*)-1-bromo-4-chloro-1,4-diphenyl-1,3-butadiene-2-*d* (97 ± 1% d_1) as described for the undeuterated compounds.

Solvolysis of (*E,Z*)-1-Bromo-4-chloro-1,4-diphenyl-1,3-butadiene. In AcOH. To 31 mg of 11*EZ*, 22.9 mg of AgOAc, and 38.3 mg of $AgBF_4$ was added 2 mL of AcOH containing 0.1 mL of Ac_2O. The mixture was refluxed for 4.5 h and cooled and 2.0 mL of a CCl_4 solution containing 1.10 mg/mL of di-*n*-butyl phthalate was added. The contents of the flask were added to a stirred flask containing 20 mL each of 5% Na_2CO_3 solution, saturated NaCl solution, ether, and pentane. After 15 min the mixture was filtered through celite, the organic layer was washed with 5% Na_2CO_3 solution and dried, and solvent was removed. The residue was dissolved in 3 mL of CCl_4 and analyzed by GLC at 185 °C. Response factors were determined using standard mixtures. Retention times for 9*Z*, 11*EZ*, 21*EZ*, 11*ZZ*, and 21*ZZ* were 4.2, 6.6, 8.2, 10.0, and 11.2 min, respectively. In the case of the deuterated isomers the reaction mixture was examined by NMR (Varian XL-100 with noise-modulated deuterium decoupling) to determine the extent of scrambling in the acetates (the vinyl protons were all well separated sharp singlets). The vinylacetylene was separated either by TLC or preparative GLC at 200 °C and analyzed for deuterium content by mass spectrometry. Analyses of three aliquots of a sample from solvolysis of 11b*EZ* (one purified by TLC, the second crystallized after the purification, and a third collected by GLC) were 78.5, 79.2, and 78.6% deuterium.

In Ac_2O. The solvolysis procedure was generally the same, except that the solvent was Ac_2O containing 1% AcOH, and the reaction was kept at 80 °C in a thermostated bath for 8–12 h.

Solvolysis of (*Z,Z*)-1-Bromo-4-chloro-1,4-diphenyl-1,3-butadiene (11*ZZ*). To 11.0 mg of 11*ZZ*, 5.6 mg of AgOAc, and 17.7 mg of $AgBF_4$ was added 2 mL of AcOH containing 0.1 mL of Ac_2O. The mixture was refluxed with stirring under N_2 for 12 h. Workup was the same as for the *E,Z* isomer. The crude product mixture was separated by preparative TLC into hydrocarbon and acetate fractions. Two milliliters of CCl_4 solution containing 1.988 mg of di-*n*-butyl phthalate was added to each fraction. Each fraction was analyzed by GLC. The estimated errors for the determination of the product yields are ±1% for 11*EZ* and ±2% for 11*ZZ*. This variation in yield is caused by decomposition during the reaction. The errors are larger for 11*ZZ* because of longer reaction time. The analysis of the products from the deuterated compounds was the same as for the *E,Z* isomer.

(*E*)-1-Phenyl-1-propene. Propiophenone was reduced to 1-phenyl-1-propanol with $LiAlH_4$. The alcohol was eliminated by distillation from $NaHSO_4$.[27] The olefin was obtained in 78% yield, pure by NMR and greater than 95% isomerically pure.

1,2-Dibromo-1-phenylpropane. (*E*)-1-Phenyl-1-propene was treated with Br_2 in CCl_4 at 0 °C.[10b] The crystalline residue after evaporation of the CCl_4 is a mixture of diastereomers erythro–threo about 5:1. The erythro isomer can be crystallized to purity, mp 66–67

°C. Erythro: NMR δ 2.04 (d, J = 6 Hz, 3 H), 4.54 (dq, J = 11, 6 Hz, 1 H), 5.00 (d, J = 11 Hz, 1 H), 7.37 (m, 5 H). Threo: NMR δ 1.65 (d, J = 7 Hz, 3 H), 5.17 (d, J = 5 Hz, 1 H) in the mixture.

(*E*)-1-Bromo-1-phenyl-1-propene (29*E*). *erythro*-1,2-dibromo-1-phenylpropane was dehydrohalogenated with alcoholic KOH at 55 °C to give 91% of (*E*)-1-phenyl-1-propene, 1% of (*Z*)-1-phenyl-1-propene, and 8% of 2-bromo-1-phenyl-1-propene. The vinyl bromide was stored in dry ice at −78 °C because it isomerized in the freezer at −20 °C.

The 2-deuterated bromide was made in an analogous manner starting with deuterated propiophenone.

Solvolysis of (*E*)-1-Bromo-1-phenyl-1-propene in AcOH. A mixture of 19 mg of **29*E***, 23 mg of AgOAc, 48 mg of $AgBF_4$, 1 mL of AcOH, and 0.1 mL of Ac_2O was stirred in a sealed tube at 70 °C for 0.5 h. The reaction mixture was worked up and analyzed by GLC. The relative retention times were 3.4 min for **31**, 5.9 min for **29*E***, 7.4 min for **30*E***, and 8.4 min for **30*Z*** with the temperature programmed at 4 °C per min 40–100 °C.

Photochemical Isomerization of 9*Z* to 9*E*. A solution of 70 mg of **9*Z*** in 3 mL of cyclohexane was irradiated with a Hanovia high-pressure Hg lamp through Pyrex for 0.5 h. GLC analysis showed a 56:44 ratio of *E*/*Z* isomers. The two isomers were separated by preparative TLC. The *E* isomer was eluted slightly faster with pentane: NMR δ 6.28 (s, 1 H), 7.2–7.5 (m, 8 H), 7.9–8.1 (m, 2 H); IR 2182 cm^{-1}. Anal. Calcd for $C_{16}H_{11}Cl$: *m/e* 238.0549. Found: *m/e* 238.0551.

Elimination of a Mixture of 9*Z* and 9*E*. Relative Rates. A 74-mg mixture of **9*Z*** and **9*E***, 21:79, was stirred at room temperature in 5 mL of EtOH containing 0.5 mL of 1.5 N KOH in EtOH. After 58 h 97% of the *Z* isomer and only 7% of the *E* isomer had been converted to diphenyldiacetylene. This gives a relative rate of elimination k_Z/k_E = 66. 1,4-Diphenylbutenyne (30 mg) was used as a standard in the GLC analysis.

(*E,E*)-1-Bromo-4-chloro-1,4-diphenyl-1,3-butadiene (11*EE*). To 15 mL of ether was added 0.04 mL of *n*-butyllithium (1.58 M in hexane) followed by 0.367 g (1.0 mmol) of (*E,E*)-1,4-dibromo-1,4-diphenyl-1,3-butadiene (**32*EE***).[13] After the solid had dissolved, the solution was cooled to 0 °C and 0.76 mL of *n*-butyllithium was added dropwise with magnetic stirring. After 3 min 263 mg(1.1 mmol) of hexachloroethane was added, the cooling bath was removed, and after 10 min the reaction was worked up. The solid was crystallized from hexane: 227 mg; 71% yield; mp 108–9 °C. Anal. Calcd for $C_{16}H_{12}BrCl$: *m/e* 317.9811. Found: *m/e* 317.9808.

Solvolysis of (*E,E*)-1-Bromo-4-chloro-1,4-diphenyl-1,3-butadiene. To 0.133 g of **11*EE***, 0.489 g of $AgBF_4$, and 0.065 g of AgOAc was added 8 mL of AcOH and 0.4 mL of Ac_2O. The mixture was stirred at reflux for 75 min. After the usual workup, the products were partially separated by preparative TLC. The plate was eluted with 5% ether–pentane three times. The solvolysis was run to 70% completion and the recovered yield was 68%. The volatile products consisted of 10% **9*E***, separated from starting material by GLC, and two acetates. The minor acetate, **21*EE***, 18% of the product mixture, was separated from **21*ZE*** by GLC: mp 68–69 °C (hexane); NMR δ 2.08 (s, 3 H), 5.98, 6.58 (Abq, J = 11.9 Hz), 7.1–7.6 (m, 10 H); IR 1766 cm^{-1}. Anal. Calcd for $C_{18}H_{15}ClO_2$: *m/e* 298.0760. Found: *m/e* 298.0758. The major acetate, **21*ZE***, comprised 72% of the product mixture: mp 71–2 °C (hexane); NMR δ 2.29 (s, 3 H), 6.30, 6.52 (ABq, J = 11.6 Hz), 7.0–7.5 (m, 10 H); IR 1768 cm^{-1}. Anal. Calcd for $C_{18}H_{15}ClO_2$: *m/e* 298.0760. Found: *m/e* 298.0756. The structure of the acetates was confirmed by cleavage to the ketone, **24a*E***, with methyllithium; mp 27–30 °C; NMR δ 3.68 (d, J = 7.5 Hz, 2 H), 6.30 (t, 7.5 Hz, 1 H), 7.2–7.6 (m, 8 H), 7.84 (dd, J = 8, 2.5 Hz, 2 H); IR 1685 cm^{-1}. Anal. Calcd for $C_{16}H_{13}ClO$: *m/e* 256.0655. Found: *m/e* 256.0653.

Preparation and Solvolysis of the Vinyltriazene (36*ZZ*) from 11*ZZ*. To a stirred flask under nitrogen containing 2 mL of ether was added 0.03 mL of *n*-butyllithium solution (1.65 M) followed by 149 mg (0.47 mmol) of **11*ZZ***. The solution was cooled to −10 °C and 0.31 mL of *n*-butyllithium solution (0.51 mmol) was added dropwise. After a few minutes 66 mg (0.56 mmol) of phenyl azide was added dropwise causing the solution to turn deep-red in color. After 5 min this solution was added with a syringe to a stirred flask containing 20 mL of AcOH and 1 mL of Ac_2O. The AcOH solution was poured into a separatory funnel containing 25 mL of ether, 25 mL of pentane, and 50 mL of 0.5 N HCl solution. The organic layer was washed three times with 50 mL of water followed by 5% Na_2CO_3 solution and saturated NaCl solution. The organic layer was dried (Na_2SO_4) and solvent was removed. The crude product mixture was separated by preparative TLC with 5% ether–pentane elution yielding in order of increasing polarity: fraction 1, 4 mg of **11*ZZ*** (3%); fraction 2, 25 mg, an 8:3 mixture of **22*ZE*** (15%) and **9*Z*** (6%); fraction 3, 16 mg of **21*EZ*** (12%); fraction 4, 33 mg of **21*ZZ*** (24%). The overall recovery was 60%.

Preparation and Solvolysis of the Vinyltriazene (37*ZZ*) from 33*ZZ*.[13] To a stirred flask under nitrogen containing 3 mL of ether was added 0.03 mL of *n*-butyllithium solution (1.65 M) followed by 302 mg (0.91 mmol) of **33*ZZ***. The solution was cooled to −10 °C and 0.62 mL of *n*-butyllithium solution (1.02 mmol) was added dropwise. After a few minutes 128 mg (1.08 mmol) of phenyl azide was added dropwise (deep-red color). After 5 min this solution was added by syringe to a stirred flask containing 40 mL of AcOH, 2 mL of Ac_2O, and 0.35 g of NaOAc (0.1 M NaOAc solution). The workup was as described above for the solvolysis of the triazene from **11*ZZ***. The results were similar when NaOAc was omitted from the AcOH quench. The crude product mixture was purified by preparative TLC with 5% ether–pentane elution three times. The overall recovery was 80%. Four fractions were removed from the plate in order of increasing polarity:

Fraction 1, 10 mg, containing a 1:1 mixture of 1,4-diphenylbutadiene (3%) and (*Z,E*)-1-methylthio-1,4-diphenyl-1,3-butadiene (2%) (NMR δ 2.01 (s, 3 H), 6.54 (d, J = 10.7 Hz, H_2), 6.55 (d, J = 15.8 Hz, H_4), 7.0–7.6 (m, 11 H)) was identical to the material prepared by lithiation of **33*ZZ*** and quenching with water.

Fraction 2, 25 mg, was mainly 39*Z* (11%) containing a small amount of **35** (1%). This fraction was further separated by preparative TLC elution with pentane four times to yield in order of decreasing polarity 22 mg of **39*Z*** (NMR δ 2.14 (s, 3 H), 5.94 (s, 1 H), 7.2–7.6 (m, 10 H), IR 2180 cm^{-1}. Anal. Calcd for $C_{17}H_{14}S$: *m/e* 250.0816. Found: *m/e* 250.0815) and **35** which was purified by preparative GLC to yield 2 mg, mp 151–152 °C (lit.[17] mp 153–154 °C). This material also had identical TLC R_f and GLC retention time with authentic 2,5-diphenylthiophene (**35**). Anal. Calcd for $C_{16}H_{12}S$: *m/e* 236.0660. Found: *m/e* 236.0656.

Fraction 3, 159 mg, contained three thio acetates: **38*ZZ*** 42%, **38*EZ*** 15%, **38*EE*** 2%. This mixture was further separated by preparative TLC, elution with 7.5% ether–pentane four times, to yield, in order of decreasing polarity, pure **38*ZZ*** which was crystallized from ether–pentane: mp 121–122 °C; NMR δ 2.03 (s, 3 H), 2.23 (s, 3 H), 6.54, 7.18 (ABq, J = 11 Hz, 2 H), 7.3–7.7 (m, 10 H); IR 1770 cm^{-1}. Anal. Calcd for $C_{19}H_{18}O_2S$: C, 73.52; H, 5.84. Found: C, 73.59; H, 5.88. This thio acetate was identical by NMR to that formed in 20% yield by treatment of **33*ZZ*** sequentially with *n*-butyllithium (−78 °C), MoOPH (−78 °C), and Ac_2O (−78 to 25 °C). No other isomeric thio acetate was detected in this oxidation of the vinyllithium derivative. Preceding **38*ZZ*** on the plate, **38*EZ*** was eluted: NMR δ 2.02 (s, 3 H), 2.15 (s, 3 H), 6.60, 6.80 (ABq, J = 11 Hz, 2 H), 7.2–7.6 (m, 10 H); IR 1767 cm^{-1}. Anal. Calcd for $C_{19}H_{18}O_2S$: *m/e* 310.1027. Found: *m/e* 310.1033. The minor isomer, **38*EE***, could not be obtained in pure form and was eluted along with **38*ZZ***. It was tentatively identified as the *E,E* isomer in the NMR spectrum of the mixture having an AB quartet at δ 5.84, 6.22 (J = 11.5 Hz).

Fraction 4, 24 mg, 9%, contained a fourth thio acetate, **38*ZE***: NMR δ 2.19 (s, 3 H), 2.30 (s, 3 H), 6.23, 6.31 (ABq, J = 11 Hz, 2 H), 7.0–7.6 (m, 10 H); IR ($CHCl_3$) 1760 cm^{-1}. Anal. Calcd for $C_{19}H_{18}O_2S$: *m/e* 310.1027. Found: *m/e* 310.1033. Photolysis of **38*ZZ*** gave this isomer (**38*ZE***).

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Registry No.—**8**, 65943-09-1; **9*E***, 65943-10-4; **9*Z***, 52516-81-1; **10*E***, 65943-11-5; **10*Z***, 65943-12-6; **11a*EZ***, 52516-75-3; **11a*ZZ***, 52516-76-4; **11a*EE***, 65943-13-7; **11b*EZ***, 65943-14-8; **11b*ZZ***, 65943-15-9; **11c*EZ***, 65943-16-0; **11c*ZZ***, 65943-17-1; **17a**, 5407-91-0; **17b**, 65943-18-2; **18*Z***, 52516-77-5; **18*E***, 65943-19-3; **19**, 65943-20-6; *erytho*-**20**, 52516-78-6; *threo*-**20**, 65943-21-7; **21a*EZ***, 52516-80-0; **21a*EZ***, 52516-79-7; **21*EE***, 65943-22-8; **21*ZE***, 65943-23-9; **22*ZE***, 14533-17-6; **22*ZZ***, 65943-24-0; **23**, 65943-25-1; **24a*Z***, 65942-93-0; **24a*E***, 65943-08-0; **24b*Z***, 65942-94-1; **27**, 65942-95-2; **28**, 65942-96-3; **29a*E***, 31076-47-8; **29b*E***, 65942-97-4; **30a*E***, 7642-42-4; **30a*Z***, 13266-91-6; **31**, 673-32-5; **32*EE***, 7641-45-4; **33*ZZ***, 55373-72-3; **33*ZE***, 65942-98-5; **35**, 1445-78-9; **36*ZZ***, 65943-06-8; **37*ZZ***, 65969-55-3; **38*ZZ***, 65942-99-6; **38*EE***, 65943-00-2; **38*EZ***, 65943-01-3; **38*ZE***, 65943-02-4; **39*Z***, 65943-03-5; 1-phenyl-1-butyn-3-one, 1817-57-8; 3-bromo-1-phenylpropane, 637-59-2; (*Z,Z*)-1,4-dichloro-1,4-diphenyl-1,3-butadiene, 55373-69-8; (*E,Z*)-1,4-dichloro-1,4-diphenyl-1,3-butadiene, 65943-04-6; 1,1-dichloro-1,4-diphenylbutane-*2,2-d*$_2$, 65943-05-7; (*E*)-1-phenyl-1-propene, 873-66-5; propiophenone, 93-55-0; 1-phenyl-1-propanol, 93-54-9; *erythro*-1,2-dibromo-1-phenylpropane, 21087-19-4; *threo*-1,2-dibromo-1-phenylpropane, 21087-20-7; (*Z,E*)-1-methylthio-1,4-diphenyl-1,3-butadiene, 65943-07-9; 1,4-diphenylbutadiene, 886-65-7.

References and Notes

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$$\%\ \text{D in } \mathbf{9}Z \text{ from } \mathbf{11b} = \frac{k_c}{k_c + k_{eH}}\left(\frac{R}{R+1}\right) + \frac{k_{eH}}{k_c + k_{eH}} = \left(\frac{1}{P_H + 1}\right)\left(\frac{R}{R+1}\right) + \frac{P_H}{P_H + 1}$$

$$\%\ \text{D in } \mathbf{9}Z \text{ from } \mathbf{11c} = \frac{k_c}{k_c + k_{eD}}\left(\frac{R}{R+1}\right) = \left(\frac{1}{P_D + 1}\right)\left(\frac{R}{R+1}\right)$$

where $R = k_H/k_D$ for deprotonation of chlorolium ion **13**; k_c = rate constant for **12** → **13**; k_{eH} = rate constant for **12** → **9Z**, k_{eD} = rate constant for **12** → **9Z** where **12** is deuterated; $P_H = k_{eH}/k_c$ and $P_D = k_{eD}/k_c$; and $P_H/P_D = k_{eH}/k_{eD}$, which is the isotope effect for deprotonation of vinyl cation **12**. To solve these equations, it is necessary to assume a value for either R or P_H/P_D. Once the equation is solved, the fraction of **9Z** formed from chlorolium ion is given by $1/(1 + P_H)$.
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Synthetic and Kinetic Studies on Tricarbonates and Dicarbonates[1]

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The synthesis and properties of di-1-adamantyl tricarbonate (**5**), dicarbonate (**6**), and monocarbonate (**7**) are described. The kinetics of the thermal conversion of **6** to **7** have been measured and the activation parameters determined. Some systematic errors in the previously reported kinetics of the tri- and dicarbonates **1**, **2**, **3**, and **4** are corrected and the mechanisms of the thermal reactions are discussed. Some substituted phenoxycarbonyl derivatives of amino acids, prepared from *tert*-butyl aryl dicarbonates, are described.

In earlier studies,[3–7] the preparation and reactions of a hitherto unknown class of compounds, the di-*tert*-butyl tricarbonates **1** and **2**, were described, along with convenient syntheses of the corresponding dicarbonates **3** and **4**. The utility of the latter for preparing *t*-BOC and thio-*t*-BOC derivatives of amino acids was pointed out;[8] the oxygen dicarbonate[4] has been widely adopted for this purpose,[9] and the reagent is commercially available[10] as well as readily synthesizable in the laboratory.[7,8] The present paper reports further studies on the novel tricarbonates and on other carbonate derivatives.

Di-1-adamantyl tricarbonate (**5**) was prepared as a pure crystalline compound from the sodium salt of 1-adamantanol as shown in eq 1. When heated to approximately 110 °C, **5** melted with decomposition to yield approximately 75% of 2 equiv of carbon dioxide and a mixture of di-1-adamantyl dicarbonate (**6**) and di-1-admantyl carbonate (**7**). Subsequent heating of this mixture above 150 °C led to the formation of only the monocarbonate **7** and 2 equiv of carbon dioxide. Attempts to effect the thermal stepwise transformation of **5** to **6** to **7** were not successful, although a variety of solvents and temperatures was utilized. Thermal decomposition of **5** always led to a mixture of **6** and **7** in addition to carbon dioxide. However, as was the case with **2**, reaction of **5** with a tertiary base in carbon tetrachloride gave solely the corresponding dicarbonate **6** (eq 2).

Examination of the decomposition of pure dicarbonate **6** at approximately 170 °C indicated that the monocarbonate

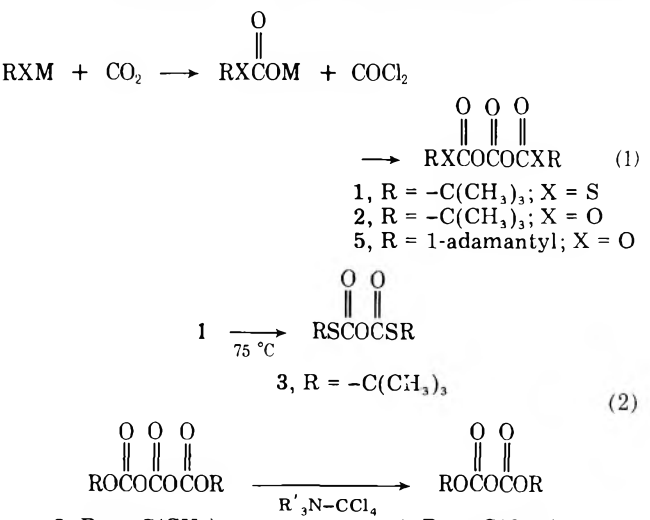

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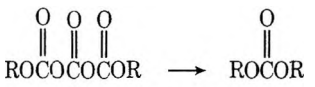
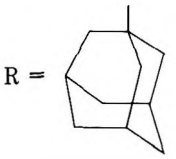
Table I. Kinetics of the Decomposition of 1-Adamantyl Dicarbonate 6 to 1-Adamantyl Monocarbonate 7

Temp,[a] °C	Concn[b]	First order $k \times 10^5$ s^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
135.9 ± 0.2	0.0164	9.16 ± 0.05		
	0.0316	9.62 ± 0.18		
146.1 ± 0.1	0.0214	25.5 ± 0.3	32.2	1.2
	0.0229	63.7 ± 0.3		
156.3 ± 0.1	0.0273	66.6 ± 0.6		
100[c]		0.19		

[a] Corrected temperatures. [b] Molar concentration in benzonitrile. [c] Extrapolated.

7 and carbon dioxide were the only products (eq 3). Therefore, a kinetic study of this decomposition, in which the decrease

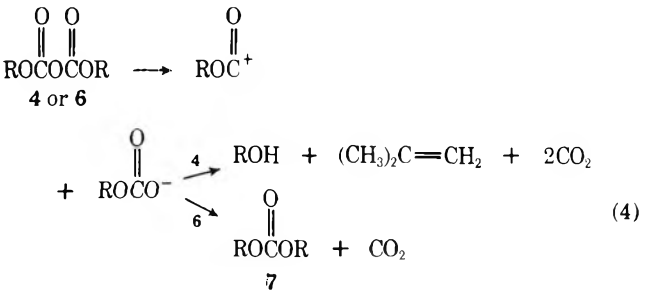




in the carbonyl absorption at 1806 cm^{-1} with benzonitrile as solvent was followed, led to the kinetic results in Table I.

$$6 \xrightarrow{170\ ^{\circ}C} 7 + CO_2 \qquad (3)$$

During this study, we reexamined the original kinetic study on the compounds **1, 2, 3,** and **4** and found that a systematic error had been made in the calculation of the rate constants. Therefore, all rate constants and activation parameters have been recalculated from the original data and the corrected results are presented in Table II. There are some interesting implications which can be drawn from the comparision of the decomposition of the 1-adamantyl dicarbonate **6** with the *tert*-butyl dicarbonate **4.** The very similar activation parameters for the two decompositions support a similar mechanism for decomposition. Since the adamantyl system would not be expected to form a free carbonium ion, decomposition probably occurs by initial scission of an internal carbonyl oxygen bond and subsequent loss of carbon dioxide followed by either recombination or proton abstraction and decarboxylation again (eq 4). Furthermore, the corresponding

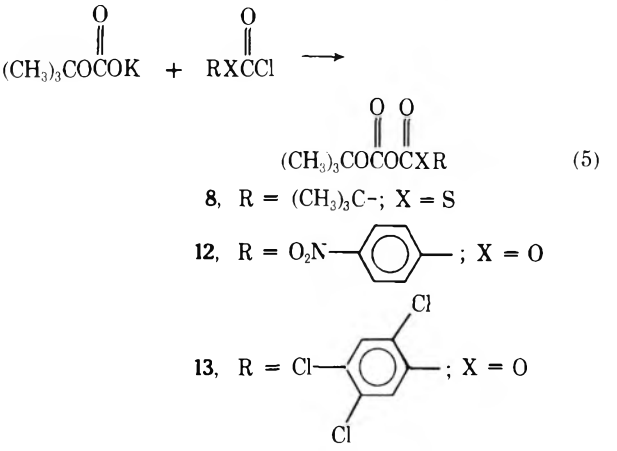


(4)

thiol dicarbonate **3,** the thiol tricarbonate **1,** and the oxygen tricarbonate **2** would appear thus to decompose via a concerted process such as the originally suggested cyclic transition states,[5] on the basis of thier activation parameters.

Attempts to prepare the di- and tricarbonates from 2-adamantanol led to the desired product as evidenced by IR, but analytically pure material could not be obtained. Decomposition of these materials appeared to parallel the corresponding 1-adamantyl system, although quantitative amounts of carbon dioxide were not obtained.

Because of the differences in the mode of decomposition of **3** and **4,** *tert*-butylthiol *tert*-butyl dicarbonate (**8**) was prepared for study following eq 5. It was obtained analytically



(5)

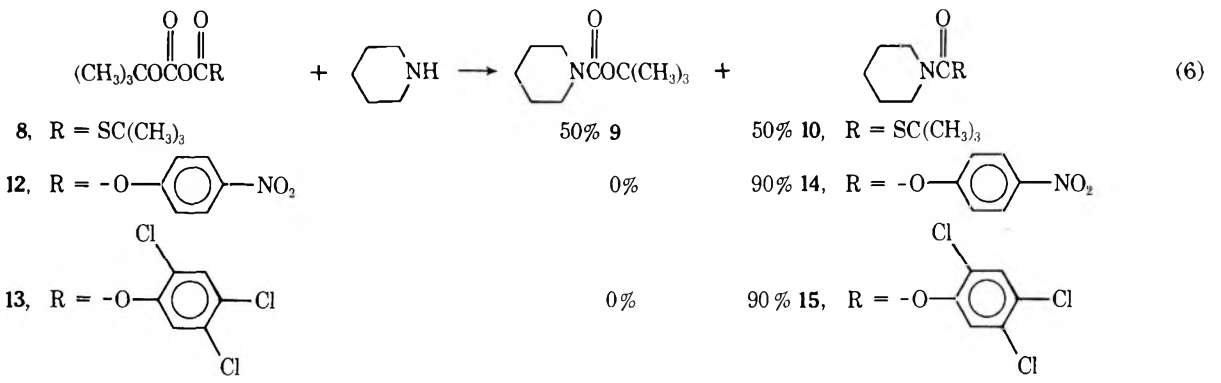
pure and was characterized as having carbonyl absorptions at 1795 and 1730 cm^{-1}.[8,11] Reaction of **8** with piperidine gave an approximately equimolar ratio of carbamate **9** and thiocarbamate **10** (eq 6) as shown by IR.

A crude determination of the decomposition rate of **8** at 162 °C gave a first-order rate constant of 2.0×10^{-4} s^{-1}, a figure which is quite similar to the rate constants for the symmetrical

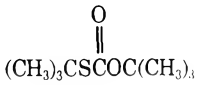
Table II. Corrected Kinetics[3] of the Decomposition of tert-butyl Di- and Tricarbonates[a] (Each Published[3] First-Order Rate Constant Should Be Multiplied by 2.303; Revised Activation Parameters Are Given Below)

	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
A. RSCOCOCSR → RSCOCSR + CO_2		
In decalin	27.1	−5.2 (105.5 °C)[b]
In chlorobenzene	24.2	−7.2 (82.4 °C)[b]
B. ROCOCOCOR → ROH + $(CH_3)_2C{=}CH_2$ + $3CO_2$		
In decalin	27.8	−4.1 (114.4 °C)[a]
C. RSCOCSR → RSCSR + CO_2		
In decalin	28.8	−9.0 (151.8 °C)[b]
D. ROCOCOR → ROH + $(CH_3)_2C{=}CH_2$ + $2CO_2$		
In decalin	33.7	2.5 (149.4 °C)

[a] R = *tert*-butyl. [b] Corrected temperature ±0.1 °C.



dicarbonates **3** and **4** at equivalent temperatures. Four separate measurements of the carbon dioxide evolved during decomposition gave a range of 172 to 130% with an average of 147% of 1 equiv. Observed products from the decomposition included carbon dioxide, *tert*-butyl dithiocarbonate, *tert*-butyl alcohol, isobutene, di-butyl carbonate, and *tert*-butyl mercaptan. During the rate determination, a peak at 1710 cm^{-1} increased in intensity through about half the reaction period and then decreased during the remainder of the reaction. This peak did not correspond to any of the above compounds; therefore we suggest that it is due to *tert*-butylthiol *tert*-butyl carbonate (**11**); further, we demonstrated that this



11

can be obtained as the major product with only minor amounts of other materials when the decomposition was carried out overnight at room temperature with Dabco present. All of this information suggests some decomposition by both an ionic chain process and an intramolecular pathway, with the chain process controlling the final product distribution. A change to a polar solvent led to a rapid increase in the decomposition rate and strongly supports the occurrence of an ionic chain process. We feel that these experiments add support to the earlier suggestion that these tertiary di- and tricarbonates containing sulfur can decompose via an intramolecular route, while the corresponding oxygen systems decompose only by the ionic chain.

As an extension of the above study, *tert*-butyl *p*-nitrophenyl dicarbonate (**12**) and *tert*-butyl 2,4,5-trichlorophenyl dicarbonate (**13**) were prepared as shown in eq 5 and their reactivity with amino compounds was examined. Contrary to the reactivity of **8**, both **12** and **13** reacted with piperidine to yield exclusively the corresponding phenoxycarbamates **14** and **15** (eq 6). Subsequently, dicarbonates **12** and **13** were treated with a series of amino acid esters to give the results shown in Table III. Several points are worthy of note. First, **12** and **13** did not attack primary or phenolic hydroxyl groups, primary thiols, or indole nitrogens and attacked only α-amino nitrogens, except for histidine, where the imidazole imino group reacted along with the α-amino group. All of the derivatives were crystalline compounds except for the serine and proline esters. Also, the reaction was carried out very easily at room temperature under mild conditions except for the alanine ester which was refluxed overnight. Attempts to remove the *N*-*p*-nitrophenoxycarbonyl group from **16** with aqueous sodium carbonate and piperidine led to a quantitative yield of *p*-nitrophenol but no isolable glycine ester. However, Wieland[12] reports the removal of the analogous *m*-nitrophenoxycarbonyl grouping by photolysis in the presence of trifluoroacetic acid.

Although chemically interesting, these new dicarbonates are inferior to **3** and **4** as blocking agents. Investigations toward the production of dicarbonates with greater water solubility such as those from 2-hydroxypyridine and numerous other compounds were undertaken, but we were unable to isolate any new dicarbonates with superior physical properties. A water-soluble dicarbonate would be of considerable usefulness in selective alteration of enzymes or proteins.

Experimental Section

Instrumentation was as previously described;[5,13] analyses were by Galbraith Laboratories.

Di-1-adamantyl Tricarbonate (5). A three-necked 1000-mL flask was fitted with a mechanical stirrer, a calibrated addition funnel, and a glass tube for introducing N_2 or CO_2 under the solution surface. This system was flamed while being flushed with dry N_2. A 50% suspension of NaH in mineral oil (5.3 g, 0.11 mol) was washed with three 25-mL portions of freshly distilled THF to remove the mineral oil. The

Table III. R′OC(O)NHCH(R)COOR″; Prepared from *tert*-Butyl *p*-Nitrophenyl Dicarbonate (12) or *tert*-Butyl 2,4,5-Trichlorophenyl Dicarbonate (13)

Registry no.	Compound	R′	Amino acid	R″	Characterization	Mp,[f] °C	Yield
2185-07-1	16	NPC[a]	Gly	Et	*c,d,e*	95.5–97	87
65815-64-7	17	NPC	L-Ala	Me	*c,d,e*	98–101	78
65815-65-8	18	NPC	L-Ser	Me	*c*	—	65[g]
65815-66-9	19	NPC	D-Try	Et	*c,d,e*	132–133	89
65815-67-0	20	NPC	L-Tyr	Me	*c,d,e*	110–111.5	93
51247-40-6	21	TPC[b]	Gly	Et	*c,d,e*	116–117	86
65815-68-1	22	TPC	L-Ala	Me	*c,d,e*	101–102	86
65815-69-2	23	TPC	D-Try	Et	*c,d,e*	143–144	88
65815-70-5	24	TPC	L-Tyr	Me	*c,d,e*	157.5–158.5	96
65815-71-6	25	TPC	L-Pro	$C_6H_5CH_2$	*c,d*	—	105[g]
65815-72-7	26	TPC	L-CysH	Et	*c,d,e*	90–91	97
65859-22-5	27	TPC	L-His	Me	*c,d,e*	67–70	52

[a] *p*-$NO_2C_6H_4$. [b] 2,4,5-$Cl_3C_6H_2$. [c] Correct IR spectrum. . [d] Correct NMR spectrum. [e] Correct elemental analysis. [f] Recrystallized from chloroform–hexane. [g] Did not purify.

washed NaH was placed in 100 mL of THF and 15.2 g (0.1 mol) of 1-adamantanol in 50 mL of THF, and 150 mL of benzene was added over a 30-min period. The solution was heated under reflux for 2 h. It then was cooled by an ice–salt bath, at −15 to −20 °C, and CO_2 was bubbled into the solution for 1 h. A thick gel resulted. A solution of 8 mL of phosgene in 28 mL of benzene was added dropwise to the resulting gel with vigorous stirring over a period 10–15 min. The cooled solution was stirred for 1 h and N_2 was bubbled through the cooled solution for an additional hour.

A yellow solid remained after solvent was removed at or below 0 °C. The solid was washed with pentane to give a white solid. Evaporation of the filtrate yielded additional white solid. The combined total was 16.0 g (80%) of di-1-adamantyl tricarbonate, which decomposed on melting at 109–110 °C with gas evolution. Recrystallization from a small amount of CCl_4 and large amount of pentane did not change the melting point. The IR spectrum (CCl_4) showed carbonyl bands at 1840, 1800, and 1775 cm^{-1} and the NMR spectrum (CCl_4) showed two broad peaks at 1.72 and 2.20 ppm.

Anal. Calcd for $C_{23}H_{30}O_7$: C, 66.01; H, 7.23. Found: C, 66.28; H, 7.24.

Di-1-adamantyl Dicarbonate (6) from the Tricarbonate and Dabco. A solution of 1.27 g of di-1-adamantyl tricarbonate in 8 mL of CCl_4 was placed in a 25-mL flask fitted with a magnetic stirrer and 0.004 g of freshly sublimed Dabco was added. Rapid evolution of carbon dioxide began at once. The reaction mixture was stirred at room temperature for 45 min to complete the loss of CO_2 and then 4 mL of water, containing sufficient citric acid to make the aqueous layer slightly acidic, was added. The layers were separated, the organic layer was dried, and the solvent was removed at room temperature with a rotary evaporator. Recrystallization from a small amount of chloroform and a large amount of pentane solution gave 0.82 g (74%) of white solid of dicarbonate, mp 120–121.5 °C. The IR spectrum ($CHCl_3$) showed carbonyl absorptions at 1806 and 1755 cm^{-1} and the NMR spectrum ($CDCl_3$) showed two broad peaks at 1.65 and 2.16 ppm.

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.07. Found: C, 70.36; H, 7.95.

Similar results were obtained with triethylamine as catalyst instead of Dabco.

Thermal Decomposition of Di-1-adamantyl Tricarbonate. a. In the Absence of Solvent. The apparatus consisted of a two-necked flask equipped with a condenser attached to the top of which were a $CaSO_4$ drying trap and a U tube, containing ascarite, connected in series. Di-1-adamantyl tricarbonate (0.525 g) was placed in the flask and a stream of pure dry nitrogen passed through the apparatus slowly via the side arm. (The nitrogen was passed through a concentrated sulfuric acid trap and tubes of ascarite prior to entry into the apparatus.) Then the decomposition flask was immersed in an oil bath and heated at approximately 112–114 °C. The passage of nitrogen was continued until the weight of ascarite in the U tube, which was attached to the top of the condenser, remained constant (1.5 h). The weight of carbon dioxide evolved was 0.0842 g (76% of 2 molecules). Raising the oil bath temperature to 150 °C and continuing to pass the nitrogen for another 2 h, the weight of carbon dioxide evolved totally was 0.1151 g (104% of 2 mol).

b. In Solvent. In an attempt to limit the reaction to the formation of dicarbonate only, a number of runs were made using various solvents (carbon tetrachloride, chlorobenzene, toluene, dioxane, and methylcyclohexane) at their boiling points. In all cases, the tricarbonate, **5**, decomposed to a mixture of dicarbonate, **6**, and monocarbonate, **7**, in various ratios. This mixture was separated by high-pressure liquid chromatography and was compared to the IR spectra of pure di- and monocarbonate.

Kinetic Studies on Di-1-adamatyl Dicarbonate. Commercially available benzonitrile was dried with $CaCl_2$ and distilled from P_2O_5 in an all-glass apparatus. The middle portion of 96 °C (40 mm) of the distillate was collected, n^{25}_D 1.5258 (lit.[14] n^{20}_D 1.5282).

The kinetic runs were carried out essentially as described previously.[5,13]

tert-Butyl tert-Butylthiol Dicarbonate (8). The following is a modification of the procedure of Degering.[15] For 30 min dry carbon dioxide was passed into an ice bath cooled three-necked round-bottomed flasked equipped with a mechanical stirrer charged with potassium *tert*-butoxide (4.5 g, 0.04 mol) in 100 mL of dry THF. A solution of *tert*-butylthiol chlorocarbonate (6.1 g, 0.04 mol) in 30 mL of dry THF was then added dropwise with vigorous stirring over a 30-min period and the resulting mixture was refluxed for 3 h. The solution was filtered through a medium-fritted filter and the volume was reduced in vacuo to yield 5.85 g of a material which appeared to be a mixture of at least three components on the basis of its IR spectrum. Distillation under reduced pressure led to three different fractions: the first mainly *tert*-butylthiol chlorocarbonate, bp 45 °C (12 mm); the second a mixture of di-*tert*-butyldithiol carbonate and the title compound, 55–75 °C (1 mm); and the third a fraction of 2.4 g (26%), bp 76–78 °C (1 mm), whose IR spectrum was consistent with the title compound. The NMR spectrum[16] showed a broad singlet at 1.54 ppm in carbon tetrachloride and the neat IR spectrum showed a carbonyl doublet at 1795 (s) and 1730 cm^{-1} (m). A correct elemental analysis was obtained.

Decomposition of *tert*-Butyl *tert*-Butylthiol Dicarbonate (8). These studies were carried out in the same manner which has been described previously.[5,13]

Representative Studies Utilizing *tert*-Butyl *p*-Nitrophenyl Dicarbonate (12) and *tert*-Butyl 2,4,5-Trichlorophenyl Dicarbonate (13). The following are representative of each of the reactions utilizing **12** and **13**.

1. *p*-Nitrophenyl Chloroformate. A stirred solution of 40 g (0.4 mol, ~32 mL) of phosgene in 200 mL of benzene at −10 °C was treated with 48.0 g (0.345 mol) of *p*-nitrophenol, followed by 42 g (0.348 mol) of *N,N*-dimethylaniline at such a rate that the reaction temperature was maintained at 5–10 °C during the addition. The mixture was stirred at room temperature overnight, then was poured into 40 g of ice, and the suspension was filtered. The organic layer in the filtrate was separated, washed with 10% brine (30 mL), 2 N HCl (30 mL), and 10% brine (3 × 30 mL), and dried with $MgSO_4$. The benzene solution was evaporated and yielded 59 g of *p*-nitrophenol chloroformate. The crude product was washed with hexane to give 56 g (80%) of white solid, mp 78.5–80 °C (lit.[17] 81–82 °C). The IR spectrum (CCl_4) showed carbonyl band at 1790 cm^{-1}.

2. *tert*-Butyl *p*-Nitrophenyl Dicarbonate (12). Potassium *tert*-butoxide (9.0 g, 0.08 mol) was dissolved in 140 mL of freshly distilled THF at room temperature in a three-necked 500-mL flask which had been flamed and flushed with dry nitrogen. Dry carbon dioxide was passed through the solution, which was cooled with an ice–salt bath (−15 to about −20 °C), with vigorous stirring for 30 min. A solution of 16.1 g (0.08 mol) of *p*-nitrophenyl chloroformate in 80 mL of THF was added dropwise over a 15-min period. The reaction mixture was stirred at 0 °C for 2 h and then raised to 5–10 °C for another hour. The precipitate was removed by suction filtration through a fritted-glass filter funnel of medium porosity, which had previously been cooled with ice-cold pentane. The precipitate was washed thoroughly with ice-cold pentane and the solution was completely evaporated at a temperature below 0 °C in a rotary evaporator under reduced pressure by a rotary pump to give a white crude product. This product was dissolved in CCl_4 and then filtered. A white solid of 2.6 g of di-(*p*-nitrophenyl) carbonate was isolated, showing a carbonyl band at 1780 cm^{-} ($CHCl_3$).

The filtrate was evaporated at or below 0 °C by a vacuum pump, washed with pentane, and 14.4 g (64%) of *tert*-butyl *p*-nitrophenyl dicarbonate was obtained. The dicarbonate decomposed on melting at 69.5–70.5 °C with gas evolution. The IR spectrum ($CHCl_3$) showed carbonyl bands at 1835 and 1780 cm^{-1}, and the NMR spectrum (CCl_4) showed peaks at 1.6 (s, 9 H), 7.6 (d, 2 H), and 8.5 (d, 2 H) ppm.

Anal. Calcd for $C_{12}H_{13}NO_7$: C, 50.88; H, 4.59. Found: c, 51.07; H, 4.44.

***N*-(*p*-Nitrophenoxycarbonyl)piperidine (14).** To a solution of 1.13 g (0.004 mol) of *tert*-butyl *p*-nitrophenyl dicarbonate in 3 mL of THF was added dropwise a solution of 0.68 g (0.008 mol) of piperidine in 4 mL of THF, with stirring at 0 °C. The reaction mixture was stirred at room temperature overnight. The solvent was evaporated at a reduced pressure, and the residue was washed with pentane and was recrystallized from chloroform–pentane giving 0.90 g (90%) of yellowish crystals of *N*-(*p*-nitrophenoxycarbonyl)piperidine, mp 91.5–93 °C. The IR spectrum ($CHCl_3$) contained a band at 1720 cm^{-1}. The NMR spectrum ($CDCl_3$) in ppm: 1.70 (broad s, 6 H); 3.75 (broad m, 4 H); 7.60 (d, 2 H); 8.55 (d, 2 H).

Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.60; H, 5.60. Found: C, 57.59; H, 5.69.

***N*-(*p*-Nitrophenoxycarbonyl)glycine Ethyl Ester.** Glycine ethyl ester hydrochloride (1.40 g) was suspended in 20 mL of $CHCl_3$, and 0.84 g of $NaHCO_3$ in 20 mL of H_2O was added. Sodium chloride (2 g) was added, and then 2.83 g of *tert*-butyl *p*-nitrophenyl dicarbonate dissolved in a few milliliters of $CHCl_3$; the mixture was stirred at room temperature overnight. The two layers were separated, and the aqueous layer was extracted with $CHCl_3$; the $CHCl_3$ solution was dried, filtered, and evaporated at room temperature. The milk-white solid was recrystallized from $CHCl_3$–hexane to give 2.3 g (87%) of white crystals of *N*-(*p*-nitrophenoxycarbonyl)glycine ethyl ester, mp 95.5–97 °C.

The IR spectrum (CCl_4) showed -NH stretch at 3440 cm^{-1} and

carbonyl bands at 1740 and 1760 cm^{-1}. The NMR spectrum ($CDCl_3$) in ppm: 1.33 (t, 3 H); 4.10 (d, 2 H); 4.30 (q, 2 H); 5.73 (broad, 1 H); 7.38 (d, 2 H); 8.30 (d, 2 H).

Anal. Calcd for $C_{11}H_{12}N_2O_6$: C, 49.25; H, 4.48, Found: C, 49.05; H, 4.54.

***tert*-Butyl 2,4,5-Trichlorophenyl Dicarbonate (13).** A suspension of 18.3 g (0.15 mol) of potassium *tert*-butoxide in 200 mL of THF was cooled with ice–salt. Carbon dioxide was passed into the suspension with vigorous stirring for 30 min. A solution of 39.0 g (0.15 mol) of 2,4,5-trichlorophenyl chloroformate in 120 mL of THF was added dropwise. The reaction mixture was stirred at 0 °C for 2 h and 5–10 °C for another 1–5 h. Insoluble materials were removed, and the filtrate was evaporated at reduced pressure. The crude product was recrystallized from 400 mL of pentane and then from 280 mL of pentane to give 21.1 g (41%) of *tert*-butyl 2,4,5-trichlorophenyl dicarbonate, mp 65.5–66.5 °C.

The IR spectrum (CCl_4) showed carbonyl bands at 1835 and 1770 cm^{-1}, and the NMR spectrum (CCl_4) showed peaks at 1.62 (s, 9), 7.66 (s, 1 H), and 7.81 (s, 1 H) ppm.

Anal. Calcd for $C_{12}H_{11}Cl_3O_5$: C, 42.17; H, 3.22. Found: C, 42.21; H, 3.28.

Registry No.—**1**, 22085-39-8; **2**, 24424-95-1; **3**, 22085-40-1; **4**, 24424-99-5; **5**, 65815-73-8; **6**, 65815-74-9; **7**, 65815-75-0; **12**, 60416-11-7; **13**, 60450-67-1; **14**, 65815-76-1; glycine ethyl ester HCl, 623-33-6; 1-adamantanol, 768-95-6; *tert*-butylthiol chlorocarbonate, 13889-95-7; di-*tert*-butyldithiol carbonate, 16118-32-4; *p*-nitrophenyl chloroformate, 7693-46-1; *p*-nitrophenol, 100-02-7; di-*p*-nitrophenyl carbonate, 5070-13-3; 2,4,5-trichlorophenyl chloroformate, 4511-19-7.

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Influence of the Steric Requirements of the Nucleophile on the Transition State Structure of E2 Reactions. A Kinetic Study of the Eliminations from 1-Bromo-2-arylethanes and 1-Chloro-1-phenyl-2-arylethanes Promoted by Sodium 2,6-Di-*tert*-Butylphenoxide

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The kinetics of the eliminations from 1-bromo-2-arylethanes and 1-chloro-1-phenyl-2-arylethanes promoted by sodium 2,6-di-*tert*-butylphenoxide in DMF–Me_2SO (9:1 v/v) have been investigated. With the first series of substrates values of ρ (+2.44), k_H/k_D (9.0), and Br/Cl leaving-group effect (146) have been evaluated which turn out to be quite similar to those (+2.64, 7.6, and 120, respectively) calculated for the corresponding reactions promoted by sodium phenoxide. The reaction of 1-chloro-2-arylethanes with sodium 2,6-di-*tert*-butyl phenoxide also exhibits a ρ value (+2.30) which is very similar to that (+ 2.40) of the same reaction with sodium phenoxide. From these results it is possible to conclude that with both series, the transition state structure of the E2 reaction is substantially unaffected by the steric requirements of the nucleophile. The influence of steric effects on the elimination rate is also not very large, sodium 2,6-di-*tert*-butylphenoxide being only 200-fold less reactive than sodium phenoxide.

The study of elimination reactions promoted by sodium phenoxides in a dipolar aprotic solvent provides a very useful tool for investigating the effect of the nature of the nucleophile on the mechanism of E2 reactions. Accordingly, unequivocal information on the effect of the nucleophile basicity upon the transition state structure of E2 reactions has been recently obtained by the study of eliminations from 2-arylethyl derivatives[1-3] induced by phenoxides of different basicity in DMF.

A continuation of this investigation with the purpose of acquiring information also on the effects of the steric requirements of the nucleophile appears worthwhile since it is recognized that these effects can be of importance in determining geometrical and positional orientation of E2 reactions.[4-9] Moreover it has been recently suggested[10] that the steric requirements of the base might play a significant role in producing the "anti-Thornton" behaviors observed in several reactions involving slow proton transfer.[11]

In this paper we report the results of a kinetic study of the eliminations from 1-bromo-2-arylethanes, 1-chloro-1-phenyl-2-arylethanes, and 1-chloro-2-phenylethane promoted by sodium 2,6-di-*tert*-butylphenoxide in DMF–Me_2SO mixed solvent. 2,6-Di-*tert*-butylphenoxide is a sterically very hindered base that has been found to produce a positional orientation much different from that anticipated by its basic strength in the reaction with 2-iodobutane.[6] In the case of

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Table I. Effect of the Base Concentration on the Rate Constants for the Elimination Reactions of 1-Chloro-1,2-diphenylethane Induced by Sodium 2,6-Di-*tert*-butylphenoxide in DMF–Me_2SO (9:1 v/v) at 30 °C

[Nucleophile], M	k_2, M^{-1} s^{-1}
0.023	6.22×10^{-3}
0.032	5.86×10^{-4}
0.045	5.06×10^{-4}
0.065	4.40×10^{-4}
0.055	5.81×10^{-5} [a]
0.065	7.55×10^{-4} [b]

[a] In the presence of $NaClO_4$ (0.85 M). [b] In the presence of 18-crown-6 ether (0.082 M).

1-chloro-1-phenyl-2-arylethanes and 1-chloro-2-phenylethane also the reactions with sodium phenoxide have been investigated.

Results

Sodium 2,6-di-*tert*-butylphenoxide has been prepared by the reaction of NaH with an excess (about 20%) of 2,6-di-*tert*-butylphenol in Me_2SO and its concentration was determined by acidimetric titration. In the kinetic runs a Me_2SO solution of sodium 2,6-di-*tert*-butylphenoxide has been mixed with a DMF solution of the substrate in order to obtain a DMF–Me_2SO (9:1 v/v) final mixture. The kinetic data obtained in this mixed solvent should be comparable with those previously obtained in pure DMF for the reaction of 1-bromo-2-arylethanes with sodium phenoxide.[1,2] Of course, the DMF–Me_2SO mixed solvent was used also for the reactions of sodium phenoxide with 1-chloro-1-phenyl-2-arylethanes and 1-chloro-2-phenylethane studied in the present work.

In the reactions of 1-bromo-2,2-dideuterio-2-phenylethane and 1-chloro-1,2-diphenylethane with sodium 2,6-di-*tert*-butylphenoxide the yield of olefin (styrene and *trans*-stilbene, respectively) was practically quantitative. Moreover, a quantitative yield of *p*-methyl-*trans*-stilbene was obtained in the reaction of 1-chloro-1-phenyl-2-*p*-tolylethane with sodium phenoxide. It is therefore fully justified to assume a quantitative yield of olefin also in the other reactions investigated.

Kinetics have been followed by potentiometric titration of the halide ions formed during the reaction. In all cases an excess of base (at least tenfold) was used.

When the base was sodium phenoxide the kinetic complications due to the not complete dissociation of this salt were overcome by carrying out the reaction in the presence of $NaClO_4$ (0,85 M).[2] In these conditions regular first-order kinetics were obtained and the second-order rate constant (k_2) does not change when the base concentration is changed. Ion pairing, however to a much smaller extent, is present also with sodium 2,6-di-*tert*-butylphenoxide. In the reactions promoted by this base the first-order plots exhibited an excellent linearity but a slight decrease of k_2 values with increasing the base concentration was observed. Moreoever the rate of elimination increases in the presence of a crown ether and decreases in the presence of $NaClO_4$. Some representative data for the reaction of 1-chloro-1,2-diphenylethane are reported in Table I. Thus, the structural effects in the reactions with sodium 2,6-di-*tert*-butylphenoxide were evaluated by comparing kinetic data obtained at the same base concentration.

The kinetic results for all reactions investigated are collected in Tables II and III.

Discussion

Since sodium phenoxide and sodium 2,6-di-*tert*-butylphenoxide are associated to a different extent, an approximate estimate of their reactivity ratio is only possible by comparing the kinetic data obtained, with 1-chloro-1,2-diphenylethane as the substrate, in the presence of 18-crown-6 ether which should convert most of the ion pairs into dissociated ions. From this comparison (Tables I and III) it turns out that sodium 2,6-di-*tert*-butylphenoxide is about 200-fold less reactive than sodium phenoxide. This is a quite significant factor but not very large. Clearly the rate of an E2 reaction appears to be much more sensitive to changes in the basicity of the nucleophile[12] than to changes in its steric requirements.

Another observation is that in going from 1-chloro-2-phenylethane to 1-chloro-1,2-diphenylethane the rate increases threefold with sodium phenoxide but only 1.2-fold with sodium 2,6-di-*tert*-butylphenoxide (see Tables II and III). Probably with the more hindered nucleophile the favorable electronic effect of the α-phenyl group is nearly completely counterbalanced by an adverse steric effect.

The data of Table II allow the calculation of the values of the Hammett reaction constant, ρ, the deuterium kinetic isotope effect (k_H/k_D), and the bromide/chloride leaving group effect (k_{Br}/k_{Cl}) for the reactions of 1-bromo-2-arylethanes with sodium 2,6-di-*tert*-butylphenoxide. These values are reported in Table IV and compared with the corresponding ones for the reaction with sodium phenoxide. We immediately see that the two reactions exhibit very similar

Table II. Rate Constants for the Elimination Reactions of 1-Bromo-2-arylethanes and 1-Chloro-2-phenylethane Induced by Sodium Phenoxide and Sodium 2,6-Di-*tert*-butylphenoxide in DMF–Me_2SO (9:1 v/v)

Nucleophile	Registry no.	Substrate	Registry no.	Temp, °C	k_2, M^{-1} s^{-1} [a]
Sodium phenoxide[b]	139-02-6	$C_6H_5CH_2CH_2Br$	103-63-9	30	4.29×10^{-2}
		$C_6H_5CH_2CH_2Cl$	622-24-2	30	3.58×10^{-4}
Sodium 2,6- di-*tert*-butylphenoxide[c]	7175-96-4	$C_6H_5CH_2CH_2Br$		0	5.98×10^{-3}
		$C_6H_5CD_2CH_2Br$	23088-37-1	0	5.67×10^{-4}
		p-$CH_3C_6H_4CH_2CH_2Br$	6529-51-7	0	3.25×10^{-3}
		p-$OCH_3C_6H_4CH_2CH_2Br$	14425-64-0	0	1.84×10^{-3}
		p-$BrC_6H_4CH_2CH_2Br$	1746-28-7	0	3.28×10^{-2}
		$C_6H_5CH_2CH_2Br$		10	1.36×10^{-2}
		$C_6H_5CD_2CH_2Br$		10	1.31×10^{-3}
		$C_6H_5CH_2CH_2Br$		20	3.49×10^{-2}
		$C_6H_5CD_2CH_2Br$		20	3.87×10^{-3}
		$C_6H_5CH_2CH_2Br$		30	7.31×10^{-2}
		$C_6H_5CD_2CH_2Br$		30	8.78×10^{-3}
		$C_6H_5CH_2CH_2Cl$		30	4.99×10^{-4}

[a] Average of at least two determinations. The average error is ±4%. [b] In the presence of $NaClO_4$ (0.85 M). [c] The base concentration was ca. 0.024 M.

Table III. Kinetic Data for the Elimination Reactions of 1-Chloro-1-phenyl-2-arylethanes with Sodium Phenoxide and Sodium 2,6-Di-*tert*-butylphenoxide in DMF–Me_2SO (9:1 v/v) at 30 °C

Nucleophile	Substrate[a]	Registry no.	k_2, M^{-1} s^{-1}[b]
Sodium phenoxide[c]	H	4714-14-1	1.08×10^{-3}
	H		1.56×10^{-1}[d]
	p-CH_3	4714-15-2	6.04×10^{-4}
	p-Cl	4714-17-4	5.05×10^{-3}
	p-NO_2	4781-42-4	1.52
Sodium 2,6-di-*tert*-butylphenoxide[e]	H		5.86×10^{-4}
	p-CH_3		4.30×10^{-4}
	p-Cl		2.65×10^{-3}
	p-NO_2		6.64×10^{-1}

[a] H refers to 1-chloro-1,2-diphenylethane. [b] Average of at least two determinations. The average error is ±2%. [c] In the presence of $NaClO_4$ (0.85 M). The base concentration was in the range 0.03–0.1 M. [d] In the presence of 18-crown-6 ether (0.081 M). [e] The base concentration was 0.03 M for p-H, p-CH_3, and p-Cl derivatives. For the p-NO_2 derivative the concentration was 0.015 M.

Table IV. Isotope Effects, Hammett Parameters, and Leaving Group Effects for Elimination Reactions of 1-Bromo-2-arylethanes with Sodium Phenoxide and Sodium 2,6-Di-*tert*-butylphenoxide in DMF–Me_2SO (9:1 v/v)

Nucleophile	Temp, °C	k_H/k_D[a]	ρ	k_{Br}/k_{Cl}[b]
Sodium phenoxide	0		+2.64[c,d]	
	21	7.6		
	30			120
Sodium 2,6-di-*tert*-butylphenoxide	0	10.5	+2.44[e]	
	10	10.4		
	20	9.0		
	30	8.3		146

[a] The probable error is ±8%. [b] Reactivity ratio between 2-phenylethyl bromide and 2-phenylethyl chloride. [c] Reference 2. The solvent in this case was DMF. [d] $r = 0.996$; $S = 0.059$. [e] $r = 0.989$; $S = 0.096$.

values of ρ and k_{Br}/k_{Cl}, which suggests that the structures of the transition state of the two eliminations closely resemble each other with respect to the carbanion character and the extent of carbon–leaving group bond breaking. At most a very small decrease of the carbanion character of the transition state for the reaction with sodium 2,6-di-*tert*-butylphenoxide could be suggested.

The k_H/k_D value is slightly larger in the reaction with sodium 2,6-di-*tert*-butylphenoxide than in that with sodium phenoxide. However, in the light of the very similar values of ρ and k_{Br}/k_{Cl} it seems unlikely that the transition states of the two reactions have a significantly different degree of C–H bond breaking. We feel that a larger tunneling contribution in the reaction with the more hindered base could be a more reasonable suggestion even though a study of the temperature dependence (between 0 and 30 °C) of k_H and k_D (Table II) was inconclusive in this respect, since the A_H/A_D value (1.20) turned out to be affected by too large an error (±3.76).

From the data of Table III values of +2.40 ($r = 0.999$, $S = 0.082$) and +2.30 ($r = 0.997$, $S = 0.128$) are calculated for the reactions of 1-chloro-1-phenyl-2-arylethanes with sodium phenoxide and sodium 2,6-di-*tert*-butylphenoxide, respectively. The similarity in the ρ values suggests that also in this system the two eliminations are characterized by transition states having a similar degree of carbanion character.

Thus the present work allows the conclusion that in spite of the effect on the reaction rate and on the positional and geometrical orientation, the steric requirements of the nucleophile do not significantly influence the transition state structure of the elimination reactions of β-phenyl activated alkyl halides. It seems therefore very unlikely that the repulsive interaction between the base and the substrate may play a significant role in determining the appearance of "anti-Thornton" patterns in E2 reactions.

Finally, the similar behavior of eliminations from 1-bromo-2-arylethanes and 1-chloro-1-phenyl-2-arylethanes with respect to changes in the steric requirements of the nucleophile is noteworthy since, in contrast, these two reaction series have been found to respond in a much different way when the nucleophile was changed from associated *t*-BuOK to crown ether complexed *t*-BuOK.[13] In the light of the present results this phenomenon cannot be due to a different response of the two series to the large difference in the steric requirements of complexed and uncomplexed *t*-BuOK.[7]

Experimental Section

Materials. 1-Bromo-2-phenylethane and 1-chloro-2-phenylethane were redistilled commercial samples (Fluka).

1-Bromo-2,2-dideuterio-2-phenylethane was prepared as described by Saunders and Edison;[14] the mass spectrum showed that the sample contained 1.92 atoms of D/molecule.

1-Bromo-2-arylethanes and 1-chloro-1-phenyl-2-arylethanes were available from previous studies.[13]

$NaClO_4$ (anhydrous, BDH) was used without further purification.

2,6-Di-*tert*-Butylphenol (Fluka) was recrystallized from *n*-hexane at −20 °C, mp 37–37.5 °C.

18-Crown-6 ether (Fluka) was purified by recrystallization from *n*-hexane, mp 38.5–39.5 °C.

Sodium phenoxide was prepared by treating phenol (C. Erba, RPE) with an equimolecular amount of NaOH in water. Water was removed at reduced pressure and the residue was recrystallized twice from dry acetone. Before use, sodium phenoxide was kept at 100 °C (0.1 mmHg) for 4 hr.

Base–Solvent Solutions. The solution of sodium 2,6-di-*tert*-butylphenoxide in Me_2SO was prepared as described by Bartsch, Weigers, and Guritz.[15] A portion of this solution (10 mL) was poured into a 100-mL volumetric flask and diluted to the calibration mark with DMF (C. Erba, RPE). The final concentration of sodium 2,6-di-*tert*-butylphenoxide was determined by titration with H_2SO_4 (0.01 N). Sodium phenoxide and $NaClO_4$ were weighed into a 100-mL volumetric flask. Me_2SO (10 mL) was added and the solution was diluted to the calibration mark with DMF.

Kinetic Study. The formation of bromide and chloride ions was followed by potentiometric analysis with $AgNO_3$. In the case of the very reactive 1-chloro-1-phenyl-2-*p*-nitrophenylethane the elimination was followed by a batchwise procedure.

Olefin Analysis. The yields of styrene in the reaction of 1-bromo-2-phenylethane with sodium 2,6-di-*tert*-butylphenoxide and of *trans*-stilbene in the reaction of 1-chloro-1,2-diphenylethane with the same base were determined by GPC analysis using a 20% LAC 728 (3 m) column in the former case and a 10% SE 30 (1 m) column in the second. The internal standards were isopropylbenzene and biphenyl, respectively.

The yield of *p*-methyl-*trans*-stilbene in the reaction of 1-chloro-1-phenyl-2-*p*-tolylethane with sodium phenoxide was determined spectrophotometrically. The olefin was extracted with *n*-heptane from the reaction mixture and the optical density of the *n*-heptane solution (after dilution to 25 mL) was determined at 297.5 nm.[16]

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Kinetics of the Baeyer–Villiger Reaction of Acetophenones with Permonophosphoric Acid[1]

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The Baeyer–Villiger reaction of acetophenones with permonophosphoric acid (H_3PO_5) has been studied kinetically in acetonitrile at 30 °C. The sole product, the corresponding aryl acetate, which is a product via aryl migration, is obtained almost quantitatively. The yields are much higher than those obtained by means of the other peroxycarboxylic acid oxidations. The rate equation is $v = k_2$[acetophenones][H_3PO_5]. The reaction is catalyzed by H_2SO_4, the rate being correlated with the acidity function (H_0). The rate-determining step is a migration step under these conditions. The apparent rate for ring-substituted acetophenones affords a Hammett ρ value of −2.55 (σ). The migration step seems to be a concerted process.

The preparation of permonophosphoric acid was discovered by Schmidlin and Massini in 1910.[2] Since then various techniques for its preparation,[3,4] decomposition mechanisms,[5] and dissociation constants[6,7] have been reported, but only a few reports have appeared on the oxidation of organic compounds, which were confined to oxidations of aromatic amines.[8] Recently, we have reported[9] on the oxidation of phenol, anisole, and toluene with permonophosphoric acid in acetonitrile; the oxidation rates for phenol and anisole (ArH) were expressed as $v = k$[ArH][H_3PO_5]$^2h_0$, where h_0 is Hammett's acidity function.

In the present paper, our study on the oxidations of organic compounds with H_3PO_5 was extended to the Baeyer–Villiger (B–V) reaction, in which we chose acetophenone and ring-substituted acetophenones as substrates. Ordinary B–V reactions using peroxycarboxylic acids were well studied,[10–12] where the rate equation is expressed as $v = k$[ketone][peracid]. The reaction is acid-catalyzed.[12,13] The rate-determining step may be either addition of peracid to carbonyl or migration from the adduct, depending on the substrate.[14]

This report summarizes our kinetic data on the B–V reaction of acetophenones with H_3PO_5. It was found that H_3PO_5 is a strong and excellent reagent for the B–V reaction, the rate being determined by a concerted migration which is catalyzed by strong acid.

Results and Discussion

The reaction of 0.2 molar equiv of acetophenones with H_3PO_5 was conducted in MeCN at 30 °C. The corresponding aryl acetates were obtained, and the yields were as follows: *p*-MeO, 70%; *p*-Me, 98%; H, 91%; *p*-Cl, 95%. But the corresponding methyl benzoates were not detected. Therefore, only the aryl group migrates, giving aryl acetate in agreement with the migratory apptitude observed with other peracid reactions.[10] No reaction occurred with *p*-nitroacetophenone, which has a strong electron-withdrawing group.

$$p\text{-}XC_6H_4\overset{O}{\overset{\|}{C}}Me + H_3PO_5 \xrightarrow[\text{in MeCN}]{30\ ^\circ C} pX\text{-}C_6H_4O\overset{O}{\overset{\|}{C}}Me + H_3PO_4 \quad (1)$$

The rates for the H_2SO_4-catalyzed B–V reaction satisfied the second-order kinetics as shown in eq 2. But in the absence

$$v = k_2[C_6H_5COMe][H_3PO_5] \quad (2)$$

of H_2SO_4, the integral rate order was not observed because of the variation of the acidity of the system with the change of initial concentration of H_3PO_5, which is a fairly strong acid ($K_{1a} = 8 \times 10^{-2}$, $K_{2a} = 3 \times 10^{-6}$, and $K_{3a} = 2 \times 10^{-13}$ at 25 °C)[7] comparable to phosphoric acid.

A comparison of yields and rate constants with those by some other percarboxylic acids is shown in Table I. It is evident that H_3PO_5 is superior to peracetic acid and perbenzoic acid in yield and reaction rate.

Effect of Acidity. The correlation between rate constant k_2 and acidity constant H_0 of the solution was measured for the H_2SO_4-catalyzed reaction of acetophenone. A plot of log k_2 vs. $-H_0$ gave a straight line with a slope of 0.75 as shown

Table I. Comparison of the B–V Reactions of Acetophenone

Peracid	Yield, %	Rate constant
H_3PO_5[a]	91	2.9×10^{-3} M^{-1} s^{-1}
$PhCO_3H$	63[b]	1.47×10^{-5} M^{-1} s^{-1}[c]
CH_3CO_3H	33[d]	
CF_3CO_3H[e]	Quantitative	2.7×10^{-2} M^{-2} s^{-1}[f]

[a] In MeCN at 30 °C; $H_0 = -0.64$. [b] In $CHCl_3$ at 23–26 °C: S. L. Friess, *J. Am. Chem. Soc.*, **71**, 14 (1949). [c] In MeCN at 25 °C: S. L. Friess and N. Farnham, *J. Am. Chem. Soc.*, **72**, 5518 (1950). [d] In MeCN at 25 °C: W. von E. Doering and L. Speers, *J. Am. Chem. Soc.*, **72**, 5515 (1950). [e] In $ClCH_2CH_2Cl$ at 29.8 °C: M. F. Hawthorne and W. D. Emmons, *J. Am. Chem. Soc.*, **80**, 6398 (1958). [f] $v = k$[CF_3CO_3H][CF_3CO_2H][R_1R_2CO].

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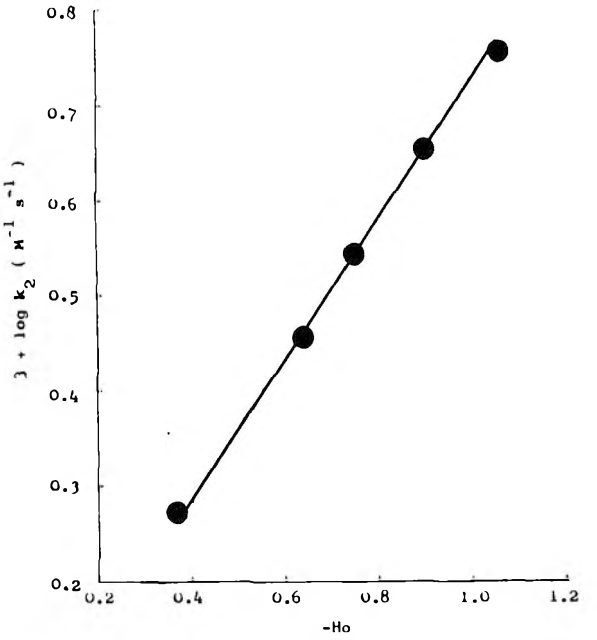
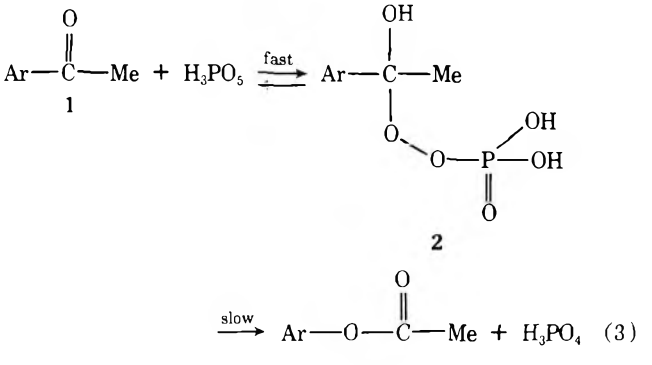


Figure 1. Effect of acidity on the second-order rate constant (k_2) in MeCN at 30 °C.

in Figure 1. This relation suggests that a proton participates in the transition state.

Substituent Effect. The effect of a ring substituent on the second-order rate constant (k_2) in rate equation $v = k_2[p\text{-}X\text{-}C_6H_4COMe][H_3PO_5]$ was studied at a constant acidity function ($H_0 = -0.64$) in MeCN at 30 °C. The rate data are listed in Table II. A Hammett plot of log k_2 vs. σ was linear with $\rho = -2.55$ and correlation coefficient = 0.991. This ρ value has the same sign as that for the trifluoroperacetic acid reactions ($\rho = -1.45$ with σ).[13] If the addition of peracid anion was rate determining, a positive ρ value would be expected, but this is not the case. Hence, the migration step seems to be rate determining.



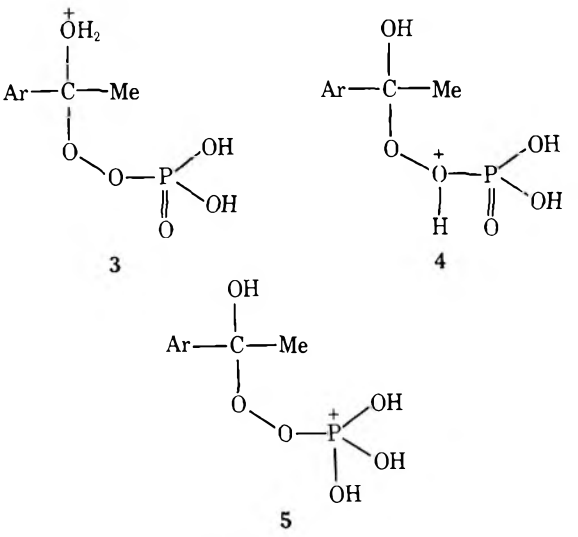
It is generally accepted[15] that a straight line plot of log k vs. $-H_0$ with a slope over 0.8 suggests unimolecular acid catalysis (A1), while a line with a slope below 0.8 suggests bimolecular acid catalysis (A2). Further, the deviation of slope from unity is often observed on account of steric and solvent effects. In our case, the linear relation of log k_2 vs. $-H_0$ with a slope of 0.75 indicates undoubtedly the participation of a proton in the transition state. Three protonated states for the adducts of permonophosphoric acid, **3–5**, are conceivable.

A pathway via **3** necessitates for product formation the separation of oppositely charged species (phosphoric acid anion), which should be a difficult process. A pathway via **4** or **5** does not require the separation of opposite charges, but at the same time a pathway via **4** requires the protonation at

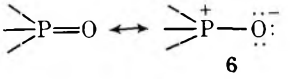
Table II. Second-Order Rate Constants for the Reaction of Acetophenones with H_3PO_5[a]

Substituent	Registry no.	σ	$10^3 k_2$, $M^{-1} s^{-1}$
MeO	100-06-1	−0.27	13.7
Me	122-00-9	−0.17	9.8
H	98-86-2	0	2.9
Cl	99-91-2	+0.23	0.72

[a] In MeCN at 30 °C; $H_0 = -0.64$.



the proximity of the electron-attracting phosphorus atom, which should also pass through a fairly high energy barrier. In the last case, a pathway via **5**, the P=O bonding is a d_π–p_π bonding which is expressed as **6**, where the oxygen atom can



be easily protonated. Therefore, among these three types, a pathway via **5** seems to be most appropriate.

The σ^+ correlation is generally observed in reactions in which the apparent positive charge is generated at the reaction center, and the charge is delocalized by aromatic resonance. In our case, the observed correlation of log k_2 vs. σ rather than σ^+ suggests that the generation of positive charge is poor on account of migration of an aryl group, which is concerted with the leaving of phosphoric acid; i.e., the migration does not occur stepwise after the complete elimination of phosphoric acid. The concerted process has been postulated by several workers, especially Hawthorne-Emmons[13] and Palmer-Fry.[16]

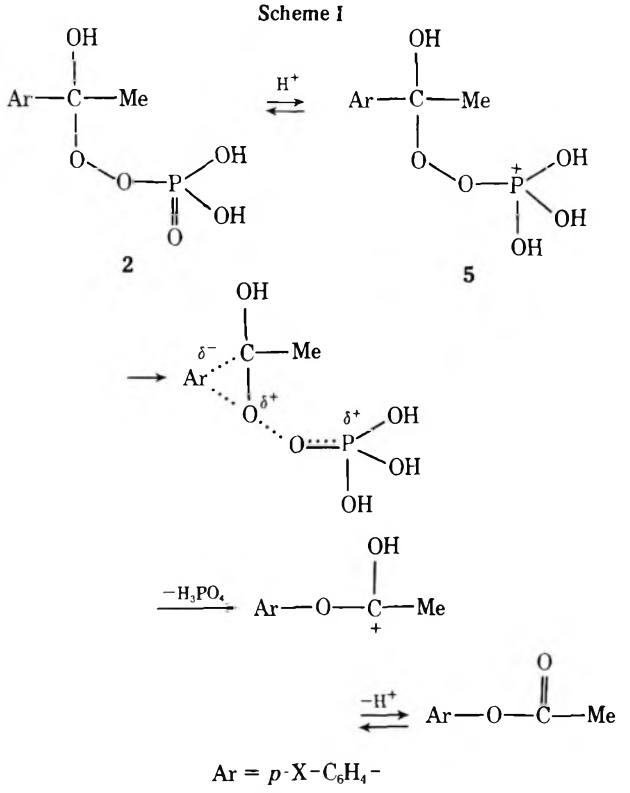
These considerations suggest the reaction mechanism as shown in Scheme I. The high reactivity of H_3PO_5 also is explained by this mechanism; i.e., the migration step is accelerated by the elimination of phosphoric acid because P–O bonding would have the strong tendency for the formation of P=O, which is very stable.[17]

Experimental Section

Materials. Acetonitrile was distilled over P_2O_5 (bp 81–82 °C). All organic reagents were protected carefully from atmospheric moisture. Acetophenone and *p*-nitroacetophenone were of guaranteed grade and were used without further purification. Other acetophenones were prepared by Friedel–Crafts acylation[18] and purified by fractionation. Boiling points for these ketones are as follows: *p*-MeO-C_6H_4COMe, 155–157 °C (26 mm); *p*-Me-C_6H_4COMe, 119–120 °C (30 mm); *p*-Cl-C_6H_4COMe, 124–125 °C (24 mm).

Preparation of Permonophosphoric Acid. To a suspension of P_2O_5 (14.2 g) in MeCN (30 mL) was added an MeCN (10 mL) solution

Scheme I



Ar = p-X-C_6H_4-

of 90% H_2O_2 (7.5 g) with stirring at −5 to −10 °C for 1 h. The mixture was stirred at room temperature for an additional 6 h. The solution contained 2–2.5 M H_3PO_5, and ca. 0.2 M H_2O_2 remained. The content of permonophosphoric acid was estimated iodometrically[19] before use, and that of H_2O_2 was estimated by $KMnO_4$ titration.[19] The oxidation with contaminated H_2O_2 was negligible because the reaction rate of a B–V reaction with H_2O_2 was smaller than 0.05 of that with H_3PO_5 (at $H_0 = -0.76$; $k_2(H_2O_2) = 1.2 \times 10^{-4}$ M^{-1} s^{-1}, $k_2(H_3PO_5) = 3.5 \times 10^{-3}$ M^{-1} s^{-1}).

Baeyer–Villiger Reaction. The Baeyer–Villiger reactions of acetophenones were carried out in MeCN at 30 °C. The aryl acetates produced were identified by GC–MS (a Shimadzu GCMS 7000 gas chromatograph–mass spectrometer; Silicone OV-17, 5% Shimalite W, 2.5 mm × 1.1 m). Mass spectral data were as follows: p-MeO, m/e 166, 124, 109, 43; p-Me, m/e 150, 108, 43; H, m/e 136, 94, 66, 43; p-Cl, m/e 170, 128, 43. These data agree with those of the corresponding aryl acetates.[20] No mass peaks corresponding to methyl benzoates were detected because GLC and GC–MS peaks of authentic samples of methyl benzoates did not agree with those of the products. The yields were measured by GLC (a Yanaco G 180 gas chromatograph; Silicone OV-17, 5% Shimalite W, 2.5 mm × 1.1 m). The rate was determined iodometrically by the disappearance of H_3PO_5 together with UV analysis (a Hitachi 124 spectrophotometer) of the remaining reactants.

Acidity Function.[21] All solutions were prepared before use. The indicator ratio (I) for p-nitroaniline in MeCN in the presence of H_2SO_4 was determined by means of UV spectrophotometry, and the acidity function (H_0) was calculated from the indicator ratio by eq 4 and 5. The H_0 values obtained are listed in Table III. Log K_B^{MeCN} (indicator constant) = 0.954. ϵ_N is the molecular extinction coefficient of p-nitroaniline at the absorption peak λ_N 364 nm in neutral solution and $\epsilon_N = 16\,400$. ϵ_A is the molecular extinction coefficient of p-nitroaniline at the peak in acid solution at λ_A (nm). ϵ_S is the molecular extinction coefficient of nitrobenzene in the same solvent at λ_A (nm).

$$H_0 = \log K_B^{MeCN} - \log I \quad (4)$$

$$I = (\epsilon_N - \epsilon_A)/(\epsilon_A - \epsilon_S) \quad (5)$$

Table III. Acidity Functions (H_0) for MeCN–H_2SO_4 Derived from the Indicator Ratio of p-Nitroaniline at 30 °C

C_A,[a] N	λ_A, nm	ϵ_A	ϵ_S	I	H_0
0.026	362	794	50	21	−0.37
0.051	357	464	60	39	−0.64
0.103	350	385	75	52	−0.76
0.154	347	307	82	72	−0.90
0.206	340	250	96	105	−1.07

[a] C_A, concentration of H_2SO_4 (N); I, indicator ratio.

Registry No.—H_3PO_5, 13598-52-2; p-methoxyphenyl acetate, 1200-06-2; p-tolyl acetate, 140-39-6; phenyl acetate, 122-79-2; p-chlorophenyl acetate, 876-27-7.

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Kinetics Studies of the Pyrolysis Reactions of Ethyl Aroyl(1-aroyl-1,2-dihydro-2-quinolyl)acetates

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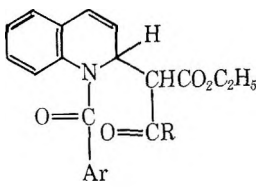
When ethyl benzoyl(1-benzoyl-1,2-dihydro-2-quinolyl)acetate (**1a**) is heated in benzene solution, it is converted to a mixture of quinoline and ethyl *O*-benzoylbenzoylacetate (**2a**). The first-order rate constant at 76.4 °C is 1.95×10^{-6} s^{-1}. The rate is increased about ninefold when the more polar solvent, acetonitrile, is used in place of benzene. Substituent effects are also relatively small, and the presence of either electron-withdrawing or electron-donating substituents on either of the phenyl groups of **1a** causes an increase in the rate of thermolysis. These and other data suggest that spin-paired diradicals are formed as unstable intermediates in these reactions. Only one of the two possible geometrical isomers of **2** has been isolated from each pyrolysis reaction mixture, and, in the case of the thermolysis of ethyl benzoyl(1-*p*-methoxybenzoyl-1,2-dihydro-2-quinolyl)acetate (**1c**), the olefin has been assigned the structure of (*Z*)-ethyl *O*-(*p*-methoxybenzoyl)benzoylacetate, (*Z*)-**2c** (which is thermodynamically more stable than (*E*)-**2c**), on the basis of NMR spectral considerations.

Ethyl benzoyl(1-benzoyl-1,2-dihydro-2-quinolyl)acetate (**1a**) and ethyl aceto(1-benzoyl-1,2-dihydro-2-quinolyl)acetate (**1b**) have been obtained by the reaction of benzoyl chloride with ethyl benzoylacetate and ethyl acetoacetate, respectively, in quinoline solution.[1] It was also reported that **1a** and **1b** undergo pyrolysis to give quinoline and the *O*-acylated products, **2a** and **2b**, respectively. Whereas the earlier studies



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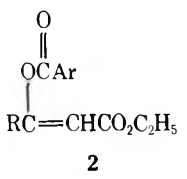

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a, R = Ar = C_6H_5
b, R = CH_3; Ar = C_6H_5
c, R = C_6H_5; Ar = *p*-$MeOC_6H_4$
d, R = C_6H_5; Ar = *m*-ClC_6H_4
e, R = *p*-$MeOC_6H_4$; Ar = C_6H_5
f, R = *p*-$NO_2C_6H_4$; Ar = C_6H_5
g, R = C_6H_5; Ar = *p*-MeC_6H_4
h, R = *p*-FC_6H_4; Ar = C_6H_5
i, R = *p*-$NO_2C_6H_4$; Ar = *m*-ClC_6H_4

were carried out in order to obtain additional evidence about the mechanism of *O*-acylation of β-keto esters in the presence of tertiary amines,[2-8] the present study is concerned mainly with the scope and mechanism of the thermolysis reaction **1** → **2**.

Results

Seven new compounds of type **1** (**1c–i**) have been prepared and subjected to thermolysis in refluxing benzene for periods of 6–12 days. In each case, the product **2** was isolated in yields ranging from 41–89%. The rates of thermolysis at 76.4 ± 0.2 °C were also determined, and the results are summarized in Table I.

The rates of thermolysis of **1a** were measured at 76.4 ± 0.1 °C in solvents of different polarities. The solvents, specific rate constants, and dielectric constants, respectively are as follows: benzene, 1.95×10^{-6} s^{-1}, 2.28; *o*-chlorotoluene, 4.22×10^{-6} s^{-1}, 4.45; acetonitrile, 17.1×10^{-6} s^{-1}, 37.5.

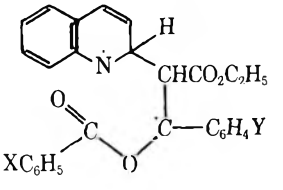
The rates of thermolysis of **1a** in *p*-xylene were measured at three different temperatures, and the results are as follows: 76.4 ± 0.2 °C, 11.3×10^{-6} s^{-1}; 86.4 ± 0.2 °C, 30.2×10^{-6} s^{-1}; 96.4 ± 0.2 °C, 84.6×10^{-6} s^{-1}. From these data, $\Delta H^{\ddagger}$ was calculated to be 26.6 ± 4.0 kcal mol^{-1} and $\Delta S^{\ddagger}$ at 76.4 °C to be −5.97 ± 4.05 cal mol^{-1} deg^{-1}.

Discussion

In a formal sense, the thermolysis of **1** to **2** plus quinoline may be classified as $\pi^2 + \pi^2 + \sigma^2 = \sigma^2 + \sigma^2 + \pi^2$ skeletal rearrangements.[9-11] However, the question remains whether these transformations are fully concerted,[12] involve a considerable degree of charge separation in the transition state, or involve spin-paired diradicals as unstable intermediates.

The possibility that the transition state for the conversion of **1** to **2** plus quinoline is characterized by a large degree of charge separation can be discounted readily. The relatively small change in rate with change in polarity of the solvent, the relatively small substituent effects, and the fact that the presence of either electron-donating or electron-withdrawing substituents in **1** lead to an increase in rate all support this conclusion.

As the massive exchanges between Huisgen[13] and Firestone[14-16] testify, it is a much more difficult matter to distinguish between a concerted process and one in which a spin-paired diradical is formed as an unstable intermediate. The small effects of changes of solvent polarity and of substituents on rate and the negative value of $\Delta S^{\ddagger}$ mentioned under Results are consistent with either mechanism. However, the fact that all of the substituents listed under formula **1**, regardless of whether they are electron withdrawing or electron donating, cause an increase in the rate of pyrolysis is more readily explained by the spin-paired diradical concept than by the assumption of a synchronous process.[17] In particular, the conversion of **1** (R = C_6H_4Y and Ar = C_6H_4X) to **2** via the spin-paired diradical **3** should show a stronger rate-enhancing



3

effect of the substituent Y than that of X.[18] Examination of the data provided in Table I shows that the effect of Y is indeed greater than that of X, although, as expected, X also exerts some influence on the rate. Of course, more conclusive evidence will be required before a final decision about the mechanism can be reached.

In all of the thermolysis reactions of **1**, only one geometrical

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Table I. Rate Data for the Thermolysis of Compounds of Type 1 at 76.4 ± 0.2 °C

1	$k \times 10^6$, s^{-1} [a]	Rel rate
a	1.95 ± 0.04	1.00
c	5.32 ± 0.05	2.73
d	17.3 ± 0.40	8.87
e	15.5 ± 0.20	8.21
f	26.2 ± 1.50	13.4
g	2.99 ± 0.02	1.53
h	6.59 ± 0.12	3.38
i	35.0 ± 0.10	17.9

[a] Average deviation based on at least three determinations. As against these average deviation values, the corresponding P.M. values would probably indicate a deviation of about ±5–10%.

isomer of **2** resulted. Ethyl *O*-(*p*-methoxybenzoyl)benzoylacetate (**2c**) was chosen as the model for the determination of the geometry. The product of the thermolysis of **1c** had a mp of 95.0–95.3 °C, and it exhibited a vinyl proton resonance at δ 6.38 in its NMR spectrum. When subjected to irradiation by the procedure of Zechmeister and McNeely,[19] a mercury lamp and a vycor filter being used, the geometrical isomer of mp 109–110 °C was obtained, and it exhibited a vinyl proton resonance at δ 6.06.

A modification of the method of Pascual, Meir, and Simon,[20] which has also been discussed by Jackman and Sternhell,[21] can be used to determine the configurations of the two geometrical isomers of **2c**. The strict use of the additive constants of Pascual, Meir, and Simon[20] indicates that the *Z* isomer (vinylic proton cis to phenyl) would have a value of vinylic proton resonance at δ 0.20 units downfield from that of the *E* isomer. In addition, one can compare cis-to-phenyl and trans-to-phenyl proton shifts in a series of known olefins (the fundamental basis of the method of Pascual, Meir, and Simon[20]) and arrive at the conclusion that the cis-to-phenyl proton should resonate 0.47 ppm downfield relative to a trans-to-phenyl proton. By either rationale, it follows that the compound of mp 95.0–95.3 °C formed directly by the thermolysis of **1c** is (*Z*)-**2c**. This is the thermodynamically more stable isomer, and, by analogy, the more stable isomer of **2** may be assumed to be formed in all of the thermolysis reactions of **1**. It is not unreasonable that this should be so if a spin-paired diradical unstable intermediate is the precursor of the olefin.

As a control experiment, *E*-(**2c**), mp 109–110 °C, was subjected to the conditions of the thermolysis of **1c**, which gave (*Z*)-**2c** exclusively. No isomerization of the less stable (*E*)-**2c** to the more stable (*Z*)-**2c** was observed. Thus, (*Z*)-**2c** was formed directly from **1c** in the thermolysis reaction, and the result is related to the configuration of the transition state.[22]

Experimental Section

General. Melting points were obtained with a Mel-temp apparatus and are uncorrected. Infrared spectra were recorded on a Backmann IR-5, IR-10, or Acculab-2 spectrometer. ^{1}H-NMR spectra were obtained with either a Varian A-60 or a Perkin-Elmer R-12 spectrometer. Chemical shifts are reported as parts per million (δ) vs. Me_4Si as an internal standard in $CDCl_3$ solutions. UV spectra were obtained by use of a Perkin-Elmer Model 202 spectrometer. UV measurements for kinetics studies were obtained with a Cary Model 14 or a Beckmann Model DK2 spectrometer. Elemental analyses were carried out by the Microanalysis Laboratory, University of Massachusetts, Amherst, Mass.

Preparation of Compounds of Type 1. Quinoline (Eastman) was distilled at reduced pressure (bp 63–64 °C at 1 mm) and collected over Drierite. Commercially available substituted benzoyl chlorides were used without further purification and commercially available substituted ethyl benzoylacetates were dried over Drierite and used without further purification.

Ethyl Benzoyl(1-benzoyl-1,2-dihydro-2-quinolyl)acetate (1a). The preparation of **1a** was carried out as previously reported.[1,7] Recrystallization of the crude product from absolute ethanol gave material of mp 154–155 °C, somewhat higher than the value previously reported:[7] ^{1}H NMR δ 1.01 (t, 3 H), 3.85 (dq, 2 H), 4.60 (d, 1 H), 6.02 (dd, 1 H), 6.10–7.85 (16 H); IR, carbonyl peaks at 1741, 1690, and 1650 cm^{-1}. Anal. Calcd for $C_{27}H_{23}NO_4$: C, 76.22; H, 5.45; N, 3.29. Found: C, 75.98; H, 5.29; N, 3.36.

Ethyl Benzoyl(1-*p*-methoxybenzoyl-1,2-dihydro-2-quinolyl)acetate (1c). The procedure was the same as for **1a**. Quinoline (129 g, 1.0 mol), ethyl benzoylacetate (96 g, 0.5 mol), and *p*-methoxybenzoyl chloride (85 g, 0.5 mol) gave 111 g (49%) of **1c**: mp 137.1–138.5 °C; ^{1}H NMR δ 1.00 (t, 3 H), 3.75 (s, 3 H), 3.85 (2 H), 4.67 (d, 1 H), 5.90–7.90 (16 H); IR, carbonyl peaks at 1730, 1685, and 1640 cm^{-1}. Anal. Calcd for $C_{28}H_{25}NO_5$: C, 73.83; H, 5.53; N, 3.08. Found: C, 73.75; H, 5.62; N, 3.07.

Ethyl Benzoyl[1-(3-chlorobenzoyl)-1,3-dihydro-2-quinolyl]acetate (1d). From 59 g (0.5 mol) of quinoline, 42.8 mL (0.25 mol) of ethyl benzoylacetate, and 27.9 mL (0.25 mol) of *m*-chlorobenzoyl chloride there was obtained 74.1 g (64%) of **1d**: mp 141.5–142.8 °C after recrystallization from ethanol; ^{1}H NMR δ 1.04 (t, 3 H), 3.88 (dq, 2 H), 4.60 (d, 1 H), 5.90–7.97 (16 H); IR, carbonyl peaks at 1740, 1690, and 1650 cm^{-1}. Anal. Calcd for $C_{27}H_{22}NO_4Cl$: C, 71.13; H, 4.72; N, 2.98; Cl, 7.55. Found: C, 70.96; H, 4.73; N, 3.00; Cl, 7.60.

Ethyl *p*-Methoxybenzoyl(1-benzoyl-1,2-dihydro-2-quinolyl)acetate (1e). From 0.5 mol of quinoline, 0.25 mol of ethyl *p*-methoxybenzoylacetate, and 0.25 mol of benzoyl chloride there was obtained 59.5 g of **1e**: mp 157.7–158.1 °C after recrystallization from ethanol; ^{1}H NMR δ 1.02 (t, 3 H), ca. 3.82 (2 H), 3.89 (s, 3 H), 4.60 (d, 1 H), 5.92–7.92 (16 H); IR, carbonyl peaks at 1740, 1685, and 1650 cm^{-1}. Anal. Calcd for $C_{28}H_{25}NO_5$: C, 73.83; H, 5.53, N, 3.08. Found: C, 73.73; H, 5.55; N, 2.93.

Ethyl *p*-Nitrobenzoyl(1-benzoyl-1,2-dihydro-2-quinolyl)acetate (1f). From 0.1 mol of quinoline, 0.05 mol of ethyl *p*-nitrobenzoylacetate (dissolved in 75 mL of anhydrous ether), and 0.05 mol of benzoyl chloride there was obtained 2.6 g (11%) of **1f** as pale yellow crystals: mp 138.5–140.0 °C after recrystallization from ethanol; ^{1}H NMR δ 1.01 (t, 3 H), 3.86 (dq, 2 H), 4.60 (d, 1 H), 6.02–8.22 (16 H); IR, carbonyl peaks at 1740, 1698, and 1650 cm^{-1}. Anal. Calcd for $C_{27}H_{22}N_2O_6$: C, 68.92; H, 4.71; N, 5.96. Found: C, 68.72; H, 4.57; N, 5.98.

Ethyl Benzoyl(1-*p*-methylbenzoyl-1,2-dihydro-2-quinolyl)acetate (1g). From 0.156 mol of quinoline, 0.078 mol of ethyl benzoylacetate, and 0.078 mol of *p*-toluyl chloride there was obtained 8.47 g (25%) of **1g**: mp 147–148 °C after crystallization from ethanol; ^{1}H NMR δ 1.02 (t, 3 H), 2.3 (s, 3 H), 3.87 (dq, 2 H), 4.62 (d, 1 H), and 5.90–7.85 (16 H); IR, carbonyl peaks at 1730, 1683, and 1640 cm^{-1}. Anal. Calcd for $C_{28}H_{25}NO_4$: C, 76.52; H, 5.73; N, 3.19. Found: C, 76.54; H, 5.64; N, 2.83.

Ethyl *p*-Fluorobenzoyl(1-benzoyl-1,2-dihydro-2-quinolyl)acetate (1h). From 0.114 mol of quinoline, 0.057 mol of benzoyl chloride, and 0.057 mol of ethyl *p*-fluorobenzoylacetate there was obtained 9.68 g (38%) of **1h**: mp 169–170 °C after crystallization from ethanol; ^{1}H NMR δ 1.02 (t, 3 H), 3.88 (dq, 2 H), 4.57 (d, 1 H), 5.92–7.90 (16 H); IR, carbonyl peaks at 1725, 1670, and 1635 cm^{-1}. Anal. Calcd for $C_{27}H_{22}NFO_4$: C, 73.12; H, 5.00; F, 4.28; N, 3.16. Found: C, 72.56; H, 5.27; F, 4.20; N, 3.16.

Ethyl *p*-Nitrobenzoyl[1-(*m*-chlorobenzoyl)-1,2-dihydro-2-quinolyl]acetate (1i). From 0.12 mol of quinoline, 0.06 mol of ethyl *p*-nitrobenzoylacetate, and 0.06 mol of *m*-chlorobenzoyl chloride there was obtained 12.25 g (40.3%) of yellow **1i**: mp 132.5–133.5 °C after crystallization from acetone; ^{1}H NMR δ 1.01 (t, 3 H), 3.88 (dq, 2 H), 4.54 (d, 1 H), 5.90–8.30 (15 H); IR, carbonyl peaks at 1730, 1691, and 1648 cm^{-1}. Anal. Calcd for $C_{27}H_{21}N_2O_6Cl$: C, 64.22; H, 4.21; N, 5.55; Cl, 7.03. Found: C, 63.48; H, 4.62; N, 5.78; Cl, 6.66.

Ethyl β-Benzoxycinnamate (2a). A solution of 5.00 g (0.012 mol) of ethyl benzoyl(1-benzoyl-1,2-dihydro-2-quinolyl)acetate (**2a**) in 2.5 mL of dry benzene was refluxed. The solution gradually turned from colorless to a deep yellow color. After 12 days the reflux was discontinued and 50 mL of ether was added. The ether–benzene layer was extracted thoroughly with cold 10% HCl, cold 10% NaOH, and finally with water. The organic layer was then dried over Drierite and evaporated. The residue was dissolved in hot absolute ethanol and then cooled. A white crystalline solid was collected and identified as ethyl β-benzoxycinnamate by comparison with the physical properties of an authentic sample. The melting point was 85.5–86.5 °C and a mixture melting point test with an authentic sample[5] showed no depression. The IR spectrum was identical with that of the authentic sample.[5] The yield was 2.59 g (72.5%).

Ethyl β-*p*-Anisoxycinnamate (2c). The procedure was the same

as for **2a**. From 3.0 g (0.0067 mol) of ethyl benzoyl(1-*p*-methoxybenzoyl-1,2-dihydro-2-quinolyl)acetate (**1c**) there was obtained 1.46 g (67.9%) of **2c**, a white crystalline solid, mp 90–95 °C. Recrystallization from absolute ethanol yielded a sample of mp 95.0–95.3 °C: ^{1}H NMR δ 1.15 (t, 3 H), 3.88 (s, 3 H), 4.12 (q, 2 H), 6.38 (s, 1 H), 6.82–8.30 (m, 9 H); IR, carbonyl peaks at 1715 and 1735 cm^{-1}. Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 70.04; H, 5.48.

Ethyl β-*m*-Chlorobenzoxycinnamate (2d). From 3.0 g (0.0065 mol) of ethyl benzoyl(1-*m*-chlorobenzoyl-1,2-dihydro-2-quinolyl)-acetate there was obtained 1.83 g (84.5%) of **2d**, a white crystalline solid, mp 86.5–87.5 °C. Recrystallization from absolute ethanol yielded a sample of mp 86.5–87.5 °C: ^{1}H NMR 1.18 (t, 3 H), 4.18 (q, 2 H), 6.41 (s, 1 H), 7.20–8.18 (m, 9 H); IR, carbonyl peaks at 1750 and 1720 cm^{-1}. Anal. Calcd for $C_{18}H_{15}ClO_4$: C, 65.35; H, 4.57; Cl, 10.73. Found: C, 65.25; H, 4.51; Cl, 10.70.

Ethyl β-Benzoxy-*p*-methoxycinnamate (2e). From 3.9 g (0.0067 mol) of ethyl *p*-anisoyl(1-benzoyl-1,2-dihydro-2-quinolyl)acetate (**1e**) there was obtained 1.55 g (72.1%) of **2e**, a white crystalline solid, mp 110–112 °C. Recrystallization from absolute ethanol yielded a sample of mp 111.5–112.8 °C: ^{1}H NMR δ 1.12 (t, 3 H), 3.83 (s, 3 H), 4.12 (q, 2 H), 6.28 (s, 1 H), 6.83–8.25 (m, 9 H); IR, carbonyl peaks at 1750 and 1720 cm^{-1}. Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.93; H, 5.56. Found: C, 69.91; H, 5.72.

Ethyl β-Benzoxy-*p*-nitrocinnamate (2f). From 0.50 g (0.0011 mol) of ethyl 4-nitrobenzoyl(1-benzoyl-1,2-dihydro-2-quinolyl)acetate (**1f**) there was obtained 0.32 g (88.9%) of **2f**, yellow crystalline solid, mp 67.1–68.0 °C. Recrystallization from absolute ethanol yielded a sample of mp 67.1–68.0 °C: ^{1}H NMR δ 1.17 (t, 3 H), 4.18 (q, 2 H), 6.52 (s, 1 H), 7.25–8.50 (m, 9 H); IR, carbonyl peaks at 1749 and 1720 cm^{-1}.

Anal. Calcd for $C_{18}H_{15}NO_6$: C, 63.34; H, 4.46; N, 4.10. Found: C, 63.29; H, 4.62; N, 4.00.

Ethyl β-*p*-Methylbenzoxycinnamate (2g). From 1.5 g (0.0034 mol) of ethyl benzoyl(1-*p*-methylbenzoyl-1,2-dihydro-2-quinolyl)-acetate (**1g**) there was obtained 0.74 g (71%) of **2g**, a pale yellow crystalline solid, mp 97.5–99.0 °C. Recrystallization from absolute ethanol yielded material of mp 97.5–99.0 °C: ^{1}H NMR δ 1.12 (t, 3 H), 2.35 (s, 3 H), 4.06 (q, 2 H), 6.30 (s, 1 H), 7.00–8.10 (m, 9 H); IR, carbonyl peaks at 1738 and 1710 cm^{-1}. Anal. Calcd for $C_{19}H_{18}O_4$: C, 73.53; H, 5.85. Found: C, 73.30; H, 5.79.

Ethyl β-Benzoxy-*p*-fluorocinnamate (2h). From 1.50 g (0.0034 mol) of ethyl 4-fluorobenzoyl(1-benzoyl-1,2-dihydro-2-quinolyl)-acetate (**1h**) there was obtained 0.435 g (41%) of **2h**, a white crystalline solid, mp 90.2–91.0 °C. Recrystallization from absolute ethanol gave material of mp 90.2–91.0 °C: ^{1}H NMR δ 1.13 (t, 3 H), 4.13 (q, 2 H), 6.30 (s, 1 H), 6.95–7.32 (m, 9 H); IR, carbonyl peaks at 1738 and 1705 cm^{-1}. Anal. Calcd for $C_{18}H_{15}FO_4$: C, 68.78; H, 4.81; F, 6.05. Found: C, 68.99; H, 5.38; F, 6.17.

Ethyl β-m-Chlorobenzoxy-*p*-nitrocinnamate (2i). From 1.5 g (0.0030 mol) of ethyl 4-nitrobenzoyl[1-(3-chlorobenzoyl)-1,2-dihydro-2-quinolyl]acetate (**1i**) there was obtained 0.655 g (58.5%) of **2i**, a pale yellow crystalline solid, mp 98.5–99.5 °C. Recrystallization from absolute ethanol yielded a sample of mp 98.5–99.5 °C: ^{1}H NMR δ 1.20 (t, 3 H), 4.28 (q, 2 H), 6.48 (s, 1 H), 7.50–8.50 (m, 8 H); IR, carbonyl peaks at 1725 and 1700 cm^{-1}.

Anal. Calcd for $C_{18}H_{14}NClO_6$: C, 57.53; H, 3.76; N, 3.73; Cl, 9.43. Found: C, 57.53; H, 3.82; N, 3.92; Cl, 9.58.

(*E*)-Ethyl β-Anisoxycinnamate. Ethyl β-anisoxycinnamate (1.0 g) from the pyrolysis of **1c** was dissolved in 100 mL of benzene and photolyzed by means of a Hanovia medium pressure mercury lamp having a vycor filter, the lamp being centered in the well of the reaction chamber. The reaction was followed by observing the disappearance of **2c** by use of VPC.

By use of TLC, 50% Skelly F–50% Ether being used as eluent, three spots were observed under UV light, one being the starting material and one trailing the starting material. The benzene was evaporated, and the residue was orange in color and smelled of a ketone. The residue was dissolved in 10 mL of hot ethanol and cooled. There was obtained 0.65 g (65%) of one product only, which melted sharply at 109–110 °C. Its NMR spectrum showed the same integration (9:3:3:2:1) as did the spectrum of the starting material, but the vinylic proton absorption had been shifted from δ 6.38 to 6.06. In all other respects, the NMR spectra were essentially the same.

The assignment of *E* and *Z* configurations was made on the basis of the observed ^{1}H-NMR shift of the vinylic proton according to the method of Pascual, Meir, and Simon[20] and also discussed by Jackman and Sternhell.[21]

Attempts to effect thermal isomerizations of the (*E*) isomer to the (*Z*) isomer were made by two methods. First, a purely thermal isomerization was attempted by refluxing 0.3 g of (*E*)-**2c** in benzene for 4 days. The 0.3 g of starting compound was recovered unchanged by evaporation of the solvent and recrystallization of the residue from ethanol. The product isolated exhibited a mp of 109–110.5 °C, and there was no change in its NMR absorption from that of the starting material, the *E* isomer.

To determine if the quinoline present in the reaction mixture was affecting the product formation, a solution of 0.3 g (0.0092 mol) of (*E*)-**2c** and 0.12 g of quinoline in benzene was refluxed for 6 days. At the end of 6 days the solvent was evaporated and the recovered starting material was purified by recrystallization from hot ethanol. The melting point of the product was 108–109 °C. The NMR spectrum showed no change from that of the starting material. Therefore, exposure to the reaction conditions does not cause conversion of (*E*)-**2c** to (*Z*)-**2c**.

Kinetics Studies

Materials. The preparation of the various 1,2-dihydroquinoline adducts (**1a–i**) has been described previously. Solvent purification was accomplished as follows: Benzene was distilled from sodium and collected over molecular sieves. Prior to kinetics experiments, it was distilled once more and the first 5–10 mL of distillate was discarded. Acetonitrile and o-chlorotoluene were distilled prior to use. Xylene was distilled from sodium prior to use.

Procedure. Two procedures were used to determine relative reaction rates.

1. In a 100-mL volumetric flask was placed 1.5–1.8 × 10^{-5} mol of a given 1,2-dihydroquinoline adduct. A given solvent contained in a round-bottom flask, purified as previously described, was placed in a constant temperature bath at 76.4 °C for 30 min. A 100-mL pipette was then used to transfer 100 mL of the solvent (usually benzene) at 76.4 °C into the 100-mL volumetric flask. The volumetric flask was swirled twice and immediately fitted with a rubber septum cap, secured with copper wire, and clamped in the constant temperature bath. Zero time was defined as the instant of complete delivery of the 100 mL of solvent. At 2- to 4-h intervals, a 2.00-mL aliquot was removed by the use of a hypodermic syringe fitted with a 9-in. needle. Quenching was accomplished by discharging the 2.00-mL aliquot into the wall of a 15-mL test tube which was maintained in a 20 °C bath. The UV measurement was taken directly from the aliquot. To check on the accuracy of quenching, samples were left at room temperature for 24 h with no detectable change in spectrum.

2. In a 250-mL volumetric flask was placed 3.3–4.1 × 10^{-5} mol of a given 1,2-dihydroquinoline adduct. The mass was then diluted to the 250-mL mark with a given solvent. The solution was swirled for 5 min and then 4.0-mL aliquots were pipetted into 36-cm lengths of Pyrex tubing which were sealed at one end and were then capped with a rubber stopper. Each 4.0-mL aliquot was placed in a constant temperature bath (76.4, 86.4, 96.4 °C). The zero time was defined as the instant that the tube was delivered into the constant temperature bath. Each tube represented one determination and from 12 to 15 samples were used to evaluate one kinetics run. The samples were quenched by removal from the constant temperature bath and cooling under cold tap water. The UV measurement was taken directly from the aliquot for all samples except **1i**. In the case of **1i** it was necessary to dilute 2.00 mL of benzene.

The rates were determined by following the growth of a quinoline absorption peak at 314 mμm by use of either a Cary Model 15 spectrophotometer or a Beckman Model DK2A spectrophotometer.

A calibration curve was constructed by taking the UV spectra of solutions of known concentrations of stoichiometric quantities of products (quinoline and **2a**) and starting material (**1a**) in benzene at 314 mμm. The plot was found to fit Beer's law.

From the UV spectrum of the aliquot and the calibration

curve, the concentration of quinoline at each time, t, could be determined.

Results. For the determination of substituent effects and solvent effects, all kinetics experiments were carried out at 76.4 ± 0.2 °C. To obtain the Arrhenius plot (ln k vs. $1/t$) additional runs were made at 86.4 ± 0.2 and 96.4 ± 0.2 °C.

Rate data of each kinetics experiment are shown in Table I. The method of least squares was used to derive the average slope of each reaction plot from the raw data.

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Registry No.—**1a,** 56346-06-6; **1c,** 65815-43-2; **1d,** 65815-44-3; **1e,** 65815-45-4; **1f,** 65815-46-5; **1g,** 65815-47-6; **1h,** 65815-48-7; **1i,** 65815-49-8; **2a,** 65847-84-9; (*Z*)-**2c,** 65815-50-1; (*E*)-**2c,** 65815-51-2; **2d,** 65815-52-3; **2e,** 65815-53-4; **2f,** 65815-54-5; **2g,** 65847-83-8; **2h,** 65815-55-6; **2i,** 65815-56-7; quinoline, 91-22-5; ethyl benzoylacetate, 94-02-0; *p*-methoxybenzoyl chloride, 100-07-2; *m*-chlorobenzoyl chloride, 618-46-2; ethyl *p*-methoxybenzoylacetate, 2881-83-6; benzoyl chloride, 98-88-4; ethyl *p*-nitrobenzoylacetate, 838-57-3; *p*-toluyl chloride, 874-60-2; ethyl *p*-fluorobenzoylacetate, 1999-00-4.

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(22) There are two chiral centers in **1,** but we have found no evidence for the formation of two racemates in any of the condensation reactions. Owing to the facile reversibility of condensation in reactions of this type,[6-8] and also owing to the acidity of the hydrogen bonded to one of the chiral carbon atoms, interconversion of diastereomers would occur readily. Thus, it is probable that the thermodynamically more stable racemate is being formed in each of the reactions giving rise to **1.** However, we have no solid evidence which permits us to decide which of the racemates is the more stable in each case. Also, examination of space filling models for each of the possible diastereomers of **1** suggests no obvious explanation for the exclusive formation of (*Z*)-**2** in thermolysis.

Rate of Deprotonation of Phenylnitromethane by Hydroxide Ion in Aqueous Dimethyl Sulfoxide and Aqueous Methanol[1]

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The rates of deprotonation of phenylnitromethane by hydroxide ion in aqueous dimethyl sulfoxide and aqueous methanol have been measured at 20, 30, and 40 °C under pseudo-first-order conditions using the stopped-flow technique. The various solvents (vol %) used, the second-order rate constants ($k_2 \times 10^{-2}$ M^{-1} s^{-1}) found at the three temperatures, ΔH^* (kcal/mol), and ΔS^* (cal/mol deg), respectively, are as follows: 20% methanol, 1.54, 2.97, 5.78, 11.4, −9.4; 50% methanol, 2.22, 4.39, 8.44, 11.6, −8.3; 33.3% Me_2SO, 3.22, 6.43, 9.42, 9.2, −15.5; 50% Me_2SO, 13.8, 20.8, 36.9, 8.3, −15.8; and 66.7% Me_2SO, 10.47, 17.03, 24.60, 7.2, −15.6. A plot of log k_2 (25 °C) vs. ΔpK for the aqueous Me_2SO solutions gave a least-squares slope (β) of 0.58 (r = −0.997). The Brønsted β coefficient calculated on the basis of the enhanced basicity of hydroxide ion in these mixtures thus agrees closely with that obtained for aqueous solutions by variation in the type and strength of the bases employed. The constancy of the entropy of activation in Me_2SO–water mixtures suggests that solvent reorganization is very similar in each solvent and that the differences in rate can be attributed to the increased strength of the interaction between the solvent and the incipient water molecule.

Interest in proton transfer reactions is promoted by their formal simplicity. The accumulated evidence points to the mechanism shown in eq 1–3, in which charge types are not shown.[2]

$$\mathrm{H\text{-}A + B \rightarrow \{A\text{-}H \cdots B\}} \quad (1)$$

$$\mathrm{\{A\text{-}H \cdots B\} \xrightarrow{1} \{A \cdots H\text{-}B\}} \quad (2)$$

$$\mathrm{\{A \cdots H\text{-}B\} \xrightarrow{2} A + H\text{-}B} \quad (3)$$

Species **1** and **2** represent hydrogen-bonded encounter complexes, and reactants and products can be free species or ion pairs.

Carbon acids are expected to behave qualitatively differently than oxygen or nitrogen acids because of the inability of the former to hydrogen bond in the encounter complex. Both carbonyl[3] and nitro compounds[4] have been studied extensively with a view toward defining the structure of the transition state in deprotonation reactions in aqueous solution. Many weaker acids have been studied in nonaqueous

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Table I. Rate Constants for Phenylnitromethane Reacting with Hydroxide Ion

Solvent[a]	t, °C	$k_2 \times 10^{-3}$, $M^{-1}\ s^{-1}$[b]	n[c]	r[d]
Water[e]	25.0	0.151		
20.0% MeOH	20.0	0.154 ± 0.023	5	0.999
	25.0	0.215		
	30.0	0.297 ± 0.054	6	0.997
	40.0	0.578 ± 0.169	6	0.996
50.0% MeOH	20.0	0.222 ± 0.038	5	0.999
	25.0	0.314		
	30.0	0.439 ± 0.084	5	0.999
	40.0	0.844 ± 0.244	5	0.999
33.33% Me_2SO	20.0	0.322 ± 0.041	7	0.995
	25.0	0.448		
	30.0	0.643 ± 0.202	6	0.994
	40.0	0.942 ± 0.252	6	0.999
50.00% Me_2SO	20.0	1.38 ± 0.21	5	0.999
	25.0	1.73		
	30.0	2.08 ± 0.22	5	0.998
	40.0	3.69 ± 0.18	4	0.999
66.67% Me_2SO	20.0	10.47 ± 1.79	5	0.997
	25.0	13.28		
	30.0	17.03 ± 2.36	5	0.998
	40.0	24.60 ± 0.89	5	0.999

[a] Volume percent. [b] The values in this column are least-squares slopes for the plot of pseudo-first-order rate constants vs. hydroxide ion concentration. The deviation given is the difference between the least-squares slope and the k_2 calculated for the point furtherest from the line. Values at 25 °C are interpolated from the Arrhenius equation. [c] Number of different hydroxide ion concentrations used. [d] Correlation coefficient truncated at three decimal places. [e] Taken from ref 7.

solutions.[2b,5] For the deprotonation of nitro compounds, Bordwell and his co-workers have concluded that in the transition state the proton is approximately half-transferred, even for reactions of fairly large $\Delta G°$ values, and that rehybridization of the carbon center has progressed only slightly from sp^3 to sp^2. These conclusions were based on substituent effects on both rate and equilibria in the ionization of substituted aryl nitromethanes and aryl nitroethanes,[6a] deuterium isotope effects,[6b] and structural effects on the protonation rates of nitronate anions.[6c] Keefe and Munderloh have supported this view, based on their study of the reaction of phenylnitromethane and its deuterated analogue with 15 bases in aqueous solution.[7]

Bell and Cox have reported an interesting study of the inversion of (−)-methone in Me_2SO–water mixtures.[8] They were able to correlate rate changes in these solvents with the enhanced basicity of hydroxide ion, as reflected in H_- values.[9] The Brønsted β value for the reaction calculated from these variations in the basicity of the medium agreed quite closely with that determined for acetone reacting in aqueous solution with bases of strengths approaching that of hydroxide ion.

Our interest in extending this latter approach to the study of phenylnitromethane was twofold. We wanted to see if the Brønsted β coefficient determined in this fashion would agree with the one determined in the standard manner by Keefe and Munderloh and if the activation parameters found for the reaction in aqueous Me_2SO would be interpretable in terms of the previously suggested structure of the transition state.[6b] The results of this study are described below.

Experimental Section

Phenylnitromethane was prepared by the procedure of Kornblum, Smiley, Blackwood, and Iffland.[10] The crude product boiled at 75–85 °C (3.5 mm) and a redistilled sample had bp 68–69 °C (0.7 mm). Stock solutions were prepared by dissolving weighed amounts in the appropriate Me_2SO–water mixtures or in absolute methanol. Three different concentrations were prepared in each solvent mixture by dilution of a small aliquot of the stock solution with solvents containing excess potassium hydroxide. Molar absorptivities were obtained from the slope of the linear plot ($r > 0.996$) of absorbance vs. concentration. In aqueous methanol, the anion showed λ_{max} at 293.5 nm with $\log a = 4.33$. The appropriate values in aqueous Me_2SO are as follows: 33.3% Me_2SO, 300 nm, 4.38; 50.0% Me_2SO, 303 nm, 4.31; 66.7% Me_2SO, 308.5 nm, 4.25.

Dimethyl sulfoxide (Aldrich Chemical Co.) was stirred overnight with calcium hydride and distilled at 20 mm. A middle-boiling fraction had bp 86 °C. Aqueous mixtures were prepared by mixing appropriate volumes of Me_2SO or reagent grade (Mallinckrodt) methanol with distilled, demineralized, freshly boiled water. Solutions of potassium hydroxide were prepared by diluting aliquots of carbonate-free, ~1 M base in either water or 33.33% (v/v) Me_2SO with appropriate solvent to prepare ~0.1 M solutions. These were standardized against potassium acid phthalate and were subsequently diluted to the concentration range of 10^{-2}–10^{-4} M for use in kinetic studies.

Deprotonation kinetics were followed by ultraviolet spectroscopy using a Durrum stopped flow spectrophotometer. The analogue photomultiplier output representing absorbance changes was stored in a Physical Data Model 514A, 10-bit transient recorder and was analyzed by means of a varian 620-1 computer. Runs were made under pseudo-first-order conditions, with base concentrations ranging from 10 to 100 times that of the nitro compound. Good first-order kinetics were followed, and analyses characteristically were made using 3 half-lives. Data were analyzed using the expression in eq 4, in which S_∞ and S_t represent a signal proportional to the absorbance at infinity and at time t, respectively.

$$\ln (S_\infty - S_t) = -k_\Psi t + \ln (S_\infty - S_0) \quad (4)$$

Least-squares analysis of the regression of $\ln (S_\infty - S_t)$ on time gave correlation coefficients better than −0.99. Such analyses typically utilized 300–600 data points.

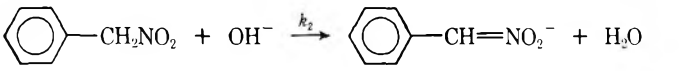
The second-order rate constants were calculated by use of eq 5, in which $\{OH^-\}$ represents the constant concentration of hydroxide ion.

$$k_\Psi = k_2\{OH^-\} \quad (5)$$

A plot of k_Ψ vs. $\{OH^-\}$ is linear ($r > 0.994$) and must pass through the origin. Because of this latter requirement, the origin was included as a fixed data point in the analysis.

Results and Discussion

The rates of deprotonation of phenylnitromethane, eq 6, by hydroxide ion in a variety of Me_2SO–water and methanol–water mixtures have been determined at 20, 30, and 40 °C, using the stopped flow technique. The second-order rate constants are collected in Table I. The rate constant is relatively insensitive to the change from water to methanol–water, as seen from a mere doubling of k_2 at 50 vol % (30.9 mol %) methanol. In contrast, the change from water to 66.67 vol % (33.63 mol %) Me_2SO results in an 88-fold increase in k_2. These findings are consistent with changes in the basicity of the media.



(6)

Bowden[9] has summarized much previous work dealing with acidity and basicity in strongly basic media. The basicity of a medium is given by the expression in eq 7, in which pK_a refers to the ionization of an indicator in water and the concentration terms refer to ionization in the medium in question.

$$H_- = pK_a - \log (\{HA\}/\{A^-\}) \quad (7)$$

H_- therefore represents the increase in the basicity of the medium over pure water brought about by changing activity coefficients. Methanol–water mixtures are anomalous in that there is a *very slight decrease* in H_- at a given hydroxide ion concentration in changing from pure water to pure methanol. The basicity of aqueous methanol solutions is therefore not expected to deviate significantly from that of pure water.

On the other hand, Me_2SO–water mixtures show an orderly

Table II. ΔpK's for Phenylnitromethane and Water in Aqueous Me_2SO at 25 °C

Solvent[a]	Mol % of Me_2SO[b]	log k_2	ΔpK[c]	Excess basicity[d]
Water	0	2.18[e]	−8.83	0.00
33.33% Me_2SO	11.24	2.65	−9.76	0.96
50.00% Me_2SO	20.21	3.24	−10.83	1.87
66.67% Me_2SO	33.63	4.12	−12.14	3.09

[a] Volume percent. [b] All calculations involving densities used those of J. M. G. Cowie and P. M. Toporowski, *Can. J. Chem.*, **39**, 2240 (1961). [c] Calculated from eq 9 with pK for phenylnitromethane of 6.88 (ref 6a). [d] Excess basicity is defined as $H_- - pK_w - \log\{OH^-\} + \log a_{H_2O}$ (ref 11). [e] Taken from ref 7.

increase in H_- from 12.04 for 0.011 M hydroxide ion in pure water to ~22.5 for the same concentration in 95 mol % Me_2SO, and Cox and Stewart[11] have shown that H_- rises rapidly as the last traces of water are removed from the mixture. The enhanced basicity in aqueous Me_2SO is attributed to the competition between hydroxide ions and Me_2SO molecules for hydrogen bond formation with donor water molecules, resulting in an increase in the activity of the hydroxide ion as the Me_2SO content increases.[9]

In their study of the inversion of (−)-methone, Bell and Cox[8] derived ΔpK values as a function of solvent composition based on eq 8 and 9.

$$pK_{H_2O} = H_- + \log(\{H_2O\}/\{OH^-\}) \quad (8)$$

$$\Delta pK = pK^0_{SH} - H_- - \log(\{H_2O\}/\{OH^-\}) \quad (9)$$

Equation 8 gives the expected change in the ionization constant of water, while eq 9 gives the difference in pK between the ionization of (−)-menthone in water and the ionization of water in aqueous Me_2SO mixtures. A plot of log k_2 vs. ΔpK, the usual Brønsted relationship, gave a slope of 0.48 as the Brønsted β coefficient. This compared well with the β value of 0.54 which had been determined for acetone reacting in water with bases of strength up to that of hydroxide ion.

Analogous ΔpK values for the present study are shown in Table II. These values were calculated by use of 6.88 as the pK for phenylnitromethane in water.[6a] The H_- values used were obtained by linear interpolation of those reported by Bowden.[9] The assumption of Bell and Cox that $H_- - \log\{OH^-\}$ is independent of the small hydroxide ion concentrations used in this study was also made. A plot of log k_2 vs. ΔpK gave a least-squares slope (β) of 0.58 ($r = -0.997$). Not surprisingly, a plot of log k_2 vs. excess basicity, as defined by Cox and Stewart,[11] was also linear ($r = 0.996$) and gave nearly the same slope (0.63). Keefe and Munderloh[7] have tabulated the results for the reaction of phenylnitromethane with 14 oxygen and nitrogen bases and with fluoride ion in aqueous solution. They reported a Brønsted β coefficient of 0.57. The agreement between the β value determined in their study and the one reported here indicates that the measurement of deprotonation rates as a function of aqueous Me_2SO composition provides a satisfactory approach to the determination of β for nitro compounds, just as it does for ketones.

It has been pointed out on the basis of both theory[6a,12] and experiment[4c,6a] that Brønsted coefficients are not necessarily good indicators of transition state structure in proton-transfer reactions, despite the fact that Brønsted plots sometimes show the expected curvature.[2a,13] Whether or not a Brønsted plot shows curvature is frequently open to interpretation, and Kemp and Casey[14] have argued that most proton transfers that have been studied give plots that are linear over remarkably large ΔpK ranges. In contrast, Hupe and Wu[15] have recently reported a definitive case in which distinct curvature is seen in the Brønsted plot for deprotonation of 4-(*p*-nitrophenoxy)-2-butanone by an homologous set of bases. They suggest that curvature due to changes in transition state bond orders is essentially not observable over the ΔpK range accessible with the single substrate and homologous set of catalysts typically employed in constructing a Brønsted plot. Instead, they propose that curvature may result from a compromise between the forces of charge stabilization by solvent molecules and the unfavorable energy required to leave solvent molecules in position after proton transfer has occurred.

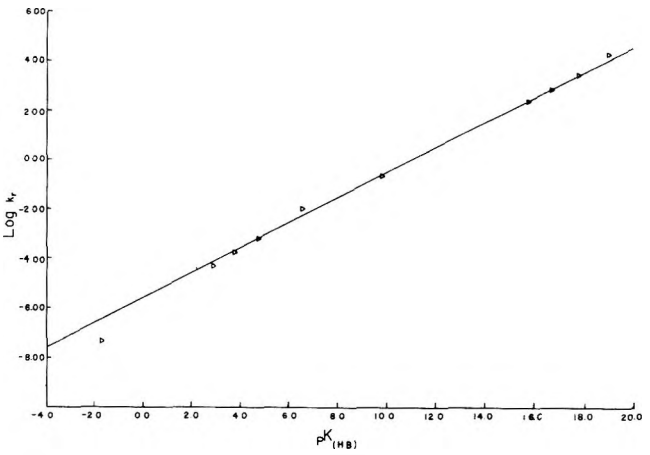


Figure 1. Plot of the logarithm of the rate constant (25 °C) vs. pK for the conjugate acids of oxygen bases used for the deprotonation of phenylnitromethane. Because the point for water ($pK_{(HB)} = -1.86$) deviates significantly, this point was not included in the calculation of the least-squares line shown. The data points for aqueous solutions were taken from ref 7.

In this connection it is interesting to examine the combined data of Keefe and Munderloh[7] and the present study. Reanalysis of the previously reported results by means of a plot of log k_2 vs. pK_{HB} gave a slope of 0.56 with a correlation coefficient of 0.974, which reflects a slight scatter of points. A plot containing only the seven points for oxygen bases gave a β of 0.53 with $r = 0.987$. Addition of the three points for aqueous Me_2SO solutions results in a β of 0.50 and r of 0.994. Interestingly, visual inspection of the plot, shown in Figure 1, reveals that the point for hydroxide ion in water is cleanly on the line, although that for water falls somewhat below it. These combined data clearly indicate that there is no curvature in this case for a series of homologous bases representing a difference of ~16 pK units. The continued linearity of the plot is remarkable for two reasons. First, the activation parameters for the reaction in water differ significantly from those for the reaction in aqueous Me_2SO (vide infra), which suggests that solvational factors are greatly different in the two types of solvents. Consequently, a difference in w_r (the energy required to bring the reactants together, including solvational energy[15]) might have been expected, and this could have modified the slope and/or the intercept in passing to the mixed solvents. Second, the H_- scale in the range presently applied is based on changes in the ionization constants of aromatic amines. Because these acids are structurally dissimilar to carbon acids nonparallel changes in ionization behavior might have been expected. Again, in this respect, phenylnitromethane compares to (−)-methone in introducing no irregularities. Despite these possible complications, the plot continues linearly even though the reaction is carried out under very different solvational circumstances. This behavior is compatible with the interpretation that lack of curvature stems from the essential lack of rehybridization of the central carbon atom as the transition state is reached. Curvature may possibly mean that there is extensive charge delocalization accompanied by structural reorganization as the transition state is attained.

Table III. Activation Parameters for the Deprotonation of Phenylnitromethane by Hydroxide Ion at 25 °C

Solvent[a]	E_a[b]	ΔH^*[b]	ΔS^*[c]
Water[d]	12.2	11.6	−9.4
20.00% MeOH	12.0	11.4	−9.4
50.00% MeOH	12.2	11.6	−8.3
33.33% Me_2SO	9.8	9.2	−15.5
50.00% Me_2SO	8.9	8.3	−15.8
66.67% Me_2SO	7.8	7.2	−15.6

[a] Volume percent. [b] Kcal/mol. [c] Cal/mol deg. [d] Taken from ref 7.

The activation parameters for the deprotonations are collected in Table III. Again, there is a close correspondence between the values for the reaction in aqueous methanol and in pure water. The presence of Me_2SO in the solvent mixture causes a trend toward smaller activation enthalpies. Differences in reaction rate constants are based solely on the enthalpy differences, because the entropy of activation for the reaction is virtually identical in the three mixtures studied and is more negative than in water and methanol–water mixtures.

Caldin, Jarczewski, and Leffek[16] reported activation parameters for the reactions in acetonitrile solution of *p*-nitrophenylnitromethane with tri-*n*-butyl- and triethylamine. These reactions have enthalpies of 6.0 and 6.7 kcal/mol and entropies of −25.2 and −22.1 cal/(mol deg), respectively. The low enthalpies of activation were attributed to the weakness of the bond between the hydrogens and the aliphatic carbon atom, and the large negative entropies of activation were interpreted as an indication of a transition state that is more strongly solvated than the initial state. The values in Table III seem to reflect the same solvational phenomena, in that the enthalpies of activation and entropies of activation are smaller in the mixed solvents than in water. If the proton is partly transferred in the transition state, loosening of the C–H bond and partial formation of an O–H bond should render the proton more susceptible to solvational interaction in the transition state than when it is firmly bonded to the carbon atom in the reactant. Thus, the difference in attractive solvational interactions between incipient water molecule and the hydroxide ion is greater than that between the incipient phenylmethanenitronate anion and the phenylnitromethane molecule. This effect is progressively magnified as the Me_2SO content increases, resulting in progressively decreasing enthalpies of activation. Structural tightening in the solvent is also apparently associated with these interactions, producing relatively large, negative entropies of activation. The constancy of ΔS^* in the three mixtures studied cannot be interpreted unambigously at present.

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Registry No.—Phenylnitromethane, 622-42-4; hydroxide ion, 14280-30-9; dimethyl sulfoxide, 67-68-5; methanol, 67-56-1.

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Chemical Studies on Carcinogenic Nitrosamines. 1. Hydrolysis of α-Acetoxynitrosamines

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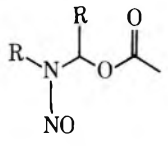
α-Hydroxynitrosamines have been implicated as activated carcinogens. Protected derivatives of these species were found to undergo two mutually exclusive reactions on treatment with simple nucleophiles. Attack at the α carbon resulted in hydrolysis or methanolysis, while attack at the carbonyl carbon by *n*-propylamine, for example, yielded *N*-*n*-propylacetamide and the unstable α-hydroxynitrosamine. The hydrolysis and methanolysis appear to occur via an S_N1 reaction, involving a resonance-stabilized benzylnitrosimminium ion. The deacylation by primary amines was found to be strongly activated by the nitrosamino group, probably via an inductive effect.

Nitrosamines are believed to be activated in vivo to a proximate carcinogen. One possibility for this process that has been frequently discussed is α hydroxylation, following which, decomposition could provide several powerfully electrophilic species capable of alkylating nucleic acids (Scheme I). α-Acetoxynitrosamines (1) are currently receiving considerable attention since on hydrolysis they may give rise to the elusive α-hydroxynitrosamines. Indeed, it has been conclusively demonstrated that such derivatives (1) are both carcinogenic



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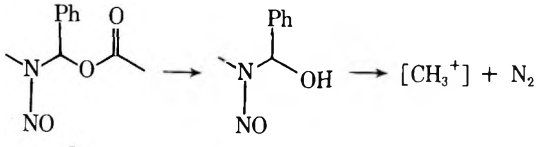
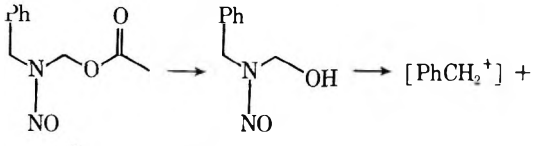
and capable of directly causing bacterial mutations without prior enzymatic activation, an observation that has been attributed to their prior hydrolysis to the α-hydroxynitrosamines.[1-3] Recently[1b] we demonstrated that the two structural isomers of α-acetoxymethylbenzylnitrosamine possessed markedly different mutagenic activity, i.e., **2** was a powerful bacterial mutagen, whereas **3** was essentially inactive, the expected hydrolysis schemes for these compounds being shown in eq 1 and 2.[4]



2

+ PhCHO + OH^- (1)

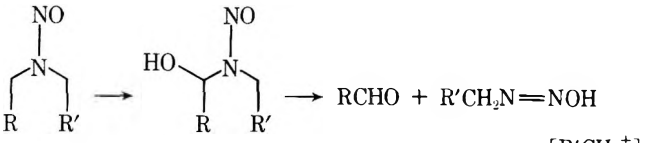


3

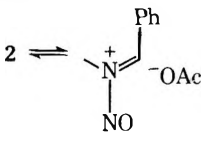
+ CH_2O + OH^- (2)

In experiments to effect mild hydrolysis of the ester functions of these two compounds, they were both treated in a buffered solution with hog liver esterase. Both compounds hydrolyzed readily, but **2** reacted three times more rapidly. The relative lability of **2** was much more apparent in the absence of enzyme. While **3** was stable in aqueous neutral solution, **2** displayed a half-life of only 19 min in water. Rapid hydrolysis of **2** was also apparent in pH 8 buffer, while **3** hydrolyzed some 32-fold more slowly. In weakly acidic solutions

Scheme I



(pH 3), **2** again hydrolyzed extremely rapidly, while **3** was stable. We attribute the striking reactivity of **2** to its ability to form a highly resonance-stabilized benzylnitrosimminium ion, **4** (eq 3). This type of S_N1 process, via imminium ion,[12] **4**,



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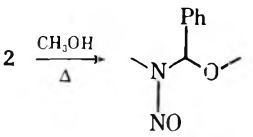
involving fission at the alkyl–oxygen bond, is unlikely to be operative for **3**, as the resultant cation would lack benzylic stabilization. It is instead more likely that the slow hydrolysis of **3** in pH 8 buffer involves the more conventional acyl–oxygen fission.

To further investigate the behavior of **2** and **3** toward nucleophilic substitution, each compound was treated with dry methanol at reflux for about 24 h (eq 4). The methyl ether **5**



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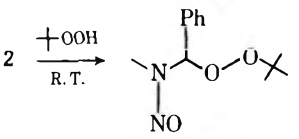

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was cleanly produced from **2** in quantitative yield (79% isolated); no reaction occurred at 25 °C with or without *p*-toluenesulfonic acid catalysis. When isomer **3** was refluxed with dry methanol, however, only the starting material was recovered. Again it appears that **2** yields the cation **4**, which is trapped by methanol, while **3** cannot likewise react. Additionally, **2** was treated with *tert*-butyl hydroperoxide for 2 weeks at room temperature (eq 5). The α-peroxynitrosamine **6** formed in nearly quantitative yield. If a sufficiently mild

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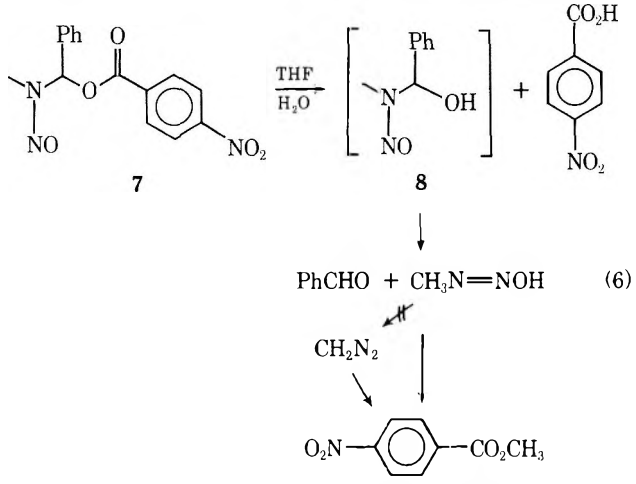
reductive method can be found, this compound could prove to be a precursor of the α-hydroxynitrosamine **8**. Exchange of the acyloxy function was found to occur when **2** was refluxed in methylene chloride solution with an excess of chloroacetic acid. The identity of methyl(α-chloroacetoxybenzyl)nitrosamine was confirmed by comparison with an authentic sample prepared in standard fashion.

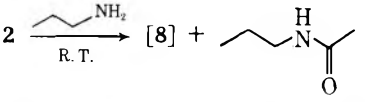
In an effort to trap ion **4** with water, we hydrolyzed the nitrosamine **7** in THF containing 1 equiv of H_2O at reflux. Under these conditions, methyl *p*-nitrobenzoate was isolated in 75% crude yield. It seems likely that initial replacement of *p*-nitrobenzoate by hydroxyl is followed by collapse of the α-hydroxynitrosamine to methyl diazotate, which directly alkylates the *p*-nitrobenzoic acid (eq 6). In addition, re-



(6)

placement of the water in the hydrolysis experiment with deuterium oxide gave methyl *p*-nitrobenzoate, containing no deuterium, thereby eliminating diazomethane as a possible alkylating intermediate.[5]

In sharp contrast to the above behavior, when nitrosamine **2** was exposed to neat *n*-propylamine at room temperature for 5 min, a smooth exothermic reaction occurred (eq 7). *N*-*n*-



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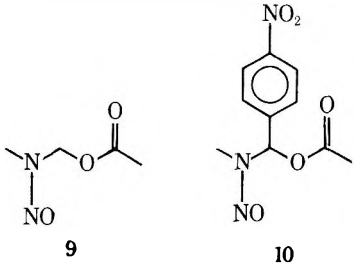
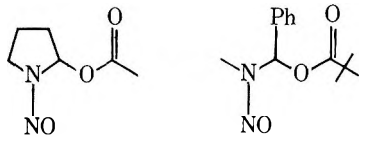
Propylacetamide was isolated in quantitative yield and a mixture of benzaldehyde and *N*-benzylidene-*n*-propylamine was also isolated. These products clearly result from nucleophilic attack at the carbonyl carbon, followed by spontaneous decomposition of the α-hydroxynitrosamine **8**, vide supra. The resulting benzaldehyde is incompletely converted to the imine under the reaction conditions.

The generality of this exothermic reaction of α-acetoxynitrosamines with *n*-propylamine was demonstrated. Thus, α-acetoxydimethylnitrosamine (**9**), prepared according to



9 **10**

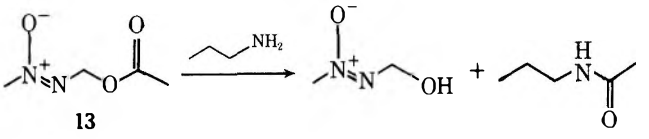
Keefer,[2a] reacted as rapidly with *n*-propylamine as did **2** to give a 68% isolated yield of the amide. Nitrosamine **3** gave an exothermic reaction on treatment with the amine at 25 °C, resulting in an inseparable mixture of the amide and an unknown aromatic impurity. Nitrosamine **10** reacted readily at 0 °C in like fashion. The cyclic α-acetoxynitrosamine **11** similarly gave a 77% isolated yield of *n*-propylacetamide.



11 **12**

The reaction with *n*-propylamine is subject to steric effects. The α-pivalate **12** reacted exclusively at the carbonyl carbon to give cleanly a 1:1 mixture of *n*-propylpivalamide and *N*-benzylidene-*n*-propylamine. However, the reaction required 40 h at reflux (48 °C) to reach completion. Though a steric effect is not unexpected, its magnitude is remarkable.

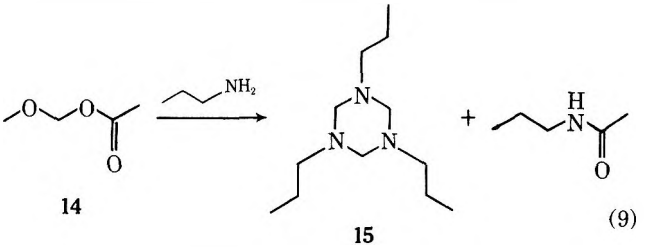
The nature of the carbonyl activation by an α-nitrosamino functionality was probed by replacing the nitrosamino group by other functional groups possessing the same inductive effect. Thus, methylazoxymethanol acetate (**13**), which is isomeric with **9**, was treated with *n*-propylamine (eq 8) under the



13

(8)

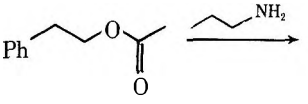
usual conditions. The reaction was complete within 35 min at 25 °C without any noticeable exotherm, and the resulting methylazoxymethanol and *n*-propylacetamide could not be separated by preparative TLC. Methoxymethyl acetate (**14**) was similarly exposed to *n*-propylamine (eq 9). In this ex-



14 **15**

(9)

periment an exothermic reaction occurred to produce a quantitative yield of *n*-propylacetamide and hexahydro-1,3,5-tripropyl-*s*-triazine (**15**). Apparently, the liberated formaldehyde is converted to the imine, which spontaneously trimerizes under the reaction conditions. As an unactivated control 2-phenylethyl acetate (**16**) was treated with the amine under the usual conditions (eq 10). No reaction occurred and

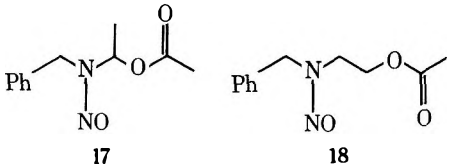


(10)

16

the ester was recovered unchanged. These experiments imply that the observed carbonyl activation by the α-nitrosamino group is purely an inductive effect.

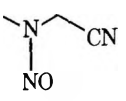
The importance of the α position with regard to this carbonyl activation was studied by comparing the reactivity of benzyl(α-acetoxyethyl)nitrosamine (**17**) and benzyl(β-acetoxyethyl)nitrosamine (**18**). The α-acetoxy isomer **17** gave the



17 **18**

usual exothermic reaction with *n*-propylamine, resulting in the isolation of a 78% yield of *n*-propylacetamide, while under identical conditions the β-acetoxy isomer **18** gave no exotherm and was only about 50% complete (NMR). In the latter experiment, a 46% isolated yield of the liberated alcohol was

realized and 12% of the unreacted starting material was recovered. The difference in reactivity between **17** and **18** is reminiscent of the hydrolysis of α- and β-cyanonitrosamines recently reported by Harrington and co-workers.[6] They observed a rate enhancement in the hydrolysis of the cyano group which was due to interaction with the nitrosamino function. Furthermore, they found that the rate of hydrolysis



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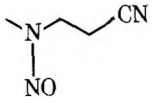

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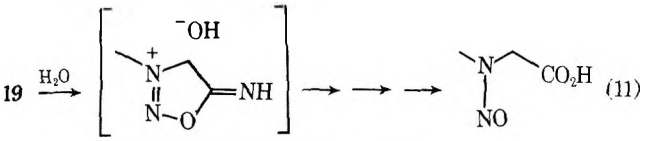
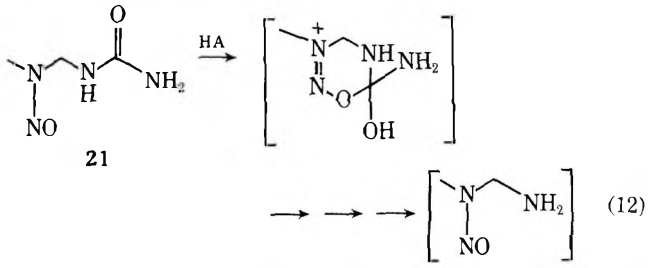
was 500 times faster for the α-isomer **19** than for the β-isomer **20**. They invoked a five-membered cyclic intermediate in the α case (eq 11) and a six-membered cyclic intermediate in the



(11)

β case. This type of cyclic intermediate (eq 12) was also suggested by Michejda and co-workers in the hydrolysis of α-ureidonitrosamines (**21**).[7]



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(12)

The correlation of this carbonyl activation with the IR stretching frequency of the ester C=O group was examined. The α-acetoxynitrosamines **2**, **3**, **9**, and **17** have C=O stretching bands at 1750 cm^{-1} and all react exothermically with *n*-propylamine at room temperature. Nitrosamine **10**, with an unusually high carbonyl stretch at 1765 cm^{-1}, also reacted readily. The cyclic α-acetoxynitrosamine **11** and the α-pivaloxynitrosamine **12** have C=O stretches at 1740 cm^{-1}. The former reacted exothermically under the usual conditions; the latter was very sluggish, but this can be attributed to steric effects. The β-acetoxynitrosamine **18** has a C=O stretch at 1740 cm^{-1} and reacted slowly under conditions where the α-isomer **17** reacted exothermically and completely. Methylazoxymethanol acetate (**13**) has a C=O stretch at 1750 cm^{-1} and reacted as rapidly as the α-acetoxynitrosamines. The control compound, 2-phenylethyl acetate (**16**) has a "normal" C=O stretch at 1735 cm^{-1} and failed to react under the usual conditions. Methoxymethyl acetate (**14**) has a C=O stretch at 1745 cm^{-1} and reacted exothermically with *n*-propylamine as did the α-acetoxynitrosamines. From these data we may conclude that acetate esters having an α-nitrosamino group, α-azoxy group, or α-methoxy group (1745–1750 cm^{-1}) are sufficiently activated to react exothermically and rapidly with *n*-propylamine, while those having a β-nitrosamino group (1740 cm^{-1}) react slowly. Normal esters having C=O stretching at 1735 cm^{-1} or lower do not react under these conditions. Since the inductively similar, but structurally dissimilar, nitrosamino, azoxy, and methoxy groups activate equally well, it appears that the carbonyl activation which we have observed with the nitrosamino group is purely an inductive effect and does not involve a cyclic intermediate.

Experimental Section

General. Solvents and commercially available starting materials were reagent grade and were used as received unless specified otherwise. Thin-layer chromatograms were run on Analtech analytical silica gel plates. Preparative plates were prepared from EM Laboratories plate silica gel. Melting points were taken with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 700 instrument, and NMR spectra were recorded with a Varian T-60 or a Hitachi Perkin-Elmer R22 spectrometer using tetramethylsilane as an internal standard (δ 0). The high-resolution mass spectra were obtained through the courtesy of Dr. Catherine E. Costello at M.I.T. The microanalyses were performed by Robertson Laboratory, Florham Park, N.J.

Hydrolysis of 2 and 3. Compounds **2** and **3** (5 μmol) were dissolved in 1.0 mL of buffer (20 mM trimethylamine hydrochloride, pH 8.0) at room temperature, and 5 units of esterase was added. [EC 3.1.1.1. hog liver esterase (Sigma): 1 unit hydrolyzes 1 μmol of butyrate per min at pH 8.0 and 25 °C]. Similar solutions of **2** and **3** were prepared, without the addition of enzyme, in distilled water, in buffer, and in 0.001 N HCl (pH 3.0). The disappearance of **2** and **3** with time, and the concomitant appearance of the products benzaldehyde and benzyl alcohol, respectively, was monitored by HPLC with UV detection at 254 nm. Chromatography was performed on a reverse-phase μC_{18}-Bondapak column (Waters Associates, Milford, Mass.) using a mobile phase of MeOH–H_2O (50:50), delivered at 1.5 mL/min. The decreasing size of the absorption peaks due to **2** and **3** from successive aliquots allowed determination of the amount of each compound remaining at a given time under each reaction condition. In all cases, hydrolyses were first order with respect to **2** and **3**. Linear regression analysis of the data gave the following results:

	Half-lives $\left(\text{times at which } \frac{[\text{compound}]}{[\text{compound}]_0} = \frac{1}{2}\right)$			
	In water	In acid, pH 3.0	In buffer, pH 8.0	In buffer, pH 8.0, with enzyme
2	19 min	17 min	26 min	16 min
3	stable	stable	16 h	1 h

Methyl(α-acetoxybenzyl)nitrosamine (2) was prepared as previously described.[1b] Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 58.06; H, 5.81; N, 12.98.

Benzyl(acetoxymethyl)nitrosamine (3) was prepared as previously described.[1b] Anal. Calcd for $C_{10}H_{12}N_2O_3$: C, 57.69; H, 5.81; N, 13.45. Found: C, 57.80; H, 6.01; N, 12.76.

Treatment of 2 with Methanol; Methyl(α-methoxybenzyl)-nitrosamine (5). Compound **2** (1.0 mmol, 0.208 g) was dissolved in dry methanol (4 mL) and allowed to stand at 25 °C. After 1 h, TLC analysis indicated that no reaction had occurred; however, refluxing for 16 h resulted in a complete reaction. The solvent was removed in vacuo, giving 0.224 g of yellow liquid which was purified by preparative TLC on silica gel (hexane–ethyl acetate, 2:1). This gave 0.142 g (79%) of pure methyl(α-methoxybenzyl)nitrosamine (**5**), which was a very pale-yellow oil. By NMR integration, the compound exists almost exclusively as the *E* isomer: IR (film) 2950 (w), 1470 (s), 1350 (s), 1210 (s), and 1110 (s) cm^{-1}; NMR ($CDCl_3$) δ 2.77 (s, 3 H), 3.47 (s, 3 H), 6.65 (s, 1 H), and 7.29 (s, 5 H). The high-resolution mass spectrum did not show a molecular ion. A satisfactory peak was obtained for the loss of CH_3O. Anal. Calcd for $C_8H_9N_2O$: 149.07148 ($M^+ - CH_3O$). Found: 149.07250.

Treatment of 2 with Methanol and *p*-Toluenesulfonic Acid. Compound **2** (0.50 mmol, 0.104 g) was dissolved in dry methanol (2 mL) at 25 °C and one crystal of *p*-toluenesulfonic acid was added. The acid dissolved and the pale-yellow solution was allowed to stand for 22 h without any detectable reaction by TLC.

Treatment of 3 with Methanol. Compound **3** (0.60 mmol, 0.125 g) was dissolved in dry methanol (5 mL) and refluxed for 24 h without any detectable reaction by TLC or NMR. The starting material was quantitatively recovered.

Methyl(α-*tert*-butylperoxybenzyl)nitrosamine (6). Compound **2** (2 mmol, 0.4164 g) was stirred in *tert*-butyl hydroperoxide (8 mL) under N_2 for 2 weeks. A crude yellow liquid of high purity was obtained by simple removal of the hydroperoxide in vacuo. It was rinsed with several portions of CH_2Cl_2 and dried in vacuo. Filtration through a short column of silica with hexane–ether (9:1) removed a small amount of baseline impurity to give, after drying, 0.451 g (95%) of **6**. By NMR integration, the compound exists as a mixture of *E*:*Z* isomers (approximately 98:2, respectively): IR (film) 1470 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.33 (s, *E*-$C(CH_3)_3$), 2.84 (s, *E*-CH_3), 3.68 (s, *Z*-CH_3), 2.84 (s, *E*-CH_3), 3.68 (s, *Z*-CH_3), 7.30 (s, *E*-CH), and 7.37 (s, *E*-C_6H_5).

Anal. Calcd for $C_{12}H_{18}N_2O_3$: C, 60.49; H, 7.61; N, 11.76. Found: C, 60.58; H, 7.93; N, 11.32.

Methyl(α-chloroacetoxybenzyl)nitrosamine. This compound was prepared according to Wiessler.[8] Passage through a short column

of silica gel with benzene elution gave a yellow liquid which crystallized on standing (86%). By NMR integration the compound exists as a mixture of *E*:*Z* isomers (approximately 95:5, respectively). The analytical sample was recrystallized from hexane: mp 58–60 °C; IR ($CHCl_3$) 1765 cm^{-1}; NMR ($CDCl_3$) δ 2.84 (s, *E*-CH_3), 3.59 (s, *Z*-CH_3), 4.18 (s, *Z*-CH_2), 4.26 (s, *E*-CH_2), 7.47 (s, *E*-C_6H_5), 8.41 (s, *E*-CH).

Anal. Calcd for $C_{10}H_{11}ClN_2O_3$: C, 49.50; H, 4.57; N, 11.57; Cl, 14.61. Found: C, 49.43; H, 4.52; N, 11.78; Cl, 14.60.

Treatment of 2 with Chloroacetic Acid. Compound 2 (1.0 mmol, 0.208 g) and chloroacetic acid (10 mmol, 0.945 g) were dissolved in methylene chloride (1 mL). The resulting solution was allowed to stand at 25 °C for 3.5 h without any detectable reaction by TLC. After refluxing for 19 h the reaction solution was worked up by pouring into a separatory funnel containing methylene chloride (20 mL) and saturated sodium bicarbonate (30 mL). The organic layer was separated, washed with water, and dried over sodium sulfate. The solvent was removed in vacuo, yielding 0.153 g of yellow liquid which by NMR was a 3:2 mixture of chloroacetoxynitrosamine and benzaldehyde (probably formed on workup). A trace of starting acetoxy compound was also present. Since the mixture could not be separated on an analytical TLC plate, no purification was attempted.

Methyl(α-*p*-nitrobenzoyloxybenzyl)nitrosamine (7). This compound was prepared in 55% crude yield according to Wiessler.[8] By NMR integration, the compound exists as a mixture of *E*:*Z* isomers (approximately 96:4, respectively). Recrystallization from benzene–hexane gave a 49% yield of 7: mp 115–116 °C (lit.[8] mp 115–116 °C); NMR ($CDCl_3$) δ 3.02 (s, *E*-CH_3), 3.73 (s, *Z*-CH_3), 8.37 (s, $(ABq)_2$, *E*-C_6H_4), and 8.62 (s, *E*-CH).

Hydrolysis of Methyl(α-*p*-nitrobenzoyloxybenzyl)nitrosamine (7). Compound 7 (0.50 mmol, 0.157 g) and water (0.50 mmol, 0.009 g) were dissolved in distilled THF (0.5 mL) and allowed to stand for 45 min at 25 °C without any detectable reaction by TLC. Refluxing for 23 h followed by removal of the solvent in vacuo gave 0.068 g (75%) of pale-yellow solid which by NMR was found to be pure methyl *p*-nitrobenzoate. Purification by preparative TLC on silica with hexane–ethyl acetate (9:1) afforded 0.036 g of pale-yellow crystals, mp 93–94 °C (lit.[9] mp 95–96 °C). The mixture melting point with an authentic sample of methyl *p*-nitrobenzoate was 93–94 °C.

Hydrolysis of 7 with D_2O. Compound 7 (0.50 mmol, 0.157 g) and deuterium oxide (0.50 mmol, 0.010 g) were dissolved in distilled THF (1.5 mL), and the solution was refluxed for 30 h, after which time most of the solvent had evaporated. The reaction was found to be incomplete by TLC, so an additional (0.50 mmol) portion of D_2O and more THF (1.5 mL) were added, and refluxing was continued for an additional 26 h after which time the reaction was still incomplete. Removal of the solvent in vacuo gave 0.130 g of pale-yellow solid, which by TLC contained benzaldehyde, methyl *p*-nitrobenzoate, and starting material. Preparative TLC on silica with hexane–ethyl acetate (9:1) gave 0.038 g (42%) of pure methyl *p*-nitrobenzoate, mp 93–94 °C. An NMR spectrum of this material was identical with that from the hydrolysis experiment with H_2O; no 1:1:1 triplet characteristic of $-CH_2D$ was observed.[10]

Control for the Hydrolysis of 7. Methanol (1.0 mmol, 0.040 mL) and *p*-nitrobenzoic acid (1.0 mmol, 0.167 g) were dissolved in distilled THF (1 mL). The resulting solution was refluxed for 21 h. The solvent was removed in vacuo, giving 0.151 g of recovered *p*-nitrobenzoic acid, mp 238–240 °C. The starting *p*-nitrobenzoic acid melted at 239–240 °C.

Treatment of 2 with *n*-Propylamine. Compound 2 (3.0 mmol, 0.634 g) was dissolved in *n*-propylamine (Eastman) (5 mL) and allowed to stand for 5 min at ambient temperature. TLC analysis at this time revealed that the reaction was complete. The excess amine was removed in vacuo, giving a 0.791 g of yellow liquid which was found to give two major spots on TLC. Preparative TLC as above gave 0.194 g of pale-yellow liquid (44%) in the upper band, which was identified as a 2:1 mixture of *N*-benzylidene-*n*-propylamine and benzaldehyde (NMR). The lower band gave 0.308 g (100%) of *n*-propylacetamide, which was identified by comparison of the IR and NMR spectra to those from an authentic sample.

Methyl(acetoxymethyl)nitrosamine (9). This compound was prepared in 9% yield as described by Keefer.[2a] The NMR spectrum of the crude product was identical with that reported by Keefer and revealed no impurities.

Treatment of Methyl(acetoxymethyl)nitrosamine (9) with *n*-Propylamine. Compound 9 (1.0 mmol, 0.132 g) was dissolved in *n*-propylamine (1 mL). TLC analysis after 3 min revealed that the reaction was complete. After 20 min, the excess amine was removed in vacuo, yielding 0.170 g of yellow oil. Preparative TLC on silica using chloroform–methanol (10:1) gave 0.069 g (68%) of pure *n*-propylacetamide, which was identified by comparison of the IR and NMR spectra with those from an authentic sample.

Treatment of Benzyl(acetoxymethyl)nitrosamine (3) with *n*-Propylamine. Compound 3 (3.0 mmol, 0.624 g) was dissolved in *n*-propylamine (2 mL). The usual exothermic reaction occurred and after 18 min the excess amine was removed in vacuo. This afforded 0.818 g of yellow liquid which by NMR contained *n*-propylacetamide and an unknown aromatic impurity, which was not benzyl-*n*-propylamine or benzyl alcohol. Filtration of the crude product through a short column of silica, followed by preparative TLC, gave a mixture of *n*-propylacetamide and the aromatic impurity. The usual solvent systems failed to separate these two compounds.

Methyl(α-acetoxy-*p*-nitrobenzyl)nitrosamine (10) was prepared on a 50-mmol scale by the method of Wiessler.[8] Compound 10 was purified by washing with saturated sodium bisulfite, followed by column chromatography [silica gel H, EM reagent; benzene–ether (19:1)] in 11% yield as light-yellow crystals. By NMR integration the compound exists as a mixture of *E*:*Z* isomers (approximately 95:5, respectively). The analytical sample was recrystallized from hexane–chloroform: mp 108–109 °C; IR ($CHCl_3$) 1765 (s) and 1480 (s) cm^{-1}; NMR ($CDCl_3$) δ 2.29 (s, *Z*-CH_3), 2.36 (s, *E*-CH_3), 2.89 (s, *E*-CH_3), 3.64 (s, *Z*-CH_3), 8.06 ($(ABq)_2$, J_{AB} = 9 Hz, $\Delta\nu_{AB}$ = 0.583 ppm, *E*-C_6H_4), and 8.46 (s, *E*-CH).

Anal. Calcd for $C_{10}H_{11}N_3O_5$: C, 47.43; H, 4.38; N, 16.60. Found: C, 47.43; H, 4.41; N, 16.80.

Treatment of 10 with *n*-Propylamine. Compound 10 (0.5 mmol, 0.127 g) was added at 0 °C to *n*-propylamine (3 mL). Analytical TLC (eluent either ether or benzene) of an aliquot (taken immediately after mixing) showed the complete disappearance of starting material. Concentration in vacuo gave a clean 1:1 mixture of *n*-propylacetamide and *N*-(*p*-nitrobenzylidene)-*n*-propylamine as determined by NMR.

α-Acetoxynitrosopyrrolidine (11) was prepared as previously described.[1a]

Treatment of α-Acetoxynitrosopyrrolidine (11) with *n*-Propylamine. Pure 11 (0.221 mmol, 0.035 g) was dissolved in *n*-propylamine (0.5 mL), resulting in an immediate exotherm. After 2 min, TLC showed that the reaction was complete. After 14 min, the excess amine was removed in vacuo to give 0.061 g of yellow liquid which by NMR was essentially pure *n*-propylacetamide. Preparative TLC on silica with hexane–ethyl acetate (2:1) afforded 0.017 g (77%) of pale-yellow oil whose IR spectrum was identical with that from an authentic sample of amide.

Methyl(α-pivaloyloxybenzyl)nitrosamine (12) was prepared on a 10-mmol scale by the method of Wiessler.[8] Compound 12 was purified by column chromatography (silica gel H; EM reagent; benzene–ether, 19:1) in 29% yield as a light-yellow liquid. By NMR intergration, the compound exists as a mixture of *E*:*Z* isomers (approximately 97:3, respectively): IR (film) 1740 (s) and 1475 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.34 (s, *E*-$C(CH_3)_3$), 2.86 (s, *E*-CH_3), 3.60 (s, *Z*-CH_3), 7.48 (s, *E*-C_6H_5), and 8.36 (*E*-CH).

Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19. Found: C, 62.53; H, 7.20; N, 11.09.

Treatment of 12 with *n*-Propylamine. Compound 12 (0.571 mmol, 0.143 g) was dissolved in *n*-propylamine (3 mL). Analytical TLC after stirring for 1 h at ambient temperature indicated no reaction; 40 h at reflux was necessary to effect complete reaction. The reaction was conveniently followed by analytical TLC [benzene–ether (9:1)]. Concentration in vacuo gave a clean 1:1 mixture of *N*-(*n*-propyl)pivalamide and *N*-benzylidene-*n*-propylamine as determined by NMR.

Treatment of Methylazoxymethanol Acetate (13) with *n*-Propylamine. Compound 13 (0.50 mmol, 0.0661 g) was dissolved in *n*-propylamine (1 mL) as usual. After 35 min at 25 °C (no exotherm or color change), the excess amine was removed in vacuo to give 0.113 g of pale-yellow liquid. NMR analysis revealed that the crude product was a 1:1 mixture of *n*-propylacetamide and methylazoxymethanol.[11] The reaction was complete. Preparative TLC on silica ($CHCl_3$–CH_3OH, 8:1) failed to separate the two products.

Treatment of Methoxymethyl Acetate with *n*-Propylamine. To a 10-mL flask were added methoxymethyl acetate (Eastman) (0.312 g, 3.0 mmol) and *n*-propylamine (3 mL). The resulting colorless solution became warm to the touch after 2 min. After standing at ambient temperature for 30 min, the excess amine was removed in vacuo, giving 0.506 g (98%) of yellow liquid, which contained no ester by IR and appeared to be a mixture of *n*-propylacetamide and hexahydro-1,3,5-tripropyl-s-triazine (3:1) by NMR. A Sadtler NMR spectrum (8949) for the triazine was superimposable on the unknown signals in the mixture NMR. Attempted separation of the two products on silica using hexane–ethyl acetate (1:1) gave 0.337 g (theoretical 0.303 g) of pale-yellow liquid from the band with

the same R_f as *n*-propylacetamide. An NMR spectrum revealed that the amide still contained a small amount of triazine.

Treatment of 2-Phenylethyl Acetate (16) with n-Propylamine. To a 10-mL flask were added 2-phenylethyl acetate (0.279 g, 1.7 mmol) and anhydrous *n*-propylamine (2 mL). The resulting colorless solution, from which no heat was evolved, was allowed to stand at room temperature for 30 min before the amine was removed in vacuo. This gave 0.272 g (99%) of pale-yellow liquid, which by NMR was pure unchanged starting material.

Benzyl(α-acetoxyethyl)nitrosamine (17). This compound was prepared using the method developed by Keefer[2a] by substituting acetaldehyde for paraformaldehyde. The crude black product obtained as described by Keefer was filtered through silica with benzene to give 13.7 g (31%) of yellow liquid which by TLC and NMR contained benzyl acetate (major) and **17** (minor). Distillation at 0.7 mm and 50–54 °C gave 8.7 g (29%) of pure benzyl acetate. The residue, which was predominantly **17** (5.0 g, 11%), was purified by preparative TLC on silica using hexane–ethyl acetate (9:1). From 0.539 g of crude **17**, 0.303 g of pure material was obtained. By NMR integration, the compound exists almost exclusively as the *E* isomer: IR (film) 3000 (m), 1750 (s), 1480 (s), 1380 (s), 1220 (s), and 1070 (s) cm^{-1}; NMR ($CDCl_3$) δ 1.82 (d, J = 6 Hz, *E*-CH_3), 2.02 (s, *E*-CH_3), 4.85 (ABq, J_{AB} = 15 Hz, $\Delta\nu_{AB}$ = 0.342 ppm, *E*-CH_2), and 6.9–7.5 (m, 6 H).

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60; mol wt, 222.10044. Found: C, 59.84; H, 6.44; N, 12.33; mol wt, 222.10127.

Treatment of 17 with n-Propylamine. Compound **17** (1.36 mmol, 0.303 g) was treated with *n*-propylamine (2 mL) as described above for 30 min. The usual exothermic reaction occurred to give after workup 0.428 g of yellow-orange oil, which was found by NMR to contain *n*-propylacetamide and an unknown aromatic impurity. Preparative TLC with hexane–ethyl acetate (2:1) gave from the area just above the baseline 0.107 g (78%) of yellow liquid which was pure amide by NMR.

***N*-Nitroso-*N*-benzylethanolamine.** *N*-Benzylethanolamine (Aldrich) (3.0 mmol, 0.453 g) and distilled triethylamine (3.3 mmol, 0.458 mL) were dissolved in methylene chloride (3 mL), and the resulting solution was cooled in an ice bath while flushing with N_2. After 10 min nitrosyl chloride (1.44 M, 3.3 mmol) in methylene chloride was added via syringe and the bath was removed. The mixture was allowed to come to 25 °C over a 30-min period before adding excess dry ether. The mixture was filtered and the filtrate concentrated to dryness in vacuo to give 0.536 g (99%) of yellow liquid which was quite pure by TLC. Filtration of a benzene solution through a small column of silica (15 g) removed the high running impurities. The alcohol was eluted with benzene–ether (4:1) to give 0.378 g (70%) of pale-yellow liquid which was pure product by NMR. By NMR integration, the compound exists as a mixture of *E*:*Z* isomers (approximately 39:61, respectively): IR (film) 3400 (broad), 2950 (w), 1460 (m), and 1145 (s) cm^{-1}; NMR ($CDCl_3$) δ 3.40 (broad s, 1 H), 3.62 (s, *Z*-A_2B_2), 4.02 (m, *E*-A_2B_2), 4.85 (s, *E*-CH_2), 5.32 (s, *Z*-CH_2), and 6.9–7.4 (m, 5 H).

Anal. Calcd for $C_9H_{12}N_2O_2$: mol wt, 180.08987. Found: mol wt, 180.08918.

Benzyl(β-acetoxyethyl)nitrosamine (18). *N*-Nitroso-*N*-benzylethanolamine (0.833 mmol, 0.150 g) was dissolved in acetic anhydride (1 mL) and a trace of concentrated H_2SO_4 was added from a capillary tube. The yellow solution was allowed to stand overnight at 25 °C, after which time the acetylation was found to be complete by TLC. Removal of the excess acetic anhydride and acetic acid in vacuo gave 0.157 g (85%) of yellow liquid which was pure (**18**) by NMR. By NMR integration, the compound exists as a mixture of *E*:*Z* isomers (approximately 51:49, respectively): IR (film) 2975 (m), 1740 (s), 1460 (m), and 1240 (s) cm^{-1}; NMR ($CDCl_3$) δ 2.05 (s, *Z*-CH_3), 2.07 (s, *E*-CH_3), 3.90 (m, *Z*-A_2B_2), 4.38 (s, *E*-A_2B_2), 4.90 (s, *E*-CH_2), 5.38 (s, *Z*-CH_2), and 7.0–7.5 (m, 5 H).

Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60; mol wt, 222.10044. Found: C, 58.98; H, 6.41; N, 12.26; mol wt, 222.10156.

Treatment of 18 with n-Propylamine. Compound **18** (0.707 mmol, 0.157 g) was dissolved in *n*-propylamine (1 mL) and allowed to stand at 25 °C for 30 min before removing the excess amine in vacuo. This gave 0.345 g of yellow liquid which by NMR was a mixture of *n*-propylacetamide, **18**, and *N*-nitroso-*N*-benzylethanolamine. Preparative TLC on silica using benzene–ether (4:1) gave 0.019 g (12%) of starting ester (NMR) and 0.058 g (46%) of *N*-nitroso-*N*-benzylethanolamine (NMR). The amide was not isolated.

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Registry No.—**2**, 53198-46-2; **3**, 63531-81-7; (*E*)-**5**, 65815-21-6; (*E*)-**6**, 65815-22-7; (*E*)-**6**, 65815-24-9; (*E*)-**7**, 65815-25-0; (*Z*)-**7**, 65815-26-1; **9**, 56856-83-8; (*E*)-**10**, 65815-28-3; (*Z*)-**10**, 65815-30-7; **11**, 59435-85-7; (*E*)-**12**, 65815-31-8; (*Z*)-**12**, 65815-32-9; **13**, 592-62-1; **14**, 4382-76-7; **15**, 13036-81-2; **16**, 103-45-7; **17**, 65815-34-1; **18**, 65815-36-3; methyl-(*E*)-(α-chloroacetoxybenzyl)nitrosamine, 65815-38-5; methyl-(*Z*)-(α-chloroacetoxybenzyl)nitrosamine, 65815-39-6; chloroacetoxynitrosamine, 65815-40-9; methyl *p*-nitrobenzoate, 619-50-1; *p*-nitrobenzoic acid, 62-23-7; *n*-propylamine, 107-10-8; *N*-benzylidine-*n*-propylamine, 6852-55-7; *n*-propylacetamide, 5331-48-6; *N*-(*p*-nitrobenzylidene)-*n*-propylamine, 25105-59-3; *N*-(*n*-propyl)-pivalamide, 41391-97-3; methylazoxymethanol, 590-96-5; (*E*)-*N*-nitroso-*N*-benzylethanolamine, 65815-41-0; (*Z*)-*N*-nitroso-*N*-benzylethanolamine, 65815-42-1; *N*-benzylethanolamine, 104-63-2.

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Reactions of Diaryliodonium Fluoroborates with Inorganic Anions

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Reactions of diphenyliodonium and phenyl-*p*-tolyliodonium fluoroborates with sodium nitrite, sodium azide, sodium thiocyanate, and potassium cyanide have been investigated. Nitrobenzene was obtained in 72–76% yield by treatment of diphenyliodonium fluoroborate with sodium nitrite in aqueous dioxane for 50 h at 100 °C. Phenyl azide was obtained in 97–99% yield by reaction of the iodonium salt with sodium azide at 80 °C for 2 h in the same solvent. Phenyl thiocyanate was obtained in 97–98% yield and phenyl isothiocyanate in 0.28–0.30% yield by treatment of the iodonium salt with sodium thiocyanate in the same solvent for 24 h at 100 °C. The reaction with potassium cyanide proved to be more troublesome, but a 42% yield of benzonitrile was ultimately obtained by reaction of the iodonium salt with potassium cyanide in aqueous dioxane for 50 h at 100 °C, 5 equiv of 1,1-diphenylethylene being added to the reaction mixture to suppress a competing free-radical chain reaction leading to benzene as a major product. Competition reactions have also been carried out, and interpretations of the results are presented.

In the reactions of sodium alkoxides with diaryliodonium salts, a radical chain reaction, which produces aromatic hydrocarbons, usually competes with the S_NAr reaction,[2] which gives alkyl aryl ethers.[3] In fact, the aromatic hydrocarbon products frequently are formed in greater yields than the alkyl ethers, unless radical traps are used as additives to inhibit the chain reactions. The most efficient inhibitor of the chain reactions leading to hydrocarbon products proved to be 1,1-diphenylethylene in the alkoxide reactions. By way of contrast, Beringer and his colleagues[4] have provided examples of reactions of diaryliodonium salts with simple, inorganic anions which appear to involve only an S_NAr reaction. For example, the reaction of diphenyliodonium bromide with sodium nitrite in aqueous solution gave nitrobenzene in 66% yield, while the reaction of phenyl-*o*-nitrophenyliodonium bromide with the same reagent afforded *o*-dinitrobenzene in 84% yield. No benzene was reported to have been formed. On the other hand, the reaction of diphenyliodonium bromide with potassium cyanide in ethanol solution gave but a 23% yield of benzonitrile (actually isolated as benzoic acid), thus suggesting the incursion of a major competing reaction.

In order to gain some insight into the factors determining whether the reaction of a diaryliodonium salt with a relatively simple inorganic anion will proceed mainly by an S_NAr reaction or by (presumably) a radical chain reaction, we decided to investigate in some depth the reactions of diphenyliodonium fluoroborate with sodium nitrite, sodium azide, sodium thiocyanate, and potassium cyanide, respectively.[5]

As shown in Table I, nitrobenzene was obtained in 72–76% yield by treatment of diphenyliodonium fluoroborate with sodium nitrite in aqueous dioxane at 100 °C for a prolonged period. In like manner, the corresponding reaction with sodium thiocyanate afforded phenyl thiocyanate in 97–98% yield, a trace amount (0.3%) of phenyl isothiocyanate also being detected. Phenyl azide was obtained in 97–99% yield by reaction of the iodonium salt with sodium azide at 80 °C for 2 h in the same solvent. The reaction with potassium cyanide proved to be more troublesome, but a 42% yield of benzonitrile was ultimately obtained by reaction of diphenyliodonium fluoroborate with the cyanide salt in aqueous dioxane at 100 °C for a prolonged period, 5 equiv of 1,1-diphenylethylene also being added to the reaction mixture to suppress a competing free-radical chain reaction.

It is clear from the data presented in Table I that aromatic hydrocarbon formation is a major competing reaction only when potassium cyanide is used as the inorganic salt. In the absence of 1,1-diphenylethylene as an additive, benzene is produced in 69% yield as against a 5% yield of benzonitrile. However, in the presence of a relatively large amount of 1,1-diphenylethylene, the yield of benzene drops to 5%, and the yield of benzonitrile increases to 42%. Very little benzene is formed in the reactions of diphenyliodonium fluoroborate with sodium nitrite, sodium thiocyanate, or sodium azide, even in the absence of 1,1-diphenylethylene. However, even these small amounts of benzene produced are decreased markedly when 1,1-diphenylethylene is present.

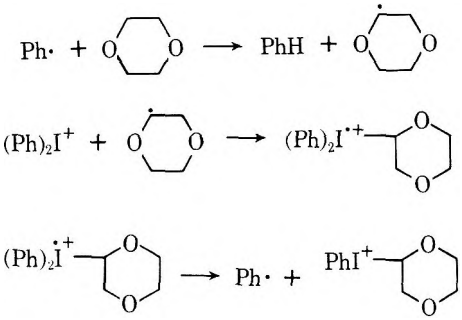
The initiation step of the radical chain reaction leading to the formation of benzene in the reaction of the diphenyliodonium ion with the cyanide ion probably consists of an electron-transfer reaction.[8] However, the formation and subsequent dissociation of a hypervalent iodine intermediate, $(C_6H_5)_2ICN$, may represent the detailed mechanism of the electron transfer process.[9] In any event, the concept of electron transfer permits one to suggest a fundamental reason why the reaction of diphenyliodonium fluoroborate with cyanide ion is more complex than those with nitrite, thiocyanate, and azide ions, respectively. It would be anticipated on the basis of the values of E_n (nucleophile constant characteristic of an electron donor) provided by Edwards[10] that the cyanide ion ($E_n = 2.79$) should be a more powerful electron transfer agent than the nitrite ($E_n = 1.73$), the thiocyanate ($E_n = 1.83$), or the azide ($E_n = 1.58$) ion; i.e., the order of E_n values parallels that of the abilities of the anions to quench fluorescence of a variety of fluorescent materials, which, in turn, parallels the abilities of the anions to function as electron-transfer agents.[11] Thus, the steps in the radical chain reaction may be postulated as:

(1) Initiation

$$PhI^+Ph + CN^- \rightarrow (Ph)_2I\cdot + \cdot CN$$

$$(Ph)_2I\cdot \rightarrow PhI + Ph\cdot$$

(2) Propagation



(3) Termination

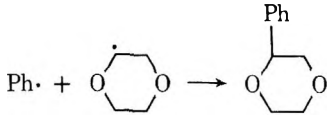
0022-3263/78/1943-2432$01.00/0

Table I. Reactions of Diphenyliodonium Fluoroborate with Inorganic Reagents in Dioxane–Water (70:30) in Sealed Tubes

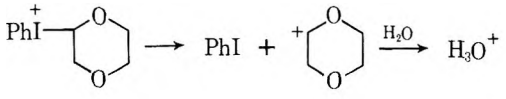
Inorganic reagent	Registry no.	Temp, °C	Time, h	Special conditions	% yield of products							
					$PhNO_2$[e]	PhN_3[f]	PhCN[g]	PhSCN[h]	PhI[i]	PhH[j]	PhOH	PhPh
$NaNO_2$	7632-00-0	100	50	Air	76				78	2.3	0.6	Trace
$NaNO_2$		100	50	Argon	72				77	2.3	0.7	Trace
$NaNO_2$		100	50	Argon, DPE[a]	75				79	1.3	0.6	Trace
NaN_3	26628-22-8	80	2	Air		99			100	0.8	Trace	Trace
NaN_3		80	2	Argon		98			96	0.9	Trace	Trace
NaN_3		80	2	Argon, DPE[b]		97			97	0.4	Trace	Trace
KCN	151-50-8	100	50	Air			5.3		99	69	5.0	2.7
KCN		100	50	Argon			8.8		98	76	0.4	6.0
KCN		100	50	Argon, DPE[b]			32		98	19	0.8	24
KCN		100	50	Argon, DPE[c]			42		97	5	0.9	26
NaSCN	540-72-7	100	24	Air				98[d]	98	0.6	Trace	Trace
NaSCN		100	24	Argon				97[d]	99	0.8	Trace	Trace
NaSCN		100	24	Argon, DPE[b]				98[d]	98	0.2	Trace	Trace

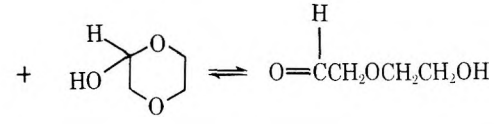
[a] 0.56 equiv of 1,1-diphenylethylene (DPE) present, of which 100% was recovered unchanged. [b] 1.0 equiv of DPE present, of which 100% was recovered unchanged. [c] 5.0 equiv of DPE present, of which 100% was recovered unchanged. [d] 0.28–0.30% yield of PhNCS also detected. [e] Registry no. 98-95-3. [f] Registry no. 622-37-7. [g] Registry no. 100-47-0. [h] Registry no. 5285-87-0. [i] Registry no. 591-50-4. [j] Registry no. 71-43-2.

$$2Ph\cdot \longrightarrow PhPh$$



(4) Subsequent reactions





Evidence in support of this mechanism consists of the following. (1) Reports by Bachofner, Beringer, and Meites[12,13] indicate that the first of three polarographic waves in the electroreduction of the diphenyliodonium cation corresponds to the process $Ph_2I^+ + e^- \rightleftharpoons PhI\cdot$. Also, Beringer and Bodlaender[14] have shown that various metal ions, such as Cu(I), Ti(III), and Cr(II), are capable of transferring an electron to Ph_2I^+ to form essentially $Ph_2I\cdot$. Thus, the ability of the diphenyliodonium ion to accept an electron in an electron-transfer process is established. (2) Significant amounts of biphenyl have been detected.[15] This represents one of the possible chain termination products of a reaction involving phenyl radicals as chain carriers. Furthermore, independent evidence has been presented that $Ph_2I\cdot$ readily dissociates to give Ph· + PhI.[12-14,16] (3) The formation of benzene is inhibited when 1,1-diphenylethylene is added to the reaction mixture.[15] (4) A significant yield of hydronium ion was detected by titration of the reaction mixture with standard base, and undoubtedly some HCN gas was lost when the ampule was opened. (5) The molar amount of iodobenzene produced when 1 equiv of 1,1-diphenylethylene is present in the reaction mixture[17] equals the sum of the molar amounts of benzonitrile and benzene and twice that of biphenyl. (6) It is well known that dioxane readily gives up a hydrogen atom to reactive radicals to produce

as an intermediate.[18]

Since azide, thiocyanate, and nitrite ions have but little tendency to enter into an electron-transfer reaction with the diphenyliodonium cation, then, by default, S_NAr reactions predominate, leading to high yields of phenyl azide, phenyl thiocyanate, and nitrobenzene, respectively.

Data for the reactions of nitrite, azide, thiocyanate, and cyanide ion, respectively, with phenyl-*p*-tolyliodonium fluoroborate are presented in Table II. As expected for an S_NAr reaction, the ratio of nitrobenzene to *p*-nitrotoluene produced in the reaction with nitrite ion was found to be about 5:2. In like manner, the ratio of phenyl azide to *p*-azidotoluene produced in the azide reaction was about 7:3, the ratio of phenyl thiocyanate to *p*-tolyl thiocyanate was also about 7:3 in the thiocyanate reaction, and the ratio of benzonitrile to *p*-cyanotoluene produced in the cyanide reaction was about 5:1. These ratios fall within the ranges reported for other typical S_NAr reactions in which there is a competition between attack of a nucleophile at a phenyl group vs. a *p*-tolyl group.[2,19-21] It is also significant that the ratios of benzene to toluene produced in these reactions are nearly 1:1. This is indicative of their origin by a radical process, i.e., a similar lack of discrimination in the formation of the hydrocarbons has been observed in other, related radical reactions.[2,19-23]

In the reaction of phenyl-*p*-tolyliodonium fluoroborate with potassium cyanide (Table II), it should be noted that the biaryls produced consist of a mixture of biphenyl (2.6%), *p*-methylbiphenyl (1%), and di-*p*-tolyl (0.8%). These results reinforce the concept that the biaryls do indeed result from chain termination reactions and not from an otherwise conceivable intramolecular decomposition of the hypervalent intermediate, $C_6H_5I(CN)C_6H_4CH_3$-*p*, which would have produced only *p*-methylbiphenyl.[24]

A recent report[25] indicates that the relative rates of reaction of N_3^-, NO_2^-, and SCN^- with 1-iodo-2,4-dinitrobenzene in methanol solution at 50 °C are about 100, 5, and 1, respectively. Our results with diaryliodonium cations as the aromatic substrates also suggest that the azide reactions are distinctly more rapid than the nitrite or thiocyanate reactions.[26] In order to provide a direct comparison of the reactivities of the anions, we carried out competition reactions in which 5 equiv of each of two salts were caused to react with 1 equiv of diphenyliodonium fluoroborate for a relatively brief period of time at a relatively low temperature, thereby limiting the reaction to about 35% of completion in most cases. The results are summarized in Table III. In direct comparison, it was found that azide ion is about 14.7 times more reactive than nitrite ion,

Table II. Reactions of Phenyl-*p*-tolyliodonium Fluoroborate with Inorganic Reagents in Dioxane–Water (70:30) in Sealed Tubes

Inorganic reagent	Temp, °C	Time, h	Special conditions	% yield of products							
				PhX	Tol–X	PhH	PhMe	PhI	Tol-I	Biaryls	Other products
$NaNO_2$	100	50	Air	41[a]	18[b]	0.4	0.4	23	44	Trace	Phenols[c]
$NaNO_2$	100	50	Argon	48[a]	21[b]	0.5	0.4	24	48	Trace	Phenols[d]
$NaNO_2$	100	50	Argon, DPE[e]	52[a]	21[b]	0.3	0.4	24	57	Trace	Phenols[f]
NaN_3	80	2	Air	69[h]	29[i]	0.3	Trace	29	67	Trace	Phenols[g]
NaN_3	80	2	Argon	65[h]	24[i]	0.6	0.3	30	67	Trace	Phenols[g]
NaN_3	80	2	Argon, DPE[j]	70[h]	29[i]	0.2	Trace	26	71	Trace	Phenols[g]
KCN[k]	78	50	Argon	25[l]	5.0[m]	23	21	45	52	4.4[n]	Ethers[o]
KCN[k]	100	50	Air	2.4[l]	0.5[m]	24	28	33	40	1.7[p]	Phenols[q]
KCN[k]	100	50	Argon	3.4[l]	0.7[m]	28	28	32	40	1.7[p]	Phenols[q]
KCN[k]	100	50	Argon, DPE[r]	15[l]	3.2[m]	9.6	8.5	21	31	3.4[p]	Phenols[q]
NaSCN	100	24	Air	70[s]	29[t]	1.1	0.7	30	68	Trace	phenols[u]
NaSCN	100	24	Argon	69[s]	30[t]	1.2	0.8	31	68	Trace	Phenols[u]
NaSCN	100	24	Argon, DPE[j]	71[s]	32[t]	0.3	0.2	32	69	Trace	phenols[u]

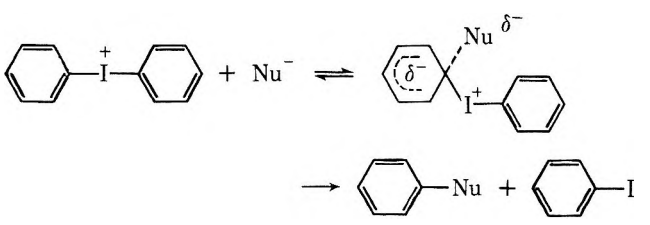
[a] Nitrobenzene. [b] *p*-Nitrotoluene. [c] Phenol (0.2%), *p*-cresol (1.5%). [d] Phenol (0.5%), *p*-cresol (1.8%). [e] 0.5 equiv of 1,1-diphenylethylene (DPE) present, of which 100% was recovered. [f] Phenol (0.6%), *p*-cresol (1.8%). [g] Phenol (trace). [h] Phenyl azide. [i] *p*-Azidotoluene. [j] 1.0 equiv of DPE present. [k] Reaction carried out in ETOH–H_2O (80:20). [l] Benzonitrile. [m] *p*-Cyanotoluene. [n] Biphenyl (2.6%), *p*-methylbiphenyl (1%), di-*p*-tolyl (0.8%). [o] Phenetole (14%), *p*-methylphenetole (5%). These products arise by aromatic S_N reaction of OEt^- with the diaryliodonium cation. Origin of OEt^- is $CN^- + EtOH \leftrightharpoons HCN + OEt^-$. [p] Biphenyl (0.9%), *p*-methylbiphenyl (0.4%), di-*p*-tolyl (0.4%). The same ratio of biaryls obtained in all three experiments. [q] Phenol (0.5%), *p*-cresol (1.9%). [r] 2.0 equiv of DPE present, of which 100% was recovered. [s] Phenyl thiocyanate (0.3% phenyl isothiocyanate was also detected). [t] Tolylthiocyanate (trace of *p*-tolyl isothiocyanate was also detected). [u] Traces of phenol and *p*-cresol were detected.

Table III. Competition Reactions of Diphenyliodonium Fluoroborate with Inorganic Reagents in Dioxane–Water (70:30) in Sealed Tubes

Inorganic reagents[a]	Temp, °C	Time, h	Special conditions	% yield of products							
				PhN_3	$PhNO_2$	PhCN	PhSCN	PhI	PhH	PhOH	PhPh
$NaNO_2$ vs.	25	2	Argon, DPE[b]	21	2.4			26	2.4	0.03	Trace
NaN_3	100	2	Argon, DPE[b]	42	2.9			48	2.3	Trace	Trace
KCN vs. NaN_3	25	2	Argon, DPE[b]	29		0.7		32	3.7	0.08	Trace
	100	2	Argon, DPE[b]	40		2.0		48	5.0	1.4	Trace
$NaNO_2$ vs. KCN	25	2	Argon, DPE[b]		29	2.9		34	3.3	Trace	Trace
	100	2	Argon, DPE[b]		36	6.0		47	3.0	0.04	Trace
NaN_3 vs. NaSCN	100	2	Argon, DPE[c]	68			5.0	74	0.9	1.5	Trace
$NaNO_2$ vs. NaSCN	100	2	Argon, DPE[c]		66		9.0	76	0.9	1.2	Trace

[a] 5.0 equiv of each inorganic salt present. [b] 0.5 equiv of DPE present, of which 100% was recovered unchanged. [c] 1.0 equiv of DPE present, of which 100% was recovered unchanged.

about 13.5 times more reactive than thiocyanate ion, and about 20 times more reactive than cyanide ion toward the diphenyliodonium cation. In like manner, nitrite ion was found to be seven times more reactive than thiocyanate ion and six times more reactive than cyanide ion. Thus, toward the diphenyliodonium ion, the order of nucleophilic reactivities is $N_3^- > NO_2^- > SCN^-, CN^-$, in qualitative agreement with Parker's results.[25] The greater degree of reactivity of N_3^- over NO_2^- and SCN^- in the reaction with 1-iodo-2,4-dinitrobenzene as against that with the diphenyliodonium cation suggests that the transition state for the former reaction is somewhat tighter than that for the latter; i.e., Parker[27] has provided evidence that the tighter the transition state in an S_NAr reaction, the greater is the difference in reactivity between two nucleophiles of different nucleophilicities. Thus, we suggest that the transition state for the S_NAr reaction of the diphenyliodonium ion with a nucleophile is a relatively early one as depicted below; i.e., a significant degree of negative charge remains on the attacking nucleophile in the transition state, and this permits a favorable electrostatic interaction with the positively charged iodine atom to occur, thus lowering the energy of the transition state.



Since the negative charge of the attacking anion is more extensively delocalized in the S_NAr transition state of the reaction with 1-iodo-2,4-dinitrobenzene than in that of the reaction with the diphenyliodonium ion, the former transition state would be tighter than the latter. Thus, a greater spread in relative rates for the reactions with N_3^-, NO_2^-, and SCN^- would be expected in the 1-iodo-2,4-dinitrobenzene reaction than in the diphenyliodonium fluoroborate reaction.[28] Of course, the different solvents used for the two systems also affect the relative rates.[25,27]

Experimental Section

Diphenyliodonium Fluoroborate. Material of mp 134–136 °C was prepared by the method of Beringer et al.[29]

Phenyl-*p*-tolyliodonium Fluoroborate. This salt, mp 121–123 °C, was prepared by the method of Neilands.[30]

Typical Reaction Procedures. To 2 mL of dioxane–water (70:30) was added 5.0×10^{-4} mol of the diaryliodonium fluoroborate and 7.0×10^{-4} mol of sodium nitrite. The sealed tube was placed in an oil bath maintained at 100 °C and allowed to remain there for 50 h. After completion of the reaction, the tube was opened, neutralized with 85% phosphoric acid (usually requiring only 1 drop from a micropipet), and immediately analyzed on a Hewlett-Packard 5830A flame ionization gas chromatograph equipped with either a 6-ft 10%-SE 30,

80–100 Chromosorb W or a 6-ft 5%-FFAP, 80–100 Chromosorb W column. Product identities were determined by comparison of retention times with those of known compounds and by "mixture VPC tests."

To assure maximum reproducibility, the reactions were carried out in batches of four to eight at a time. The yields of the reaction products were determined from the areas of the peaks which constitute part of the data output of the gas chromatograph. Three standard solutions, having compositions near the approximate value obtained from the reaction mixture, were then prepared for each component and subjected to VPC analysis; the approximate areas were obtained and plotted graphically vs. composition. The actual product compositions were then obtained directly from the graphs.

Detection of Acid Following KCN Reactions. In a control experiment, a solution of diphenyliodonium fluoroborate in dioxene–water was subjected to the conditions specified in Table I for the KCN reactions. No acid could be detected by titration with standard NaOH solution. When the actual reaction with KCN was carried out, the yield of H_3O^+ was found to be 30%.

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Registry No.—Diphenyliodonium fluoroborate, 313-39-3; phenyl-*p*-tolyliodonium fluoroborate, 2665-59-0; *p*-nitrotoluene, 99-99-0; *p*-azidotoluene, 2101-86-2; *p*-cyanotoluene, 104-85-8; *p*-tolyl thiocyanate, 5285-74-5; toluene, 108-88-3; *p*-iodotoluene, 624-31-7.

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(2) J. F. Bunnett, *J. Chem. Educ.*, **51**, 312 (1974), and references cited therein.
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(15) The fact that the amount of biphenyl increases sharply when 1,1-diphenylene is present (Table I) suggests that the clefin combines with the phenyl radical to produce a relatively long lived molecule which serves as a reservoir for phenyl radicals. One possible sequence of reactions is the following:

$$(C_6H_5)_2C{=}CH_2 + C_6H_5{\cdot} \rightleftarrows (C_6H_5)_2\dot{C}CH_2C_6H_5$$

$$(C_6H_5)_2\dot{C}CH_2C_6H_5 + C_6H_5{\cdot} \rightarrow C_6H_5C_6H_5 + (C_6H_5)_2C{=}CH_2$$

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(17) We have pointed out in a previous paper[3] that ordinarily the material balance in reactions of diphenyliodonium salts with nucleophiles is excellent only when at least 1 equiv of 1,1-diphenylethylene is present in the reaction mixture. Among other effects, the olefin inhibits destruction of iodobenzene by a free-radical chain reaction.
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(26) Bunnett[2] suggests that S_NAr reactions usually occur only when the aryl halide is activated by the presence of strongly electron withdrawing groups (such as nitro or diazonio) ortho or para to the site of nucleophilic attack. Inasmuch as 1-iodo-2,4-dinitrobenzene falls within the scope of this limitation, and since the reactivity profiles of this compound and of diaryliodonium salts toward the three nucleophiles are similar, it follows that the latter reactions are also of the S_NAr type. Furthermore, the only other conceivable mechanism which could give the same products, the $S_{RN}1$ mechanism,[2] can be ruled out because of the lack of inhibition by 1,1-diphenylethylene and other radical traps.[3] Data presented previously[3] also indicate that formation of arynes as intermediates is not a reasonable possibility.
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(28) The direct estimate of the N_3^-/SCN^- reactivity ratio, for example, does not agree well with the indirect estimate with relay via the nitrite ion. This is probably attributable to the fact that the percent error in the determination of the minor component is much greater than that for the major component. For example, the yield of PhN_3 is probably 68 ± 2% and that of PhSCN 5 ± 2% in the appropriate competition reaction cited in Table III. Thus, the N_3^-/SCN^- reactivity ratio might range between 9 and 24 in the direct comparison, and the discrepancy would be magnified in the indirect estimate. However, there is no ambiguity in the given order of reactivities of N_3^-, NO_2^-, and SCN^- toward the diphenyliodonium ion. The reaction with cyanide ion is so complex that its position on the relative reactivity scale must be considered doubtful.
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Mixed Dehydrotrimerization of Biphenyl–Mesitylene by Aluminum Chloride–Cupric Chloride[1a]

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Coupling of biphenyl and mesitylene in the presence of aluminum chloride–cupric chloride provided an oligomer, 2,4,6,2‴,4‴,6‴-hexamethyl-*p*-quaterphenyl, as the main product. This apparently comprises the first example of dehydrotrimerization of two aromatic substrates to form a mixed product. Mechanistically, the process presumably entails initial formation of a radical cation from biphenyl, which then effects electrophilic attack on mesitylene, followed by fixation of the intermediate to a second mesitylene in a similar sequence of steps. Authentic material was obtained by reaction of mesitylene with *N,N'*-dinitroso-*N,N'*-diacetylbenzidine.

The Ullmann reaction comprises the classical method for joining aromatic nuclei.[2] Biaryls have also been synthesized by other routes involving aryl halides[3] or organometallic compounds.[4] Another approach consists of free-radical arylation.[5] Over the years, a substantial number of reagents have been found which effect dehydrodimerization of aromatic

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Table I. Influence of Variables on Yield in the Biphenyl–Mesitylene Reaction[a]

$CuCl_2$, mol	$AlCl_3$, mol	Biphenyl–mesitylene–$CuCl_2$–$AlCl_3$ (molar ratio)	Time, h	Crude product, g
0.1	0.2	1:3:1:2	2	9[b]
0.1	0.2	1:3:1:2	15	9[b]
0.2	0.4	1:3:2:4	2	10[b]
0.3	0.6	1:3:3:6	2	12[c,d]
0.4	0.8	1:3:4:8	2	13.5[c]

[a] Biphenyl (0.1 mol), mesitylene (0.3 mol), chlorobenzene (120 mL), room temperature. [b] Sticky, dark brown, tar-like mass. [c] Black-green solid which turned to a tar-like mass when dried at 110 °C. [d] Product used for analyses and separation (33% pure **1**).

Table II. Ionization[29] and Polarographic[28] Oxidation Potentials

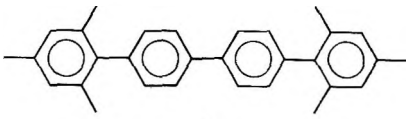
Compd	Registry no.	IP, eV	$E_{1/2}$, V
Biphenyl	92-52-4	8.27	1.48
Mesitylene	108-67-8	8.39	1.53
Benzene	71-43-2	9.24	2.04

substrates, including lead(IV) acetate,[6,7] cobalt(III) or manganese(III) trifluoroacetate,[8] cerium(IV) trifluoroacetate,[9] thallium(III) trifluoroacetate,[10] tellerium(IV) chloride,[11] Pd(II) salts,[12] nitric acid,[13] and electrochemical methods.[14] The prior literature[15] most pertinent to our work entails the use of catalyst–oxidant combinations, e.g., aluminum chloride–cupric chloride, ferric chloride, or molybdenum pentachloride. There is only a meager number of previous reports dealing with mixed coupling by dehydrodimerization (or polymerization). These involve use of ferric chloride,[16] lead(IV) acetate,[6,7] and aluminum chloride–cupric chloride.[17,18]

The purpose of the present investigation was to effect mixed coupling of biphenyl and mesitylene and to investigate the mechanistic features.

Results and Discussion

Experimental. Biphenyl and mesitylene were coupled by means of aluminum chloride as catalyst and cupric chloride as oxidant, providing a product which was shown by thin layer chromatography (TLC) to be a complicated mixture. The major component isolated was a trimer-type oligomer, 2,4,6,2‴,4‴,6‴-hexamethyl-*p*-quaterphenyl (**1**).



1

Three methods were used for purification. The combination of Soxhlet extraction–chromatography–crystallization was preferred to sublimination or repeated crystallization. A portion of the crude product was extracted first with methanol, then with *n*-pentane, and finally with hexane. In addition to bimesityl, the "dimer" fraction apparently contained isomers of the type p-$C_6H_5C_6H_4C_6H_2(CH_3)_3$ and p-$C_6H_5C_6H_4CH_2C_6H_3(CH_3)_2$, based on mass spectral,[19] IR, and NMR data. 2,4,6-Trimethyl-*p*-terphenyl[7] (**2**) may be a component. Since the system contains a powerful Lewis acid catalyst, there could well be some rearrangement entailing methyl migration.[20] The major fraction (15–20% yield based on biphenyl) was shown to be **1** from NMR, mass, IR, and UV spectra, similarity to spectral data[21] for **2**, and comparison with authentic material. Since the ortho substituents oppose coplanarity of the rings, maximum absorption was observed at 267.5 nm in the UV spectrum, in contrast to the value of 294 nm for *p*-quaterphenyl.[22] This effect is also seen for **2** which exhibited

Table III. Lowest Energy Absorption Maxima for Donor–Acceptor or Charge-Transfer Complexes[30]

Donor	γ_{max}, cm^{-1} TCNE[a]	Chloranil
Biphenyl	20 000	23 000
Mesitylene	21 700	23 300
Benzene	26 000	29 900

[a] Tetracyanoethylene.

Table IV. Relative Rates of Electrophilic Aromatic Substitution

Compd	Relative rate: Bromination	Nitration	pK_B
Mesitylene	1.89×10^8[b]	10^3[c]	0.4
Biphenyl	1.00×10^3[d]	40[e]	5.5
Benzene	1.00	1.0	9.2

[a] Reference 31, pp 272 and 279. [b] Reference 32. [c] Reference 33. [d] Reference 34. [e] Reference 35.

absorption at 248 nm[21] (cf. 276 nm for *p*-terphenyl). An alternate procedure for **1** comprised reaction of mesitylene with *N,N'*-dinitroso-*N,N'*-diacetylbenzidine (<7% yield based on benzidine). This route gave a lower yield, involves more steps, and entails handling of carcinogenic and unstable reagents.

This is the first preparation of **1**. Trimer-type products have been observed previously in the oligomerization of biphenyl to form *p*-sexiphenyl[23] and of mesitylene to yield trimesityl.[8] A significant difference is that these cases represent homocoupling whereas compound **1** is derived from the first observed mixed coupling of two different monomers to form a "trimer" (dehydrotrimer). Since inexpensive, readily available starting materials, mild conditions, and relatively uncomplicated techniques are involved, this provides a convenient, one-step synthesis of this novel substance.

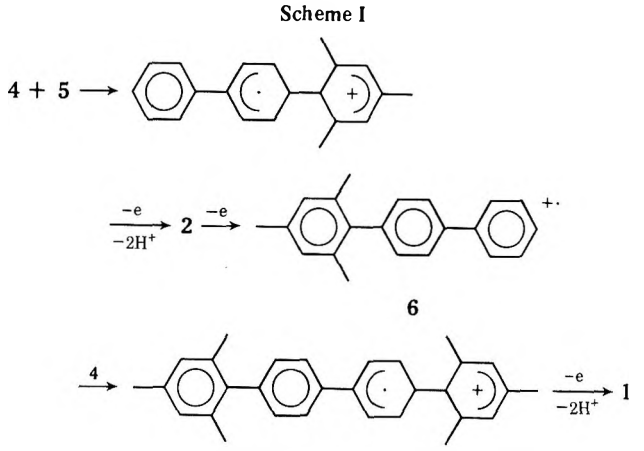
The reaction of biphenyl with mesitylene was investigated in some detail with the aim of determining optimum conditions (Table I).

The reaction was quite sensitive to changes in the amounts of catalyst and oxidant. A biphenyl–mesitylene–$CuCl_2$–$AlCl_3$ molar ratio of 1:3:4:8 gave crude product of highest yield and best appearance; with this molar ratio, hydrogen chloride evolution was most vigorous. Lesser amounts of metal halides produced a lower yield of crude product which was more difficult to purify. Extension of the reaction time to 15 h did not give a higher yield of crude product.

Mechanism. Most of the processes for direct nuclear coupling of aromatic hydrocarbons apparently involve radical cation intermediates, e.g., in the case of aluminum chloride–cupric chloride,[24,25] ferric chloride,[16,26] or molybdenum pentachloride.[27] Various means have been used[28] to measure the ease of organic oxidation entailing removal of an electron, namely, ionization potential (Table II), polarographic oxidation potential (Table II), and lowest energy absorption maxima for donor–acceptor or charge-transfer complexes (Table III). The IP, $E_{1/2}$, and γ_{max} values all indicate that biphenyl (**3**) should be somewhat more readily oxidized than mesitylene (**4**). These data, in addition to product distribution, lead to the conclusion that essentially only biphenyl is oxidized to a radical cation, C_6H_5–$C_6H_5^{+\cdot}$ (**5**). Once **5** is formed, it can interact with a neutral aromatic molecule. From Table IV we note that the rate of electrophilic attack on mesitylene is much larger than for biphenyl. All these data indicate that **5** attacks mesitylene much faster than biphenyl via an electrophilic route, forming **2** (Scheme I). Subsequently, **2** should be oxidized even more easily than biphenyl to form radical cation **6** which can, in turn, become affixed to another mesitylene molecule in a similar sequence to generate the major product **1**. Thus **2** apparently serves as precursor of **1**. Further oxidative coupling of **2** with another mesitylene molecule would also be favored by the presence of excess alkylbenzene. Note that only very minor amounts (~1% yield) of bimesityl were formed, which comprises additional evidence against generation of mesitylene radical cation to any significant degree.

It should be recognized that disagreement exists concerning the mode of attack by the radical cation upon a neutral aromatic molecule. Nyberg ($FeCl_3$)[16,36] and Kovacic ($AlCl_3$–$CuCl_2$)[24] favor cationic attack whereas Norman et al.[6] [lead(IV) acetate] as well as Mano and Alves[25] ($AlCl_3$–$CuCl_2$) argue that radical involvement occurs.[37] There is only a small difference between biphenyl and mesitylene in relation to

Scheme I



reactivity toward a radical species (relative rate: mesitylene, 6.2; biphenyl, 4.0; benzene, 1.0).[5]

Emphasis should be placed on the fact that aromatic cation radicals are versatile species about which there is much less known than the simpler, more familiar, reactive intermediates. It may be that, depending upon the aromatic substrate and conditions, several processes can occur which produce the same coupled product:[38] (1) reaction of the cation radical with an aromatic molecule (Scheme I); (2) conversion of the cation radical (by loss of an electron) to a dication, followed by combination with an aromatic molecule; or (3) dimerization of cation radicals. The pathway outlined in Scheme I appears to apply most commonly in related situations.[38]

Experimental Section

Materials. Biphenyl (practical) and mesitylene (reagent grade) were obtained from Aldrich Chemical Co., chlorobenzene (99%) from Matheson Coleman & Bell, aluminum chloride (anhydrous powder) from Fisher Scientific Co., and cupric chloride (reagent grade) from Mallinckrodt Chemical Works (dried at 110–120 °C for at least 24 h prior to use). Nitrogen was high purity industrial grade. Alumina (neutral, 80–200 mesh) was supplied by Fisher Scientific Co.

Analytical Procedures. IR spectra were obtained with a Beckman IR-8 spectrophotometer (calibrated with the 1601.8-cm^{-1} band of polystyrene). A Varian T-60 instrument was used to record NMR data which are reported in ppm (δ) (in CCl_4 unless otherwise indicated) relative to tetramethylsilane as internal standard. Mass spectra were obtained with a Hitachi RMU-6E (70 eV unless otherwise indicated) and UV spectra with a Cary 17 instrument. Column chromatography was conducted with a Bulcher automatic fraction collector. Melting points (uncorrected) were measured with a Thomas–Hoover capillary apparatus or Berl block. Gas chromatography was performed on an 8 ft, 15% SE-30 on Chromosorb W, column. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

General Procedure. (a) Biphenyl (15.4 g, 0.1 mol), mesitylene (41.8 mL, 0.3 mol), and chlorobenzene (120 mL) were placed in a 250-mL, three-necked flask fitted with a thermometer, gas inlet, stirrer, and condenser, previously flushed with nitrogen. Anhydrous $AlCl_3$ (53.44 g, 0.8 mol) and anhydrous $CuCl_2$ (53.84 g, 0.4 mol) were then added. The reaction mixture was stirred under nitrogen at room temperature for 2 hr during which time it turned purple. The mixture was then poured into 800 mL of ice-cold 6 M HCl and steam distilled. The organic residue was pulverized with water in a blender and washed continuously with 6 M HCl until the wash became colorless and then with water until a negative test ($AgNO_3$) for chloride ion was obtained. The crude product was a black-green solid, yield 13.5 g (88% based on biphenyl).

Product Purification. (a) Extraction–Chromatography–Crystallization. A portion (2 g) of the black-green solid product, from preparation (a), was placed in a Soxhlet apparatus and extracted for 4 h with methanol. Removal of solvent yielded a light-yellow solid which contained mainly biphenyl and bimesityl as determined by ions at *m/e* 154 and 238 in the mass spectrum (10 eV).

Continuous extraction of the methanol-insoluble residue for 6 h with *n*-pentane gave 1.65 g of yellow-brown shiny solid which consisted of a complex mixture. This mixture (1 g) was separated by column chromatography with a 2.5-cm column and 150 g of neutral alumina (diameter/height = 0.06). The eluent was initially petroleum ether (bp 30–60 °C). The polarity of the eluent was gradually increased by the addition of toluene up to 5%. Twenty-minute fractions and a flow rate of 0.6 cm^3/min were used. The progress of the separation was followed by TLC (fraction, wt in g): A, 0.05; B, 0.02; C, 0.04; D, 0.04; E, 0.38; F, 0.03; G, 0.03; H, 0.06; I, 0.04; J (column residue), 0.2.

Fraction A was recrystallized from methanol. Cooling in a methanol–dry ice bath yielded white crystals: mp 42–60 °C; mass spectrum *m/e* 272 (10 eV), 273 (29), 272 (M^+, 100), 271 (11), 257 (40), 242 (26), 241 (23), 215 (17), 167 (29), 165 (20), 149 (77), 113 (20), 104 (17), 85 (29), 83 (26), 71 (49); NMR δ 0.8 (d, impurity), 1.2–1.4 (m, impurity), 1.8 (s), 2.1 (s), 2.5–2.7 (m, impurity), 3.9–4.2 (m, impurity + possible dibenzylic methylene signal at δ 4.0), 6.65 (s, isolated aromatic hydrogens), 6.8 (s, isolated aromatic hydrogens), 7.0–7.6 (m, aromatic hydrogens).

Fraction C was recrystallized from methanol. Cooling in a methanol–dry ice bath yielded white crystals: mp 66–68 °C; mass spectrum *m/e* 272 (10 eV), 273 (33), 272 (M^+, 100), 271 (16), 257 (42), 242 (27), 241 (25), 181 (13), 279 (17), 165 (19), 149 (21), 91 (13), 85 (17), 83 (15), 71 (23); NMR δ 0.81 (d, impurity), 1.2–1.4 (m, impurity), 2.01 (s, 6, *o*-CH_3), 2.29 (s, 3, *p*-CH_3), 2.5–2.7 (m, impurity), 3.9–4.2 (m, impurity), 6.85 (s, 2, $(CH_3)_3C_6\mathbf{H}_2$), 7.10–7.66 (m, aromatic hydrogens).

Fraction E (1) was recrystallized from hexane. Cooling in a methanol–dry ice bath precipitated white needles: mp 233–235.5 °C; a methanol–dry ice bath precipitated white needles: mp 233–235.5 °C; NMR δ 2.01 (s, 12, *o*-CH_3), 2.29 (s, 6, *p*-CH_3), 6.85 (s, 8, $(CH_3)_3C_6\mathbf{H}_2$), and 7.14–7.75 (AB pattern, 8, J = 4 Hz, C_6H_4); mass spectrum *m/e* 390 (10 eV), 391 (29), 390 (M^+, 100), 375 (21), 360 (18), 345 (13), 330 (7), 315 (6), 272 (7), 209 (13), 195 (35), 187 (14), 181 (17), 180 (31), 179 (29), 172 (14), 165 (17), 91 (10); IR (KBr) 1600 (w), 1390 (w), 1370 (w), 1100 (w), 1478 (m), 1000 (m), 845 (m), 817 (s), 742 (w), 734 (w); UV λ_{max} (cyclohexane) 267.5 nm (log ϵ 4.46).

When petroleum ether (bp 30–60 °C) was added to fraction H, an insoluble shiny, white crystalline solid was isolated, mp 283–285 °C. Fractions other than A, C, and E were not examined in detail.

The residue from the previous *n*-pentane extraction was then further extracted with hexane to give 0.23 g of a brown solid which when subjected to TLC (alumina, petroleum ether) showed only one spot with R_f 0.06; this fraction was not investigated thoroughly.

(b) Vacuum Sublimation. Sublimation of preparation (a) at 200–240 °C (0.15–0.1 mm) gave about 30% recovery of material, mp 230–235 °C (crystallized from benzene and then from hexane). The NMR spectrum was the same as that of fraction E.

(c) Repeated Recrystallization. The crude product was extracted with *n*-pentane, and the insoluble residue was extracted with *n*-hexane. The hexane soluble material was repeatedly crystallized from hexane to give a white solid, mp 232–235 °C. The spectral data were identical to those of fraction E.

1 from Benzidine and Mesitylene. *N,N'*-Diacetylbenzidine.[39] A mixture of benzidine (25 g, 0.136 mol) (carcinogenic), 150 mL of acetic acid–acetic anhydride (1:1), and about 0.2 g of zinc powder was refluxed for 20 min. After an additional 100 mL of the acylating mixture was added, reflux was continued for another 20 min. The cooled mixture was added to 700 mL of ice–water and filtered. After the solid was heated in 700 mL of boiling water for 40 min, filtration provided 33.6 g (92%) of amide, mp 332–333 ° C (lit.[40] mp 327–330 °C).

***N,N'*-Dinitroso-*N,N'*-diacetylbenzidine.**[41a] A mixture of the amide (33.5 g, 0.13 mol), sodium acetate (21.3 g, 0.32 mol), P_2O_5 (2.5 g), glacial acetic acid (400 mL), and acetic acid (200 mL) was stirred vigorously in an ice bath for 0.5 h. Addition of nitrosyl chloride[41b] (17 g, 0.26 mol) in 50 mL of acetic anhydride during 15 min produced a bright yellow color. After 20 min, the mixture was added to ice–water (1.5 L), filtered (slow process), and dried overnight away from light, yielding a yellow solid, 40 g. In order to effect separation from unchanged or incompletely nitrosated amide, the material was extracted in 1-g portions with chloroform and the solvent was removed as rapidly as possible under vacuum, providing a mustard-colored solid[42,43] (4 g total of crude product): IR (KBr) ~1700 (CO) cm^{-1}; NMR ($CDCl_3$) δ 7.40 (m, AB pattern, 8, ArH), 3.02 (s, 6, CH_3CO).

1 from *N,N'*-Dinitroso-*N,N'*-diacetylbenzidine.[44] The bisnitroso compound was divided into 2-g (0.0063 mol) portions. One part was stirred vigorously with mesitylene (100 mL) for 12 h at 30 °C. The other part was treated similarly for 4 h at 60 °C. After each cooled mixture was filtered from ~0.4 g of solid, mesitylene was removed by distillation and steam distillation. The sticky, red, residual masses were combined in CH_2Cl_2 solvent, since TLC indicated close similarity. Elution through a silica gel column (1 in. × 24 in.) with CH_2Cl_2 provided an orange semisolid (1.1 g) which on stirring with hexane (15 mL) afforded 0.25 g (<7% yield from the bis(nitroso)precursor) of yellow solid, mp 220–230 °C. Preparative TLC (120 mg) on neutral alumina entailing multiple development with hexane followed by extraction with CH_2Cl_2 gave 90 mg of material, mp 235–237 °C. Two

crystallizations from benzene–hexane afforded white crystals, mp 236–237 °C.

Anal. Calcd for $C_{30}H_{30}$: C, 92.31; H, 7.69. Found: C, 92.21; H, 7.74.

The IR and NMR spectra were essentially identical to those of the product formed by dehydrotrimerization.

A second fraction, 15 mg, mp 79–82 °C, of slightly higher R_f value, exhibited a molecular ion (*m/e* 272) in the mass spectrum corresponding to the molecular weight of 2 (lit.[21] mp 88–91 °C).

Acknowledgment. We are grateful to the National Science Foundation, Polymers Program, Division of Materials Research, Grant No. DMR75-06788, for support of this work, to Mr. Paul Karges for mass spectral data, and to Dr. Kathryn N. McFarland for assistance.

Registry No.—**1**, 65879-27-8; $CuCl_2$, 7447-39-4; $AlCl_3$, 7446-70-0; TCNE, 670-54-2; chloranil, 118-75-2; chlorobenzene, 108-90-7; benzidine, 92-87-5; *N,N'*-dinitroso-*N,N'*-diacetylbenzidine, 61444-52-8.

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Rhodium Catalysis of Allylic Oxidations with Molecular Oxygen. β-Silyl-2-cycloalkenones

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Rhodium catalyzed autoxidation of cycloalkenes with allylic carboethoxyl, isopropyl, and trimethylsilyl substituents is examined. Reaction of 3-(trimethylsilyl)cycloalkenes with molecular oxygen in the presence of tris(triphenylphosphine)rhodium(I) chloride is regiospecifc and affords β-silylcycloalken-2-ones in good yields. A new rhodium-catalyzed allylic oxidation reaction is reported which utilizes *tert*-butyl hydroperoxide as oxidizing agent.

Ten years ago, chlorotris(triphenylphosphine)rhodium(I) (**1**) was shown to catalyze allylic oxidation of olefins[1,2] by molecular oxygen. Cyclohexen-3-one and water are major products of the catalyzed autoxidation of cyclohexene. Since **1** forms coordination complexes with oxygen, it was considered that the catalyst might function by activating molecular oxygen. That is, coordination of oxygen would be prerequisite for catalysis. However, $Rh(CO)(PPh_3)_2Cl$, which interacts only weakly with oxygen, shows similar catalytic activity and product distribution as **1**.[3] Furthermore, autoxidations of cyclohexene catalyzed by cobalt(II) carboxylates yield almost identical product mixtures as reactions catalyzed by **1**, and the latter reactions are completely inhibited by 2% of hydroquinone[4a] as is rhodium(I) promoted autoxidation of tetramethylethylene.[4b] These observations suggest that autoxidations catalyzed by **1**, in analogy with cobalt, are free radical chain reactions in which the metal complex initiates chains by inducing decomposition of hydroperoxides. How-

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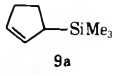
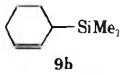
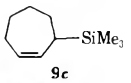
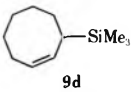
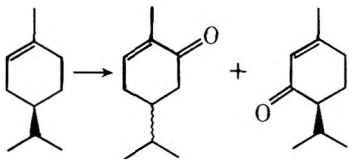
Table I. Synthesis of 3-(Trimethylsilyl)cycloalkenes

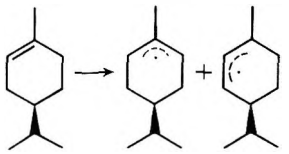
Silane	Registry no.	Bp (yield, %)	^{1}H NMR (in CCl_4)
 9a	14579-08-9	140–146 °C (94)	0.00 (s, 9 H, $SiCH_3$), 1.68–258 (m, 5 H, CH_2's, CH), 5.66 (s, 2 H, CH=CH)
 9b	40934-71-2	69–72 °C (10 mm) (54)	0.00 (s, 9 H, $SiCH_3$), 1.3–2.2 (broad m, 7 H, CH_2's, CH), 5.60 (s, 2 H, CH=CH)
 9c	66085-02-7	85–95 °C (8 mm) (32)	0.00 (s, 9 H, $SiCH_3$), 1.3–2.4 (broad m, 9 H, CH_2's, CH), 5.53–5.75 (m, 2 H, CH=CH)
 9d	20083-09-4	60–70 °C (0.45 mm) (22)	0.00 (s, 9 H, $SiCH_3$), 1.1–2.5 (broad m, 11 H, CH_2's, CH), 5.2–5.9 (m, 2 H, CH=CH)

ever, for metal-catalyzed autoxidation, inhibitors could operate by reaction with the catalyst rather than by scavenging radicals.[4d] Further evidence considered to support allyl radical intermediates was obtained from the autoxidation of (+)-carvomenthene (**2**) promoted by **1**.[5] This reaction gives carvotanacetone (**3**) and piperitone (**4**), and several derived al-



2 **3** **4**

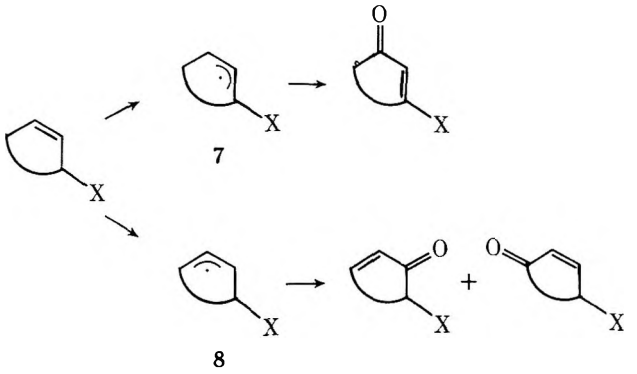
cohols. Though **2** is not racemized under the reaction conditions, **3** is completely racemic. A symmetrical intermediate, such as the radical **5**, is thus implicated in the pathway from **2** to **3**. An analogous intermediate **6** leads to **4**. However,



2 **5** **6**

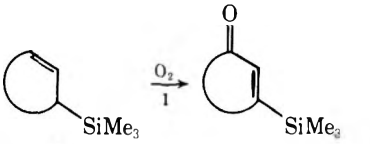
η^3-allylrhodium intermediates (i.e., rhodium complexes of **5** and **6**), which also could explain formation of racemic **3**, have not been ruled out.

Molecular oxygen is an inexpensive oxidant for organic synthesis. Homogeneous catalysis enhances the utility of this reagent by permitting controlled oxidations under mild conditions. However, such oxidations (e.g., **2** → **3** + **4**) generally give complex product mixtures which are difficult to separate since hydrogen atom abstraction and subsequent capture of intermediate allyl radicals are nonregiospecific. It seems reasonable that an allylic substituent which facilitates hydrogen abstraction should promote oxidation and favor products from allyl radicals of type **7** over those from **8**. We



7 **8**

now report that **1** catalyzes regiospecific oxidation of cyclic allylsilanes (**9**) to afford β-silyl-2-cycloalkenones (**10**) in good yields.

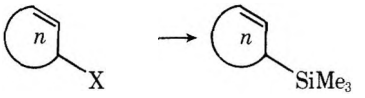


9 **10**

Results and Discussion

Rhodium catalyzed oxidations of cycloalkenes with allylic substituents including carboethoxyl, isopropyl, and trimethylsilyl groups were examined. Only the trimethylsilyl derivatives underwent synthetically valuable oxidations in goods yields. Oxygen is an oxidizing reagent of choice, but we also discovered that *tert*-butyl hydroperoxide can serve as the oxidizing reagent with chlorotris(triphenylphosphine)rhodium(I) (**1**) as a catalyst.

Synthesis of 3-(Trimethylsilyl)cycloalkenes. Hydrosilation of 1,3-cyclopentadiene with trichlorosilane and methylation of the resulting 3-(trichlorosilyl)cyclopentene with methylmagnesium bromide afford 3-(trimethylsilyl)cyclopentene (**9a**) in moderate yield.[6] Alternatively, 1,3-cyclopentadiene is readily converted into 3-chlorocyclopentene (**11a**),[7] and **9a** is prepared by addition of an equimolar mixture

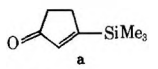
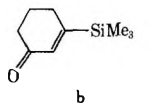
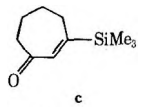
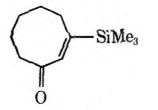


11a, $n = 5$; X = Cl — **9a**, $n = 5$
b, $n = 6$; X = Br — **b**, $n = 6$
c, $n = 7$; X = Br — **c**, $n = 7$
d, $n = 8$; X = Br — **d**, $n = 8$

of **11a** and chlorotrimethysilane in tetrahydrofuran (THF) to magnesium turnings.[8] We obtained **9a** in excellent yield (see Experimental Section) by a modification of the latter procedure. Thus, **11a** in THF is added to a mixture of magnesium turnings and a solution of excess chlorotrimethylsilane in THF. This procedure, which is the method of choice, is noteworthy since allylic silanes are useful synthons for organic synthesis.[4b,9] This method is analogous to that reported for the synthesis of **9b** from **11b**.[10] The method is less satisfactory for the seven- and eight-membered analogues **9c** and **9d** (see Table I).

Rhodium(I) Catalyzed Autoxidation of 3-Substituted Cycloalkenes. A slow stream of oxygen was bubbled through solutions of tris(triphenylphosphine)rhodium(I) chloride (1 mol %) in pure olefin at 100 °C. Reaction progress was monitored by gas–liquid phase chromatography (GLPC). Complete

Table II. Rhodium Catalyzed Autoxidation of 3-(Trimethylsilyl)cycloalkenes

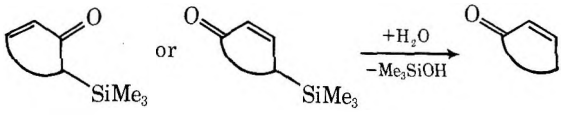
Oxidation[a] product 10	Registry no.	Bp (yield, %)[b]	^{1}H NMR (in CCl_4)
 a	66085-03-8	90 °C (9.5 mm) (83)	0.20 (s, 9 H, $SiCH_3$), 1.95–2.34 (m, 2 H, CH_2), 2.50–2.83 (m, 2 H, CH_2), 6.25 (t, 1 H, J = 2.0 Hz, CH)
 b	66085-04-9	84 °C (4.0 mm) (81)	0.13 (s, 9 H, $SiCH_3$), 1.70–2.50 (m, 6 H, CH_2's), 5.90 (m, 1 H, CH)
 c	66085-05-0	72 °C (0.68 mm) (84)	0.13 (s, 9 H, $SiCH_3$), 1.62–1.90 (m, 4 H, 2 CH_2), 2.33–2.62 (m, 4 H, 2 CH_2), 6.15 (m, 1 H, CH)
 d	66085-06-1	38% SM recovered[c] (60)	0.14 (s, 9 H, $SiCH_3$), 1.40–2.10 (broad s, 6 H, 3 CH_2), 2.45–2.80 (broad s, 4 H, 2 CH_2), 6.24 (s, 1 H, CH)

[a] Oxidation reactions run at 97 °C. Times required for completion: entry (time, h) **10a** (1.5), **10b** (1.5), **10c** (4.5), **10d** (2); were determined by GLPC monitoring of the reactions with a 1/8 in. × 10 ft column filled with 10% SE-30 on 60/80 Chromosorb W at 200 °C. [b] Yields are for pure products isolated by distillation except for **10d** (see Experimental Section). [c] By the *tert*-butyl hydroperoxide method (see text).

oxidation of the allylic silanes **9a–9c** required 1.5–4.5 h. The β-silylcycloalkenone products **10a–10c** were separated from catalyst by transfer under reduced pressure (0.2 mm) into a cold trap (−78 °C), and isolated in good yields by distillation under reduced pressure (see Table II). The recovered catalyst showed unattenuated activity for promoting autoxidation of a second batch of 3-(trimethylsilyl)cycloalkene.

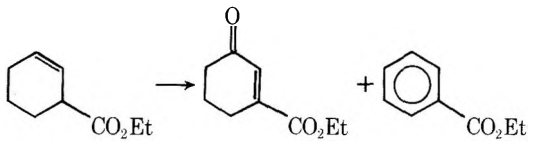
Autoxidation of 3-(trimethylsilyl)cyclooctene (**9d**) promoted by rhodium catalyst **1** was sluggish. We discovered that inclusion of *tert*-butyl hydroperoxide (*t*-BHP) in the autoxidation reaction mixtures noticeably increased the rate of oxidation. Thus, with two equivalents of *t*-BHP **9d** underwent 62% conversion upon heating with oxygen for 2 h. The yield of ketone **10d** was 60% according to GLPC analysis of the reaction mixture.

Although only isomerically pure β-silyl-α,β-unsaturated ketones were isolated, we considered the possibility that minor amounts of isomeric α′- or γ-silyl-α,β-unsaturated ketones may be formed. These products are expected to be selectively destroyed by facile protodesilation under the reaction con-



ditions.[11] However, meticulous examination of the oxidation product mixture from 3-(trimethylsilyl)cyclopentene (**9a**) revealed no trace of 2-cyclopenten-1-one.

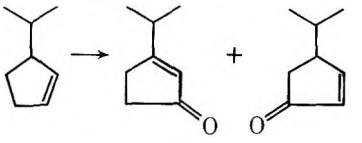
Autoxidation of ethyl cyclohex-2-enecarboxylate (**12**) also was facilitated by *t*-BHP in addition to the rhodium complex



12 13

(**1**). Thus, **12** underwent 51% conversion upon heating with oxygen for 5 h in the presence of **1** and 2 equiv of *t*-BHP. The only ketone product was ethyl 3-oxo-1-cyclohexene-1-carboxylate (**13**) in 77% yield. Also, ethyl benzoate was produced in 23% yield. Attempted complete conversion of **12** resulted in decreased yields of **13** which apparently is slowly destroyed upon prolonged heating of the reaction mixture.

Autoxidation of 3-isopropylcyclopent-1-ene (**14**) in the presence of **1** resulted in 58% conversion after 4 h. Two isomeric oxidation products, 3-isopropylcyclopent-2-en-1-one (**15**) and 4-isopropylcyclopent-2-en-1-one (**16**), were produced



14 15 16

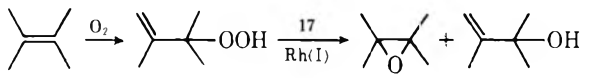
in 42% and 11% yields, respectively. Again, attempted complete conversion of the alkene resulted in decreased yields of enone products. The lack of complete regiospecificity in the oxidation of **14** shows that the isopropyl group does not promote cleavage of an allylic carbon–hydrogen bond as effectively as a carboethoxyl or trimethylsilyl group. In fact, the ratio of **15** to **16** observed may be an overestimate of the actual regiospecificity of hydrogen atom abstraction from **14** since the complex **1** promotes isomerization of **16** into **15**.[12]

Autoxidation of 3-(Trimethylsilyl)cyclopentene Initiated by Benzoyl Peroxide. If autoxidations catalyzed by **1** are free radical chain reactions in which the metal complex serves only to initiate chains (e.g., by inducing decomposition of hydroperoxides), then similar autoxidations should be possible with other radical initiators such as benzoyl peroxide. A slow stream of oxygen was bubbled through a solution of benzoyl peroxide (1 mol %) in pure 3-(trimethylsilyl)cyclopentene (**9a**) at 100 °C for 4 h. Transfer of the oxidation product into a cold trap as above gave 3-(trimethylsilyl)cyclopent-2-en-1-one (**10a**), isomerically pure, but in only 12% yield. In addition, 3-(trimethylsilyl)cyclopent-2-en-1-ol was obtained in 28% yield. The remaining products consisted of a nonvolatile viscous oil. No trace of 2-cyclopenten-1-one was detected. Thus, the same high regioselectivity is observed in autoxidations promoted by benzoyl peroxide and by the rhodium catalyst **1**. This suggests that the regioselectivity in both reactions is totally determined by the silyl substituent. That is, an olefin–rhodium interaction need not be invoked to explain the regioselectivity of the rhodium catalyzed oxidations.

Rhodium(I) Catalyzed Allylic Oxidation of 3-(Trimethylsilyl)cyclopentene with *tert*-Butyl Hydroperoxide. One function of rhodium in promoting autoxidation of

olefins is believed to be catalysis of hydroperoxide decomposition to produce chain-initiating radicals.[3-5] Hydroperoxides are intermediate products which may arise via capture of allyl radicals with molecular oxygen. In some cases, allylic hydroperoxides can be isolated from rhodium promoted autoxidation of olefins.[4] Although rhodium(I) forms complexes with molecular oxygen, it has been argued that the catalytic action of rhodium(I) complexes in allylic oxidation of olefins does not involve activation of oxygen by coordination.[3-5] However, recent work suggests that this question deserves further scrutiny.[4d] Coordination of the olefin substrate by the metal catalyst is definitely not a prerequisite for catalysis.[4b]

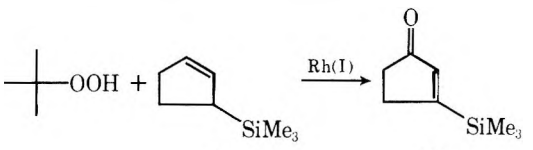
Besides generating chain-initiating radicals, the interaction of hydroperoxide intermediates with the rhodium catalyst can also result in oxidation of the olefin substrate. For example, a rhodium(I) catalyst promotes a reaction between a hydroperoxide intermediate (18) from autoxidation of tetramethylethylene (17) and the olefin 17 to afford epoxide and tertiary allylic alcohol 20.[4b] Similarly, 17 or styrene reacts with *t*-BHP



17 18 19 20

in the presence of a rhodium catalyst, but in the absence of oxygen, to afford 19 or styrene oxide, respectively, as well as *tert*-butyl alcohol.[13]

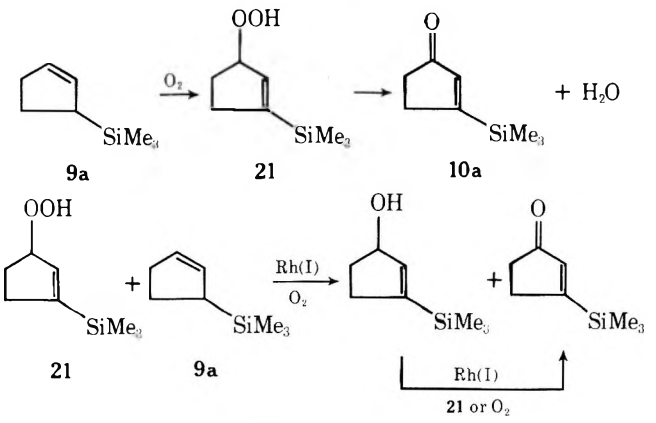
It was of interest to determine if hydroperoxides react with 3-substituted cycloalkenes (e.g., 9) in the presence of rhodium catalyst 1 to afford allylic oxidation products (e.g., 10). Thus, allylsilane **9a** was heated with 2 equiv of *t*-BHP and 1 mol %



9a 10a

of the rhodium catalyst 1 *in the absence of molecular oxygen.* After 20 h at 74 °C, **9a** underwent 87% conversion to **10a** in 57% yield.

The ketone **10a** could be produced exclusively by loss of water from an intermediate hydroperoxide 21 in the autox-



idation of **9a** catalyzed by rhodium(I). However, the reaction described above between *t*-BHP and **9a** to give **10a** suggests that some of the **10a** produced in the reaction of **9a** with molecular oxygen may arise via a rhodium catalyzed reaction of 21 with **9a**. The dependence of reaction products and kinetics from cyclohexene on reaction conditions shows the mechanistic complexity of some rhodium promoted autoxidations.[1,4d] Our demonstration that hydroperoxides can serve as oxidizing agents in rhodium promoted allylic oxidations further complicates the mechanistic picture for rhodium catalysis of autoxidations.

Whatever the mechanism, the ready availability of allylsilanes, mild reaction conditions, regiospecificity of the rhodium promoted autoxidations, and the good yields of pure β-silylcycloalken-2-ones obtained make this approach attractive for preparative purposes. Moreover, methods described previously for synthesis of β-silyl-α,β-unsaturated ketones are *not* applicable for preparation of *cyclic* silyl enones.[14] The versatility of vinylsilanes in organic synthesis increases the potential applications of this approach.[15] In addition, vinylsilanes are readily protodesilylated to afford the corresponding olefins. Thus, **10a** gives 2-cyclopentenone quantitatively by reaction with dry HCl in THF.

Experimental Section

General. All preparative GLPC work was performed with a Varian Model 90-P chromatograph using a 6 ft × ¼ in. column filled with 15% SE-30 silicone oil on 60/80 Chromosorb W. Analytical GLPC work was performed with a Varian series 1200 chromatograph using a 10 ft × ⅛ in. column filled with 10% SE-30 silicone oil on 60/80 Chromosorb W. ^{1}H NMR spectra were recorded with a Varian A60A or HA-100 with Fourier transform using CCl_4 as solvent and 1% Me_4Si as internal standard. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz.

Synthesis of Cyclic Allylsilanes. General Procedure. Chlorotrimethylsilane (64.7 mL, 0.51 mol), magnesium (18.7 g, 0.77 mmol), and THF (250 mL, freshly distilled from sodium benzophenone ketyl) were placed into a flame-dried three-necked flask fitted with reflux condenser, addition funnel, mechanical stirrer, and nitrogen inlet tube. The mixture was cooled to 5 °C in an ice bath. The addition funnel was charged with the allyl halide (0.51 mol) and dry THF (500 mL), and cooled with a dry ice jacket. The resulting solution was added dropwise over several hours. The reaction was allowed to warm to room temperature and was stirred overnight. The reaction product was washed with water (5 × 100 mL) and the aqueous layers were backwashed with pentane (50 mL). The combined organic fractions were washed with saturated NaCl (100 mL) and dried ($MgSO_4$). After filtering, the solvent was removed by rotary evaporation and the product was distilled. Physical constants are listed in Table I.

3-(Trimethylsilyl)cyclopentene (9a) and 3-(trimethylsilyl)-cyclohexene (9b) were reported previously.[8,10]

3-(Trimethylsilyl)cycloheptene (9c). Anal. Calcd for $C_{10}H_{20}Si$: C, 71.34; H, 11.97. Found: C, 70.76; H, 11.56.

3-(Trimethylsilyl)cyclooctene (9d). Anal. Calcd for $C_{11}H_{22}Si$: C, 72.44; H, 12.16. Found: C, 72.44; H, 12.38.

Rhodium Catalyzed Autoxidations: β-Silyl-2-cycloalkenones. The procedure for oxidation of 3-(trimethylsilyl)cyclopent-1-ene is typical. 3-(Trimethylsilyl)cyclopent-1-ene (500 mg, 3.56 mmol) and 1 (33 mg, 1 mol %) were placed in a 5-mL round-bottom flask equipped with reflux condenser, stirring bar, and oxygen inlet tube such that the gas was slowly bubbled in under the liquid surface. The mixture was then heated for 1.5 h with stirring at 97 °C (oil bath). After cooling, the reaction mixture was vacuum transferred to remove the catalyst. For larger scale reactions the product was distilled under reduced pressure. Physical data are given in Table I.

3-(Trimethylsilyl)cyclopent-2-en-1-one (10a). Anal. Calcd for $C_8H_{14}SiO$: C, 62.27; H, 9.14. Found: C, 62.58; H, 9.12.

3-(Trimethylsilyl)cyclohex-2-en-1-one (10b). Anal. Calcd for $C_9H_{16}SiO$: C, 64.22; H, 9.58. Found: C, 64.24; H, 9.70.

3-(Trimethylsilyl)cyclohept-2-en-1-one (10c). Anal. Calcd for $C_{10}H_{18}SiO$: C, 65.85; H, 9.95. Found: C, 65.61; H, 10.02.

Oxidation of 3-Isopropylcyclopent-1-ene. 3-Isopropylcyclopent-1-ene (14) (500 mg, 4.54 mmol) and 1 (42 mg, 1 mol %) were placed in a 5-mL round-bottomed flask fitted with reflux condenser and oxygen inlet tube as described above. The mixture was heated with magnetic stirring in an oil bath at 97 °C for 4 h. After vacuum transfer the following major components were isolated by GLPC: entry, absolute % yield (relative GC retention time); starting material **14**, 42% (1.0); 4-isopropylcyclopent-2-en-1-one (**16**), 11% (2.0); 3-isopropylcyclopent-2-en-1-one (**15**), 42% (2.6). The enone **15** was characterized by the identity of its ^{1}H NMR spectrum with that reported.[16] The structural assignment for the isomeric enone **16** is based on its ^{1}H NMR spectrum: (CCl_4) δ 0.95 and 0.99 (6 H, 2 doublets, J = 6 Hz, 2 CH_3's, 1:1 mixture of diastereomers), 1.74 (1 H, m, CH), 1.92 (1 H, dd, J = 4, 18 Hz, CH_2), 2.30 (1 H, dd, J = 6, 18 Hz, CH_2), 2.70

(1 H, m, CH), 6.10 (1 H, dd, J = 2, 6 Hz, C-2 vinyl), 7.52 (1 H, dd, J = 2, 6 Hz, C-3 vinyl).

4-Isopropylcyclopent-2-en-1-one (**16**) was further characterized by isomerization to **15** in the presence of rhodium(I) complex (**1**). A small sample of 4-isopropylcyclopent-2-en-1-one (**16**) was isolated by GLPC and placed in a sealed NMR tube with **1** (5 mg) and CCl_4. The tube was heated at 80 °C. The ^1H NMR spectrum of the solution after 15 h showed only 3-isopropylcyclopent-2-en-1-one (**15**).

Oxidation of 3-(Trimethylsilyl)cyclopent-1-ene (9a) with Recovered Catalyst. The rhodium containing residue, from oxidation of **9a** with oxygen, and 3-(trimethylsilyl)cyclopent-1-ene (500 mg, 3.56 mmol) were placed in a flask fitted with reflux condenser and oxygen inlet tube as described above. The resulting mixture was heated in an oil bath at 98 °C. After 1 h the reaction was complete, yielding 467 mg (85%) of vacuum transferred product (90% pure by GLPC).

Rhodium Catalyzed Oxidation of 9a with *tert*-Butyl Hydroperoxide. 3-(Trimethylsilyl)cyclopent-1-ene (**9a**) (100 μL), undecane (20 μL, as internal standard), and *tert*-butyl hydroperoxide (200 μL) were vacuum sealed in a Pyrex tube and heated in an oil bath at 74 °C for 20 h. GLPC analysis of the crude reaction mixture showed 13% starting material and 50% of β-trimethylsilyl-2-cyclopentenone (**10a**).

***tert*-Butyl Hydroperoxide Assisted Autoxidation of 3-(Trimethylsilyl)cyclooct-1-ene.** 3-(Trimethylsilyl)cyclooct-1-ene (**9d**) (500 mg, 2.54 mmol), **1** (23 mg, 1 mol %), and *tert*-butyl hydroperoxide (510 μL, 5.08 mmol) were placed in a 10-mL round-bottomed flask equipped with reflux condenser, magnetic stirring bar, and oxygen inlet tube as previously described. The resulting mixture was heated in an oil bath at 96 °C for 2 h. The reaction product was then analyzed by GLPC (see Table I). A sample of **10d** was isolated for analysis by GLPC.

3-(Trimethylsilyl)cyclooct-2-en-1-one (10d). Anal. Calcd for $C_{11}H_{20}SiO$: C, 67.28; H, 10.27. Found: C, 67.52; H, 10.52.

***tert*-Butyl Hydroperoxide Assisted Oxidation of Ethyl Cyclohex-2-enecarboxylate (12).** Ethyl cyclohex-2-enecarboxylate (**12**)[17] (500 mg, 3.24 mmol), **1** (30 mg, 1 mol %), and *tert*-butyl hydroperoxide (0.70 mL, 6.48 mmol) were placed in a 5-mL round-bottom flask fitted with reflux condenser and O_2 delivery tube as described above and heated in an oil bath at 96 °C for 5 h. The following components were isolated by GLPC: entry, absolute yield % (relative GC retention time); starting material **12**, 34% (1.0); ethyl benzoate, 15% (1.1); ethyl 3-oxo-1-cyclohexene-1-carboxylate (**13**), 51% (2.1). The enone **13** was characterized by the identity of its ^1H NMR spectrum with that reported.[18]

Protonolysis of 3-(Trimethylsilyl)cyclopent-2-en-1-one (10a). A typical protonolysis procedure follows. 3-(Trimethylsilyl)cyclopent-2-en-1-one (500 mg, 3.24 mmol) in dry THF (15 mL) was saturated with dry HCl and boiled under reflux under nitrogen for 14 h. The reaction was quenched with saturated $NaHCO_3$ (15 mL) and extracted into pentane (25 mL). The organic layer was dried ($MgSO_4$), and the solvent was removed by rotary evaporation. A quantitative yield of cyclopentenone was obtained.

Benzoyl Peroxide Initiated Autoxidation of 3-(Trimethylsilyl)cyclopentene. The olefin **9a** (2.5 g, 18 mmol) and benzoyl peroxide (43 mg) were placed in a 15-mL round-bottom flask equipped with reflux condenser, oxygen inlet tube which entered through the top of the condenser, and gas outlet near the top of the condenser. Oxygen was slowly bubbled in under the liquid surface while the reaction mixture was heated at 97 °C (oil bath) for 4 h. The volatile products were then transferred under reduced pressure (0.2 Torr) into a cold receiver (−78 °C). Yields were determined by ^1H NMR analysis of the product mixture, and **3-(trimethylsilyl)cyclopent-2-en-1-ol** was isolated by preparative gas–liquid phase chromatography. ^1H NMR: (CCl_4) δ 0.07 (9 H, s, $SiMe_3$), 1.33–2.58 (5 H), 4.57–4.88 (H, m, CH–O), 5.85–6.02 (H, m, vinyl). Anal. Calcd for $C_8H_{16}SiO$: C, 61.47; H, 10.32. Found: C, 61.56; H, 10.38.

Acknowledgment. We thank the National Science Foundation for generous support of our investigations on homogeneous catalysis in organic synthesis.

Registry No.—**1**, 14694-95-2; **11a**, 96-40-2; **11b**, 1521-51-3; **11c**, 36291-49-3; **11d**, 7422-06-2; **12**, 55510-68-4; **13**, 25017-79-2; **14**, 4276-45-3; **15**, 1619-28-9; **16**, 54814-23-2; chlorotrimethylsilane, 75-77-4; 3-(trimethylsilyl)cyclopent-2-en-1-ol, 66085-07-2.

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Reactions Involving Electron Transfer. 12. Effects of Solvent and Substituents upon the Ability of Lithium Diorganocuprates to Add to Enones[1]

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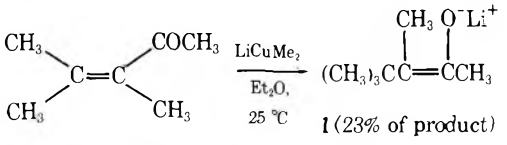
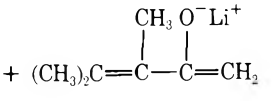
A series of enones, **7**, **8**, and **3**, with progressively more negative reduction potentials has been used to study the effects of solvent (or other donor ligands) and the nature of the substituent R upon the ability of cuprate reagents, $LiCuR_2$, to form conjugate adducts from unsaturated carbonyl compounds. Good donor solvents (THF, DME, DMF) retarded or inhibited conjugate addition; the best yields of conjugate adducts were obtained with mixtures of Et_2O–Me_2S or Et_2O–pentane as the reaction solvent. The limiting reduction potentials (E_{red}) for successful conjugate additions varied with the nature of the cuprate reagent, $LiCuR_2$, in the following way: $E = -2.35$ V, R = *n*-Bu or CH_2=CH–; $E_{red} = -2.2$ to -2.3 V, R = Ph, *sec*-Bu, or Me; $E_{red} = -2.1$ V, R = *t*-Bu; and $E_{red} = -2.0$ to -2.1 V, R = CH_2=$CHCH_2$. Three side reactions have been observed in reactions of $LiCuR_2$ reagents with enones whose E_{red} values cause conjugate addition to be marginally successful. The most common side reaction was formation of the metal enolate of the starting enone. With *sec*-Bu and *t*-Bu cuprate reagents a second side reaction, resulting from thermal decomposition of the cuprate reagent, produced 1,2 and/or 1,4 reduction products of the starting enone. A third side reaction observed with *t*-Bu and allyl cuprate reagents was the formation of 1,2-addition products. This latter side reaction, also related to decomposition of the cuprate reagents, was significantly enhanced by the use of impure Cu(I) salts to prepare the cuprate reagents. Additional experiments are provided to support the idea that the *soluble* metal enolates from enones and $LiCuMe_2$ are Li enolates and not Cu(I) enolates.

Previous study[2] of the reaction of lithium dimethylcuprate ($LiCuMe_2$)[3] with various α,β-unsaturated carbonyl compounds in ether solution has demonstrated that the reduction potential (E_{red} vs. SCE in an aprotic solvent) of the unsaturated carbonyl compound should be within the range -1.3 to -2.3 V in order to obtain the conjugate addition product in good yield. More easily reduced substrates (E_{red} less negative than -1.3 V) typically yield reduction products rather than conjugate adducts, while more difficultly reduced substrates (E_{red} more negative than -2.3 V) either fail to react or, more commonly, react with $LiCuMe_2$ to form the enolate (e.g., **2**) of the starting material (e.g., **3**). This latter circumstance results in an apparent recovery of "unchanged" starting material after hydrolysis of the reaction mixture. Most unsaturated carbonyl compounds of interest as synthetic intermediates have E_{red} values within the range -1.8 to -2.5 V.[4] Consequently, it was of interest to extend our study of the upper limit of E_{red} values for successful conjugate addition to include the use of reaction solvents other than Et_2O and the use of cuprates, $LiCuR_2$, where the reagent substituent R is not a methyl group. This paper reports our study of these solvent and substituent effects.

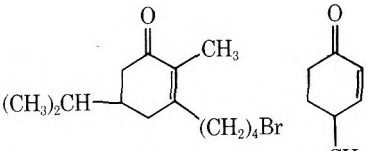


3 (E_{red} −2.35 V) **1** (23% of product)



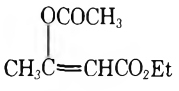
2 (77% of product)

Choice of Reaction Solvent. The coupling reaction of $LiCuR_2$ reagents with alkyl halides is accelerated by changing the reaction solvent from Et_2O to a better donor solvent[5] such as THF or an Et_2O–HMP [$(Me_2N)_3PO$] mixture,[6] while the mechanistically related coupling of $LiCuR_2$ with alkyl tosylates and epoxides is retarded by the use of THF rather than Et_2O.[7] Previous observations relating to the conjugate addition of $LiCuR_2$ reagents to unsaturated carbonyl compounds suggest that the presence of good donor solvents or donor ligands may be deleterious.[8] For example, in the reaction of the enone **4**[8a] (calcd[4] $E_{red} = -2.3$ V) with $LiCuMe_2$ an increasing fraction of the enone was recovered as the solvent was changed from PhH to Et_2O to THF. Similarly, lower yields of conjugate adducts were obtained with THF rather than Et_2O as the solvent for reaction of several enones[8c] (calcd[4] $E_{red} = -2.1$ to -2.2 V) with $LiCuMe_2$. The addition of 2–3 molar equiv of the donor ligand, 12-crown-4-polyether, was found[8b] to inhibit the addition of $LiCuMe_2$ to enone **5** (calcd[4] $E_{red} = -2.1$ V) and the addition of $LiCuEt_2$ to ester **6** (calcd[9] $E_{red} = -2.3$ V).



4

5

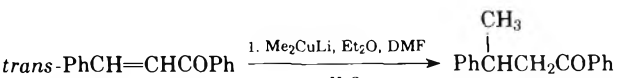


6

To examine the effect of solvent on conjugate addition in a more systematic way, the set of enones **7**, **8**, and **3** (Scheme I) with progressively more negative reduction potentials was used. These enones were allowed to react with $LiCuMe_2$ in Et_2O and in mixtures of Et_2O with poorer (pentane, PhH, CH_2Cl_2, Me_2S) or better (THF, DME) donor solvents. The results, summarized in Table I, demonstrate that for the most difficulty reduced enone **3** there is a clear advantage in using a mixed solvent containing as much pentane as can be added without precipitating the cuprate reagent. Furthermore, there is a clear disadvantage to adding a better donor solvent such as THF or DME. With the more easily reduced enone **8**, use of an Et_2O–pentane mixture rather than pure Et_2O as the solvent offered no advantage, but the deleterious effect of

Scheme I

CH_3CH=$CHCOCH_3$ **7** ($E_{red} = 2.08$ V)
$(CH_3)_2C$=$C(CH_3)COCH_3$ **3** ($E_{red} = -2.35$ V)
$(CH_3)_2C$=$CHCOCH_3$ **8** ($E_{red} = -2.21$ V)
$(CH_3)_2C$=$C(CH_3)COCH_2D$ **9**



10 ($E_{red} = -1.41$ V) **11** (75% yield)

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Table I. Reaction of $LiCuMe_2$ with the Enones 7, 8, and 3 at 10–30 °C in Various Solvents

Solvent	Reaction product (% yield)		
	trans-$CH_3CH{=}CHCOCH_3$ (7; E_{red} = −2.08 V)	$(CH_3)_2C{=}CHCOCH_3$ (8; E_{red} = −2.21 V)	$(CH_3)_2C{=}C(CH_3)COCH_3$ (3; E_{red} = −2.35 V)
Et_2O–pentane (1:3.4 v/v)		$(CH_3)_3CCH_2COCH_3$ (13; 88%)	$(CH_3)_3CCH(CH_3)COCH_3$ (12; 59%) + 3 (26%)
Et_2O–PhH (1:5 v/v)			12 (37%) + 3 (62%)
Et_2O–Me_2S (1:5 v/v)			12 (31%) + 3 (62%)
Et_2O–CH_2Cl_2 (1:3.3 v/v)			12 (25%) + 3 (63%)
Et_2O	$(CH_3)_2CHCH_2COCH_3$ (14; 94%)[a]	13 (93%)	12 (21%)[b] + 3 (72%)
Et_2O–THF (1:5 v/v)	14 (98%)	13 (51%) + 8 (39%)	3 (96%)
Et_2O–DME (1:5 v/v)	14 (84%)	13 (45%) + 8 (45%)	3 (100%)

[a] This experiment was described by H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966). [b] This experiment was originally reported in ref 2b; the range of product compositions was 15–30% of 12 and 70–85% of 3.

adding better donor solvents (THF or DME) was still apparent. In these experiments the recovered starting material (e.g., 3) resulted from a relatively slow reaction [precipitation of $(CH_3Cu)_n$] to form the enolate 2 that was reconverted to the starting ketone 3 by hydrolysis with H_2O or to the monodeuterio ketone 9 by quenching in a D_2O–DOAc mixture.

Since the usual preparative route to $LiCuR_2$ reagents (reaction of CuI or CuBr with 2 molar equiv of RLi) produces a solution containing the cuprate reagent accompanied by an equivalent amount of LiI or LiBr, it might be supposed that the deleterious effect of THF or DME arises from the increased ability of these solvents to complex with Li^+ (from LiI or LiBr). If this extra Li^+ were a catalyst for the conjugate addition, then coordination of the Li^+ with a good donor ligand could retard or inhibit the reaction (cf. ref 7). We were able to disprove this hypothesis by demonstrating that the same amount of conjugate adduct 12 was formed from the enone 3 using either an Et_2O solution of the usual cuprate reagent ($LiCuMe_2$ + LiBr) or an Et_2O solution of $LiCuMe_2$ from which 95% of the LiBr had been removed.[6b,10]

Only with the most easily reduced enone 7 was it possible to demonstrate that addition of one of the donor solvents, THF or DME, had no deleterious effect on conjugate addition. Since stable solutions of $LiCuMe_2$ in mixtures of Et_2O and DMF can be prepared,[2c] it was also possible to examine the effect of a very good[5] donor solvent on the conjugate addition reaction. Using $LiCuMe_2$ in an Et_2O–DMF mixture (1:3 v/v) we did not detect the conjugate adduct from any of the enones 7, 8, or 3 and only obtained a conjugate adduct 11 in this solvent mixture with the very easily reduced (and difficultly enolizable[11]) enone 10.

Consideration of these results indicates that the choice of reaction solvent can be a very important factor in obtaining good yields of conjugate adducts from cuprate reagents and unsaturated carbonyl compounds. This is particularly true in the rather common circumstance where the estimated[4] E_{red} value for the unsaturated carbonyl is more negative than −2.1 V. In such cases the presence of good donor solvents (e.g., THF or DME) or good donor additives (e.g., DMF or HMP) may either lower the yield or completely inhibit the formation of a conjugate adduct. In general the best choice of reaction solvent would appear to be either pure Et_2O or an Et_2O–Me_2S mixture. Dilution of these cuprate solutions with a hydrocarbon cosolvent (e.g., pentane) before use is clearly desirable whenever the estimated[4] E_{red} value for the unsaturated carbonyl compound is more negative than −2.2 V.

The Effect of the Substituent R in $LiCuR_2$. In order to survey the effect of the group R in a cuprate reagent, $LiCuR_2$, upon limiting substrate E_{red} value for successful conjugate addition, we have studied the reactions of the enones 7, 8, and 3 with a representative group of cuprate reagents, 15–21 (see Table II). In performing these reactions we selected reaction temperatures 5–10 °C below the temperature at which significant thermal decomposition of the cuprate reagent began in order to minimize subsequently discussed side reactions. Although successful conjugate additions require only 1 molar equiv of $LiCuR_2$ reagent for each mole of enone,[2g] we used an excess of $LiCuR_2$ in each of these reactions to minimize the possibility that portions of the starting enones 7, 8, or 3 were recovered because of adventitious destruction of a portion of the $LiCuR_2$ reagent. Furthermore, we used reaction times well in excess of those normally needed for complete reaction. Thus, we believe that any unchanged enone found among the reaction products represents the portion of enone that was converted to its enolate (e.g., 2 from 3) rather than undergoing conjugate addition. In most cases this relatively slow enolate formation was the major side reaction when conjugate addition was retarded or inhibited. Whenever practical, we used mixtures of Et_2O with Me_2S or Me_2S plus a hydrocarbon (pentane, hexane, or cyclohexane) as the reaction solvent in order to optimize the proportion of conjugate adduct 12–14 or 22–34 (see Table II) in the product.

The results of this series of reactions, summarized in Table II, suggest that the following limiting E_{red} values are appropriate for the various cuprates studied: −2.35 V, $LiCu(Bu\text{-}n)_2$ and $LiCu(CH{=}CH_2)_2$; −2.2 to −2.3 V, $LiCuPh_2$, $LiCu(Bu\text{-}sec)_2$, and $LiCuMe_2$; −2.1 V, $LiCu(Bu\text{-}t)_2$; −2.0 to −2.1 V, $LiCu(CH_2CH{=}CH_2)_2$. This *order of ability* to undergo conjugate addition with an enone having a certain E_{red} value (*n*-Bu ~ $CH_2{=}CH_2$ > Ph ~ *sec*-Bu ~ Me > *t*-Bu > allyl) generally parallels the *order of relative rates* for conjugate addition determined in several sets of competition experiments. When limited amounts of several enones were allowed to react with solutions containing both $LiCuMe_2$ and $LiCu(CH{=}CH_2)_2$, the relative rate of R group transfer was $CH_2{=}CH$ > Me.[2b,12] In competition experiments involving addition to enone 8 the order was *n*-Bu > *sec*-Bu > *t*-Bu and the order *n*-Bu ~ *sec*-Bu > *t*-Bu > Ph was reported for competitive additions to $CH_2{=}CHCOCH_3$.[13,14] These relative rate orders were consistent with our order of reactivity except for the positions of $LiCuPh_2$ and $LiCu(Bu\text{-}t)_2$, where our data clearly indicated $LiCuPh_2$ to be more reactive, not less reactive, than $LiCu(Bu\text{-}t)_2$. Although this difference might be interpreted to mean that the reactivity order changed in mixed cuprates such as LiCu(Ph)Bu-*t* [formed from $LiCuPh_2$ and $LiCu(Bu\text{-}t)_2$], the facts that the earlier relative rate study[13] was performed at a temperature (0 °C) where thermal decomposition of $LiCu(Bu\text{-}t)_2$ would be extensive and used an enone ($CH_2{=}CHCOCH_3$) that would be a very efficient trap for alkyl radicals led us to reexamine these relative rates. Reaction of the enone 8 (Scheme II) with an excess of an equimolar mixture of $LiCuPh_2$ and $LiCu(Bu\text{-}t)_2$ indicated that the relative rates of R group transfer were Ph > *t*-Bu, as our previous data suggested.

Table II. Reaction of $LiCuR_2$ Reagents with the Enones 7, 8, and 3 in Et_2O or Et_2O–Hexane Solution

$LiCuR_2$[d] (solvent)	Reaction temp, °C	Reaction products (% yield)[e]: *trans*-CH_3CH=$CHCOCH_3$ (7; E_{red} = −2.08 V)	$(CH_3)_2C$=$CHCOCH_3$ (8; E_{red} = −2.21 V)	$(CH_3)_2C$=$C(CH_3)COCH_3$ (3; E_{red} = −2.35 V)
$LiCu(Bu\text{-}n)_2$ (15) (Et_2O–Me_2S–hexane, 1:3:3 v/v/v)	−20 to −30		*n*-$BuC(CH_3)_2CH_2COCH_3$ (22; 83%)	*n*-$BuC(CH_3)_2CH(CH_3)COCH_3$ (23; 74%) + 3 (5%)
$LiCu(CH{=}CH_2)_2$ (16) (Et_2O–Me_2S–THF, 1:1:1 v/v/v)	−20 to −35		CH_2=$CHC(CH_3)_2CH_2COCH_3$ (24; 72%)[a]	CH_2=$CHC(CH_3)_2CH(CH_3)COCH_3$ (25; 55%) + 3 (17%)[b]
$LiCuPh_2$ (17) (Me_2S–Et_2O, 1:3 v/v)	10–27		$PhC(CH_3)_2CH_2COCH_3$ (26; 77%)	$PhC(CH_3)_2CH(CH_3)COCH_3$ (27; 48%) + 3 (43%)
$LiCu(Bu\text{-}sec)_2$ (18) (Et_2O–Me_2S–cyclohexane, 1:1:2 v/v/v)	−50 to −55	*sec*-$BuCH(CH_3)CH_2COCH_3$ (28, 87%)	*sec*-$BuC(CH_3)_2CH_2COCH_3$ (29; 77%)	*sec*-$BuC(CH_3)_2CH(CH_3)COCH_3$ (30; 17–43% + 3 (19–45%) + other products
$LiCuMe_2$ (19) (Et_2O)	10–30	$(CH_3)_2CHCH_2COCH_3$ (14; 94%)[c]	$(CH_3)_3CCH_2COCH_3$ (13; 93%)	$(CH_3)_3CCH(CH_3)COCH_3$ (12; 21%) + 3 (72%)
$LiCu(Bu\text{-}t)_2$ (20) (Et_2O–Me_2S–pentane, 1:1:1 v/v)	−55 to −65	*t*-$BuCH(CH_3)CH_2COCH_3$ (31; 74%)	*t*-$BuC(CH_3)_2CH_2COCH_3$ (32; 4%) + 8 (59–62%) + other products	
$LiCu(CH_2CH{=}CH_2)_2$ (21) (Et_2O–Me_2S, 3:1 v/v)	−30 to −70	CH_2=$CHCH_2CH(CH_3)CH_2COCH_3$ (33; 10–16%) + 7 (48–53%) + 35 (12–18%)	CH_2=$CHCH_2C(CH_3)_2CH_2COCH_3$ (34; 1%) + 8 (6%) + 36 (71%)	

[a] This experiment is reported in ref 2f. [b] This experiment is described in ref 2b. [c] This experiment is described by H. O. House, W. L. Respess, and G. M. Whitesides, *J. Org. Chem.*, **31**, 3128 (1966). [d] Registry no.: **15**, 24406-16-4; **16**, 22903-99-7; **17**, 23402-69-9; **18**, 23402-73-5; **19**, 15681-48-8; **20**, 23402-75-7; **21**, 21500-57-2. [e] Registry no.: **7**, 3102-33-8; **28**, 21409-93-8; **14**, 108-10-1; **31**, 65995-71-3; **33**, 35194-34-4; **35**, 919-98-2; **8**, 141-79-7; **22**, 49585-97-9; **24**, 1753-37-3; **26**, 7403-42-1; **29**, 66018-00-6; **13**, 590-50-1; **32**, 65995-72-4; **34**, 17123-68-1; **36**, 926-20-5; **3**, 684-94-6; **23**, 58105-39-8; **25**, 54678-05-6; **27**, 1203-12-9; **30**, 65995-73-5; **12**, 5340-45-5.

Scheme II

$(CH_3)_2C$=$CHCOCH_3$ + $LiCuPh_2$ + $LiCu(Bu\text{-}t)_2$

8 17 20

1. Et_2O, Me_2S, pentane, −62 to −72 °C
2. H_2O

→ $PhC(CH_3)_2CH_2COCH_3$ **26** (67%) + *t*-$BuC(CH_3)_2CH_2COCH_3$ + other products

32 (1.3%)

Thus, with proper attention to reaction conditions, conjugate addition to unsaturated carbonyl substrates having E_{red} values less negative than −2.3 V is likely to be a satisfactory synthetic procedure for $LiCuR_2$ reagents where the group R is primary or secondary alkyl, methyl, vinyl, or aryl. Substrates with E_{red} values less negative than −2.3 V include acetylenic ketones and esters, a fair number of ethylenic ketones, and a limited number of ethylenic esters.[4] However, the number of simple unsaturated carbonyl substrates that are likely to form conjugate adducts in good yield (E_{red} = −2.1 V or less) with $LiCuR_2$ reagents where the group R is tertiary alkyl or allyl is much more limited. In instances where the foregoing data would suggest that a satisfactory conjugate addition is doubtful, it would seem prudent to modify the unsaturated carbonyl substrate in such a way that its reduction potential will be less negative. For example, although unsaturated esters of the type **37** normally fail to give good yields of conjugate adducts with $LiCuMe_2$,[15a] the corresponding more easily reduced alkylidene malonates **38**[15a] or alkylidene cyanoacetates[15b] are satisfactory substrates. Similarly, while the reaction of enone **7** with either $LiCu(CH_2CH{=}CH_2)_2$ or with CH_2=$CHCH_2MgBr$ in the presence of a Me_2SCuBr catalyst formed the conjugate adduct **33** in only 10–20% yield, the corresponding reaction with the more easily reduced enone **39** formed the conjugate adduct **40** in 75% yield.[16]

R_2C=$CHCO_2Et$ R_2C=$C(CO_2Et)_2$

37 (calcd[4] E_{red} = −2.4 V) **38** (E_{red} = −2.1 V)

CH_3CH=$CHCOCH_3$

7 (E_{red} = −2.08 V)

CH_2=$CHCH_2CH(CH_3)CH_2COCH_3$

33

CH_3CH=$C(CO_2Bu\text{-}t)COCH_3$

39 (E_{red} = −1.8 V)

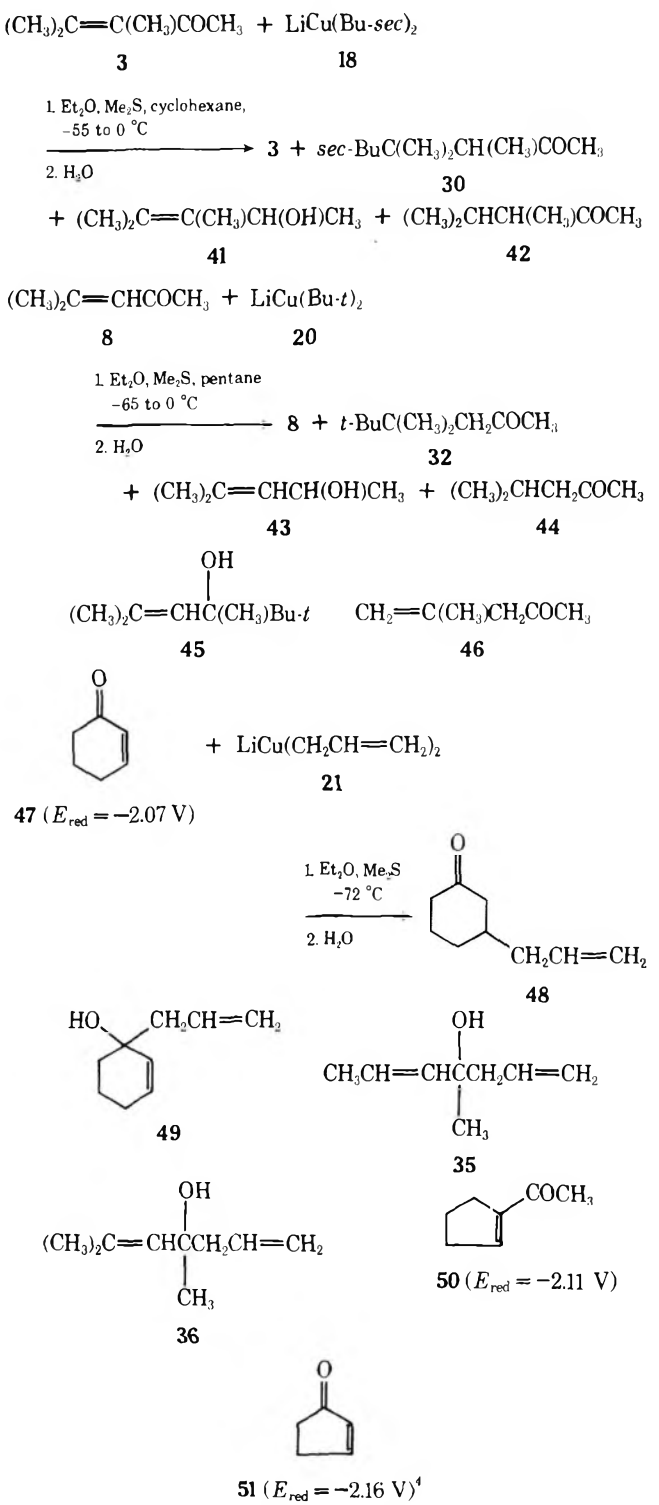
CH_2=$CHCH_2CH(CH_3)CH(CO_2Bu\text{-}t)COCH_3$

40

Side Reactions with the *sec*-Butyl, *tert*-Butyl, and Allyl Cuprates. Our study of the reaction of $LiCu(Bu\text{-}sec)_2$ with the enone **3** (Scheme III) and the reaction of $LiCu(Bu\text{-}t)_2$ with the enone **8** were both complicated by the formation of reduction products **41**–**44**. The amounts of these byproducts varied from run to run and appeared to be related to the amount of thermal decomposition of the cuprate reagent that occurred during the course of the reaction. Analogous byproducts were not observed in reactions of either of these cuprate reagents with more easily reduced enones where conjugate addition occurred readily. We are, therefore, inclined to believe that these reduction products are formed by partial thermal decomposition of *sec*-alkyl and *tert*-alkyl cuprates to form copper hydride species of the type LiCuH(R) that reduce the enones at a rate competitive with conjugate addition or enolate formation.[17]

A second side reaction, noted in the reaction of $LiCu(Bu\text{-}t)_2$ (**20**) with the enone **8** and the reaction of LiCu-

Scheme III



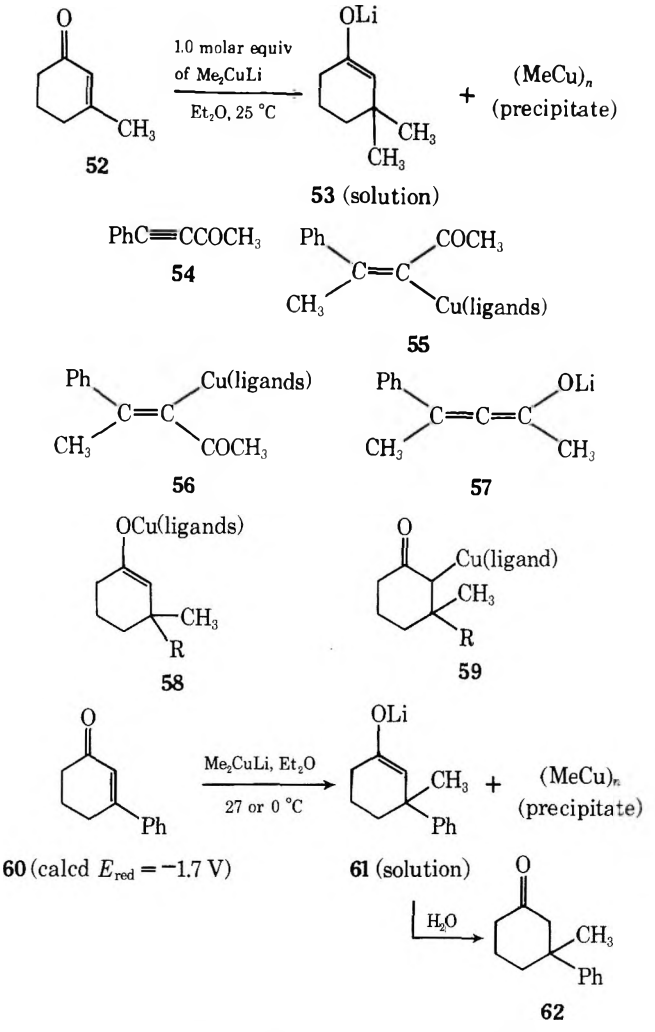
$(CH_2CH{=}CH_2)_2$ (**21**) with the enones **7**, **8**, and **47**, was the formation of 1,2 adducts **35**, **36**, **45**, and **49**. A major cause of this side reaction was the special sensitivity of the cuprates **20** and **21** to thermal decomposition when the Cu(I) salt used to prepare the cuprates contained an impurity [presumably a Cu(II) derivative]. Thus, the *t*-Bu_2CuLi (**20**) generated at −60 to −70 °C from freshly prepared (or freshly recrystallized) Me_2SCuBr was obtained as a pale orange solution that reacted with the enone **8** to form, after hydrolysis, a mixture of the starting enone **8** and the conjugate adduct **32**. However, when the cuprate **20** was prepared from samples of Me_2SCuBr that had been stored for some time before use, partial decomposition of the cuprate **20** was evident (brown-black precipitate) during its formation, even at −70 °C, and a substantial amount (20% or more) of the 1,2-adduct **45** was formed upon addition of the enone **8**. Similarly, repetition of the previously reported[18] addition of $LiCu(CH_2CH{=}CH_2)_2$ (from freshly purified Me_2SCuBr) to the enone **47** formed the conjugate adduct **48** in 91% yield, while similar reactions employing Me_2SCuBr that had been stored before use yielded mixtures containing both the ketone **48** and the alcohol **49**. These observations suggest that in the presence of small amounts of a Cu(II) compound the cuprates **20** and **21** are particularly prone to an autocatalytic decomposition[17e] that generates one of the organolithium reagents, *t*-BuLi or $CH_2{=}CHCH_2Li$, and leads to 1,2 addition as a side reaction.

Even with special care to control the reaction temperature and purity of the Cu(I) source, we have found the course of the reaction of $LiCu(CH_2CH{=}CH_2)_2$ with enones having E_{red} values of about 2.1 V to vary significantly with the structure of the enone. While high yields of conjugate adducts have been obtained from reaction of $LiCu(CH_2CH{=}CH_2)_2$ or $Li_2Cu[CH_2C(CH_3){=}CH_2]_2$[19a] with the cyclic enones **47** and **51**,[19b] reaction of $LiCu(CH_2CH{=}CH_2)_2$ with the enones **7** and **50** yielded mixtures containing comparable amounts of the starting enone, the conjugate adduct, and the 1,2 adduct. The yields of 1,4-adduct **33** (10–16%), 1,2-adduct **35** (12–18%), and recovered enone (48–53%) obtained from enone **7** and $LiCu(CH_2CH{=}CH_2)_2$ were not significantly different when the $CH_2{=}CHCH_2Li$ used to prepare the cuprate **21** was obtained from $Sn(CH_2CH{=}CH_2)_4$ and PhLi,[20a] rather than from $PhOCH_2CH{=}CH_2$ and Li,[20b] in spite of the fact that the latter reagent contains an equivalent amount of PhOLi. However, one difference dependent on the source of the $CH_2{=}CHCH_2Li$ was observed. The red precipitate, previously suggested[18,19] to be allylcopper, that resulted either when the allylcuprate solution was treated with a reactive enone or when the Cu(I) salt was treated with only 1 molar equiv of $CH_2{=}CHCH_2Li$ was observed only with the $CH_2{=}CHCH_2Li$ preparation that contained an equimolar amount of PhOLi. In reactions utilizing phenoxide-free $CH_2{=}CHCH_2Li$ [from $(CH_2{=}CHCH_2)_4Sn$], the above circumstances led to the formation of red-orange solutions but no red precipitate. These observations suggest that the above red precipitate may be some mixed cuprate cluster such as (allyl)(PhO)CuLi.

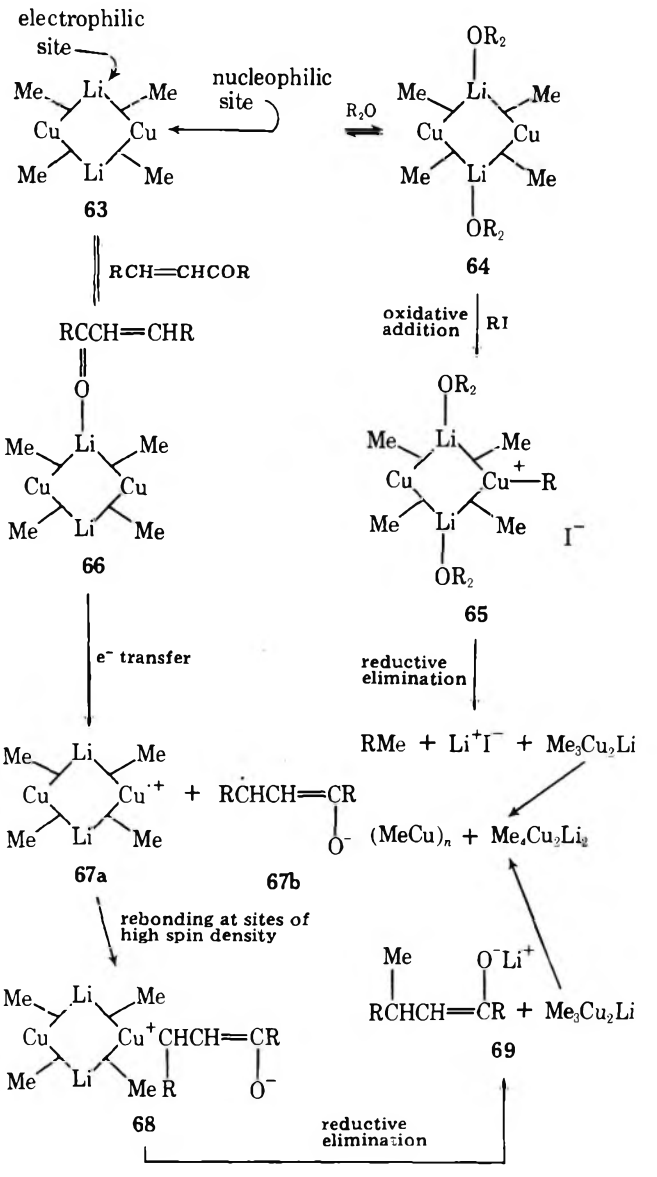
Although an early study[21] had suggested that an added Cu(I) salt was not effective in catalyzing the conjugate addition of an allyl Grignard reagent to the enone **47**, in retrospect this early Cu-catalyzed reaction, performed at 25 °C, could not have succeeded because the allylcopper reagents undergo rapid thermal decomposition at temperatures above −30 °C. When the enone **7** was allowed to react with $CH_2{=}CHCH_2MgBr$ in Et_2O at −40 to −50 °C in the presence of 27 mol % of Me_2SCuBr, the yield of 1,4-adduct **33** (13–20%) was similar to that obtained with the allylcuprate **21**. As might be expected, the yield of alcohol **35** (53–60%) was higher and the amount of recovered enone **7** (4–8%) was lower. The more easily reduced derivative (**39**) of enone **7** reacted with $CH_2{=}CHCH_2MgBr$ at −70 °C in the presence of 27 mol % of Me_2SCuBr to yield 75% of the conjugate adduct **40**.[2f] In the absence of a Cu(I) catalyst, each of the enones **7**, **8**, and **47** reacted with $CH_2{=}CHCH_2MgBr$ to give a good yield of 1,2-adduct **35**,[2f] **36**, or **49**. Both this observation and related control experiments with allyllithium indicated the product compositions reported here are not being complicated by a base-catalyzed[22] oxy-Cope rearrangement during the reaction or subsequent product isolation.

We conclude that one may expect satisfactory yields of conjugate adducts from reaction of either $LiCu(CH_2CH{=}CH_2)_2$ or $CH_2{=}CHCH_2MgBr$ accompanied by a soluble Cu(I) catalyst with unsaturated carbonyl compounds if the E_{red} values are −2.0 V or less negative. However, as the substrate E_{red} values become more negative than −2.0 V it is

Scheme IV



Scheme V



difficult to predict whether the predominant mode of reaction will be 1,2 addition or conjugate addition.[23] In such cases it appears wise to consider alternative synthetic routes to the conjugate adduct, such as the base-catalyzed oxy-Cope rearrangement[22] or the very efficient reaction of the enone with CH_2=$CHCH_2SiMe_3$ and $TiCl_4$.[24]

The Nature of the Initial Reaction Product. The reaction of the enone **52** (Scheme IV) with 1 molar equiv of $LiCuMe_2$ at 25 °C formed a suspension in which all of the enolate **53** was in solution and all of the Cu used was in the MeCu precipitate.[2g] This simple observation allows the unambiguous conclusion that the first stable product formed at 25 °C is a lithium enolate and not some type of copper enolate. However, there is clear precedent for the formation of solutions of vinylcopper enolates such as **55** and **56** (confirmed by spectral measurements) by the addition of $LiCuMe_2$ to the acetylenic ester **54**,[25] and the corresponding lithium enolate **57** is formed only upon reaction of **56** with MeLi at 25 °C. Thus, the possibility exists that the reaction of the enone **52** initially formed some type of copper enolate (e.g., **58** or **59**) that dissociated at 25 °C to form the observed lithium enolate **53** and the insoluble MeCu. We have sought more information concerning this possibility by studying the reaction of the more reactive enone **60** with 1 molar equiv of $LiCuMe_2$ at various temperatures. At both 27 and 0 °C the results with enone **60** paralleled the earlier study in forming a suspension with all the enolate **61** in solution and all of the Cu in the MeCu precipitate. Even after reaction at much lower temperatures (−44 and −72 °C) essentially all of the Cu (94–98%) remained in the precipitate along with a significant fraction (20% at −44 °C and 98% at −72 °C) of the conjugate adduct. When these cold solutions were warmed to 0 °C before hydrolysis, the mixture then contained the usual mixture with all the enolate **61** in solution and all the Cu in the precipitate. Thus, we can conclude that at 0 °C or above the conjugate adduct is a lithium enolate and even at −44 °C that portion of the conjugate adduct *in solution* is the lithium enolate. However, we have found no convincing way to decide whether the insoluble conjugate adduct present at low temperatures (−44 or −72 °C) is a lithium enolate or a copper enolate. In any case, it is clear that if a copper enolate such as **59** is formed it is much less stable than the vinylcopper enolate **56** (which was stable in solution at 25 °C).

Discussion

The effect of donor solvents (or other donor ligands) upon the reactions of $LiCuR_2$ reagents can be understood if the metal atoms in the cuprate cluster **63** (Scheme V) are considered as either electrophilic (Li atoms) or nucleophilic (Cu atoms) sites. The presence of a good donor solvent, R_2O, would increase the proportion of the solvated complex **64**. Since this solvation (**63** → **64**) would increase the electron density of the cluster, it should facilitate the oxidative addition[3a,6] of an alkyl halide at the Cu atom (**64** → **65**), leading to an increased rate of formation of coupled product, RCH_3. By contrast, the conjugate addition of the cuprate reagent to an enone is believed to proceed by initial coordination of the enone oxygen

atom with the cluster (**63** → **66**),[2a,c] followed by inner-sphere electron transfer and subsequent transformations (**66** → **67** → **68** → **69**) leading to the conjugate adduct. A good donor ligand, R_2O, would clearly compete with the enone for electrophilic coordination sites on the cuprate cluster and would, consequently, tend to diminish the concentration of the *enone–cuprate complex (66) needed for electron transfer and* subsequent conjugate addition. With difficultly reduced enones, where the electron-transfer step **66** → **67** is not especially favorable, the result of diminishing the concentration of complex **66** would be to decrease the rate of conjugate additions, allowing the usually slower competing enolate formation to become the dominant reaction. Although it is not presently clear what cuprate species is primarily responsible for the conversion of ketones to their metal enolates, it is apparent that this competing reaction is not inhibited by the presence of good donor solvents.

The order of reactivity in conjugate addition of $LiCuR_2$ reagents with various R groups (*n*-Bu ~ CH_2=CH > Ph ~ *sec*-Bu ~ *Me* > *t*-Bu > CH_2=$CHCH_2$) *differs from the reactivity* order in coupling reactions with alkyl halides (*sec*-Bu > *t*-Bu > *n*-Bu > Ph)[13] or alkyl tosylates (*sec*-alkyl and *tert*-alkyl > Ph and Me).[6c] Neither reactivity order suggests any obvious explanation. One possibility is that the size and/or geometry of the cuprate cluster $LiCuR_2$ varies with different R groups, so that the dimeric formulation **63** indicated[3] for $LiCuMe_2$ is not applicable to other cuprate reagents. If this were true then it would not be surprising to find that both the oxidation potential of the cuprate and its steric requirements for bonding with other ligands would vary with changes in the size and geometry of the cuprate cluster.

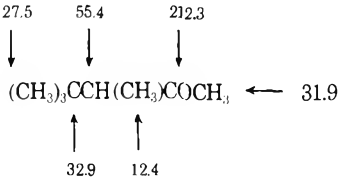
Experimental Section[26]

Preparation of Reagents. All solvents were purified by distillation from $LiAlH_4$ immediately before use. Recrystallized samples of Me_2SCuBr[2b] were used to prepare all organocopper(I) derivatives. The Me_2S was purified by distillation from $LiAlH_4$; bp 36–38 °C. Pure samples of enones 7[27] and 3[2b] were obtained as previoulsy described and a pure sample of enone 8 was obtained by fractional distillation[28] of commercial mesityl oxide: bp 127–128 °C; n^{25}_D 1.4430 (lit.[28] bp 129.8 °C; n^{20}_D 1.44575). Solutions of PhLi, obtained by reaction of PhBr with Li wire in Et_2O, were standardized by a double titration procedure[29] in which aliquots of the reagent, both before and after reaction with $BrCH_2CH_2Br$, were titrated with standard aqueous acid. The same standardization procedure[29] was used for commercial solutions of *n*-BuLi (Foote Mineral Co.) in hexane, *t*-BuLi (Lithium *Corporation of America) in pentane, and sec-BuLi (Foote Mineral* Co.) in cyclohexane. Ethereal solutions of allylmagnesium bromide, prepared in the usual way,[30] were standardized by titration with *sec*-BuOH employing 2,2′-bipyridyl as the indicator.[31] Ethereal solutions of allyllithium, containing an equivalent amount of PhOLi, were prepared by a modification of a previously described procedure[20b] in which $PhOCH_2CH$=CH_2 was allowed to react with Li in Et_2O solution. Alkoxide-free ethereal solutions of allyllithium were prepared by the previously described[20a] reaction of $(CH_2$=$CHCH_2)_4Sn$ with ethereal PhLi. In each case the amounts of allyllithium and residual base in the solutions were determined by the double titration procedure.[29] Solutions of halide-free MeLi, obtained by reaction of MeCl with Li dispersion in Et_2O, were standardized by the double titration procedure[29] or by titration with *sec*-BuOH employing 2,2′-bipyridyl as the indicator.[31] Titration for halide ion by the Volhard *procedure indicated that the LiCl content of the halide-free MeLi was* 5–6 mol %.

Freshly distilled commercial samples of enone **47** were used for electrochemical measurements employing previously described procedures.[16,32] Solutions in anhydrous DMF containing 0.5 M *n*-Bu_4NBF_4 and 1.3–4.8 × 10^{-3} M enone **47** exhibited a polarographic $E_{1/2}$ value of −2.07 V vs. SCE (n = 0.9, i_d = 7–19 μA).

The previously described[33] reaction of 3-ethoxy-2-cyclohexenone with ethereal PhMgBr followed by treatment with dilute aqueous H_2SO_4 yielded 14.8 g (78%) of the enone **60** as pale yellow plates: mp 61–62 °C (lit. mp 61–61.5,[34] 64.5–66 °C[33]); IR (CCl_4) 1670 cm^{-1} (C=O); NMR (CCl_4) δ 7.1–7.7 (5 H, m, aryl CH), 6.26 (1 H, partially resolved multiplet, vinyl CH), and 1.9–2.9 (6 H, m, aliphatic CH); UV max (95% EtOH) 217.5 (ε 9180) and 283.5 nm (ε 17 000); mass spectrum *m/e* (relative intensity) 172 (M^+, 99), 145 (25), 144 (100), 128 (20), 116 (70), 115 (72), and 102 (21).

Reactions of $LiCuMe_2$ with Enone 3 in Various Solvents. Solutions of $LiCuMe_2$, prepared from 411 mg (2.0 mmol) of Me_2S–CuBr and 2.4 mL of Et_2O containing 4.0 mmol of halide-free MeLi, were stirred at 10–25 °C for 5 min and then diluted either with 12 mL of Et_2O or with the appropriate volume (see Table I) of one of the purified cosolvents: pentane, PhH, Me_2S, CH_2Cl_2, THF, or DME. Then weighed samples of the enone **3** (~112 mg or 1 mmol) and *n*-$C_{12}H_{26}$ (~100 mg, internal standard) in 2.0 mL of the cosolvent were added and the reaction mixtures were stirred for 12 h at 25–30 °C. After the mixtures had been treated with a limited amount of H_2O (~0.3 mL) and then filtered, the resulting organic solutions were analyzed by GLC [FFAP (Regis Chemical Co.) on Chromosorb P, apparatus calibrated with known mixtures]; the retention times were: ketone **12**, 8.7 min; enone **3**, 18.6 min; *n*-$C_{12}H_{26}$, 36.8 min. Collected (GLC) samples of the ketones **3** and **12** (n^{25}_D 1.4152; lit. n^{25}_D 1.4161,[35] 1.4162[2b]) were identified with authentic samples[2b] by comparison of IR, NMR, and mass spectra and GLC retention times. The ^{13}C NMR spectrum of the ketone **12** ($CDCl_3$ solution) is summarized in the following structure; the indicated assignments are consistent with off-resonance decoupling measurements. The yields of ketone **12** and recovered enone **3** from the various reactions are summarized in Table I.



A cold (15 °C) solution of Me_2CuLi, from 3.717 g (18.1 mmol) of Me_2SCuBr, 36.2 mmol of MeLi (halide-free) in 25 mL of Et_2O, and 125 mL of THF, was treated with a solution of 1.021 g (9.12 mmol) of *the enone 3 in 10 mL of THF. The originally colorless solution* progressively turned yellow, pink, and then violet and yellow $(MeCu)_n$ began to precipitate after 10 min. After the reaction mixture had been stirred at 15–20 °C for 1 h, it was added slowly with stirring to a solution of DOAc and D_2O prepared by refluxing a mixture of 7.91 g (77.6 mmol) of freshly distilled Ac_2O and 10 mL of D_2O. The resulting mixture was filtered and extracted with three 25-mL portions of Et_2O. After the combined ethereal extracts had been washed with aqueous $NaHCO_3$, dried, and concentrated, an aliquot of the crude liquid product (1.92 g) was mixed with a known weight of *n*-$C_{12}H_{26}$ for GLC analysis. The calculated recovery of the enone **9** (or **3**) was 85% and none of the conjugate adduct **12** was detected. Short-path distillation of the remaining crude product separated 686 mg of the enone **9** containing (mass spectral analysis) 15% d_0 species, 78% d_1 species, and 7% d_2 species. The NMR spectrum (CCl_4) of this product corresponded *to the NMR spectrum of the* enone **3**, except that *the* CH_3CO singlet at δ 2.10 was largely replaced by a three-line pattern (J_{HD} = 2.2 Hz) at slightly higher field (δ 2.08),[36] corresponding to the $COCH_2D$ grouping. In a second comparable experiment, the recovered enone **9** (86% yield) contained (mass spectral analysis) 22% d_0 species and 78% d_1 species and exhibited NMR absorption comparable to that described above. As a control experiment, 755 mg (6.74 mmol) of the enone **3** in 5 mL of THF was added to a solution prepared from 10.1 mmol of Me_2CuLi, 78 mL of THF, 43 mmol of CH_3CO_2D, and 10 mL of D_2O. After the resulting mixture had been stirred at 27 °C for 2 h, the previously described isolation procedure was used to separate 491 mg of the enone **3**, bp 49–50 °C (12 mm), that contained (mass spectral analysis) 99% d_0 species and 1% d_1 species.

The following experiments were performed to compare the reaction of enone **3** with ethereal Me_2CuLi in the presence and absence of *dissolved Li^+ salts. A solution of 84 mg (0.75 mmol) of the* enone **3** and 60 mg of *n*-$C_{12}H_{26}$ in 4 mL of Et_2O was added to a cold (6 °C) solution of 1.69 mmol of Me_2CuLi and 1.69 mmol of LiBr [from 348 mg (1.69 mmol) of Me_2SCuBr and 3.38 mmol of halide-free MeLi in 8.2 mL of Et_2O]. The resulting mixture was allowed to warm from 6 to 22 °C with stirring during 20 min, quenched with H_2O, and analyzed (GLC, UCON 50HB 280X on Chromosorb P, apparatus calibrated with known mixtures). The crude product contained ketone **12** (retention time 7.1 min, 19% yield), enone **3** (12.1 min, 80% yield), and *n*-$C_{12}H_{26}$ (28.5 min). In a second comparable reaction the yields were 22% of ketone **12** and 69% of enone **3**.

Reaction of 1.03 g (5.00 mmol) of Me_2SCuBr with 4.96 mmol of halide-free MeLi in 9.2 mL of Et_2O yielded a slurry of yellow $(MeCu)_n$

that was centrifuged. After the supernatant liquid had been separated, the $(MeCu)_n$ precipitate was washed with one 6-mL portion of Et_2O and then treated with 4.65 mmol of halide-free MeLi in 9 mL of Et_2O. Aliquots of the resulting Me_2CuLi solution (0.53 M) were quenched in aqueous H_2SO_4, filtered, and titrated for halide content by the Volhard procedure; in a series of cuprate preparations, the halide concentration (mainly LiCl) was 0.023–0.030 M (4–6 mol %). After a solution of 2.65 mmol of this halide-free Me_2CuLi in 9 mL of Et_2O had been allowed to react with 84 mg (0.75 mmol) of the enone **3** as previously discribed, the product yields (GLC analysis) were 17% of ketone **12** and 81% of enone **3**. From a second comparable run, the yields were 17% of ketone **12** and 77% of enone **3**. Thus, in all of the reactions of enone **3** with Me_2CuLi in Et_2O solution the product was composed of 18–24% of the conjugate adduct **12** and 76–82% of the enone **3** (from enolate formation) irrespective of whether the solution contained a molar equivalent of LiBr.

Reaction of $LiCuMe_2$ with the Enones 7 and 8 in Various Solvents. Solutions of $LiCuMe_2$, from 411 mg (2.0 mmol) of Me_2S–CuBr and 2.4 mL of an Et_2O solution containing 4.0 mmol of MeLi, were diluted with 11 mL of either THF or DME and then treated with 2.0 mL of the same cosolvent containing weighed amounts of n-$C_{12}H_{26}$ (~80–90 mg, internal standard) and either enone **8** (~98 mg, 1.0 mmol) or **7** (~84 mg, 1.0 mmol). The resulting mixtures were stirred at 25–30 °C for 12 h and then subjected to the previously described isolation and analytical procedures.

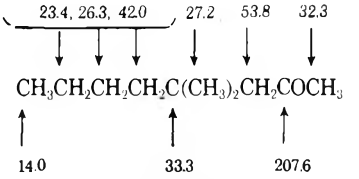
The GLC retention times (Carbowax 20M on Chromosorb P) for reactions with the enone **8** were: ketone **13**, 16.1 min; enone **8**, 29.9 min; n-$C_{12}H_{26}$, 58.9 min. The corresponding values for reactions with the enone **7** were: ketone **14**, 13.9 min; n-$C_{12}H_{26}$, 55.8 min. Collected (GLC) samples of the ketones **8**, **13**, and **14** were identified with authentic samples[2e] by comparison of GLC retention times and IR and either NMR or mass spectra. Comparable reaction and analysis procedures were used for the reaction of 1.024 mmol of the enone **8** with 2.05 mmol of Me_2CuLi in 8.7 mL of Et_2O and for the reaction of 0.997 mmol of the enone **8** with 2.76 mmol of Me_2CuLi in a mixture of 3.6 ml of Et_2O and 14 mL of pentane. The yields of the ketones **13** and **14** and the recovered enone **8** are summarized in Table I.

Reaction of $LiCuMe_2$ With the Enone 10 in Et_2O–DMF Solution. A solution of $LiCuMe_2$, prepared from 520 mg (2.53 mmol) of Me_2SCuBr and 4.95 mmol of MeLi (halide-free) in 3 mL of Et_2O, was diluted with 15 mL of anhydrous DMF and then a solution of 256 mg (1.23 mmol) of the enone **10** in 2 mL of Et_2O was added dropwise with stirring. The resulting solution, which turned red immediately upon addition of the enone, was stirred at 25 °C for 5 h; during this period the initial red solution turned green within ~10 min, but no further change and no precipitation of $(MeCu)_n$ were evident. The resulting mixture was partitioned between pentane and an aqueous solution of NH_4Cl and NH_3. The organic layer was washed with aqueous NaCl, dried, and concentrated to leave 345 mg of crude solid product containing (TLC, silica gel coating with an Et_2O–hexane eluent, 1:4 v/v) the adduct **11** (R_f 0.43) and two minor unidentified impurities (R_f 0.10 and 0.26). A 183.8-mg aliquot of the crude product was subjected to preparative TLC to separate 104.1 mg (75% yield) of the adduct **11** as colorless plates, mp 70–72 °C (lit.[18a] mp 70.5–71 °C); the product was identified with an authentic sample by comparison of IR, NMR, and mass spectra.

Reactions of Ph_2CuLi. A. With Enone 8. To a cold (10 °C) solution of 3.46 g (16.9 mmol) of Me_2SCuBr in 15 mL of Me_2S was added, dropwise with stirring and cooling during 20 min, 35.7 mL of an Et_2O solution containing 33.8 mmol of PhLi. To the resulting cold (10 °C) green solution was added 1.10 g (11.3 mmol) of enone **8**. The resulting mixture, which warmed to 34 °C and slowly became a dark green-brown color, was stirred for 1 h at 27 °C and the mixture was then partitioned between Et_2O and an aqueous solution (pH 8) of NH_3 and NH_4Cl. The organic layer was washed successively with aqueous NH_3, aqueous NaCl, and H_2O and then dried and concentrated to leave 2.16 g of crude liquid product. An aliquot was mixed with an internal standard (n-$C_{16}H_{34}$) and subjected to GLC analysis (Carbowax 20M on Chromosorb P, apparatus calibrated with known mixtures of authentic samples); the product contained n-$C_{16}H_{34}$ (retention time 6.3 min), ketone **26** (77% yield, 19.0 min), and PhPh (26.0 min). In three comparable reactions, the yields of ketone **26** were 76, 77, and 87%. A collected (GLC) sample of PhPh was identified with an authentic sample by comparison of IR and mass spectra and GLC retention times. A collected (GLC) sample of the ketone **26** was obtained as a colorless liquid, n^{25}_D 1.5118 [lit. bp 61–62 °C (1 mm),[37a] 134 °C (22 mm);[37b] n^{20}_D 1.5115[37a]]; IR (CCl_4) 1725 and 1708 cm^- (C=O); NMR (CCl_4), δ 7.0–7.5 (5 H, m, aryl CH), 2.58 (2 H, s, CH_2CO), 1.63 (3 H, s, CH_3CO), and 1.33 (6 H, s, CH_3); UV (95% EtOH) series of weak maxima (ε 60–243) in the region 239–278.5 nm; mass spectrum m/e (rel intensity) 176 (M^+, 24), 120 (20), 119 (100), 118 (38), 91 (63), and 43 (58).

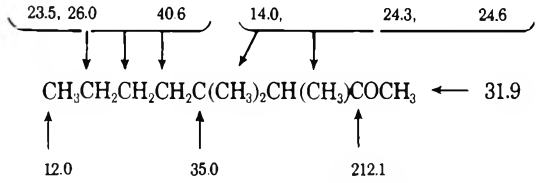
B. With Enone 3. To a solution (at 20 °C) of Ph_2CuLi, prepared from 2.303 g (11.2 mmol) of Me_2SCuBr in 7 mL of Me_2S and 28 mL of Et_2O and 28 mL of an Et_2O solution containing 22.4 mmol of PhLi, was added, dropwise and with stirring, a solution of 896 mg (8.0 mmol) of the enone **3** in 12 mL of Et_2O. The reaction mixture, a green solution containing some white solid, was stirred at 27 °C for 1 h and then subjected to the usual isolation procedure. An aliquot of the crude liquid product (1.74 g) was mixed with a known amount of internal standard (n-$C_8H_{17}Ph$) for GLC analysis (Carbowax 20 M on Chromosorb P). The product contained (GLC) the enone **3** (retention time 10.2 min, 43% recovery), n-$C_8H_{17}Ph$ (34.5 min), the ketone **27** (44.3 min, 48% yield), and PhPh (47.9 min). Collected (GLC) samples of PhPh and the enone **3** were identified with authentic samples by comparison of GLC retention times and IR and mass spectra. A collected (GLC) sample of the ketone **27** was obtained as a colorless liquid, n^{25}_D 1.4468 [lit. bp 72–75 °C (0.15 mm),[38a] 129–130 °C (5 mm),[38b] 138.5 °C (18 mm);[38c] n^{25}_D 1.4604,[38b] 1.5093[38c]]; IR (CCl_4) 1711 cm^{-1} (C=O); NMR (CCl_4) δ 7.1–7.5 (5 H, m, aryl CH), 2.91 (1 H, q, J = 7.5 Hz, CHCO), 1.68 (3 H, s, CH_3CO), 1.35 (6 H, s, CH_3), and 0.95 (3 H, d, J = 7.5 Hz, CH_3); mass spectrum m/e (rel intensity) 190 (M^+, 5) 120 (11), 119 (100), 91 (37), 43 (30), and 41 (18); UV (95% EtOH) series of weak maxima (ε 174–248) in the region 246–264 nm with an additional maximum at 289 nm (ε 56).

Reaction of n-Bu_2CuLi. A. With Enone 8. To a cold (−20 to −30 °C) solution of n-Bu_2CuLi, from 14.35 g (70 mmol) of Me_2SCuBr, 75 mL of Me_2S, and 77.5 mL of a hexane solution containing 140 mmol of n-BuLi, was added, dropwise with stirring and cooling, a solution of 4.9 g (50 mmol) of the enone **8** in 20 mL of Et_2O. The resulting dark green-brown mixture was stirred at −20 to −30 °C for 20 min and then allowed to warm to 27 °C with stirring during 15 min. This warming was accompanied by thermal decomposition of the excess cuprate with separation of Cu^0 as a black precipitate. The reaction mixture was partitioned between Et_2O and an aqueous solution (pH 8) of NH_4Cl and NH_3. The organic phase was filtered, washed successively with aqueous NH_3 and with aqueous NaCl, and then dried and concentrated by fractional distillation. The residual yellow liquid (8.046 g) contained (GLC, Carbowax 20 M on Chromosorb P) the ketone **22** (retention time 11.7 min) accompanied by two minor unidentified impurities (4.5 and 5.3 min). A 7.060-g aliquot of the product was fractionally distilled to separate 5.670 g (83%) of the ketone **22** as a colorless liquid: bp 93–95 °C (30 mm); n^{25}_D 1.4223. A collected (GLC) sample of the pure ketone **22** was obtained as a colorless liquid, n^{25}_D 1.4240 [lit.[39] bp 62–64 °C (7 mm); n^{20}_D 1.4250]; IR (CCl_4) 1716 cm^{-1} (C=O); UV max (95% EtOH) 284.5 nm (ε 21); NMR (CCl_4) δ 2.25 (2 H, s, CH_2CO), 2.04 (3 H, s, CH_3CO), and 0.8–1.5 (15 H, m, aliphatic CH including a CH_3 singlet at δ 0.97); mass spectrum m/e (rel. intensity) 156 (M^+, <1), 98 (35), 69 (30), 58 (14), 57 (36), 56 (22), 43 (100), and 41 (16). The natural abundance ^{13}C NMR spectrum of the ketone **22** ($CDCl_3$) is summarized in the following formula; the indicated assignments are consistent with off-resonance decoupling measurements.



B. With Enone 3. To a cold (−25 °C) solution of n-Bu_2CuLi, from 2.173 g (10.6 mmol) of Me_2SCuBr in 13 mL of Me_2S and 13.9 mL of a hexane solution containing 21.2 mmol of n-BuLi, was added, dropwise with stirring and cooling, a solution of 846 mg (7.55 mmol) of the enone **3** in 4 mL of Et_2O. After the resulting dark-colored solution had been stirred at −25 °C for 15 min, it was warmed to 27°C during 15 min and then subjected to the previously described isolation procedure. After an aliquot of the crude liquid product (1.94 g) had been mixed with a known weight of internal standard (n-BuPh), analysis (GLC, Carbowax 20 M on chromosorb P) indicated the presence of the starting enone **3** (retention time 8.3 min, ~5% recovery), n-BuPh (12.0 min), and the adduct **23** (18.9 min, 74% yield). A collected (GLC) sample of the ketone **23** was obtained as a colorless liquid: n^{25}_D 1.4336; IR (CCl_4) 1711 cm^{-1} (C=O); UV max (95% EtOH) 285.5 nm (ε 17); NMR (CCl_4) δ 2.49 (1 H, q, J = 7 Hz, CHCO), 2.08 (3 H, s, $COCH_3$), and 0.8–1.5 (18 H, m, aliphatic CH including a CH_3 singlet at δ 0.90); mass spectrum m/e (rel intensity) 170 (M^+, <1), 98 (19), 72 (100), 71 (15), 57 (50), and 43 (61). The natural abundance ^{13}C NMR spectrum of the ketone **23** ($CDCl_3$) is summarized in the

following formula; the indicated assignments are consistent with off-resonance decoupling measurements.



Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.47; H, 13.04.

Reaction of *t*-Bu_2CuLi. A. With Enone 8. To a cold (−72 °C) solution of 11.73 g (57.1 mmol) of freshly recrystallized Me_2SCuBr in 50 mL of Et_2O and 62 mL of Me_2S was added, dropwise with stirring and cooling during 45 min, 68.3 mL of a pentane solution containing 114 mmol of *t*-BuLi. The temperature was maintained at −72 to −65 °C during this addition. The yellow to orange precipitate that separated during the initial phase of the addition redissolved as the remainder of the *t*-BuLi was added to give an orange solution of *t*-Bu_2CuLi. A solution of 3.83 g (39.1 mmol) of the enone 8 in 10 mL of Et_2O was added, dropwise and with stirring during 10 min, to the cold solution of *t*-Bu_2CuLi while the mixture was maintained at −65 °C. During the addition of the enone 8 the solution turned red and a red precipitate separated. The resulting mixture was stirred at −60 °C for 45 min and then allowed to warm to 0 °C over a period of 20 min. During this warming thermal decomposition (separation of brown-black solid) was evident as the temperature rose above −25 °C. The reaction mixture was partitioned between Et_2O and an aqueous solution of NH_4Cl and NH_3. The organic phase was washed with aqueous NaCl, dried, concentrated, and mixed with a known weight of *n*-$C_{14}H_{30}$ (an internal standard). Analysis [GLC, 74 °C with FFAP (a modified Carbowax) on Chromosorb P, apparatus calibrated with known mixtures] indicated the presence of the starting enone 8 (retention time 2.9 min, 51% recovery), the isomerized enone **46** (2.2 min, 11% yield), the alcohol **43** (5.3 min, 10% yield), the ketone **32** (11.6 min, 3.5% yield), and *n*-$C_{14}H_{30}$ (26.2 min). A peak corresponding in retention time (1.8 min) to ketone **44**, the conjugate reduction product of enone 8, was also observed. Under the conditions used for this analysis the subsequently described alcohol **45** exhibited a GLC peak at 10.1 min. In another comparable experiment employing 1,3,5-(*i*-$Pr)_3C_6H_3$ (retention time 31.0 min) as the internal standard, the yields and retention times of the products were: **8**, 57% (3.0 min); **46**, 1.9% (2.3 min); **43**, 4.5% (5.6 min); and **32**, 4.7% (12.7 min). Collected (GLC) samples of ketones 8 and **46** and alcohol **43** were identified with authentic samples by comparison of GLC retention times and IR and mass spectra. A collected (GLC) sample of the ketone **32** was obtained as a colorless liquid, $n^{25}D$ 1.4416 [lit.[40] bp 196.1 °C; $n^{20}D$ 1.4420]; IR (CCl_4) 1715 (sh) and 1708 cm^{-1} (C=O); NMR (CCl_4) δ 2.29 (2 H, s, CH_2CO), 2.05 (3 H, s, CH_3CO), 0.97 (6 H, s, CH_3), and 0.87 (9, H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 141 (9), 123 (9), 101 (24), 100 (57), 99 (26), 98 (26), 85 (58), 83 (71), 57 (69), 55 (36), 43 (100), 41 (58), and 39 (31).

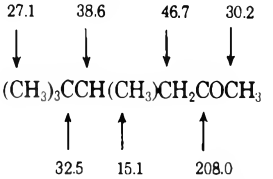
In an experiment where the cuprate reagent was prepared at −57 to −65 °C from 14.65 g (71.5 mmol) of Me_2SCuBr (*not* freshly purified), 60 mL of Me_2S, and 72.2 mL of a pentane solution containing 143 mmol of *t*-BuLi, at least partial decomposition of the cuprate occurred during its preparation. After the resulting cold (−65 °C) dark-colored mixture had been treated with a solution of 5.00 g (51.0 mmol) of the enone 8 in 20 mL of Et_2O, the resulting mixture was stirred at −60 to −65 °C for 20 min and then allowed to warm to room temperature with stirring during 15 min. After following the usual isolation procedure, the residual crude liquid product (3.63 g) contained (IR and NMR analysis) a mixture of the starting enone 8 and the alcohol **45** with little if any saturated ketone product. A 3.12-g aliquot of this crude product was distilled in a short-path still to separate 1.37 g (20%) of the pure alcohol **45** as a colorless liquid [bp 30–31 °C (0.4 mm); $n^{25}D$ 1.4510–1.4512] that was identified with the subsequently described sample by comparision of IR and NMR spectra. A collected (GLC) sample of the starting enone 8 was identified with an authentic sample by comparison of GLC retention times and IR spectra.

To obtain an authentic sample of the alcohol **45**, a solution of 153 mmol of *t*-BuLi in 135 mL of pentane was cooled to −72 °C and then a solution of 7.497 g (76.5 mmol) of the ketone 8 in 25 mL of Et_2O was added dropwise and with stirring while the temperature of the reaction mixture was maintained at −65 to −72 °C. After the resulting yellow mixture had been stirred at −72 °C for 30 min, it was warmed to −30 °C and siphoned into H_2O. This mixture was saturated with NaCl and extracted with Et_2O. After the ethereal solution had been dried and concentrated, the residue, 11.89 g of liquid containing (IR and NMR analysis) mainly the alcohol **45**, was fractionally distilled in apparatus that had been washed with aqueous NH_3 and dried before use. The alcohol **45** was collected as 3.83 g (33%) of colorless liquid: bp 28–33 °C (0.42 mm); $n^{25}D$ 1.4500–1.4508 [lit. bp 180–185 °C,[40] 46 °C (4 mm);[41a] $n^{20}D$ 1.4502[41b]]; IR (CCl_4) 3610, 3500 (OH), and 1665 cm^{-1} (weak, C=C); NMR (CCl_4) δ 5.1–5.4 (1 H, m, vinyl CH), 1.87 (3 H, d, J = 1.5 Hz, allylic CH_3), 1.72 (3 H, d, J = 1.5 Hz, allylic CH_3), 1.23 (3 H, s, CH_3), and 0.92 (9 H, s, *t*-Bu); mass spectrum *m/e* (rel intensity) 138 (13), 123 (84), 81 (85), 79 (20), 67 (34), 57 (59), 55 (42), 53 (30), 43 (55), 42 (100), and 39 (58).

Reduction of 1.02 g (10.44 mmol) of the enone 8 with 564 mg (14.9 mmol) of $LiAlH_4$ in 18 mL of Et_2O, followed by hydrolysis with a limited amount (2.2 mL) of aqueous NaOH and the usual isolation procedure, yielded 635 mg (61%) of the alcohol **43** as a colorless liquid: bp 37–45 °C (10 mm); $n^{25}D$ 1.4350 [lit.[41b] bp 63 °C (36 mm); $n^{18}D$ 1.440]; IR (CCl_4) 3608, 3420 (br, OH), and 1674 cm^{-1} (C=C); NMR (CCl_4) δ 4.1–5.3 (2 H, m, vinyl CH and CHO), 3.13 (1 H, br, OH), 1.63 (6 H, d, J = 1 Hz, allylic CH_3), and 1.11 (3 H, d, J = 6 Hz, CH_3); mass spectrum *m/e* (rel intensity) 100 (M^+, 7), 85 (100), 82 (20), 67 (73), 55 (21), 45 (25), 43 (57), 41 (77), and 39 (36).

B. With Enone 7. To a cold (−55 to −60 °C) red-colored solution of *t*-Bu_2CuLi, formed at −60 to −65 °C from 3.73 g (18.2 mmol) of Me_2SCuBr in 15 mL of Me_2S and 20.6 mL of a pentane solution containing 33.4 mmol of *t*-BuLi, was added, dropwise with stirring and cooling, a solution of 1.007 g (12.0 mmol) of the enone 7 in 6 mL of Et_2O. After the reaction mixture had been stirred at −55 °C for 30 min, it was allowed to warm to 27 °C during 30 min and then subjected to the usual isolation procedure. An aliquot of the crude liquid product (1.72 g) was mixed with a known amount of internal standard (durene) and analyzed by GLC (silicone QF_1 on Chromosorb P). The product contained (GLC) durene (retention time 12.9 min) and the ketone **31** (19.9 min, 74% yield) as well as two minor unidentified volatile by-products (3.9 and 10.8 min).

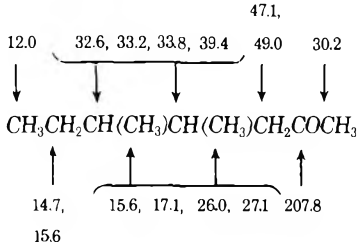
A collected (GLC) sample of the ketone **31** was obtained as a colorless liquid, $n^{25}D$ 1.4227 [lit.[42] bp 162 °C (735 mm), $n^{20}D$ 1.4275]; IR (CCl_4) 1718 cm^{-1} (C=O); UV max (95% EtOH) 277.5 nm (ε 34); NMR (CCl_4) δ 1.7–2.7 (6 H, m, aliphatic CH including a CH_3CO singlet at δ 2.05) and 0.7–0.95 (12 H, *t*-Bu singlet at δ 0.85 partially resolved from a CH_3 doublet); mass spectrum *m/e* (rel intensity) 142 (M^+, <1), 127 (7), 86 (32), 71 (36), 57 (65), 43 (100), and 41 (39). The natural abundance ^{13}C NMR spectrum ($CDCl_3$) is summarized in the following formula; the indicated assignments are consistent with off-resonance decoupling measurements.



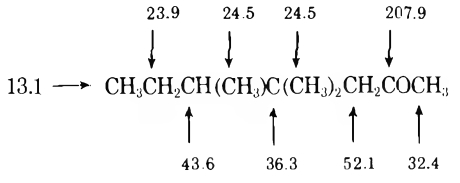
Reaction of the Enone 8 With a Mixture of *t*-Bu_2CuLi and Ph_2CuLi. A cooled (15 °C) solution of 2.02 g (9.82 mmol) of Me_2SCuBr (recrystallized before use) in 8.5 mL of Et_2O and 14.5 mL of Me_2S was treated with 8.85 mL of an Et_2O solution containing 9.82 mmol of PhLi (from PhBr and Li). The resulting greenish yellow slurry was cooled to −72 °C and 5.88 mL of a pentane solution containing 9.82 mmol of *t*-BuLi was added dropwise and with stirring while the temperature was maintained at −65 to −72 °C. After the resulting solution of the cuprates had been stirred at −70 °C for 10 min a solution of 317 mg (3.24 mmol) of the enone 8, 9.1 mg of *n*-$C_{16}H_{34}$ (internal standard), and 61 mg of 1,3,5-(*i*-$Pr)_3C_6H_3$ (internal standard) in 2 mL of Et_2O was added dropwise and with stirring at −62 to −68 °C. During the addition of the enone a red precipitate [(*t*-$BuCu)_n$] separated. The reaction mixture was stirred at −72 °C for 1 h and then was allowed to warm to 25 °C during 45 min. After the mixture had been quenched in an aqueous solution of NH_4Cl and NH_3, it was filtered to remove precipitated Cu and then extracted with Et_2O. The Et_2O solution was washed with aqueous NaCl, dried, and analyzed by GLC [FFAP (a modified Carbowax) on Chromosorb P, apparatus calibrated with known mixtures]. With the GLC column at 74 °C, the yields and retention times of the components were: enone **46**, 0.4% yield (2.5 min); enone 8, 6.4% recovery (3.5 min); alcohol **43**, 3.3% yield (5.7 min); alcohol **45**, 0.7% yield (10.5 min); ketone **32**, 1.3% yield (11.7 min); and 1,3,5-(*i*-$Pr)_3C_6H_3$ (32.2 min). With the GLC column at 141 °C the yields and retention times of the components were: *n*-$C_{16}H_{34}$ (7.9 min); ketone **26**, 67% yield (16.7 min); and PhPh (22.7 min). From a second comparable reaction the product yields were: **46**, 3.1%; **8**, 6.4%; **43**, 7.9%; **32**, 1.6%; and **26**, 77%. A collected

sample of the major product, ketone **26**, was identified with an authentic sample by comparison of GLC retention times and IR spectra. Thus the ratio of conjugate addition products **32** (*t*-Bu addition) to **26** (Ph addition) was 2:98.

Reactions of *sec*-Bu_2CuLi. A. With Enone 7. To a cold (−72 °C) mixture of 3.80 g (18.5 mmol) of Me_2SCuBr, 10 mL of Me_2S, and 10 mL of Et_2O was added, dropwise with stirring and cooling, 27.4 mL of a cyclohexane solution containing 36.9 mmol of *sec*-BuLi. After the resulting solution of *sec*-Bu_2CuLi had been stirred for 5 min at −55 °C, a solution of 1.108 g (13.2 mmol) of the enone **7** in 4 mL of Et_2O was added dropwise with stirring while the mixture was kept at −50 to −55 °C. The resulting reaction mixture was stirred at −50 °C for 20 min and then allowed to warm to 0 °C with stirring during 10 min. After the mixture had been partitioned between Et_2O and an aqueous solution of NH_3 and NH_4Cl, the organic phase was dried, concentrated, and mixed with a known weight of internal standard (tetralin). The crude product contained (GLC, Carbowax 20 M on Chromosorb P, apparatus calibrated with known mixtures) the ketone **28** (retention time 10.9 min, diastereoisomers not resolved, yield 87%), tetralin (32.1 min), and two minor unidentified alcohol (IR analysis) impurities (5.3 min and 21.0 min), but lacked a GLC peak for the starting enone **7** (4.5 min). A collected (GLC) sample of the ketone **28** was obtained as a colorless liquid, $n^{25}D$ 1.4236 [lit.[43] bp 71–73 °C (15 mm)]; IR (CCl_4) 1720 cm^{-1} (C=O); UV max (95% EtOH) 278 nm (ε 25); NMR (CCl_4) δ 1.6–2.8 (6 H, m, aliphatic CH including a CH_3CO singlet at δ 2.06) and 0.6–1.1 (12 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 142 (M^+, <1), 85 (35), 84 (59), 69 (25), 58 (26), 57 (22), 43 (100), and 41 (22). The natural abundance ^{13}C NMR spectrum ($CDCl_3$) of the ketone **28** is summarized in the following structure. Since two diastereoisomers are present in this sample, two chemical shift values are given for each carbon atom where the two diastereoisomers have different chemical shifts.

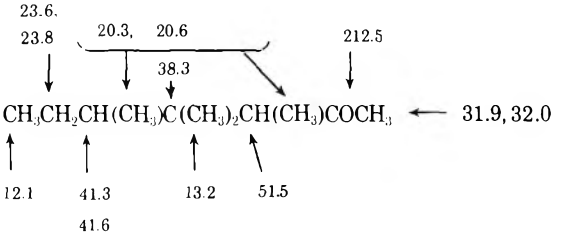


B. With Enone 8. To a cold (−50 to −55 °C) solution of *sec*-Bu_2CuLi, from 3.38 g (16.4 mmol) of Me_2SCuBr, 10 mL of Me_2S, 10 mL of Et_2O, and 23.2 mL of a cyclohexane solution containing 31.3 mmol of *sec*-BuLi, was added, dropwise with stirring and cooling, a solution of 1.096 g (11.2 mmol) of the enone **8** in 4 mL of Et_2O. After the reaction mixture had been stirred for 20 min at −50 °C and for an additional 10 min while it was allowed to warm to 0 °C, the usual isolation procedure was followed and the crude neutral product was mixed with a known amount of internal standard (sec-BuPh). The crude product contained (GLC, Carbowax 20 M on Chromosorb P, apparatus calibrated with known mixtures) *sec*-BuPh (retention time 10.9 min), the ketone **29** (18.3 min, yield 77%), and two minor unidentified impurities (5.6 and 35.0 min). A collected (GLC) sample of the ketone **29** was obtained as a colorless liquid: $n^{25}D$ 1.4330; IR (CCl_4) 1720 cm^{-1} (C=O); UV max (95% EtOH), 284 nm (ε 25); NMR (CCl_4) δ 2.36 (2 H, s, CH_2CO), 2.12 (3 H, s, CH_3CO), and 0.6–1.8 (15 H, m, aliphatic CH including a CH_3 singlet at δ 0.96); mass spectrum *m/e* (rel intensity) 141 (1), 99 (17), 98 (38), 83 (25), 57 (17), 43 (100), and 41 (12). The natural abundance ^{13}C NMR sepctrum ($CDCl_3$) of the ketone **29** is summarized in the following structure; the indicated assignments are consistent with off-resonance decoupling measurements.



Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.60; H, 12.89.

C. With Enone 3. To a cold (−68 to −72 °C) solution of *sec*-Bu_2CuLi, from 6.80 g (33.1 mmol) of Me_2SCuBr, 25 mL of Me_2S, 25 mL of Et_2O, and 45.3 mL of a cyclohexane solution containing 66.2 mmol of *sec*-BuLi, was added 2.523 g (22.5 mmol) of the enone **3** in 2 mL of Et_2O. After the resulting mixture had been stirred at −55 to −60 °C for 30 min and at −45 to −60 °C for 90 min, it was warmed to 0 °C during 10 min and then subjected to the usual isolation procedure. After the crude liquid product had been mixed with an internal standard (1,3,5-triisopropylbenzene), analysis [GLC, FFAP (Regis Chemical Co.) on Chromosorb P] indicated the presence of the ketone **42** (retention time 4.1 min, 5% yield), the starting enone **3** (9.6 min, 20% yield), the alcohol **41** (23.9 min, 13% yield), the ketone **30** (35.6 min, the two diastereoisomers were not resolved, 19% yield), and 1,3,5-(*i*-Pr)$_3C_6H_3$ (59.5 min). From a number of comparable reactions, the following ranges of yields were observed for the various products: **42**, 5–10%; **3**, 19–45%; **41**, 13–34%; **30**, 17–43%. Collected (GLC) samples of products **3**, **41**, and **42** were identified with authentic samples by comparison of IR and mass spectra and GLC retention times. A collected (GLC) sample of the ketone **30** was obtained as a colorless liquid: $n^{25}D$ 1.4430; IR (CCl_4) 1713 cm^{-1} (C=O); UV max (95% EtOH) 288 nm (ε 36); ^1H NMR (CCl_4) δ 2.5–2.9 (1 H, m, CHCO), 2.07 (2 H, s, CH_3CO), and 0.7–1.4 (18 H, m, aliphatic CH); mass spectrum *m/e* (rel intensity) 137 (1), 113 (11), 99 (11), 98 (31), 83 (23), 72 (16), 57 (34), 55 (12), 43 (100), and 41 (14). The natural abundance ^{13}C NMR spectrum ($CDCl_3$) of ketone **30** is summarized in the following structure; the indicated assignments are consistent with off-resonance decoupling measurements. Since the product is a mixture of two diastereoisomers, certain of the ^{13}C NMR signals appear as two peaks.



Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.57; H, 13.02.

To obtain an authentic sample of the alcohol **41**, 1.00 g (8.93 mmol) of the enone **3** was reduced with 177 mg (4.65 mmol) of $LiAlH_4$ in 8 mL of refluxing Et_2O for 30 min. After addition of 0.7 mL of H_2O and 0.2 mL of aqueous 15% NaOH to precipitate the metal salts, the Et_2O solution was dried, concentrated, and distilled to separate the alcohol **41** as a colorless liquid: bp 41–42 °C (12 mm); $n^{25}D$ 1.4508 [lit.[44] bp 65–68 °C (25 mm)]; IR (CCl_4) 3615 and 3470 cm^{-1} (OH); NMR (CCl_4) δ 4.72 (1 H, q, *J* = 6.5 Hz, CHO), 2.70 (1 H, s, OH), 1.4–1.8 (9 H, m, allylic CH_3), and 1.10 (3 H, d, *J* = 6.5 Hz, CH_3), mass spectrum *m/e* (rel intensity) 114 (M^+, 20), 99 (64), 96 (18), 81 (44), 79 (15), 55 (30), 53 (19), 45 (17), 43 (100), 41 (43), and 39 (25).

An authentic sample of the ketone **42** was obtained by hydrogenating a solution of 0.40 g (3.5 mmol) of the enone **3** in 8 mL of EtOH over 30 mg of a 5% Pd/C catalyst at 25 °C and 1 atm of H_2. After 8 h the H_2 uptake (3.9 mmol) ceased and the mixture was filtered and concentrated. A collected (GLC) sample of the ketone **42**[45] was obtained as a colorless liquid, $n^{25}D$ 1.4070 (lit. bp 135–140,[45a] 136–138 °C[45b]); IR (CCl_4) 1713 cm^{-1} (C=O); NMR (CCl_4) δ 1.7–2.3 (5 H, m, aliphatic CH including a CH_3CO singlet at δ 2.04) and 0.7–1.3 (9 H, m, CH_3); mass spectrum *m/e* (rel intensity) 114 (M^+, 2), 72 (22), 71 (19), 55 (12), 43 (100), and 41 (20).

Reaction of $(CH_2{=}CHCH_2)_2CuLi$. A. With Enone 47. To a cold (−72 °C) partial solution of 545 mg (2.65 mmol) of freshly purified Me_2SCuBr in 4 mL of Me_2S and 4 mL of Et_2O was added, dropwise and with stirring, a solution of 5.30 mmol of $CH_2{=}CHCH_2Li$ (from $PhOCH_2CH{=}CH_2$) in 6.3 mL of Et_2O while the temperature was maintained at −60 to −68 °C. As this addition proceeded the white precipitate (Me_2SCuBr) was replaced by a red precipitate (presumably a derivative of allylcopper) and finally a clear red solution of $(CH_2{=}CHCH_2)_2CuLi$ was obtained. To this solution was added, dropwise and with stirring, a solution 126 mg (1.31 mmol) of the enone **47** and 94 mg of PhC_8H_{17}-*n* in 4 mL of Et_2O. The resulting mixture, from which a red precipitate separated during the addition of the enone, was stirred at −72 °C for 3 h and then allowed to warm to 27 °C overnight. During the warming, decomposition of the excess cuprate reagent was evident (separation of a fine black precipitate) as the temperature of the reaction mixture rose above −30 °C. The final reaction mixture was added, dropwise and with stirring, to an aqueous solution of NH_4Cl and NH_4OH, and the resulting mixture was extracted with Et_2O. After the ethereal solution had been washed successively with aqueous 10% NaOH (to remove PhOH from the $PhOCH_2CH{=}CH_2$) and with aqueous NaCl, it was dried, concentrated, and analyzed [GLC, FFAP (Regis Chemical Co.) on Chromosorb P,

apparatus calibrated known mixtures]. The product contained the ketone **48** (retention time 11.1 min, yield 91%), PhC_8H_{17}-*n* (22.0 min), and a minor unidentified impurity (3.4 min), but did not exhibit a GLC peak corresponding to the alcohol **49** (9.6 min).

A comparable reaction was run employing the cuprate, from 3.60 g (17.5 mmol) of Me_2SCuBr, 35 mmol of $CH_2{=}CHCH_2Li$ (from $PhOCH_2CH{=}CH_2$), 23 mL of Me_2S, and 38 mL of Et_2O, with a solution of 1.20 g (12.5 mmol) of the enone **47** in 5 mL of Et_2O. After the mixture had been stirred at −72 °C for 1 h and then warmed to 0 °C during 15 min, the previously described isolation procedure separated 1.50 g of the crude product as a yellow liquid. Short-path distillation of a 1.39-g aliquot of this product separated 910 mg (57%) of the ketone **48** as a colorless liquid, n^{25}_D 1.4720–1.4721, that was identified with the previously described[18] sample by comparison of IR, NMR, and mass spectra.

A solution of 5.00 g (52.1 mmol) of the enone **47** in 10 mL of Et_2O was added, dropwise and with stirring during 20 min, to a solution containing 60 mmol of $CH_2{=}CHCH_2MgBr$ in 68 mL of Et_2O. After the resulting mixture had been stirred at 25 °C for 12 h, it was poured into aqueous NH_4Cl and extracted with Et_2O. The organic layer was dried and concentrated to leave 6.74 g of the crude alcohol **49**. Fractional distillation afforded 1.01 g of forerun [bp 35–40 °C (0.06 mm); n^{25}_D 1.5154] and 3.58 g (50%) of the pure alcohol **49** as a colorless liquid: bp 40–42 °C (0.05 mm); n^{25}_D 1.4932; IR (CCl_4) 3620, 3480 (OH), 1640 (C=C), and 912 cm^{-1} ($CH{=}CH_2$); NMR (CCl_4) δ 4.7–6.2 (5 H, m, vinyl CH), 2.48 (1 H, s, OH), and 1.0–2.3 (8 H, m, CH_2); mass spectrum *m/e* (rel intensity) 120 (6), 97 (100), 79 (32), 55 (37), 41 (33), and 39 (30).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.18; H, 10.24.

B. With Enone 8. To a cold (−65 to −72 °C) solution of $(CH_2{=}CHCH_2)_2CuLi$, from 417 mg (2.03 mmol) of Me_2SCuBr, 4.06 mmol of $CH_2{=}CHCH_2Li$ (from $PhOCH_2CH{=}CH_2$), 4 mL of Me_2S, and 9.1 mL of Et_2O, was added, dropwise and with stirring, a solution of 99 mg (1.01 mmol) of the enone **8** in 4 mL of Et_2O. The resulting solution, from which a red precipitate separated within 5 min, was stirred at −72 °C for 2 h and then allowed to warm to 27 °C during 2 h. After following the previously described isolation procedure, an aliquot of the crude product (164 mg of liquid) was mixed with a known weight of dicyclohexyl (an internal standard) for analysis [GLC, FFAP (Regis Chemical Co.) on Chromosorb P, apparatus calibrated with known mixtures]. The crude product contained the enone **8** (retention time 3.2 min, 6% recovery), the ketone **34** (8.4 min, 1% yield), the alcohol **36** (15.1 min, 71% yield), and dicyclohexyl (25.5 min). A comparable reaction of 2.00 g (20.4 mmol) of the enone with a solution of $(CH_2{=}CHCH_2)_2CuLi$ [from 6.30 g (30.7 mmol) of Me_2SCuBr and 61.3 mmol of $CH_2{=}CHCH_2Li$ (from $PhOCH_2CH{=}CH_2$)] in 30 mL of Me_2S and 40 mL of Et_2O produced 3.27 g of crude liquid product containing (GLC) the alcohol **36** accompanied by minor amounts of the enone **8** and the ketone **34**. A collected (GLC) sample of the ketone **34** was identified with an authentic sample by comparison of IR spectra and GLC retention times. Distillation of a 3.14-g aliquot of the curde product separated 1.96 g (72%) of the alcohol **36** [bp 68–74 °C (10 mm); n^{25}_D 1.4552–1.4585] that was identified with an authentic sample by comparison of IR and NMR spectra and GLC retention times.

Reaction of 2.76 g (28 mmol) of the enone **8** with 34 mmol of $CH_2{=}CHCH_2MgBr$ in 48 mL of Et_2O, followed by the usual isolation procedure, afforded 3.06 g (78%) of the alcohol **36** as a colorless liquid: bp 70–75 °C (10 mm); n^{25}_D 1.4570 [lit.[46] bp 72 °C (18 mm); n^{20}_D 1.4598]; IR (CCl_4) 3600, 3570, 3460 (OH), 1666, 1639 (C=C), and 922 cm^{-1} ($CH{=}CH_2$); NMR (CCl_4) δ 4.7–6.2 (4 H, m, vinyl CH), 2.25 (2 H, d, J = 7 Hz, allylic CH_2), 1.83 (3 H, d, J = 1 Hz, allylic CH_3), 1.6–1.8 (1 H, br, OH), 1.66 (3 H, d, J = 1 Hz, allylic CH_3), and 1.25 (3 H, s, CH_3).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 76.96; H 11.55.

Following a previously described[24] procedure, a solution of 1.00 g (8.8 mmol) of $CH_2{=}CHCH_2SiMe_3$ in 10 mL of CH_2Cl_2 was added, dropwise and with stirring during 2 min, to a cold (−78 °C) mixture of 0.78 g (8.0 mmol) of the enone **8** and 1.52 g (8.0 mmol) of $TiCl_4$ in 10 mL of CH_2Cl_2. The resulting red-brown mixture was allowed to warm to 25 °C with stirring during 40 min and then partitioned between H_2O and Et_2O. The organic solution was dried and concentrated to leave 1.60 g of crude liquid product. After an aliquot of the crude product had been mixed with a known amount of 1,3,5-(*i*-Pr)$_3C_6H_3$ (an internal standard), analysis (GLC, Carbowax 20 M on Chromosorb P, apparatus calibrated with known mixtures) indicated the presence of the enone **8** (retention time 12.8 min, 13% recovery), the ketone **34** (26.8 min, 85% yield), and 1,3,5-(*i*-Pr)$_3C_6H_3$ (108 min). Distillation of a 1.39-g aliquot of the crude product separated 641 mg (66%) of the ketone **34** as a colorless liquid: bp 45–60 °C (10 mm); n^{25}_D 1.4330 [lit.[47] bp 167–168 °C; n^{25}_D 1.4335]; IR (CCl_4) 1720 (C=O), 1639 (C=C), and 922 cm^{-1} ($CH{=}CH_2$); UV max (95% EtOH) 286 nm (ε 21); NMR (CCl_4) δ 4.7–6.2 (3 H, m, vinyl CH), 2.25 (2 H, s, CH_2CO), 1.9–2.2 (5 H, m, allylic CH_2 and $COCH_3$), and 0.98 (6 H, s, CH_3); mass spectrum *m/e* (rel intensity) 125 (7), 99 (46), 82 (75), 67 (33), 55 (28), 43 (100), 41 (36), and 39 (36).

C. With Enone 7. To a cold (−72 °C) mixture of 576 mg (2.80 mmol) of Me_2SCuBr, 6 mL of Me_2S, and 6 mL of Et_2O was added, dropwise with stirring and cooling, a solution of 5.60 mmol of $CH_2{=}CHCH_2Li$ [from $(CH_2{=}CHCH_2)_4Sn$] in 5.2 mL of Et_2O. As the lithium reagent was added the white precipitate (Me_2SCuBr) dissolved to give an orange-red solution and finally a pale yellow solution when all of the lithium reagent had been added. However, unlike the cuprate preparation using $CH_2{=}CHCH_2Li$ from $PhOCH_2CH{=}CH_2$, no red precipitate was observed when equimolar amounts of Me_2SCuBr and $CH_2{=}CHCH_2Li$ were present. To the cold (−72 °C) solution of the cuprate was added, dropwise and with stirring, a solution of 94.1 mg (1.12 mmol) of the enone **7** and 66.3 mg of *n*-$C_{12}H_{26}$ (an internal standard) in 2 mL of Et_2O. During this addition the solution developed a red-orange color, but no red precipitate was observed. The resulting solution was warmed to −50 °C, stirred for 2 h, warmed to −40 °C, and siphoned into a cold (−40 °C), stirred solution of 3 mL of HOAc in 25 mL of Et_2O. (In other runs, where the diallylcuprate reagent was allowed to warm to −30 to −35 °C before quenching, some thermal decomposition of the cuprate reagent was evident.) The resulting mixture was warmed to 25 °C and partitioned between Et_2O and aqueous $NaHCO_3$. After the ethereal layer had been washed successively with an aqueous solution (pH 8) of NH_3 and NH_4Cl and with aqueous NaCl, it was dried and concentrated for GLC analysis (UCON 50HB 280 X on Chromosorb P, apparatus calibrated with known mixtures). The product contained the enone **7** (retention time 3.4 min, 44% yield), the ketone **33** (7.6 min, 13% yield), the alcohol **35** (10.1 min, 16% yield), and *n*-$C_{12}H_{26}$ (15.1 min). In a second comparable run, where the reaction mixture was stirred at −55 to −60 °C for 45 min and then warmed to 25 °C before quenching, the yields were: 28% of enone **7**, 18% of ketone **33**, and 22% of alcohol **35**. Collected (GLC) samples of ketones **7** and **33** and alcohol **35** were identified with authentic samples[2f] by comparison of GLC retention times and IR spectra.

In an additional set of experiments $CH_2{=}CHCH_2Li$, prepared from $PhOCH_2CH{=}CH_2$, was used to prepare the diallylcuprate reagent. These preparations differed from the preparation described above in that a red precipitate separated when equimolar quantities of Me_2SCuBr and $CH_2{=}CHCH_2Li$ were present and redissolved as the second equivalent of $CH_2{=}CHCH_2Li$ was added to give a cold (−70 to −72 °C) orange solution of the diallylcuprate reagent. From a series of reactions ran for 2–3 h within the temperature range −72 to −30 °C and then quenched in a HOAc–Et_2O mixture at −40 to −30 °C, the product yields were: 48–53% of enone **7**, 10–16% of ketone 33, and 12–18% of alcohol **35**.

A solution of 1.27 mmol of $CH_2{=}CHCH_2MgBr$ in 1.73 mL of Et_2O was added, dropwise and with stirring, to a cold (−65 °C) suspension of 71.2 mg (0.35 mmol, 28 mol %) of Me_2SCuBr in 3 mL of Me_2S and 3 mL of Et_2O and the resulting pale orange solution was stirred at −60 to −65 °C for 10 min. Then a solution of 95.8 mg (1.14 mmol) of the enone **7** and 74.3 mg of *n*-$C_{12}H_{26}$ (an internal standard) in 3 mL of Et_2O was added dropwise and with stirring during 35 min while the temperature of the mixture was maintained at −48 to −52 °C. The resulting light orange suspension was stirred at −50 °C for 2 h and then warmed to −40 °C, quenched in an HOAc–Et_2O mixture at −40 °C, and subjected to the previously described isolation and analysis procedures. The yields were 8% of enone **7**, 20% of ketone **33**, and 60% of alcohol **35**. Collected (GLC) samples of the products were identified with authentic samples by comparison of IR and mass spectra and GLC retention times. In a similar reaction where an Et_2O solution of $CH_2{=}CHCH_2MgBr$ was added slowly to a cold (−72 °C) mixture of the enone **7** and 27 mol % of Me_2SCuBr the yields were 4% of enone **7**, 13% of ketone **33**, and 53% of the alcohol **35**.

Reaction of Me_2CuLi With the Enone 60. To a cold (0 °C) solution of Me_2CuLi, from 358 mg (1.74 mmol) of Me_2SCuBr, 3.48 mmol of halide-free MeLi, and 12 mL of Et_2O, was added, dropwise and with stirring, a solution of 198 mg (1.15 mmol) of the enone **60** in 4 mL of Et_2O. After the resulting red-orange solution, from which a yellow precipitate separated rapidly, had been stirred at 0 °C for 1 h, it was siphoned into a vigorously stirred aqueous solution (pH 8) of NH_4Cl and NH_3. The resulting solution was extracted with Et_2O and the ethereal extract was dried, concentrated, and mixed with a known weight of o-terphenyl (an internal standard) for GLC analysis (silicone

Table III. Reaction of Enone 60 With Me_2CuLi in Et_2O Solution

	Product yields, %					
	Supernatant solution			Precipitate		
Temp, °C	Cu	Enone **60**	Ketone **62**	Cu	Enone **60**	Ketone **62**
27	0.5	15	72	99		
0	1.5	17	68	98		
−44	1.2	4	67	98	3	17
−72	5.3	9	0.5	94	59	32

SE-52 on Chromosorb P, apparatus calibrated with known mixtures). The crude product contained the ketone **62** (retention time 12.8 min, 96% yield) and o-terphenyl (37.0 min), but none of the starting enone **60** (17.7 min) was detected. A collected (GLC) sample of the ketone **62** was obtained as a colorless liquid: $n^{25}D$ 1.5397 [lit.[48] bp 80–100 °C (0.1 mm)]; IR (CCl_4) 1719 cm^{-1} (C=O); NMR (CCl_4) δ 7.0–7.4 (5 H, m, aryl CH), 1.4–3.0 (8 H, m, CH_2), and 1.26 (3 H, s, CH_3; lit.[32] 1.28); UV (95% EtOH) series of weak maxima (ε 283 or less) in region 247–268 nm with a maximum at 282 nm (ε 87); mass spectrum *m/e* (rel intensity) 188 (M^+, 65), 173 (30), 145 (30), 131 (100), 118 (50), 117 (33), 91 (51), 55 (68), and 42 (43).

In a series of similar experiments, solutions of 1.16–1.18 mmol of the enone **60** in 5 mL of Et_2O were added, dropwise and with stirring during a period of 40–45 min, to centrifuge tubes containing 1.22–1.28 mmol of Me_2CuLi in 6.5 mL of Et_2O that were continuously cooled in baths at the temperatures indicated in Table III. In each case a yellow (27, 0, −44 °C) to orange (−72 °C) precipitate separated during the addition of the enone **60**. The resulting mixtures were stirred for 40 min at the bath temperatures indicated in Table III, centrifuged for 1–2 min, and again stored in the cooling baths while the supernatant liquid was separated from each tube with a cannula. In the experiments performed at 27 °C and at 0 °C, the precipitates were washed with two 10-mL portions of Et_2O (at 0 or 27 °C) and these washings were combined with the appropriate supernatant solutions. The separate supernatant solutions and precipitates were each hydrolyzed with water and extracted with Et_2O. Each of the Et_2O extracts was dried, concentrated, mixed with a known weight of o-terphenyl, and subjected to the previously described GLC analysis. Each aqueous phase was acidified with aqueous H_2SO_4 and HNO_3, boiled to complete the oxidation of all Cu salts to Cu(II) salts and to expel oxides of nitrogen, and then analyzed for copper by electrodeposition. The yields of Cu, the recovered enone **60**, and the ketone **62**, found in the precipitates and the supernatant solutions are presented in Table III.

To explore the solubility of the lithium enolate **61** at low temperature, the above reaction of Me_2CuLi with the enone **60** was repeated at 27 °C and the supernatnat solution was separated from the $(MeCu)_n$ precipitate by centrifugation. When this supernatant solution was cooled to 0 °C, a small amount of gray-white solid precipitated. This precipitate was separated by centrifugation, hydrolyzed, and subjected to the previously descrbed GLC analysis. The organic material obtained from this precipitate contained the enone **60** (0.4% recovery) and the ketone **62** (0.4% yield). The remaining solution was cooled to −72 °C and centrifuged to separate a white crystalline precipitate (mainly LiBr) from a pale yellow supernatant solution. The organic material obtained from this precipitate contained the enone **60** (1.1% recovery) and the ketone **62** (0.7% yield). The supernatant solution was hydrolyzed to give the enone **60** (22% recovery) and the ketone **62** (55% yield). Thus, we conclude that the lithium enolate **61** is relatively soluble in Et_2O at −72 °C in the concentration range where these experiments were performed.

Registry No.—**9**, 65995-74-6; **10**, 614-47-1; **11**, 1533-20-6; **41**, 2747-54-8; **42**, 565-78-6; **43**, 4325-82-0; **44**, 108-10-1; **45**, 65995-75-7; **46**, 3744-02-3; **47**, 930-68-7; **48**, 20498-05-9; **49**, 65995-76-8; **60**, 10345-87-6; **62**, 33026-37-8.

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Palladium-Catalyzed Arylation of Ethylene

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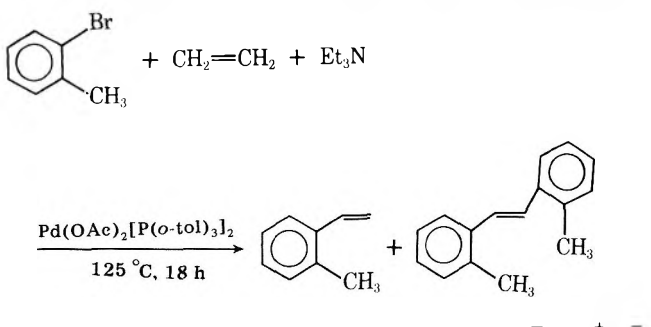
A variety of styrene derivatives and 3-vinylpyridine were prepared in moderate to good yields by the palladium–tri-o-tolylphosphine catalyzed reaction of ethylene with aryl bromides or 3-bromopyridine, respectively.

Styrene derivatives are often very useful chemical intermediates. Frequently, the synthesis of many of these derivatives is not trivial. Therefore, we thought it worthwhile to investigate the palladium-catalyzed arylation of ethylene as a simple general route to these compounds. Previously, ethylene had been successfully used in the arylation reaction but the generality of the reaction had not been determined.[1,2] This paper reports a study of the reaction employing a variety of aryl bromides.

Results and Discussion

Preliminary experiments reacting 2-bromotoluene in acetonitrile solution with ethylene using triethylamine as base and 1 mol % palladium acetate, plus 2 mol % tri-*o*-tolylphosphine (based upon the halide) as catalyst, showed that ethylene pressure was necessary to obtain good yields of o-methylstyrene. The yield of 2-methylstyrene in 20 h at 125 °C increased from 54 to 83 to 86% as the pressure of ethylene was increased from 20 to 100 to 120 psi, respectively. The reason for the lower yields at the lower pressures was that (*E*)-2,2′-



dimethylstilbene was being formed as a side product by a second arylation of the 2-methylstyrene. The yields of the stilbene decreased from 34 to 10 to 4%, respectively, in the above reactions. At pressures above about 200 psi the reaction rates decreased. At 750 psi only 40% of the styrene was formed in 20 h and 60% of the starting bromide remained unreacted. The high ethylene pressure apparently deactivates the catalyst by coordination probably decreasing the rate of oxidative addition of the 2-bromotoluene.

In one experiment, the use of triphenylphosphine rather than the tri-o-tolylphosphine gave product at only half the rate. Therefore, subsequent experiments were carried out with 100–200 psi of ethylene with tri-*o*-tolylphosphine in the catalyst.

Ethylene was arylated with seven different aryl bromides and 3-bromopyridine as shown in Table I. The isolated yields of distilled styrene products ranged from 45 to 86%. The stilbene yields were also obtained by isolation. Unreacted aryl bromides were determined by GLC. These are relatively good yields considering the fact that the reactions were carried out on only a 10–20 mmol scale and some polymerization often occurred. 3-Bromopyridine yielded the 3-vinyl derivative in 52% yield (isolated as the picrate). Styrene derivatives with methyl, nitro, acetamide, amino, formyl, and carboxyl substituents also were prepared. *o*-Divinylbenzene was obtained from *o*-dibromobenzene in 76% (isolated) yield. Thus, the palladium-catalyzed arylation of ethylene appears to be an excellent method for the preparation of a wide variety of styrene derivatives.

Experimental Section

Reagents. All of the aryl bromides were commercial products which were used without further purification. The ethylene, triethylamine, and acetonitrile were reagent grade materials and were used as received. The tri-*o*-tolylphosphine was prepared by the Grignard procedure described previously.[3] The palladium acetate was prepared by the published method.[4]

General Procedure for the Arylation of Ethylene. A 45-mL T-303 stainless steel bomb (Parr Instrument Company) containing a Teflon-coated magnetic stirring bar was charged with 20 mmol of

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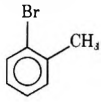
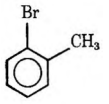
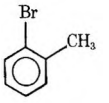
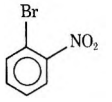
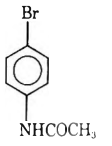
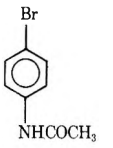
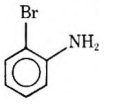
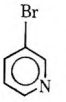
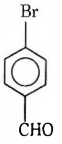
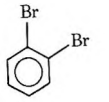
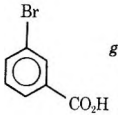
Table I. Reactions of Various Aryl Bromides with Ethylene[a,b]

Aryl bromide	Registry no.	Ethylene pressure, psi	Solvent	Time, h	% yield for product: Styrene	Stilbene	Unreacted RX (by GLC)
	95-46-5	20	5 mL of CH_3CN	20	54	34	5
		100	5 mL of CH_3CN	7	83	10	7
		120	5 mL of CH_3CN	18	86	4	10
	577-19-5	120	8 mL of CH_3CN	2	55	5	
		120	10 mL of DMF	23	59	20	
	103-88-8	120	5 mL of CH_3CN	2		48	
	615-36-1	200	10 mL of CH_3CN	30	45		15[c,d]
	626-55-1	200	10 mL of CH_3CN	66	52[b]		20
	1122-91-4	200	10 mL of CH_3CN	48	53[e]	11	
	583-53-9	200	10 mL of CH_3CN	15	78[f]		
 [g]	585-76-2	200	10 mL of CH_3CN	4	51	12	

[a] Reactions were carried out at 125 °C with 20 mmol of the aryl bromide (10 mmol of *o*-dibromobenzene), 1 mol %, based upon the aryl bromide, palladium acetate, and 2 mol % of tri-*o*-tolylphosphine. [b] Isolated as the picrate. [c] 14% aniline was also formed. [d] ~20% polymer was obtained. [e] Polymer formed also. [f] 12% *o*-Bromostyrene also formed. [g] 8 mL of Et_3N was used. [h] Registry No.—Ethylene, 74-85-1.

the aryl bromide (10 mmol in the *o*-dibromobenzene reaction), 0.045 g (0.20 mmol) of palladium acetate, 0.122 g (0.40 mmol) of tri-*o*-tolylphosphine, 5–10 mL of acetonitrile (DMF was used instead in one example because it was a better solvent for the aryl bromide), and 5 mL of triethylamine (8 mL of amine were used with *m*-bromobenzoic acid). The air in the bomb was flushed out with a stream of argon while the cap was put on. Ethylene was then added to the desired pressure with stirring to saturate the solution. The bomb was stirred magnetically in an oil bath at 125 °C until no more gas was absorbed. Additional ethylene was added periodically to keep the pressure at the initial level. The bomb was then cooled to room temperature, vented, and opened. The contents were rinsed into a round-bottomed flask with ether. Water was added to the mixture and the product was extracted with ether. The extracts were dried ($MgSO_4$) and then either distilled under reduced pressure or if solid they were recrystallized. The pot residues or the less soluble fractions from the recrystallizations contained the stilbene derivatives. These were purified by recrystallization.

Acknowledgment. Financial support for this work was provided by a grant from the National Science Foundation. We thank the Matthey-Bishop Co., Inc., for the loan of the palladium metal used in the catalyst preparations.

Registry No.—Palladium acetate, 3375-31-3; *o*-vinyltoluene, 611-15-4; 1,2-di-*o*-tolylethene, 20657-42-5; *o*-vinylnitrobenzene, 579-71-5; 1,2-bis(*o*-nitrophenyl)ethene, 6275-02-1; *N*-(*p*-vinylphenyl)acetamide, 53498-47-8; 1,2-bis(*p*-acetamidophenyl)ethene,

33267-39-9; *o*-vinylaniline, 3867-18-3; 3-vinylpyridine picrate, 66018-22-2; *p*-vinylbenzaldehyde, 1791-26-0; *o*-divinylbenzene, 91-14-5; *m*-vinylbenzoic acid, 28447-20-3.

Supplementary Material Available: Properties of the products prepared bp or mp NMR data, and molecular weights (Table II) (3 pages). Ordering information is on any current masthead page.

References and Notes

(1) R. F. Heck, *J. Am. Chem. Soc.*, **90**, 5518 (1968).
(2) K. Mori, T. Mizoroki, and A. Ozaki, *Bull. Chem. Soc. Jpn.*, **46**, 1505 (1973).
(3) C. B. Ziegler, Jr., and R. F. Heck, *J. Org. Chem.*, in press.
(4) T. A. Stephenson, S. M. Morehouse, A. R. Powell, J. P. Heffer, and G. Wilkinson, *J. Chem. Soc.*, 3632 (1965).

Synthesis of Macrocyclic Polyether–Diester Compounds with an Aromatic Subcyclic Unit[1]

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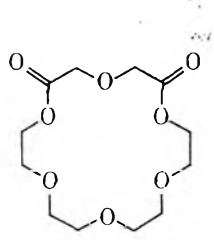
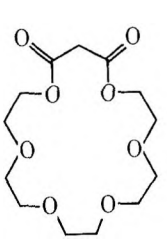
New series of macrocyclic polyether–diester ligands have been prepared by reacting isophthaloyl chloride and 5-nitroisophthaloyl chloride with tri-, tetra-, penta-, and hexaethylene glycols and one sulfur-substituted analogue (compounds **4–13**), terephthaloyl chloride with tetra-, penta-, and hexaethylene glycols (**14–16**), phthaloyl chloride with penta- and hexaethylene glycol (**17–18**), and 1,8-naphthaloyl chloride with pentaethylene glycol (**19**). All macrocyclic diesters were found to be 1:1 adducts except for the terephthalate prepared from tetraethylene glycol, which was found to be a 2:2 adduct.

The synthesis and unique cation complexing properties of the macrocyclic polyethers, first reported by Pedersen,[2] have been the object of intensive research.[3-7] The majority of work has concerned macrocyclic polyethers, the so-called crown compounds, although many aza[8] and thia crown compounds have been studied.[6,9-13]

We have recently reported the synthesis and cation complexing properties of macrocyclic polyether–diester compounds.[14,15] These compounds have proved to be of interest because stabilities for the ligand–metal complexes are somewhat different than those of the typical crown ethers. Thus, the diketo–crown compounds **1** and **2** gave stability orders of $K^+ \approx Ba^{2+}$ and $K^+ > Ba^{2+}$, respectively, while 18-crown-6 has $Ba^{2+} > K^+$.[14] The inclusion of a pyridine moiety in the macrocyclic compound (**3**) greatly increases the cation complexing ability in methanol.[15]



1



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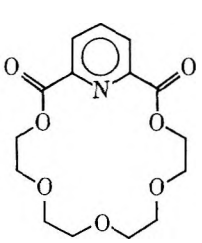
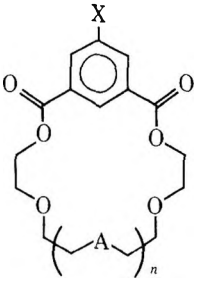


3

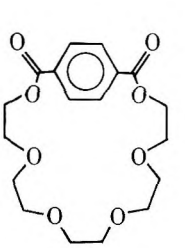
We have previously reported the synthesis of a wide variety of macrocyclic polyether–diester compounds including ether–esters,[14,16-21] thioether–esters,[15,17,19,21] ether–thiol esters,[17,21] amine–esters,[18] ether–ester–amides,[18] ester–amides,[18] and an ether–ester compound with a pyridine subcyclic unit.[15] *In this paper we are reporting the synthesis of* macrocyclic polyether–diester compounds containing benzene and, in one case, naphthalene subcyclic units (compounds **4–19**, Chart I).

Some macrocyclic diester compounds prepared from aromatic dicarboxylic acid moieties have been reported. Drewes and co-workers have prepared a number of different phthalate and bisphthalate compounds by treating the dipotassium phthalates with various alkyl dihalides.[22-26] None of their phthalate compounds contains the repeating ethylene oxide moiety, although they have reported the preparation of two

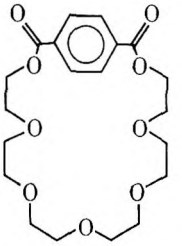
Chart I



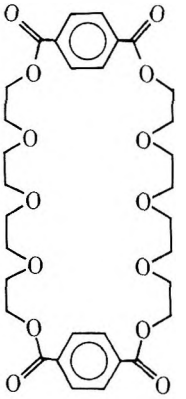
4 X = H; *n* = 0
5 X = H; A = O; *n* = 1
6 X = H; A = S; *n* = 1
7 X = H; A = O; *n* = 2
8 X = H; A = O; *n* = 3
9 X = NO_2; *n* = O
10 X = NO_2; A = O; *n* = 1
11 X = NO_2; A = S; *n* = 1
12 X = NO_2; A = O; *n* = 2
13 X = NO_2; A = O; *n* = 3



14



15



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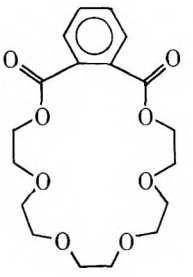
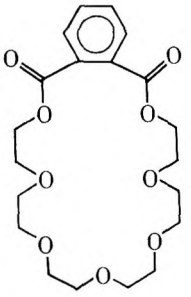
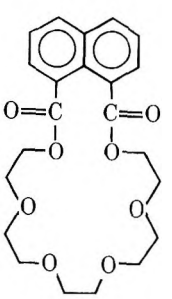


17



18



19

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polyether diesters from 2,2′-dithiodibenzoyl chloride.[27] Ehrhart has reported the synthesis of macrocyclic polyether–diester compounds by reacting phthaloyl chloride with di- and triethylene glycols.[28] These compounds are smaller versions of compounds **17** and **18**.

Only two macrocyclic compounds incorporating the isophthalate moiety have been reported. Berr reported the isolation of a bisisophthalate during the polymerization of ethylene isophthalate.[29] Frensch and Vogtle more recently have reported the synthesis of compound **5** by the same reaction reported in this paper.[30]

The preparation of macrocyclic diester compounds containing the terephthalic acid moiety is also rare. Zahn and co-workers have prepared various terephthalates and bisterephthalates by reacting terephthalic acid and various glycols.[31,32] Frensch and Vogtle also reported a terephthalate in their recent paper.[30] Compounds similar to the terephthalates but containing a methylene group between the benzene ring and each carboxyl group have been prepared by Sakamoto and Oki in their studies of hetera-*p*-carbophane systems.[33] Their synthesis also utilized the diacid chloride and various glycols.

Results and Discussion

Compounds **4–19** were prepared by reacting the diacid chloride and the appropriate glycol in benzene. The products were isolated by a hot hexane extraction followed in most cases by recrystallizing the solid product from hexane. Some solid products were sublimed. The liquid products were repeatedly separated from hot hexane until a good molecular weight was obtained.

The assigned structures are consistent with the IR and NMR spectra and the molecular weights. Isophthalates **4–8** exhibited the expected carbonyl bands in the IR at 1715 ± 5 cm^{-1}, the nitroisophthalates **9–13** at 1725 ± 5 cm^{-1}, the terephthalates **14–16** at 1720 ± 5 cm^{-1}, and the phthalates **17** and **18** at 1720 ± 5 cm^{-1}.[34] The NMR spectra of the aromatic portion of compounds **4–8** exhibited the typical isophthalate peaks[35] at δ 7.57 ± 0.02 (H_5), a doublet at δ 8.25 ± 0.05 (H_4 and H_6) and δ 8.76 ± 0.06 (H_2). The latter NMR peak for compound **4** appeared at δ 9.26 probably because of the influence of the ring ether oxygens. The typical 5-nitroisophthalate aromatic NMR peak[35] at δ 9.07 ± 0.04 was observed for compounds **9–13** except that compound **9** has an additional NMR peak at δ 9.45 probably because of the influence of the ring ether oxygens on the hydrogen on benzene carbon number 2. The typical terephthalate and phthalate aromatic NMR peaks[35] appeared at δ 8.16 ± 0.06 and 7.65 ± 0.20 for compounds **14–16** and **17** and **18**, respectively. The typical polyether–diester NMR peaks appear at δ 4.55 ± 0.10 ($COOCH_2$), 3.85 ± 0.05 ($COOCH_2CH_2$), and 3.75 ± 0.10 (OCH_2) for all compounds. For some unknown reason, the ether methylene hydrogens for compounds prepared from penta- and hexaethylene glycols (**7, 8, 12, 13, 17,** and **18**) exhibited two NMR singlets.

The NMR spectra for the terephthalates (**14–16**) are most instructive. A singlet corresponding to four hydrogens was observed to have an upfield shift from δ 3.70 to 3.46 in the NMR spectrum of compound **14**. Sakamoto and Oki also saw an upfield NMR shift in the spectra of their hetero-*p*-carbophane compounds.[33] A molecular model of compound **14** (Figure 1) shows the center ethylene moiety of the polyether chain to be directly under the benzene ring. Indeed, upfield shifts for the center hydrogens of hydrocarbon chains of the *p*-cyclophanes is common.[36] The NMR spectrum for compound **15** exhibited a triplet peak which had an upfield shift to δ 3.59. The molecular model for this compound (Figure 1) shows that the methylene hydrogens next to the center oxygen of the polyether chain are directly under the benzene ring.

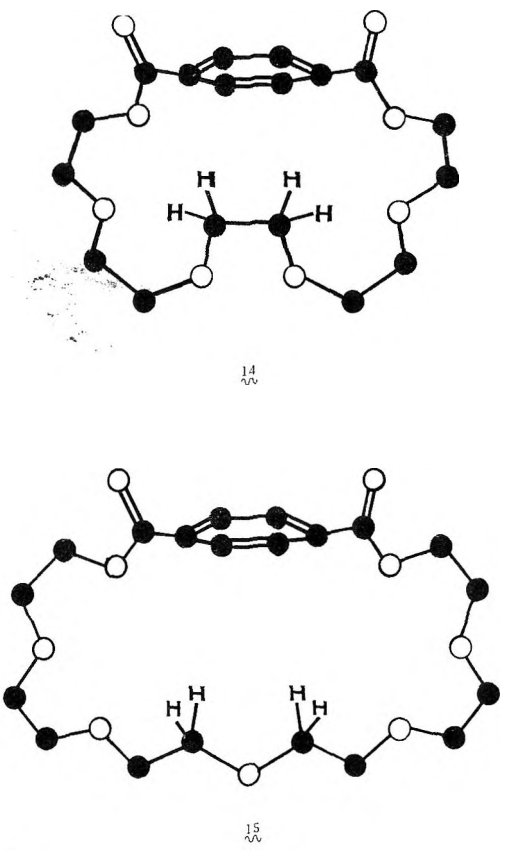
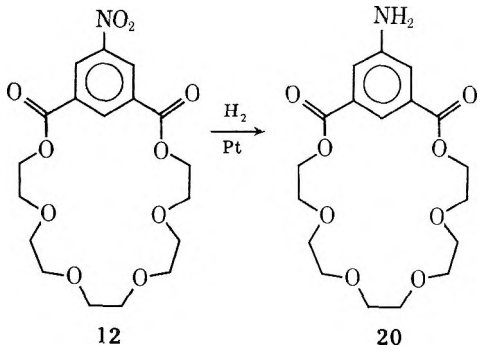


Figure 1.

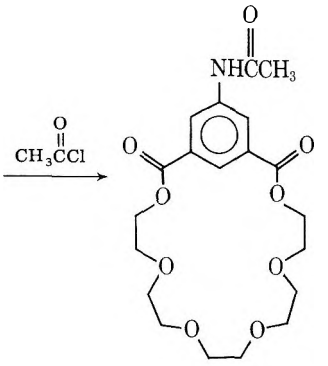
These hydrogens are not as close as those in compound **14** and the upfield shift is not as great. Compounds **14** and **15** were prepared from penta- and hexaethylene glycol, respectively. We expected to see a more pronounced upfield shift for the methylene hydrogens when we prepared a terephthalate from tetraethylene glycol. The NMR peaks corresponding to the polyether chain of the resulting compound (**16**) were essentially the same as those for the isophthalates (compounds **4–13**). This result and the fact that the molecular weight was a little more than twice that of a 1:1 adduct prove that compound **16** is a 2:2 cyclic adduct. Frensch and Vogtle have reported a 1:1 terephthalate adduct from tetraethylene glycol with essentially the same melting point as our compound **16**.[30] They gave no other physical properties. Our data as explained above conclusively demonstrates that the terephthalate prepared from tetraethylene glycol is a 2:2 adduct, not 1:1 as reported by Frensch and Vogtle.

Amino (**20**) and acetamido (**21**) derivatives of compound **12** were prepared. The preparation of these compounds demonstrates the feasibility of modifying the macrocyclic diester compounds.

A satisfactory elemental analysis could not be obtained for five of the compounds (**6, 11, 17–19**). The sulfur-containing compounds appeared to decompose as noted by the development of a distinct yellow color on standing. We have previously reported the difficulty in obtaining combustion analyses for certain sulfur-containing macrocyclic diesters.[17] The mass spectrum of compound **6** did not give a parent peak. Compound **11** exhibited a strong parent peak (385.3) in the MS probably because the ring nitro group stabilizes the two esters. We have noted the difficulty in purifying the phthalates for analysis purposes.[20] Drewes and Coleman have observed difficulty in purifying macrocyclic phthalate esters from octa-, deca-, and dodecamethylene glycols.[25] These latter compounds have a slightly smaller ring size than compounds **17** and **18**. The 1,8-naphthalene dicarboxylate (**19**) was found to be unstable to heat, forming the anhydride. This may have



12 20



21

contributed to the unsatisfactory analysis. In every case, the carbon percentage was low. This may indicate that the samples were hydrates. Some of our previous compounds were observed to have satisfactory analyses when water of hydration was postulated.[18,20]

One of the reported compounds (5) was found to be unreactive in the complexation of various metals as measured by the lack of heat of reaction in methanol. This is in contrast to compound **3**, which is very reactive toward K^+, Na^+, Ba^{2+}, and Ag^+.[15]

Experimental Section

All infrared (IR) spectra were obtained on a Perkin-Elmer Model 457 spectrophotometer. The nuclear magnetic resonance (NMR) spectra were obtained on a Varian EM-390 spectrometer in deuteriochloroform using tetramethylsilane as an internal standard. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. The molecular weights were determined by osmometry using a Hitachi Perkin-Elmer 115 molecular weight apparatus. Melting points were determined on a Thomas-Hoover capillary type melting point apparatus and are uncorrected.

Starting Materials. *o*-Phthaloyl dichloride (Aldrich), isophthaloyl dichloride (Aldrich), and terephthaloyl dichloride (Aldrich) were used as purchased. 5-Nitroisophthaloyl dichloride was prepared from 5-nitroisophthalic acid (Aldrich) using the method employed by Bennett and Wain.[37] 1,8-Naphthaloyl dichloride was prepared from 1,8-naphthalic anhydride (Aldrich) using the method of Arient and Marhan.[38]

Triethylene glycol (Baker) and tetraethylene glycol (Aldrich) were used as purchased. 1,4,10,13-Tetraoxa-7-thiatridecane was prepared from 2-(2-chloroethoxy)ethanol (Parish) using the method of Maas and co-workers.[19] Pentaethylene glycol was either purchased (Columbia) or prepared by a modification of the method of Hibbert and co-workers.[39] Sodium (73.6 g, 3.2 mol) was dissolved in 500 mL of redistilled ethylene glycol (Mallinckrodt). This solution was then warmed to 100 °C. Slowly 1,2-bis(2-chloroethoxy)ethane (301.1 g, 1.61 mol, Parish) was added. The reaction was allowed to stir at approximately 100 °C until a neutral pH was obtained (5 days). The resulting mixture was filtered on a glass frit. Distillation of the dark solution gave a colorless oil (85.4 g, 17%), bp 172–182 °C (0.7 mm). Hexaethylene glycol was prepared by the same method using redistilled diethylene glycol (Aldrich) and redistilled bis(2-chloroethyl) ether (Eastman).

General Synthesis. The appropriate glycol and acid chloride, each dissolved in 300 mL of benzene, were simultaneously dripped into 500 mL of rapidly stirring benzene at 45 °C. If diacid was present, it was filtered from the acid chloride–benzene solution before addition. The mixture was allowed to stir at 45 °C for at least 2 days, during which time HCl gas was evolved. After the reaction was complete, the benzene was removed under reduced pressure. The crude product was partially purified by continuous extraction with hot hexane.[40] The compound was further purified by recrystallizations with either hexane or a chloroform–hexane mixture, or by sublimation. Specific details are given for each compound.

3,6,9,12-Tetraoxabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,13-dione (4). Isophthaloyl dichloride (12.00 g, 0.059 mol) and triethylene glycol (8.85 g, 0.059 mol) were used. After extraction, the product (0.33 g, 2%) was purified by sublimation at 170 °C (0.5 mm) to give a white powder: mp 138–140 °C; IR 1720 cm^{-1}; NMR δ 3.84 (m, 8 H, CH_2OCH_2), 4.47 (m, 4 H, $COOCH_2$), 7.59 (m, 1 H), 8.19 (d, 2 H), 9.26 (s, 1 H).

Anal. Calcd for $C_{14}H_{16}O_6$: C, 59.99; H, 5.76; mol wt, 280. Found: C, 60.17; H, 5.77; mol wt, 281.

3,6,9,12,15-Pentaoxabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (5). Isophthaloyl dichloride (20.3 g, 0.10 mol) and tetraethylene glycol (19.4 g, 0.10 mol) were used. Purification was by repeated recrystallizations from hexane to yield the product (10.63 g, 33%), a fluffy, white, crystalline solid: mp 95.5–96.0 °C; IR 1710 cm^{-1}; NMR δ 3.72 (s, 8 H, CH_2OCH_2), 3.80 (t, 4 H, $COOCH_2CH_2$), 4.52 (t, 4 H, $COOCH_2$), 7.58 (t, 1 H), 8.27 (d, 2 H), 8.80 (m, 1 H).

Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22; mol wt, 324. Found: C, 59.41; H, 6.40; mol wt, 339.

3,6,12,15-Tetraoxa-9-thiabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (6). Isophthaloyl dichloride (5.8 g, 0.029 mol) and 1,4,10,13-tetraoxa-7-thiatridecane (6.0 g, 0.029 mol) were used. Purification was by repeatedly dissolving the product in hot hexane and letting some oil out to finally yield the product (2.06 g, 21%). An analytical sample was prepared by a microdistillation [pot 170 °C (1.0 mm)] to yield a colorless oil: IR 1720 cm^{-1}; NMR δ 2.83 (m, 4 H, SCH_2), 3.64 (t, 4 H, OCH_2), 3.82 (t, 4 H, OCH_2), 4.54 (t, 4 H, $COOCH_2$), 7.57 (t, 1 H), 8.29 (d, 2 H), 8.83 (s, 1 H).

Anal. Calcd for $C_{16}H_{20}O_6S$: mol wt, 340. Found: mol wt, 366.

3,6,9,12,15,18-Hexaoxabicyclo[18.3.1]tetracosa-1(24),20,22-triene-2,19-dione (7). Isophthaloyl dichloride (15.23 g, 0.075 mol) and pentaethylene glycol (17.9 g, 0.075 mol) were used. Purification was by repeated recrystallizations with hexane to yield the product (7.82 g, 28%), a fluffy, white, crystalline solid: mp 103.5–104.5 °C; IR 1714 cm^{-1}; NMR δ 3.64 and 3.72 (both s, 12 H, OCH_2CH_2O), 3.86 (m, 4 H, $COOCH_2CH_2$), 4.54 (t, 4 H, $COOCH_2$), 7.56 (t, 1 H), 8.30 (d, 2 H), 8.71 (m, 1 H).

Anal. Calcd for $C_{18}H_{24}O_8$: C, 58.69; H, 6.57; mol wt, 368. Found: C, 58.83; H, 6.80; mol wt, 386.

3,6,9,12,15,18,21-Heptaoxabicyclo[21.3.1]heptacosa-1(27),23,25-triene-2,22-dione (8). Isophthaloyl dichloride (10.14 g, 0.050 mol) and hexaethylene glycol (14.10 g, 0.050 mol) were used. Purification was by repeated recrystallizations with hexane to yield the product (6.40 g, 31%), a fluffy, white, crystalline solid: mp 106.5–108.5 °C; IR 1710 cm^{-1}; NMR δ 3.57 and 3.69 (both s, 16 H, OCH_2CH_2O), 3.86 (m, 4 H, $COOCH_2CH_2$), 4.54 (m, 4 H, $COOCH_2$), 7.54 (t, 1 H), 8.27 (d, 2 H), 8.70 (m, 1 H).

Anal. Calcd for $C_{20}H_{28}O_9$: C, 58.24; H, 6.83; mol wt, 412. Found: C, 58.50; H, 6.97; mol wt, 421.

16-Nitro-3,6,9,12-tetraoxabicyclo[12.3.1]octadeca-1(18),14,16-triene-2,13-dione (9). 5-Nitroisophthaloyl dichloride (5.5 g, 0.024 mol) and triethylene glycol (3.55 g, 0.024 mol) were used. The product was purified by sublimation at 150 °C (0.7 mm) to yield 0.2 g (2.6%) of light yellow solid: mp 161–163 °C; IR 1540, 1735 cm^{-1}; NMR δ 3.83 (s, 8 H, CH_2OCH_2), 4.47 (m, 4 H, $COOCH_2$), 8.95 (m, 2 H), and 9.45 (m, 1 H).

Anal. Calcd for $C_{14}H_{15}NO_8$: C, 51.69; H, 4.65; mol wt, 325. Found: C, 51.70; H, 4.79; mol wt, 326.

19-Nitro-3,6,9,12,15-pentaoxabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (10). 5-Nitroisophthaloyl dichloride (10.15 g, 0.050 mol) and tetraethylene glycol (14.10 g, 0.050 mol) were used. The product (3.08 g, 17%) was a pale yellow, crystalline solid. An analytical sample was prepared by sublimation at 175 °C (0.5 mm): mp 157–158 °C; IR 1530, 1720 cm^{-1}; NMR δ 3.74 (s, 8 H, OCH_2CH_2O), 3.83 (m, 4 H, $COOCH_2CH_2$), 4.59 (m, 4 H, $COOCH_2$), 9.04 (s, 3 H).

Anal. Calcd for $C_{16}H_{19}NO_9$: C, 52.03; H, 5.18; mol wt, 369. Found: C, 51.89; H, 5.33; mol wt, 368.

19-Nitro-3,6,12,15-tetraoxa-9-thiabicyclo[15.3.1]heneicosa-1(21),17,19-triene-2,16-dione (11). 5-Nitroisophthaloyl dichloride (9.0 g, 0.034 mol) and 1,4,10,13-tetraoxa-7-thiatridecane (7.95 g, 0.038 mol) were used. The solid was purified by recrystallization from hexane to yield a white solid which became yellow on standing (0.22

g, 1.5%): IR 1530, 1730 cm^{-1}; NMR δ 2.88 (m, 4 H, SCH_2), 3.80 (m, 8 H, OCH_2), 4.57 (m, 4 H, $COOCH_2$), 9.10 (m, 3 H).

Anal. Calcd for $C_{16}H_{19}NO_8S$: mol wt, 385. Found: mol wt, 402. MS (*m/e*): 385.3 (17.7), 193.0 (54.5), 238.1 (87.1), 342.2 (98.7), 282.1 (100).

22-Nitro-3,6,9,12,15,18-hexaoxabicyclo[18.3.1]tetracosa-1(24),20,22-triene-2,19-dione (12). 5-Nitroisophthaloyl dichloride (11.43 g, 0.050 mol) and pentaethylene glycol (11.87 g, 0.050 mol) were used. Purification was by repeated recrystallizations from hexane to yield the product (6.27 g, 30%), a fluffy, white, crystalline solid: mp 104–105 °C; IR 1530, 1720 cm^{-1}; NMR δ 3.66 and 3.72 (both s, 12 H, OCH_2CH_2O), 3.88 (m, 4 H, $COOCH_2CH_2$), 4.60 (m, 4 H, $COOCH_2$), 9.11 (s, 3 H).

Anal. Calcd for $C_{18}H_{23}NO_{10}$: C, 52.30; H, 5.61; mol wt, 413. Found: C, 52.22; H, 5.73; mol wt, 389.

Amino Derivative (20). Compound **12** (1.73 g, 0.0042 mol) was reduced with hydrogen using PtO_2 as the catalyst. The product (0.89 g, 55%) was purified by recrystallization from a chloroform/hexane mixture to yield an off-white solid: mp 128–129 °C; IR 1710, 3270, 3350 cm^{-1}; NMR δ 3.72 (d, 12 H, OCH_2CH_2), 3.85 (t, 4 H, $COOCH_2CH_2$), 4.50 (t, 4 H, $COOCH_2$), 6.5 (br s, 2 H, NH_2), 7.72 (s, 2 H), 8.14 (s, 1 H).

Amide Derivative (21). The amino compound (**20**) (0.280, 0.00075 mol) was dissolved in 10 mL of tetrahydrofuran and 0.1 g of pyridine. Acetyl chloride (0.20 g) was added. The product (0.040 g, 16%) was purified by crystallization in dilute hydrochloric acid to give pale white crystals: mp 148.5–150.5 °C; IR 1710 cm^{-1}; NMR δ 2.32 (s, 3 H, CH_3), 2.94 (br s, 1 H, NH), 3.65 (d, 12 H, OCH_2CH_2O), 3.80 (m, 4 H, $COOCH_2CH_2$), 4.44 (m, 4 H, $COOCH_2$), 8.15 (s, 1 H), 8.38 (s, 2 H).

Anal. Calcd for $C_{20}H_{27}NO_9 \cdot 3H_2O$: C, 50.10; H, 6.94. Found: C, 50.34; H, 6.62.

25-Nitro-3,6,9,12,15,18,21-heptaoxabicyclo[21.3.1]heptacosa-1(27),23,25-triene-2,22-dione (13). 5-Nitroisophthaloyl dichloride (22.52 g, 0.098 mol) and 27.60 g (0.098 mol) of hexaethylene glycol were used. Purification was by repeated crystallization from hexane to yield 2.8 g (6%) of white solid: mp 90–92 °C; IR 1530, 1720 cm^{-1}; NMR δ 3.60 and 3.66 (both s, 16 H, OCH_2CH_2O), 3.87 (m, 4 H, $COOCH_2CH_2$), 4.55 (m, 4 H, $COOCH_2$), 9.08 (m, 3 H).

Anal. Calcd for $C_{20}H_{27}NO_{11}$: C, 52.51; H, 5.95; mol wt, 457. Found: C, 52.41; H, 6.10; mol wt, 439.

3,6,9,12,15,18-Hexaoxabicyclo[18.2.2]tetracosa-20,22,23-triene-2,19-dione (14). Terephthaloyl chloride (10.15 g, 0.050 mol) and pentaethylene glycol (11.90 g, 0.050 mol) were used. Purification was by repeated recrystallization from a chloroform/hexane mixture to yield white needles (0.10 g, <1%): mp 108–109.5 °C; IR 1725 cm^{-1}; NMR δ 3.46 (s, 4 H, OCH_2CH_2O), 3.71 (m, 12 H, CH_2OCH_2), 4.51 (m, 4 H, $COOCH_2$), 8.21 (s, 4 H).

Anal. Calcd for $C_{18}H_{24}O_8$: C, 58.69; H, 6.57; mol wt, 368; Found: C, 58.68; H, 6.63; mol wt, 388.

3,6,9,12,15,18,21-Heptaoxabicyclo[21.2.2]heptacosa-23,25,26-triene-2,22-dione (15). Terephthaloyl chloride (10.15 g, 0.050 mol) and hexaethylene glycol (14.10 g, 0.050 mol) were used. Purification was by repeated recrystallizations from a chloroform/hexane mixture to yield white plates (0.44 g, 2%): mp 69–70 °C; IR 1720 cm^{-1}; NMR δ 3.59 (t, ~4 H, OCH_2CH_2O), 3.70 (s, ~12 H, OCH_2CH_2O) (total for 3.59 and 3.70 is 16 H), 3.83 (m, 4 H, $COOCH_2CH_2$), 4.52 (m, 4 H, $COOCH_2$), 8.19 (s, 4 H).

Anal. Calcd for $C_{20}H_{28}O_9$: C, 58.24; H, 6.84; mol wt, 412. Found: C, 58.31; H, 6.90; mol wt, 431.

3,6,9,12,15,22,25,28,31,34-Decaoxatricyclo[34.2.2.2^{17,20}]dotetraconta-17,19,36,38,39,41-hexaene-2,16,21,35-tetraone (16). Terephthaloyl chloride (10.15 g, 0.050 mol) and tetraethylene glycol (9.71 g, 0.050 mol) were used. Purification was by repeated recrystallizations from a chloroform/hexane mixture to yield a white solid (0.080 g, 1%): m.p. 93.5–95.0 °C; IR 1714, 1730 cm^{-1}; NMR δ 3.69 (s, 16 H, OCH_2CH_2O), 3.83 (t, 8 H, $COOCH_2CH_2$), 4.49 t, 8 H, $COOCH_2$), 8.10 (s, 8 H).

Anal. Calcd. for $C_{32}H_{40}O_{14}$: C, 59.25; H, 6.22; mol wt, 649. Found: C, 59.11; H, 6.40; mol wt, 707.

Benzo[*r*]-1,4,7,10,13,16-hexaoxacycloeicosane-17,20-dione (17). o-Phthaloyl chloride (10.14 g, 0.050 mol) and pentaethylene glycol (11.90 g, 0.050 mol) were used. Purification was by repeatedly dissolving the product in hot hexane and decanting the cold hexane to yield the product (0.07 g, <1%), a colorless oil: IR 1725 cm^{-1}; NMR δ 3.68 and 3.72 (both s, 12 H, OCH_2CH_2O), 3.85 (t, 4 H, $COOCH_2CH_2$), 4.50 (t, 4 H, $COOCH_2$), 7.45–7.80 (m, 4 H, aromatic H).

Anal. Calcd for $C_{18}H_{24}O_8$: mol wt, 368. Found: mol wt, 390.

Benzo[*u*]-1,4,7,10,13,16,19-heptaoxacyclotricosane-20,23-dione (18). o-Phthaloyl chloride (10.2 g, 0.05 mol) and hexaethylene glycol (14.1 g, 0.05 mol) were used. Purification was by repeatedly dissolving the product in hot hexane and decanting cold hexane to yield 0.08 g (0.4%) of a viscous liquid: IR 1720 cm^{-1}; NMR δ 3.62 and 3.67 (both s, 16 H, OCH_2CH_2O), 3.77 (m, 4 H, $COOCH_2CH_2$), 4.47 (m, 4 H, $COOCH_2$), 7.45–7.80 (m, 4 H).

Anal. Calcd for $C_{20}H_{28}O_9$: mol wt, 412. Found: mol wt, 402.

3,4,6,7,9,10,12,13,15,16-Decahydro-1*H*,18*H*-naphtho[1,8-*rs*]-1,4,7,10,13,16-hexaoxacycloheneicosin-1,18-dione (19). 1,8-Naphthaloyl dichloride[41] (11.51 g, 0.0455 mol) and pentaethylene glycol (10.82 g, 0.455 mol) were used. Purification was by repeated recrystallizations from hexane and then from a chloroform/hexane mixture to yield white spheres (0.070 g, <1%): mp 122–125 °C; IR 1700, 1725 cm^{-1}; NMR δ 3.68 and 3.72 (both s, 12 H, OCH_2CH_2O), 3.90 (t, 4 H, $COOCH_2CH_2$), 4.47 (t, 4 H, $COOCH_2$), 7.57 (t, 2 H), 8.07 (m, 4 H). Sublimation of the product gave only the 1,8-naphthoic anhydride.

Anal. Calcd for $C_{22}H_{26}O_8$: mol wt, 418. Found: mol wt, 465.

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Registry No.—**4**, 65930-69-0; **5**, 65745-83-7; **6**, 65930-70-3; **7**, 65930-71-4; **8**, 65930-72-5; **9**, 65930-73-6; **10**, 65930-74-7; **11**, 65930-75-8; **12**, 65930-76-9; **13**, 65930-77-0; **14**, 65930-79-2; **15**, 65930-80-5; **16**, 65930-81-6; **17**, 65930-82-7; **18**, 65930-83-8; **19**, 65930-84-9; **20**, 65930-78-1; **21**, 65930-85-0; pentaethylene glycol, 4792-15-8; 1,2-bis(2-chloroethoxy)ethane, 112-26-5; isophthaloyl dichloride, 99-63-8; triethylene glycol, 112-27-6; tetraethylene glycol, 112-60-7; 1,4,10,13-tetraoxa-7-thiatridecane, 64036-00-6; hexaethylene glycol, 2615-15-8; 5-nitroisophthaloyl chloride, 24564-72-5; terephthaloyl chloride, 100-20-9; *o*-phthaloyl chloride, 88-95-9; 1,8-naphthaloyl dichloride, 6423-29-6.

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(41) 1,8-Naphthaloyl dichloride was not very stable in a humid room.

New Synthetic Routes to *gem*-Dinitroalkanes and Derivatives[1a]

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gem-Dinitroalkanes (**3**) have been prepared by reaction of nitro olefins with organolithium reagents, followed by treatment with tetranitromethane. 2-Alkoxy-*gem*-dinitroalkanes (**2**) are obtained similarly by employing alkoxides as the basic addend. The preparation of 1-bromo derivatives of **2** and their reaction with bases are described. The ^1H and ^{13}C NMR spectra of **2** and **3** are presented and discussed.

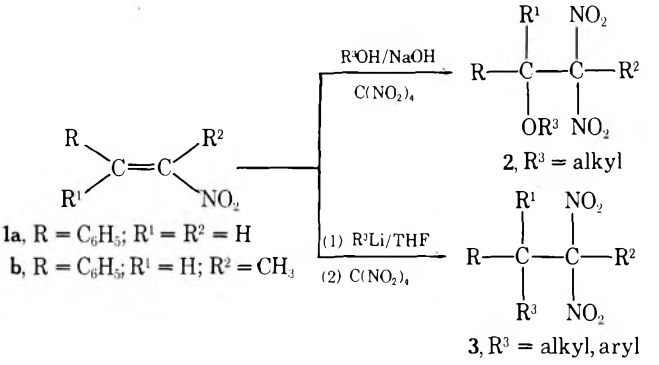
As part of a study of new synthetic routes to polynitro compounds we report a new method of preparing *gem*-dinitro compounds from nitro olefins and precursors. The principal known methods of preparation of these materials are the Kaplan–Shechter reaction (oxidative nitration of mononitroalkanes with silver nitrate),[2] the Ponzio reaction (nitration of an oxime to the pseudonitrole followed by oxidation),[3] the ter Meer synthesis (halogenation of mononitroalkanes and displacement of the halide by nitrite),[4] and alkylation of alkali metal salts of aliphatic polynitro compounds.[5] Each of these synthetic approaches has one or more shortcomings, such as low yield and/or limited scope. Terminal *gem*-dinitro compounds (1,1-dinitroalkanes) undergo reactions such as Michael condensations or Mannich reactions leading to other dinitro and polynitro materials.[6]

Recent synthesis programs in this laboratory have resulted in the facile preparation of several β-alkoxy-α,α-dinitroalkanes (*gem*-dinitro ethers) and *gem*-dinitroalkanes. Treatment of a nitro olefin (**1**) with tetranitromethane (TNM) in the presence of either an alkoxide or alkyllithium yields the corresponding *gem*-dinitro ether (**2**) or *gem*-dinitroalkane (**3**), respectively, Scheme I. The effects of alkyl substitution on the nitro olefin and various alcoholic media have been studied. A special feature of this synthesis is the introduction of two functional units in a one-pot reaction, allowing for the preparation of numerous *gem*-dinitro compounds, not easily accessible by known preparation routes.

The synthetic approach rests on well established experimental observations. Nitro olefins are excellent Michael acceptors and add numerous functional groups in a 1,2 fashion. Also, treatment of a nitronate anion with tetranitromethane, reacting as a nitronium ion source, results in the formation of dinitro and trinitro compounds.[7]

To establish the scope and limitations of this reaction with respect to addends several additions were conducted with ω-nitrostyrene (**1a**) and 2-nitro-1-phenyl-1-propene (**1b**).[8] In the preparation of dinitro ethers (**2**) alkoxides were generated

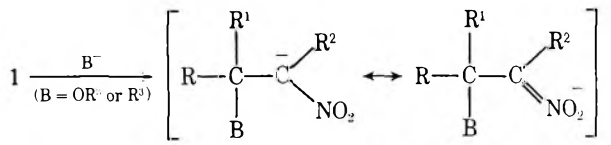
Scheme I



from an excess of the required alcohol by reaction with sodium metal or concentrated aqueous sodium hydroxide (2 mol equiv of base). A solution containing the nitro olefin (1 mol), tetranitromethane (1 mol), and the alcohol as solvent was then added slowly (0–10 °C). The dinitroalkanes (**3**) were prepared similarly in ether–tetrahydrofuran solvent at −40 °C by addition of alkyllithium reagents to the nitro olefin, followed by addition of tetranitromethane. The products were obtained as oils or low melting solids (70–90% yields of crude products). Yields of pure samples obtained by column chromatography were 20–60%. Results are summarized in Table I and indicate the versatility of the method.

The reaction is believed to proceed through anion **4**. Tetranitromethane reacts as the nitrating agent eliminating trinitromethide ion. Those 1,1-dinitroalkanes bearing an α hydrogen (**2a–d, 3a,b**) are present as their salts in the reaction mixture which must be acidified prior to workup to secure products.

Products were characterized and identified by examination of their ^1H and ^{13}C NMR spectra and infrared spectra (Tables II and III; see paragraph at end of paper about supplementary



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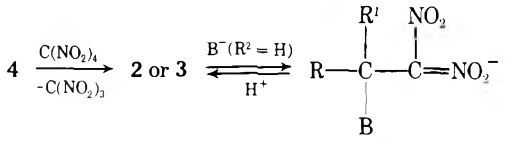
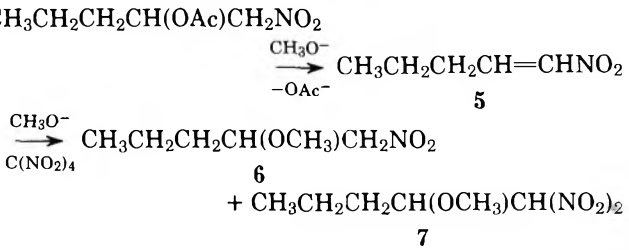


2a-d;
3a, b anion

material). Products derived from ω-nitrostyrene (**2a–d; 3a,b**) in which $R^1 = R^2 = H$ are characterized by a ^1H NMR doublet near 6.3–6.4 δ (J = 9–10 Hz). Dinitromethane and 1,1-dinitroethane are the only *gem*-dinitro compounds for which ^{13}C data have been reported previously.[9] Chemical shift assignments reported in Table *III* were made with the assistance of ^1H pulse decoupled spectra and by comparison of the chemical shifts within a series. Assignments for the ring carbon atoms were given additional support by comparison of the ortho and meta aryl carbon shieldings in known monosubstituted benzenes. Although absolute assignments are unconfirmed, the magnitude and direction of the ortho and meta carbon atom chemical shifts, with respect to benzene, are consistent with other known carbon shieldings.[10] The *gem*-dinitro carbons are characterized by a very low field signal near δ 110–120. In all compounds the characteristic asymmetric and symmetric NO_2 stretching frequencies were observed in the infrared spectra near 1560 and 1300 cm^{-1}, respectively.

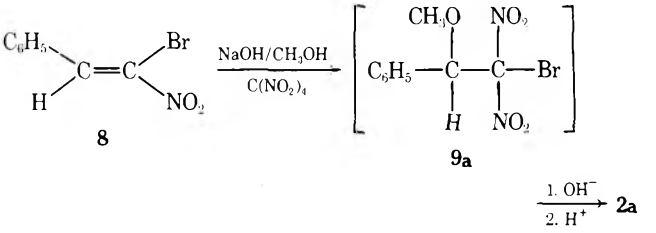
2-Acetoxynitroalkanes are convenient nitro olefin precursors[11] and may be employed in the *gem*-dinitroalkane synthesis. 2-Acetoxy-1-nitropentane with methanolic sodium hydroxide and tetranitromethane gave 1,1-dinitro-2-methoxypentane (**7**), in addition to some of the intermediate 1-nitro-2-methoxypentane (**6**). The nitro olefin **5** is readily generated in situ from the acetoxy compound by the attacking addend base. It was not possible to employ the nitro alcohol, 1-nitro-2-pentanol; much of the reactant was recovered unchanged.



Reaction of 2-nitro-1-phenyl-1-propene with phenylmagnesium bromide, followed by tetranitromethane, failed to yield the desired 1,1-diphenyl-2,2-dinitropropane. The principal reaction product proved to be a bromo derivative, $C_{15}H_{14}BrNO_2$, 2-bromo-2-nitro-1,1-diphenylpropane; its structure is supported by ^1H and ^{13}C NMR, infrared, and mass spectra. Bromide oxidation by TNM had evidently occurred in the reaction leading ultimately to bromination of the intermediate nitronate anion (**4**) to form the isolated product.

An attempt to extend the reaction to Severin's reagent, $(CH_3)_2NCH{=}CHNO_2$,[12] by reaction with phenylmagnesium bromide and tetranitromethane, gave ω-nitrostyrene but no isolable *gem*-dinitro product.

The reaction between ω-bromo-ω-nitrostyrene (**8**), tetranitromethane, and methanolic sodium hydroxide revealed that introduction of nitro and methoxy groups had occurred, but the resulting bromo compound **9a** was unstable under the reaction conditions. Bromine displacement from the dinitro-substituted carbon occurred leading to **2a** anion and the only product isolated after acidification and workup was 1,1-dinitro-2-methoxy-2-phenylethane (**2a**, 60% yield).



The scope of the new *gem*-dinitroalkane synthesis is believed to be potentially large. A wide variety of nitro olefins may be employed, with substituents alkyl, aryl, or H. Also, 2-acetoxy-1-nitroalkanes serve as convenient nitro olefin substitutes. Tetrasubstituted nitro olefins, although not examined in the present study, would be expected to react. *tert*-Butyllithium was the only organometallic addend employed which failed to yield an isolable product. Primary and secondary alkyl and aryl lithium reagents of wide variety would be expected to react normally. Alkoxides of low mo-

Table I. Properties and Yields of *gem*-Dinitro Compounds Prepared by Reactions of Scheme I

Nitro olefin 1	Addend R^3	Product, molecular formula[b]	Registry no.	Yield,[a] %	Bp/mp, °C
1a[f]	CH_3	**2a**, $C_9H_{10}N_2O_5$	65899-55-0	60	90 @ 0.7 mm
1a	CH_3CH_2	**2b**, $C_{10}H_{12}N_2O_5$	65899-56-1	44	29–30[c]
1a	$(CH_3)_2CH$	**2c**, $C_{11}H_{14}N_2O_5$	65899-57-2	38	*d*
1a	$CH_2{=}CHCH_2$	**2d**, $C_{11}H_{12}N_2O_5$	65899-58-3	37	*d*
1b[g]	CH_3	**2e**, $C_{10}H_{12}N_2O_5$	65899-59-4	42	53–55
1b	CH_3CH_2	**2f**, $C_{11}H_{14}N_2O_5$	65899-60-7	35	*d*
1b	$CH_3CH_2CH_2$	**2g**, $C_{12}H_{16}N_2O_5$	65899-61-8	20	*d*
1a	CH_3	**3a**, $C_9H_{10}N_2O_4$	65899-62-9	29	*d, e*
1a	$CH_3(CH_2)_3$	**3b**, $C_{12}H_{16}N_2O_4$	65899-63-0	45	*d*
1b	CH_3	**3c**, $C_{10}H_{12}N_2O_4$	65899-64-1	60	76–78

[a] Yields are of analytically pure samples; yields of initially isolated crude product were 70–90%. [b] Satisfactory analytical data (±0.3% for C, H, and N) and molecular weight data (±5%, by vapor osmometry in chloroform) for all compounds were submitted for review. [c] S. S. Novikov, V. M. Belikov, V. F. Dem'yanenko, and L. V. Lapshina, *Izv. Adad. Nauk SSSR, Otd. Khim. Nauk*, 1295 (1960), prepared **2b** by addition of ethanol to ω,ω-dinitrostyrene, bp 115–117 °C (3 mm); mp 31–32 °C. [d] The product was obtained analytically pure as an oil by column chromatography. [e] C. Lugercrantz, S. Forshult, T. Nilsson, and K. Torssell, *Acta Chem. Scand.*, **24**, 550 (1970), prepared **3a** by another method but gave no physical properties or details. [f] Registry no.: 102-96-5. [g] Registry no.: 705-60-2.

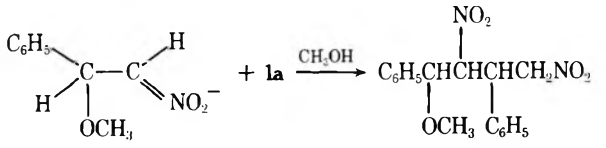
Table IV. Properties and Yields of 1-Bromo-1,1-dinitro Compounds (9)

Reactant dinitroalkane	Product, molecular formula[b]	Registry no.	Yield,[a] %	Mp, °C
2a	**9a**, $C_9H_9N_2O_5Br$	65899-65-2	91	41–43
2b	**9b**, $C_{10}H_{11}N_2O_5Br$	65899-66-3	74	*c*
2d	**9d**, $C_{11}H_{11}N_2O_5Br_3$	65899-67-4	85	*c*

[a] Yields are of analytically pure samples. [b] Satisfactory analytical data (±0.3% for C, H, N, and Br) and molecular weight data (±2% by vapor osmometry in chloroform) for all compounds were submitted for review. [c] The product was obtained analytically pure as an oil by column chromatography.

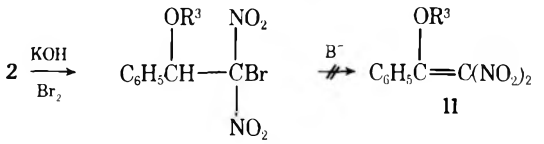
lecular weight are most convenient. Although alkoxides of C-4 and larger carbon content react, the workup and purification of product is made difficult by the low volatility of their alcohols. Phenoxide was not studied.

Interfering side reactions are few and present no problems in workup. 2-Alkoxy-1-nitroalkanes are present in small amounts in most product mixtures. A Michael addition of reactant nitro olefin leading to an alkoxy-substituted dimer is occasionally observed. In methanol solvent ω-nitrostyrene produced known[13] 2,4-dinitro-1,3-diphenyl-1-methoxybutane (**10**) in variable, low yield. With higher alcohols this side reaction is virtually absent.



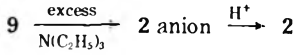
10

Acidic dinitro ethers **2a,b,d** were converted into their corresponding 1-bromo derivative (**9a,b,d**) by reaction with 10% KOH solution, followed by addition of bromine (Table IV). The alkyl compound **2d** afforded a tribromo derivative, **9d.** Treatment of **9** with triethylamine did not result in dehydrohalogenation to a dinitro olefin (**11**). Bromine attack by base occurred (as noted above) leading to **2** nitronate anion, which upon acidification gave reactant dinitro ether.

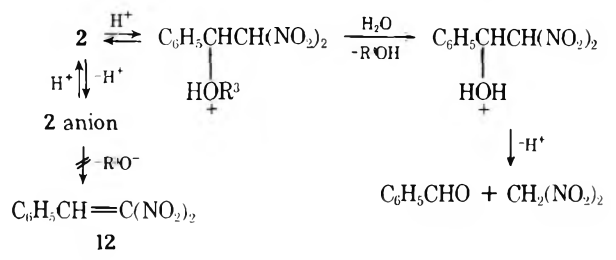


11

9a, $R^3 = CH_3$
b, $R^3 = C_2H_5$
d, $R^3 = CH_2BrCHBrCH_2$



Attempts to convert the acidic dinitro ethers **2a–d** to 1,1-dinitro olefins were unsuccessful. Treatment of **2a** with moist trifluoroacetic acid ultimately gave benzaldehyde and dinitromethane. With anhydrous trifluoroacetic acid the dinitro ether remained unchanged. The anions of acidic 1,1-dinitro ethers (**2a–d, 3a,b**) do not lose alkoxide ion to yield 1,1-dinitro olefins (**12**).



12

Experimental Section

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer grating spectrophotometer, Model 137. A Varian EM 360 or XL 100 nuclear magnetic resonance spectrometer was used for the scanning of proton and carbon spectra. Column chromatography was done on Woelm neutral silica gel with fluorescent indicator, "dry column chromatography grade." Elemental analyses and molecular weight determinations were performed by Galbraith Laboratories, Knoxville, Tenn.

Caution. All polynitro compounds are considered toxic and potentially explosive and should be handled with appropriate precautions. Tetranitromethane in hydrocarbon solvents forms an extremely hazardous mixture. In examples of preparation of acidic 1,1-dinitro compounds, the ether extracts must be washed six to ten times with 100-mL portions of water to remove the nitroform side product produced during the reaction. Insufficient washing may result in fume-offs upon concentration of the ether solutions.

The preparation of dinitro ethers employed two principal methods. These are illustrated in the preparations of **2a** and **2e.** **Method A: 1,1-Dinitro-2-methoxy-2-phenylethane (2a).** To an ice-cold solution of 4 g (0.10 mol) of NaOH dissolved in 10 mL of water and 20 mL of methanol was added dropwise a solution containing 7.5 g (0.05 mol) of ω-nitrostyrene (**1a**) and 9.8 g (0.05 mol) of tetranitromethane dissolved in 50 mL of methanol. The temperature during addition was maintained at 0–10 °C. The resulting mixture was stirred at ambient temperature for 1 h after the addition was completed. The crude reaction mixture was then poured into 100 mL of water and acidified to pH 2 or less with concentrated HCl. The crude mixture was extracted twice with two 100-mL portions of diethyl ether, the combined ether extracts washed six to ten times with 100-mL portions of water, dried over anhydrous $MgSO_4$, and concentrated on a rotary evaporator at room temperature, affording 8.5 g (75% yield) of a reddish colored oil, essntially pure dinitro ether **2a** by NMR assay. The crude product was immediately dissolved in carbon tetrachloride to avoid possible fume-offs of residual nitroform, and chromatographed on 150 g of silica using carbon tetrachloride as eluent. The first fraction was analytically pure dinitro ether (**2a**), 6.8 g (60% yield). The same procedure was also used for the preparation of compounds **2b–d.**

Occasionally the NMR spectrum of the crude material indicated the presence of traces of a second component. Trituration with cyclohexane afforded a white crystalline solid, mp 145–152 °C, 1,3-dinitro-2,4-diphenyl-4-methoxybutane (**10**). Recrystallization from a benzene/cyclohexane mixture (1:9) afforded an analytically pure sample, mp 148–149 °C (lit.[13] mp 150–151 °C: NMR ($CDCl_3$) δ 7.40, 5 H, s, C_6H_5; 4.74, 5 H, m, CH_2, CH; 3.17, 3 H, s, CH_3.

Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.85; H, 5.45; N, 8.48; mol wt 330. Found: C, 61.87; H, 5.54; N, 8.29; mol wt 321 (osmometry $CDCl_3$).

Method B: 2,2-Dinitro-1-methoxy-1-phenylpropane (2e). To 1.15 g (0.05 mol) of sodium metal dissolved in 75 mL of methanol was added dropwise with cooling (0–10 °C) a solution of 4.0 g (0.025 mol) of 2-nitro-1-phenyl-1-propene (**1b**) and 4.9 g (0.025 mol) of tetranitromethane in 25 mL of methanol. The resulting solution was stirred at room temperature for 1 h. The product was isolated and purified as described under method A above, except that acidification prior to workup was omitted. Ultimately there was obtained 2.5 g (42%) of analytically pure, white crystalline **2e**, mp 53–55 °C. The same procedure was employed to prepare **2f,g.**

Reaction of ω-Bromo-ω-nitrostyrene with Tetranitromethane. To a solution of 0.8 g (0.02 mol) of NaOH dissolved in 10 mL of water and 20 mL of methanol was added dropwise with cooling (0–10 °C) a solution of 2.28 g (0.01 mol) of ω-bromo-ω-nitrostyrene[14] and 1.96 g (0.01 mol) tetranitromethane in 30 mL of methanol. The resulting solution was stirred for 1 h at room temperature after addition was complete. The crude mixture was then acidified with concentrated HCl to pH ~1 and purified as described in the preparation of **2a** above, yielding 1.5 g (60%) of **2a.** The NMR and infrared spectra were identical with authentic **2a.**

1,1-Dinitro-2-methoxypentane (7) and 2-Methoxy-1-nitropentane (6). To a solution of 2 g (0.05 mol) of NaOH in 5 mL of water and 10 mL of methanol was added with stirring and cooling (0–10 °C) a solution of 4.4 g (0.025 mol) of 2-acetoxy-1-nitropentane[15] and 4.9 g (0.025 mol) of tetranitromethane in 15 mL of methanol. The re-

sulting mixture was stirred for an additional hour, then acidified to a pH ~2 with concentrated HCl and stirred for an additional 30 min. The crude material, 2.8 g, was isolated as described in the preparation of **2a** above. The NMR spectrum showed starting material to be absent and the presence of three products: 1-nitro-1-pentene (**5**), 2-methoxy-1-nitropentane (**6**), and 1,1-dinitro-2-methoxypentane (**7**) in a 1:4:2 ratio, respectively. Nitro olefin **5** was readily identified by comparison of its NMR spectrum with an authentic sample of known **5**[15] prepared by base elimination of the acetate group from reactant 2-acetoxy-1-nitropentane; ($CDCl_3$) δ 7.25, m, $CH{=}CH_2$; 2.28, q, CH_2; 1.27, sextet, CH_2; 0.97, t, CH_3. Compound **6** was isolated by VPC on a 20% SE 52, $\frac{3}{8}$ in. column at 175 °C with a flow rate of 120 mL/min. Pure **6** was identified by NMR: ($CDCl_3$) δ 4.51, d, CH_2NO_2; 4.05, m, CH; 3.44, s, CH_3; 1.50, m, CH_2CH_2; 0.97, m, CH_3. Product **7** could not be isolated by VPC. The NMR spectrum of the crude mixture revealed the presence of the dinitromethine group of **7** by its characteristic peak at δ 6.4 (d, J = 7.0 Hz). In addition to the dinitromethine peak, a second methoxy peak at δ 3.55 was observed. The integral ratios between the two methoxy peaks (~1:2) corresponded to that of the dinitromethine and nitromethylene peaks (~1:4).

Decomposition of 2a with Trifluoroacetic Acid. A solution of 1,1-dinitro-2-methoxy-2-phenylethane **2a** in an equal volume of moist trifluoroacetic acid was allowed to stand at room temperature. The progress of the reaction was monitored by NMR. After 3 days no reactant **2a** remained and only the following peaks were observed: δ 10.0 (s, 1 H, CHO), 7.6 (m, 5 H, C_6H_5), 6.4 (s, 2 H, CH_2), and 4.0 (s, 3 H, CH_3O), corresponding to benzaldehyde (spectrum identical with authentic sample), dinitromethane (recorded value of 6.2 in CCl_4 solvent[16]), and methyl trifluoroacetate (spectrum identical with authentic sample). When a trifluoroacetic acid/trifluoroacetic anhydride mixture was used as solvent no reaction was observed after three days and the spectrum of **2a** remained unchanged.

The preparation of dinitroalkanes is illustrated in the following description: **2,2-dinitro-3-phenylbutane (3c).** To a solution of 4.03 g (0.025 mol) of 2-nitro-1-phenyl-1-propene (**1b**) dissolved in 30 mL of dry THF (cooled to −40 °C with an acetonitrile–dry ice bath) and under a positive nitrogen atmosphere was added with stirring 22 mL (0.05 mol) of a 5% ether solution of methyllithium. The resulting solution was stirred for 1 h at −40 °C followed by the addition of 4.9 g (0.025 mol) of tetranitromethane. The solution was then allowed to warm to room temperature and stirred an additional hour. The resulting product was isolated and purified as described in the preparation of **2a** above, yielding 3.4 g (60% yield) of an analytically pure white crystalline product (**3a**), mp 76–78 °C. A similar procedure was used for the preparation of **3a** and **3b**.

2-Bromo-2-nitro-1,1-diphenylpropane. A solution containing 0.05 mol of freshly prepared phenylmagnesium bromide in 40 mL of dry THF was cooled to 0 °C and 4.07 g (0.025 mol) of 2-nitro-1-phenylpropene was added. After stirring for 1 h at this temperature 3 mL (0.025 mol) of tetranitromethane was added and the solution was stirred for an additional hour. Workup analogous to the procedures described above for **2a** afforded, after chromatography, 2.5 g, 30% of an analytical sample of 2-bromo-2-nitro-1,1-diphenylpropane as a clear yellow oil: ^1H NMR ($CDCl_3$) δ 7.39 (s, 10, C_6H_5), 5.14 (s, 1, CH), 2.28 (s, 3, CH_3); ^{13}C NMR ($CDCl_3$) δ 138.38, 137.38, 130.01, 129.87, 128.99, 128.74, 128.35, 128.18 (C_6H_5), 101.67 (C_2), 61.80 (C_1), 30.72 (CH_3); IR (film) 1575, 1295, 1100, 814, 707 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}BrNO_2$: C, 56.27; H, 4.41; N, 4.37; Br, 24.96; mol wt 320.195. Found: C, 56.19; H, 4.41; N, 4.43; Br 24.87; mol wt 320 (mass spectrum).

Reaction of 1-Nitro-2-dimethylaminoethylene with Phenylmagnesium Bromide and Tetranitromethane. To a solution of 1.16 g (0.01 mol) of 1-nitro-2-dimethylaminoethylene[12] dissolved in 20 mL of dry THF and cooled to 0 °C by an ice–salt bath was added 22 mL of 1 M solution of phenylmagnesium bromide in THF. The mixture was stirred for 15 min; 1.96 g (0.01 mol) of tetranitromethane was then added and the mixture was stirred for an additional 30 min and acidified with concentrated HCl. Following the usual workup procedure described above for **2a**, and after column chromatography on silica using $CHCl_3$ as eluent, 1.1 g of a mixture of benzaldehyde and ω-nitrostyrene (1:2 ratio) was obtained (materials identical with authentic samples).

1-Bromo-1,1-dinitro-2-methoxy-2-phenylethane (9a). To 1 g (4.4 mmol) of dinitro ether **2a** in 25 mL of a 1 N KOH solution was added 0.70 g (4.4 mmol) of bromine. The resulting mixture was stirred overnight at room temperature and extracted with two 75-mL portions of diethyl ether. The combined ether extracts were washed with two 100-mL portions of water, dried over anhydrous Na_2SO_4, and concentrated on a rotary evaporator leaving 1.23 g (91% yield) of crude **9a**. The crude material was chromatographed on 40 g of silica, using chloroform eluent, affording 1.1 g of an analytically pure oil which crystallized on standing, mp 41–43 °C. Similar procedures were used for the preparation of **9b,d**, except that 2 mol equiv of bromine was employed to obtain **9d**.

Reaction of 9a with Triethylamine. A sample of **9a** was dissolved in equal volumes of triethylamine and $CDCl_3$. The solution was allowed to stand at room temperature and the reaction was followed by NMR. The proton signal appearing at δ 5.46 gradually disappeared with the simultaneous growth of a new peak at 6.62 ppm. No further change was observed after 24 h; the material was then acidified with concentrated HCl. The NMR of the acidified material was identical with that of an authentic sample of **2a**.

Acknowledgment. The authors are indebted to R. A. Henry and D. W. Moore for technical assistance and helpful discussions.

Registry No.—**5**, 3156-72-7; **6**, 31236-66-5; **7**, 65899-68-5; **8**, 7166-19-0; **10**, 65899-69-6; tetranitromethane, 509-14-8; 2-acetoxy-1-nitropentane, 3428-90-8; 2-bromo-2-nitro-1,1-diphenylpropane, 65899-70-9; 1-nitro-2-dimethylaminoethylene, 1190-92-7; phenyl bromide, 108-86-1.

Supplementary Material Available: Proton NMR and IR spectral data for compounds **2a–g**, **3a–c** and **9a,b,d** are presented in Table II. ^{13}C NMR data for compounds **2a–g** and **3a–c** are presented in Table III (4 pages). Ordering information is given on any current masthead page.

References and Notes

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Synthesis and Reactions of Enamine *N*-Oxides

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A general synthetic route to enamine *N*-oxides (α,β-unsaturated alkylamine *N*-oxides) from the corresponding 2-chloroalkylamines is described. *N,N*-Dimethyl-1-cyclohexenylamine *N*-oxide (**3a**), *N,N*-dimethyl-1-propenylamine *N*-oxide (**3b**), and *N,N*-dimethylvinylamine *N*-oxide (**3c**) were prepared as deliquescent, white crystalline solids. The VPC decomposition and the reactions of **3a** with acylating and other reagents were investigated. The thermal reaction of **3a** (>160 °C) gave deoxygenation to the corresponding enamine and β rearrangement to 2-dimethylaminocyclohexanone. The reactions of **3a** with acetic anhydride, benzoyl chloride, and diketene gave products derived from β substitution of an intermediate acyloxyenammonium salt.

The *N*-oxides of tertiary amines have been studied since the last decade of the 19th century. Current interest in these compounds stems from their use in the detergent and polymer industry and in chemotherapy. Research efforts have also focused on reaction mechanisms and on the biochemical role of amine *N*-oxides. Various aspects of the chemistry of trialkylamine *N*-oxides have been reviewed.[2-5]

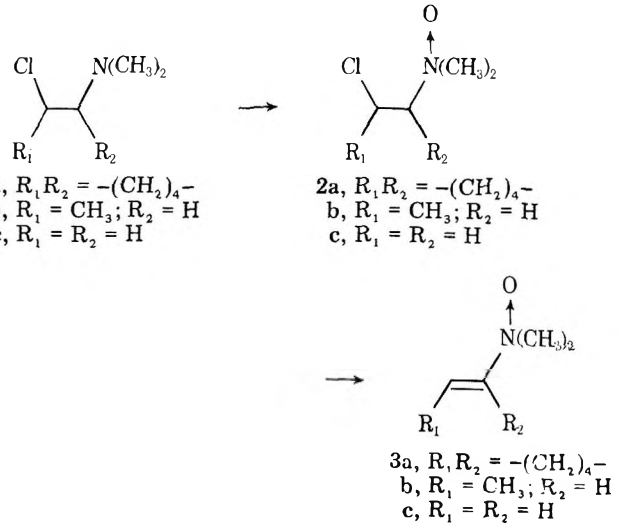
Enamine *N*-oxides (α,β-unsaturated amine *N*-oxides) are a previously unreported class of tertiary amine *N*-oxides. We wish to report a general synthetic route to enamine *N*-oxides and some reactions exhibited by one example of this class of compounds.

Results and Discussion

Synthesis of Enamine *N*-Oxides. Accumulated evidence[6] suggested that direct oxidation of an enamine would not yield the *N*-oxide. Some success had been achieved by pyrolyzing *trans*-2,3-bis(dimethylamino)norbornane *N,N*-dioxide to 2-dimethylaminonorbornene *N*-oxide;[7] however, investigations in other systems revealed that this was not a general reaction.[8]

The facile synthesis of vinylammonium salts from the corresponding 2-haloalkylammonium salts with alcoholic potassium hydroxide[9] suggested that 2-haloamine *N*-oxides might similarly be eliminated. Rate studies on the dimerization of 2-chloro- and 2-bromoalkylamines[10] suggested that it would be more convenient to work with the chlorides. Dimethylamine derivatives were chosen to exclude complications from the Cope elimination reaction.

N,N-Dimethyl-2-chlorocyclohexylamine *N*-oxide (**2a**), *N,N*-dimethyl-2-chloropropylamine *N*-oxide (**2b**), and



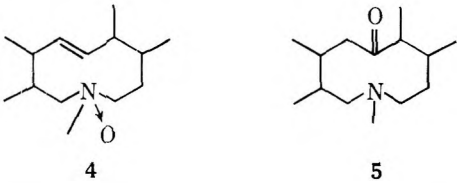
N,N-dimethyl-2-chloroethylamine *N*-oxide (**2c**)[11] were prepared as the stable hydrochloride salts from the corresponding amines **1a-c** in 54-66% yield by oxidation with *m*-chloroperbenzoic acid. Elimination of freshly dried *N*-oxide hydrochlorides was achieved without side reactions by treatment with potassium *tert*-butoxide in *tert*-butyl alcohol to give *N,N*-dimethyl-1-cyclohexenylamine *N*-oxide (**3a**), *N,N*-dimethyl-*trans*-1-propenylamine *N*-oxide (**3b**), and *N,N*-dimethylvinylamine *N*-oxide (**3c**) as solutions in *tert*-butyl alcohol. The solutions were aliquoted under argon and could be reacted directly or lyophilized and sublimed under argon to give crystalline enamine *N*-oxides **3a-c** in 45-60% yield. The trans stereochemistry of *N*-oxide **3b** was inferred from a 13-Hz vicinal coupling constant in the NMR spectrum.[12]

Enamine *N*-oxides **3a-c** are extremely deliquescent, white crystalline solids which are stable for months when stored at 0 °C under argon either as crystals or in solution. However, when the crystals are allowed to oil in air, the resultant hydrates decompose within a few hours.

Cyclohexenylamine *N*-oxide **3a**, with the largest alkyl residue, is the only enamine *N*-oxide of the three which is soluble in benzene and carbon tetrachloride. Likewise, **3a** is the most thermally stable *N*-oxide of the three, and it withstands acidification or basification at 60 °C, whereas the acid salts of **3b** and **3c** readily decompose. The attempted formation of the hydrochloride and picrate derivatives of propenylamine *N*-oxide **3b** resulted in the isolation of dimethylamine salts.

Reactions of *N,N*-Dimethyl-1-cyclohexenylamine *N*-Oxide (3a). Cyclohexenylamine *N*-oxide **3a** was chosen as a model for study of the reactions of the enamine *N*-oxide system. The reactions were run either on an aliquot of **3a** in *tert*-butyl alcohol or on freshly sublimed **3a**. After aqueous hydrolysis, yields were determined by VPC.

VPC Decomposition of 3a. Injection of a benzene solution of **3a** into the VPC instrument at injection port temperatures from 170 to 260 °C gave cyclohexanone (6%), *N,N*-dimethyl-1-cyclohexenylamine (20%), and 2-dimethylaminocyclohexanone (13%) as the major products. The formation of 2-dimethylaminocyclohexanone has precedent in the rearrangement of *N*-oxide **4** to **5** upon heating in an acidic me-



4 **5**

dium[13] and in the formation of *o*- and *p*-dimethylaminophenols from dimethylaniline *N*-oxide upon pyrolysis.[14]

Reactions of 3a with Acylating Agents. The results of the reactions of **3a** with acetic anhydride, benzoyl chloride, and diketene are consistent with the operation of one major reaction pathway (Scheme I). The initially formed acyloxyenammonium salt **6** yields the β-substitution intermediates **7** and **8**, which are hydrolyzed to the observed products, 2-

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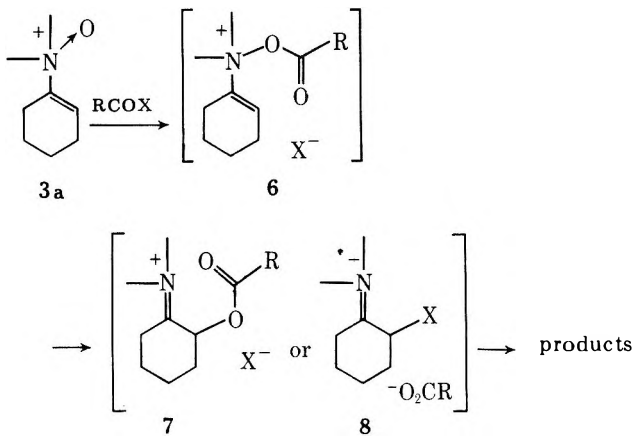
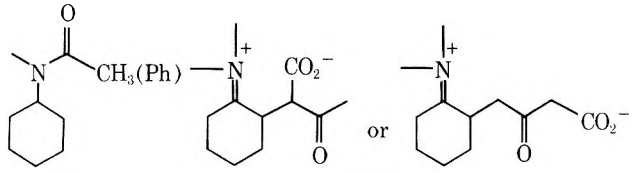
Scheme I



3a 6 7 8

substituted cyclohexanones. The detailed mechanisms for the transformations of **6** to **7** and **8** are open to speculation. No CIDNP signals were observed when the reactions were initiated in the probe of an NMR instrument, but this result does not exclude a radical mechanism. Another product, cyclohexanone, is probably the result of deoxygenation followed by hydrolysis. If some type of demethylation reaction to form hydrolyzable methylamine derivatives was occurring, one would expect to find monomethylamides in the product mixtures. However, only dimethylamides were isolated. The expected Polonovski demethylation product **9** was also absent



9 10

from the product mixtures. In the reaction with diketene, the expected intermediate **10** must decarboxylate at some stage in the reaction workup.

The reactions of trialkylamine *N*-oxides with trifluoroacetic anhydride have been studied by Potier and co-workers.[15] In a number of examples they found that the intermediate acyloxyammonium salts decomposed to give immonium trifluoroacetates as the final products. However, the reaction of **3a** with trifluoroacetic anhydride gave, after hydrolysis, 2-trifluoroacetoxycyclohexanone (32%) and cyclohexanone (18%) as the major products, a result consistent with other reactions of **3a** with acylating reagents (Scheme I). Before aqueous hydrolysis, no vinylimmonium salts corresponding to those of Potier and co-workers could be detected by NMR spectroscopy.

Other Reactions of 3a. The reaction of **3a** with *n*-butyllithium gave, after hydrolysis, cyclohexanone (48%) and formaldehyde (present in an undetermined amount in the aqueous phase). The formaldehyde presumably arose from one of the methyl groups of **3a**, a reaction which has analogy to the reactions of *N*,*N*-dimethylaniline *N*-oxides with *n*-butyllithium and phenyllithium, where monomethylanilines were the major products.[16]

Reaction of **3a** with titanium tetrachloride gave, after hydrolysis, 2-chlorocyclohexanone (47%) and cyclohexanone (19%). This result suggests a mechanism similar to the one proposed for the reaction of **3a** with acylating agents (Scheme I).

The following reagents did not react with **3a**: methyl acrylate, 2-cyclohexenone, *m*-chloroperbenzoic acid, cyclopentadiene, and diazomethane.

Experimental Section

General. Melting points were determined on a Thomas-Hoover "unimelt" capillary melting point apparatus and are corrected. The IR spectra were determined on Perkin-Elmer grating spectrophotometers, Model 237B or 337. NMR spectra were run on Varian spectrometers, Model T-60, A-60, or HA-100, and are reported in ppm downfield from tetramethylsilane as an internal standard. The mass spectra were determined on Hitachi Perkin-Elmer instruments, Model RMU-6D or RMU-6E, and the UV spectra on a Cary Model 14. VPC analyses and/or isolations were performed on F & M Scientific Hewlett-Packard research chromatographs, Model 5750 or 810 (thermal conductivity detectors), using 0.25-in columns packed with 20% silicone rubber UC-W98 on 60–80 mesh Chromosorb W, 10% Carbowax 20 M on 60–80 mesh Chromosorb P, or 15% diethylene glycol adipate (LAC 446) on 60–80 mesh Chromosorb W, or on a Wilkens Instrument and Research, Inc., Aerograph "Hy-F1" Model A-600-B instrument (flame ionization detector), using ε 0.125-in column packed with 10% Carbowax 20 M on Chromosorb W. All columns were 4–6 ft in length. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Reactions requiring an inert atmosphere were conducted in an atmosphere of nitrogen or argon, which had been passed through a column of Drierite. When anhydrous conditions were necessary, glassware was dried at 125 °C for 5 h and allowed to cool in a vacuum desiccator. Transfer of all moisture-sensitive compounds was accomplished in a dry atmosphere. Solutions were concentrated on a Büchi rotary evaporator. All solvents were reagent grade or better and were stored over Linde Type 3A or 4A molecular sieves. *tert*-Butyl alcohol was distilled from calcium hydride. Potassium *tert*-butoxide was obtained from MSA Corp. Benzene-d_6 was obtained from Aldrich Chemical Co. Gaseous HCl was dried by passage through a column of calcium chloride.

***N*,*N*-Dimethyl-2-chlorocyclohexylamine *N*-Oxide (2a) Hydrochloride.** To a stirred, ice bath cooled solution containing 20.0 g (0.12 mol) of *N*,*N*-dimethyl-2-chlorocyclohexylamine[17] (**1a**) in dry ether was added dropwise a solution containing 25.2 g (0.12 mol) of 85% *m*-chloroperbenzoic acid in dry ether. The reaction was stirred overnight at room temperature, cooled in an ice bath, and treated with 1.1 equiv of dilute HCl. After washing the ether phase with water, the combined aqueous phase was washed with ether, concentrated, dried in vacuo at 65 °C for several days, and recrystallized from acetone to give 14.3 g (54%) of **2a** hydrochloride as white crystals: mp 129–132 °C; IR (Nujol mull) 2800–2300 cm^{-1}; NMR ($CDCl_3$) δ 5.13 (m, 1), 4.53 (m, 1), 3.70 (s, 6), and 1.88 (m, 8). Picrate of **2a**: mp 153.5–157.5 °C.

Anal. Calcd for $C_{14}H_{19}ClN_4O_8$: C, 41.33; H, 4.71; Cl, 8.71; N, 13.78. Found: C, 41.32; H, 4.62; Cl, 8.81; N, 13.62.

***N*,*N*-Dimethyl-2-chloropropylamine *N*-Oxide (2b) Hydrochloride.** This was prepared similarly to **2a** to give **2b** hydrochloride in 65% yield as white prisms: mp 112–113.5 °C; IR (Nujol mull) 2800–2300 cm^{-1}; NMR (D_2O) δ 5.1–4.4 (m, 1), 4.12 (d, 2, J = 6 Hz), 3.67 (s, 6), and 1.65 (d, 3, J = 6 Hz). Picrate of **2b**: mp 117.5–120.5 °C.

Anal. Calcd for $C_{11}H_{15}ClN_4O_8$: C, 36.03; H, 4.12; Cl, 9.67; N, 15.28. Found: C, 36.18; H, 4.03; Cl, 9.54; N, 15.38.

***N*,*N*-Dimethyl-2-chloroethylamine *N*-Oxide (2c) Hydrochloride.** This was prepared similarly to **2a**, giving **2c** in 66% yield as off-white needles, mp 128–130 °C (lit.[11] mp 125–127 °C).

***N*,*N*-Dimethyl-1-cyclohexenylamine *N*-Oxide (3a).** The following represents a typical procedure. To a stirred solution containing 2.24 g (20.0 mmol) of potassium *tert*-butoxide in 40 mL of *tert*-butyl alcohol was added dropwise a solution containing 2.14 g (10.0 mmol) of **2a** hydrochloride in 20 mL of *tert*-butyl alcohol. The order of addition did not affect the yield of product. A fine precipitate formed during the addition. The reaction mixture was stirred for several hours and aliquoted into ten equal portions. Lyophilization and sublimation of an aliquot gave, typically, 70–85 mg (50–60%) of **3a** as a deliquescent, white, crystalline solid: mp 94.5–96 °C; decomposition temp, 160 °C; IR (CCl_4) 3012, 2938, 2860, 2839, 1685, 1673, 1456, 1446, 1405, 1379, 1367, 1030, 969, 937, 913, 865 cm^{-1}; NMR (C_6D_6) δ 6.75 (m, 1), 3.08 (s, 6), 2.5–2.2 (m, 2), 2.2–1.9 (m, 2), and 1.8–1.3 (m, 4); mass spectrum (80 eV), *m*/*e* (relative intensity) 141 (14), 125 (16), 124 (15), 113 (19), 110 (13), 96 (27), 84 (100), 70 (29), 68 (30), 58 (20), 56 (13), 55 (19), 44 (13), 43 (37), 42 (43), 41 (17), and 39 (18); UV max (95% ethanol) end absorption. Picrate of **3a**: mp 122–123.5 °C.

Anal. Calcd for $C_{14}H_{18}N_4O_8$: C, 45.41; H, 4.90; N, 15.13. Found: C, 45.29; H, 4.81; N, 15.04.

***N*,*N*-Dimethyl-1-propenylamine *N*-Oxide (3b).** This was prepared similarly to **3a** to give **3b** in 45% yield as a deliquescent, white, crystalline solid: mp 122–123.5 °C; decomposition temp, 122 °C; IR

($CHCl_3$) 1665, 1462, 1440, 1385, 1380, 950, 934, and 900 cm^{-1}; NMR (C_6D_6) δ 6.87 (d of q, 1, J = 13, 7 Hz), 5.92 (d of broad peaks, 1, J = 13 Hz), 2.87 (s, 6), and 1.45 (d of d, 3, J = 7, 2 Hz).

***N,N*-Dimethylvinylamine *N*-Oxide (3c).** This was prepared similarly to **3a** to give **3c** in 52% yield as deliquescent, white, feathery crystals: mp 96–100 °C; decomposition temp, 145 °C; IR ($CHCl_3$) 1650, 1465, 1450, 952, 910, and 895 cm^{-1}; NMR (C_6D_6) δ 6.3–6.1 (m, 2), 4.9–4.7 (m, 1), and 2.85 (s, 6).

Reactions of *N,N*-Dimethyl-1-cyclohexenylamine *N*-Oxide (3a). General. Except where noted, the reactions of **3a** were run under an atmosphere of nitrogen or argon either on an aliquot of **3a** in *tert*-butyl alcohol or on a sublimed sample of **3a** dissolved in benzene-d_6 in an NMR tube. Reactions were monitored by NMR spectroscopy and worked up by addition of water and extraction with $CHCl_3$. The $CHCl_3$ extract was washed with saturated NaCl and dried ($MgSO_4$ or $CaSO_4$). The products were isolated by VPC and identified by comparison of VPC retention times and spectra with those of authentic samples. The authentic samples were obtained commercially, as gifts,[18] or by synthesis using known routes. Yields are based on comparison of the VPC peak area of a known amount of hydrocarbon standard, which had been added to the reaction mixture before workup, with the product peak areas, which had been corrected by determination of the response factor of the authentic sample vs. the hydrocarbon standard.

VPC Decomposition of 3a. Injection of part of a solution containing 38.9 mg (0.28 mmol) of **3a** and 11.2 mg (0.061 mmol) of *n*-tridecane (as standard) in 0.25 mL of benzene-d_6 onto a column packed with silicone rubber UC-W98 with an injection port temperature of 270 °C and a thermal conductivity detector temperature of 230 °C gave cyclohexanone (6%), *N,N*-dimethyl-1-cyclohexenylamine (**11**; 20%), and 2-dimethylaminocyclohexanone (13%) as the major products. Coinjection of water with the sample resulted in an enhanced yield of cyclohexanone and the disappearance of **11**. Similar results were obtained at an injection port temperature of 170 °C.

Reaction of 3a with Acetic Anhydride. A 71.4-mg (0.51 mmol) sample of **3a** was treated with 57 mg (0.56 mmol) of acetic anhydride to give, after aqueous workup, cyclohexanone (4%), *N,N*-dimethylacetamide (20%), and 2-acetoxycyclohexanone (78%). Similar results were obtained when the reaction was run in *tert*-butyl alcohol or $CHCl_3$.

Reaction of 3a with Benzoyl Chloride. A 73.7-mg (0.522 mmol) sample of **3a** was treated with 80.6 mg (0.57 mmol) of benzoyl chloride to give, after aqueous workup, cyclohexanone (2%), 2-chlorocyclohexanone (25%), benzoic acid (46%), *N,N*-dimethylbenzamide (32%), and 2-benzoxycyclohexanone (20%).

Reaction of 3a with Diketene. A 50.7-mg (0.36 mmol) sample of **3a** was treated with 30.3 mg (0.36 mmol) of diketene (freshly distilled) to give, after aqueous workup with dilute HCl, cyclohexanone (15%), *N,N*-dimethylacetoacetamide (15%), and 2-acetonylcyclohexanone (14%) as the major products.

Reaction of 3a with Trifluoroacetic Anhydride. To a 46.0-mg (0.33 mmol) sample of **3a** in 1 mL of CD_2Cl_2 at −78 °C was added 68.5 mg (0.33 mmol) of trifluoroacetic anhydride. A yellow color formed immediately and gradually turned dark orange. After aqueous workup, the major products identified were 2-trifluoroacetoxycyclohexanone (32%) and cyclohexanone (18%).

Reaction of 3a with *n*-Butyllithium. A 55.8-mg (0.40 mmol) sample of **3a** was treated with 0.25 mL (0.40 mmol) of a 1.6 M solution of *n*-butyllithium in hexane. After shaking the reaction mixture for 10 min, 0.5 mL of D_2O was added. NMR analysis of the aqueous phase indicated the presence of some unreacted **3a**. Aqueous workup gave cyclohexanone (48%). The presence of formaldehyde in the aqueous phase was inferred from a VPC retention time comparison with a formalin solution on a column packed with Carbowax 20M (flame ionization detector).

Reaction of 3a with Titanium Tetrachloride. To a 34.4-mg (0.24 mmol) sample of **3a** was added 26.8 mg (0.24 mmol) of titanium tetrachloride at 0 °C. The solution turned brown immediately. After aqueous workup, the major products were 2-chlorocyclohexanone (47%) and cyclohexanone (19%).

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Registry No.—**1a**, 4580-81-8; **1b**, 108-14-5; **1c**, 107-99-3; **2a** HCl, 66172-49-4; **2a** picrate, 66172-51-8; **2b** HCl, 66172-52-9; **2b** picrate, 66172-54-1; **2c** HCl, 66172-55-2; **3a**, 66172-56-3; **3a** picrate, 66172-57-4; **3b**, 66172-58-5; **3c**, 66172-59-6; cyclohexanone, 108-94-1; *N,N*-dimethylacetamide, 127-19-5; 2-acetoxycyclohexanone, 17472-04-7; 2-chlorocyclohexanone, 822-87-7; benzoic acid, 65-85-0; *N,N*-dimethylbenzamide, 611-74-5; 2-benzoxycyclohexanone, 7472-23-3; *N,N*-dimethylacetoacetamide, 2044-64-6; 2-acetonylcyclohexanone, 6126-53-0; 2-trifluoroacetoxycyclohexanone, 66197-69-1.

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Synthesis of N,N,N′,N′-Tetrasubstituted 1,1-Diaminoethylenes and Their Thermal Rearrangement

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Various N,N,N′,N′-tetrasubstituted 1,1-diaminoethylenes (**5**) have been prepared by the reaction of N,N-disubstituted (trimethylsilylethynyl)amines (silylynamines **1**, **2**, and **3**) with secondary amines. At 200 °C in amine solvent, **5** afforded a mixture of [1,3] alkyl rearrangement products (**7**) and dealkylation products (**8** and/or **9**).

N,N,N′,N′-Tetrasubstituted 1,1-diaminoethylenes are the simplest enamines having two tertiary amino groups on the same carbon and may be useful intermediates for organic synthesis. Several 1,1-bis(disubstituted amino)ethylenes have been prepared by the reaction of a secondary amine with a ketene acetal[1] or triethyl orthoacetate,[2] dimethylacetamide

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Table I. Reaction of Silylynamine (1, 2, and 3) with Secondary Amines (4)

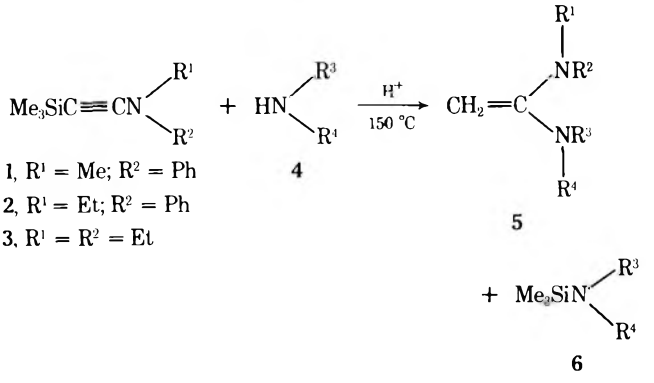
Run	Starting material: Silylynamine R^1	Silylynamine R^2	Secondary amine R^3	Secondary amine R^4	Reaction time, h	Catalyst[a]	Yield of 5, %	Compd No.
1	Me	Ph	Me	Ph	1	H^+	84	**5a**
2	Me	Ph	Et	Et	10	H^+	89	**5b**
3	Me	Ph	Et	Ph	1	H^+	78	**5c**
4	Me	Ph	*n*-Pr	Ph	3	H^+	80	**5d**
5	Me	Ph	*i*-Pr	Ph	3	H^+	63	**5e**
6	Me	Ph	Allyl	Ph	3	H^+	68	**5f**
7	Me	Ph	*n*-Bu	*n*-Bu	6	H^+	61	**5g**
8	Et	Ph	Me	Ph	1	H^+	88	**5c**
9					13		73	**5c**
10	Et	Ph	Et	Et	10	H^+	85	**5h**
11	Et	Ph	Et	Ph	2	H^+	84	**5i**
12					24		81	**5i**
13	Et	Ph	*n*-Pr	Ph	3	H^+	75	**5j**
14	Et	Ph	Allyl	Ph	2	H^+	66	**5k**
15	Et	Et	Me	Ph	1	H^+	84	**5b**
16					24		0	
17	Et	Et	Et	Et	10	H^+	82	**5l**
18	Et	Et	Et	Ph	2	H^+	75	**5h**
19	Et	Et	*i*-Pr	Ph	2	H^+	78	**5m**
20	Et	Et	Cyclohexyl	Ph	2	H^+	85	**5n**

[a] *N*-Methylaniline hydrobromide, 0.53 mol %.

Table II. N,N,N′,N′-Tetrasubstituted 1,1-Diaminoethylenes (5)[a]

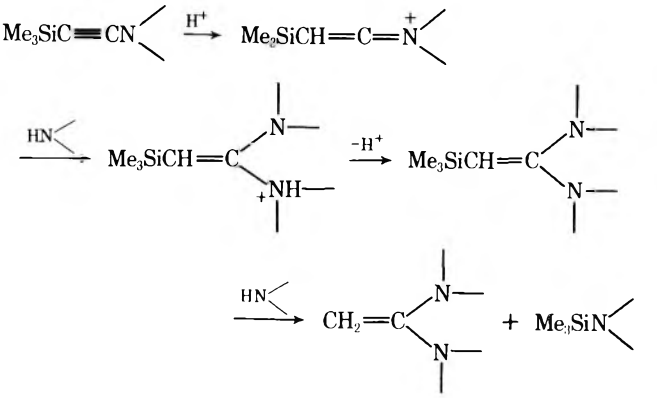
	Bp (mmHg), °C	IR(film), cm^{-1} (C=C)	NMR ($CDCl_3$), δ (CH_2=C<)
5a	118–120 (0.5)	1630	4.08 (s)
5b	138–140 (18)	1620	3.71 (s)
5c	120–122 (0.4)	1625	4.10 and 4.17 (AB, q)
5d	128–130 (0.7)	1625	4.11 and 4.18 (AB, q)
5e	125–127 (0.7)	1625	3.97 (s)
5f	132–134 (0.6)	1620	4.16 and 4.29 (AB, q)
5g	134–136 (2)	1620	3.67 (s)
5h	145–147 (20)	1620	3.74 and 3.78 (AB, q)
5i	115–117 (0.3)	1625	4.08 (s)
5j	135–137 (1)	1625	4.04 (s)
5k	120–122 (0.2)	1620	4.18–4.23 (AB, q)
5l[b]	92–94 (40)	1625	3.38 (s)
5m	91–92 (0.8)	1615	3.65 and 3.80 (AB, q)
5n	108–110 (0.3)	1615	3.66 and 3.80 (AB, q)

[a] Satisfactory analytical data (±0.4 for C, H, and N) were reported for all new compounds listed in the table. [b] Lit. bp 89–93 °C (40 mmHg), ref 1.



1, R^1 = Me; R^2 = Ph
2, R^1 = Et; R^2 = Ph
3, R^1 = R^2 = Et
4

with tetrakis(dimethylamino)titanium,[3] and tetramethylacetamidinium salt with sodium hydride.[4] These procedures have been examined for the preparation of symmetrical 1,1-diaminoethylenes, but it seems difficult to apply these to the synthesis of asymmetrical ones. In this paper, we report a new synthetic route of various types of asymmetrical N,N,N′,N′-tetrasubstituted 1,1-diaminoethylenes (**5**) by reaction of N,N-disubstituted (trimethylsilylethynyl)amines (silylynamines, **1**, **2**, and **3**)[5] with secondary amines and the thermal rearrangement of **5**.



Heating of silylynamines (**1**, **2**, and **3**) in an appropriate secondary amine at 150 °C gave the corresponding 1,1-diaminoethylenes **5** in good yields. Yields and characterizing data are summarized in Tables I and II. Addition of a catalytic amount of *N*-methylaniline hydrobromide to the reaction mixture accelerated the reaction (compare runs 8 and 9, or runs 11 and 12, in Table I). *N*,*N*-Diethyl(trimethylsilylethynyl)amine (**3**) did not react with a secondary amine in the

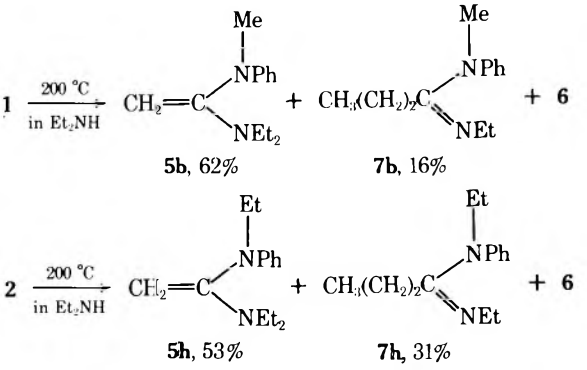
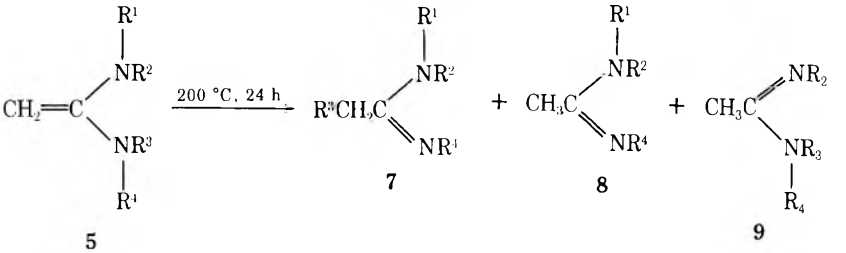


Table III



5 7 8 9

Run		R¹	R²	R³	R⁴	Solvent[a]	Yield, % Without DTBP 7	8	9	With DTBP 7	8	9
1	a	Me	Ph	Me	Ph	A	0	39		0	42	
2						B				0	8	
3	b	Me	Ph	Et	Et	A	28	0	7	37	0	0
4						C				24	0	0
5	c	Me	Ph	Et	Ph	A	34	8	31	46	0	0
6						B	0	0	0	39	0	0
7						C				34	0	0
8	d	Me	Ph	*n*-Pr	Ph	A				28	5	34
9	f	Me	Ph	Allyl	Ph	B	80	0	0			
10	h	Et	Ph	Et	Et	A				32	0	0
11	i	Et	Ph	Et	Ph	A	60	0		64	0	
12						B	0	0		45	13	
13						D	0	0		16	30	

[a] A = diethylamine, B = triethylamine, C = piperidine, D = diisopropylamine.

Table IV. Physical Properties of Amidines (7, 8, and 9)[a]

	Bp (mmHg), °C	IR (film), cm^{-1} (C=N)	NMR ($CDCl_3$), δ
7b	125–126 (22)	1625	0.74 (t, 3, $CH_3CH_2CH_2$), 1.22 (t, 3, NCH_2CH_3), 1.12–1.50 (m, 2, $CH_3CH_2CH_2$), 2.06–2.26 (m, 2, CH_2C), 3.18 (s, 3, NCH_3), 3.36 (q, 2, NCH_2), 7.00–7.50 (m, 5, aromatic H)
7c	138–140 (0.4)	1620	0.50 (t, 3, CH_3CH_2), 1.03–1.40 (m, 2, $CH_3CH_2CH_2$), 2.06–2.25 (m, 2, CH_2C), 3.33 (s, 3, NCH_3), 6.60–7.40 (m, 10, aromatic H)
7d	140–143 (0.8)	1620	0.50 (t, 3, CH_3CH_2), 0.70–1.38 (m, 4, $CH_3CH_2CH_2CH_2$), 2.06–2.30 (m, 2, CH_2C), 3.36 (s, 3, NCH_3), 6.70–7.60 (m, 10, aromatic H)
7f	121–123 (0.1)	1615	1.80–2.08 (m, 2, $=CHCH_2$), 2.12–2.40 (m, 2, CH_2C), 3.32 (s, 3, NCH_3), 4.48–4.80 (m, 2, $CH_2=$), 5.10–5.60 (m, 1, =CH–), 6.70–7.50 (m, 10, aromatic H)
7h	102–104 (10)	1620	0.72 (t, 3, $CH_3CH_2CH_2$), 1.06 (t, 3, $=NCH_2CH_3$), 1.20 (t, 3, NCH_2CH_3), 1.00–1.44 (m, 2, $CH_3CH_2CH_2$), 2.00–2.20 (m, 2, CH_2C), 3.34 (q, 2, $=NCH_2$), 3.73 (q, 2, NCH_2), 7.00–7.50 (m, 5, aromatic H)
7i	128–130 (0.5)	1620	0.50 (t, 3, $CH_3CH_2CH_2$), 1.20 (t, 3, NCH_2CH_3), 1.04–1.44 (m, 2, $CH_3CH_2CH_2$), 2.00–2.20 (m, CH_2C), 3.89 (q, 2, NCH_2), 6.80–7.60 (m, 10, aromatic H)
8a,c,d	89–92 (0.03)[b]	1625	1.66 (s, 3, CH_3C), 3.37 (s, 3, NCH_3), 6.70–7.48 (m, 10, aromatic H)
8i, 9c	96–97 (0.03)[c]	1610	1.20 (t, 3, NCH_2CH_3), 1.64 (s, 3, CH_3C), 3.92 (q, 2, NCH_2), 6.77–7.50 (m, 10, aromatic H)
9b	88–93 (0.4)	1610	1.27 (t, 6, $NCH_2CH_3 \times 2$), 1.78 (s, 3, CH_3C), 3.36 (q, 4, $NCH_2 \times 2$), 6.47–7.30 (m, 5, aromatic H)
9d	112–113 (0.13)	1620	0.88 (t, 3, $CH_3CH_2CH_2$), 1.60 (s, 3, CH_3C), 1.60 (m, 2, NCH_2CH_2), 3.81 (m, 2, NCH_2), 6.60–7.50 (m, 10, aromatic H)

[a] Satisfactory analytical data (±0.4% for C, H, and N) were reported for all new compounds listed in the table. [b] Lit.[7] bp 320–324 °C. [c] Lit.[8] bp 190–192 °C (15 mmHg).

absence of the proton catalyst (run 16). The presence of proton catalyst may assist the attack of a secondary amine to α carbon of the ynamine.

When the reaction was carried out without proton catalyst at high temperature, the reaction was complicated by competitive formation of isomers of **5**. For example, heating of **1** or **2** in an excess of diethylamine at 200 °C gave the corresponding 1,1-diaminoethylene **5b** or **5h** and its isomeric product **7b** or **7h**. The NMR spectra of **7b** and **7h** exhibited a typical signal pattern of the *n*-propyl group instead of that of the external methylene group in **5b** and **5h**. These data would be consistent with structures of *N*-methyl(or ethyl)-*N*-phenyl-*N'*-ethylbutyramidine (**7b** and **7h**). Compound **7b** was identical by spectroscopic comparison with an authentic sample prepared from *N*-ethylbutyramide (**10**) and *N*-methylaniline.

$$\underset{\mathbf{10}}{CH_3(CH_2)_2CONHEt} \xrightarrow{PCl_5} \left[CH_3(CH_2)_2\underset{Cl}{C}{=}NEt \right] \xrightarrow{PhNHMe} \mathbf{7b}$$

Amidine **7** may be formed by [1,3] rearrangement of an ethyl group from nitrogen to carbon in the initially formed **5**. Actually, heating of **5b** in diethylamine at 200 °C gave a 28% yield of **7b** (run 3 in Table III). Other 1,1-diaminoethylenes **5c** and **5i** also gave the corresponding rearrangement products **7c** and **7i** under the same reaction condition (runs 5 and 11). These ethyl migrations proceeded smoothly in diethylamine but not in triethylamine. However, in the presence of a catalytic amount of DTBP, the *N*-ethyl or *N*-*n*-propyl group of **5** migrated to give the corresponding butyr- or hexanamidine derivative in triethylamine (runs 6 and 12). The *N*-methyl group in **5** did not migrate to give the corresponding propionamidine derivatives in any cases, but the demethylation products **8** or **9** were formed.

Thermal [1,3] alkyl rearrangement may occur either by a sigmatropic shift following a suprafacial path with inversion at the migrating center or by a radical dissociation–recombination path.[6] The accelerating effect of DTBP, mentioned above, seems to suggest that the transformation of **5** to **7** proceeds via radical intermediates. From the present results, however, we cannot conclude it. 1-Allylphenylamino-1-methylphenylaminoethylene (**5f**) was converted into *N,N'*-diphenyl-*N*-methyl-4-pentenamidine (**7f**) in a high yield by heating without the aid of DTBP (run 9 in Table III).

Experimental Section

All boiling points are uncorrected. NMR spectra were recorded using a JEOL Model JNM-MH-100 spectrometer employing Me_4Si as internal standard. IR spectra were taken on a JASCO Model IRA-2 spectrometer. GLC analyses were performed on a JEOL Model JGC-1100 FID chromatograph. Fractional distillation was accomplished by a Büchi Model GKR-50 Kugelrohr distillation apparatus. All solvents were distilled in a nitrogen atmosphere just prior to use and the reactions were carried out under nitrogen atmosphere.

N,N,N',N'-Tetrasubstituted 1,1-Diaminoethylenes (5). A mixture of 10 mmol of silylynamine [*N*-methyl-*N*-(trimethylsilylethynyl)aniline (**1**), *N*-ethyl-*N*-(trimethylsilylethynyl)aniline (**2**), or *N,N*-diethyl(trimethylsilylethynyl)amine (**3**)],[5] 30 mmol of secondary amine, and 10 mg (0.53 mol %) of *N*-methylaniline hydrobromide was heated with stirring at 150 °C for 1–10 h. The reaction mixture was distilled under reduced pressure to give the corresponding **5**.

The yields and characterizing data are summarized in Tables I and II.

Thermal Reaction of 5. A solution of 7 mmol of **5** in 2 mL of amine (diethylamine, triethylamine, diisopropylamine, or piperidine) was heated with 100 mg (10 mol %) of DTBP (or without DTBP) in a sealed tube at 200 °C for 24 h. The reaction mixtures were analyzed by GLC using a 3 mm × 1 m stainless steel column filled with 10% silicone SE-30, and the yields were determined by the internal standard method. Samples of the products were isolated by fractional distillation of the reaction mixtures. The yields and characterizing data are shown in Tables III and IV.

***N*-Methyl-*N*-phenyl-*N'*-ethylbutyramidine (7b).** To a chilled suspension of PCl_5 (5.6 g, 27 mmol) in dry chloroform (30 mL) was added dropwise *N*-ethylbutyramide (2.6 g, 23 mmol) and stirring was continued for 15 min. Then a solution of *N*-methylaniline (2.42 g, 23 mmol) in chloroform (5 mL) was added and the mixture was stirred for 2 h at room temperature and an additional 2 h at reflux. After the addition of water (50 mL) to the reaction mixture, the aqueous layer was separated and made alkaline with NaOH solution and then extracted with ether. The ethereal extract was dried, concentrated, and distilled to give 1.60 g (35%) of **7b**, bp 120–122 °C (20 mm).

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Registry No.—*N*-Ethylbutyramide, 13091-16-2.

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Preparation of the Enantiomeric Forms of 9-(5,6-Dideoxy-β-D-*ribo*-hex-5-enofuranosyl)adenine[1]

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D-Allose was converted to methyl 2,3:5,6-di-*O*-isopropylidene-β-D-allofuranoside, and this in turn was hydrolyzed in an acid solution to methyl 2,3-*O*-isopropylidene-β-D-allofuranoside. Treatment of the latter with methanesulfonyl chloride gave methyl 2,3-*O*-isopropylidene-5,6-bis(*O*-methanesulfonyl)-β-D-allofuranoside. The latter was treated with sodium iodide to afford methyl 2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranoside. The isopropylidene group was hydrolyzed, the hydroxyl groups were blocked with benzoyl groups, and the methoxyl group was replaced with an acetate by acetolysis. The sugar derivative, 1-*O*-acetyl-2,3-di-*O*-benzoyl-5,6-dideoxy-D-*ribo*-hex-5-enofuranose, was condensed with 6-benzamidochloromercuripurine by the titanium tetrachloride method, and the blocking groups were removed with sodium methoxide to afford the desired nucleoside, 9-(5,6-dideoxy-β-D-*ribo*-hex-5-enofuranosyl)adenine. As an aid to NMR clarification of the configuration at the anomeric carbon atom, the 2',3'-*O*-isopropylidene derivative was prepared. D-Talose was converted to methyl 2,3-*O*-isopropylidene-5,6-bis(*O*-methanesulfonyl)-α-D-talofuranoside in several steps without isolation of the intermediates. Sodium iodide treatment of the 5,6-bis(*O*-methanesulfonate) gave methyl 2,3-*O*-isopropylidene-β-L-*ribo*-hex-5-enofuranoside, which was used to prepare 9-(5,6-dideoxy-β-L-*ribo*-hex-5-enofuranosyl)adenine by the same pathway as used to prepare the D form.

This laboratory has been engaged in a study of the chemistry and biological effects of exocyclic unsaturation of nucleosides. In addition to the 4',5' unsaturation found in decoyinine (angustmycin A) type of analogues,[2,3] this laboratory has reported the preparation of several 5',6'-unsaturated hexofuranosyl nucleosides.[4,5] Weak biological activity,

0022-3263/78/1943-2469$01.00/0

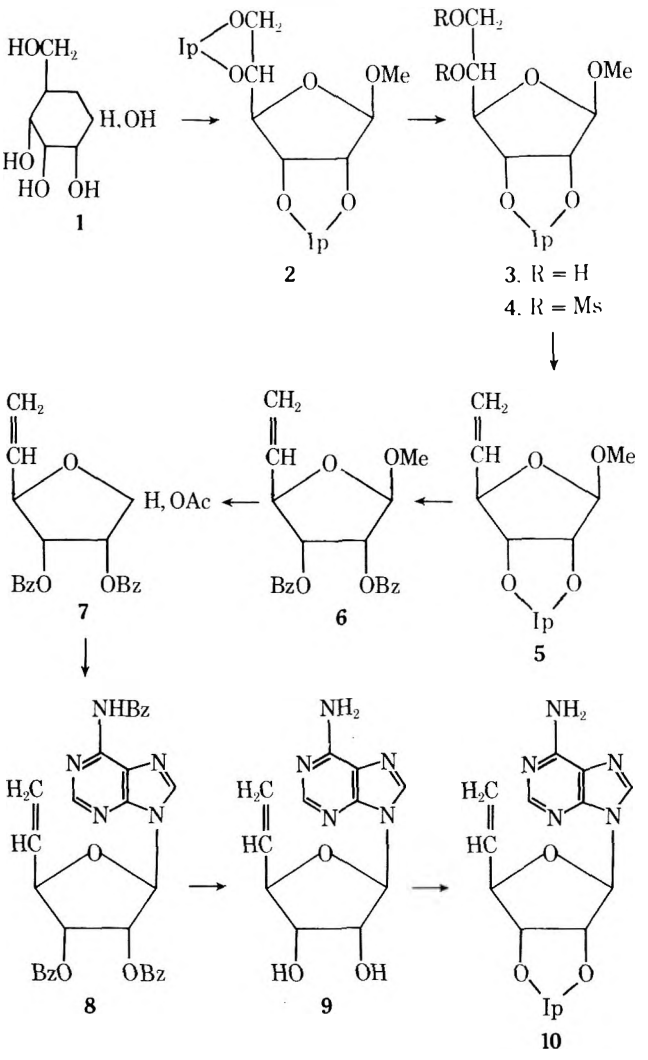
either antibacterial or antileukemic (L 1210 in culture), has been noted[5] and the two new compounds reported[5] at that time appear to have borderline activity.[6] It also seemed of interest to compare the biological and enzymatic properties of 9-(5,6-dideoxy-β-D-*ribo*-hex-5-enofuranosyl)adenine (**9**) and its enantiomer **14** to that of the enantiomeric forms of 9-(5-deoxy-β-*erythro*-pent-4-enofuranosyl)adenine reported recently.[3] Because of previous difficulties experienced during attempts to unsaturate preformed nucleosides without competitive side reactions, such as cyclonucleoside formation, the scheme of synthesis reported here again emphasizes the use of unsaturated sugar derivatives for the preparation of the desired nucleosides.

The desired starting material for the synthesis of nucleoside **9** was methyl 5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranoside (**5**). A preparation of **5** was reported a number of years ago by pyrolysis of methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside 5-*S*-methylxanthate (Chugaev reaction).[7] One problem with this approach was that methyl 6-deoxy-2,3-*O*-isopropylidene-β-D-allofuranoside had to be prepared from L-rhamnose, a fairly expensive sugar. A more serious problem was that the product of the Chugaev reaction was contaminated with sulfur-containing byproducts, and **5** could only be purified by preparative GLC. Previous experience in this laboratory has demonstrated the ease of preparation of glycosides related to **5** starting from the parent hexoses.[5] D-Allose (**1**) was, therefore, required as the starting sugar for the preparation of **5**. D-Allose has been prepared in a number of laboratories by oxidation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose followed by reduction and hydrolysis of blocking groups. The ruthenium tetraoxide oxidation procedure of Baker et al.[8] appeared to be the best method; however, in the author's hands this procedure gave low yields (~25%) and required extensive chromatography to remove colored contaminants. Utilizing this procedure as a basis and applying certain advantageous aspects of various other methods in the literature,[9] a somewhat different oxidation procedure was worked out which is presented in the Experimental Section. The reduction of the oxidation product and removal of the isopropylidene groups were accomplished as described previously[8] and D-allose was obtained in high yield.

Treatment of D-allose (**1**) with a mixture of acetone, methanol, 2,2-dimethoxypropane, and an acid catalyst[10] gave methyl 2,3:5,6-di-*O*-isopropylidene-β-D-allofuranoside (**2**) (Scheme I). In previous work,[10,11] it had been found advantageous to skip the isolation of the fully blocked intermediate and to procede directly to the next product. Therefore, a repeat of the above followed by selective hydrolysis gave a 51% yield of crystalline methyl 2,3-*O*-isopropylidene-β-D-allofuranoside (**3**). A fair amount of over hydrolysis produced D-allose and the methyl glycoside, which were present in the aqueous phase after the extraction process. By using an anion-exchange resin in the hydroxide form to neutralize the acid, it was possible to recycle the aqueous phase through the entire process at least one time to raise the total yield to over 70%. Williams[12] has reported that the acid-catalyzed methanolysis of 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose yielded both **2** and **3** as products. The physical data for **2** agreed well; however, **3** had been reported as a syrup. No elemental analysis was given and the optical rotations, which are not close, could not be compared in water due to the low solubility of crystalline **3**. The elemental analysis and NMR and IR spectra of **3** support the structure, as do the following reactions performed on it.

Treatment of **3** with methanesulfonyl chloride afforded methyl 2,3-*O*-isopropylidene-5,6-bis(*O*-methanesulfonyl)-β-D-allofuranoside (**4**) in 86% yield. Methyl 5,6-dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranoside (**5**) was

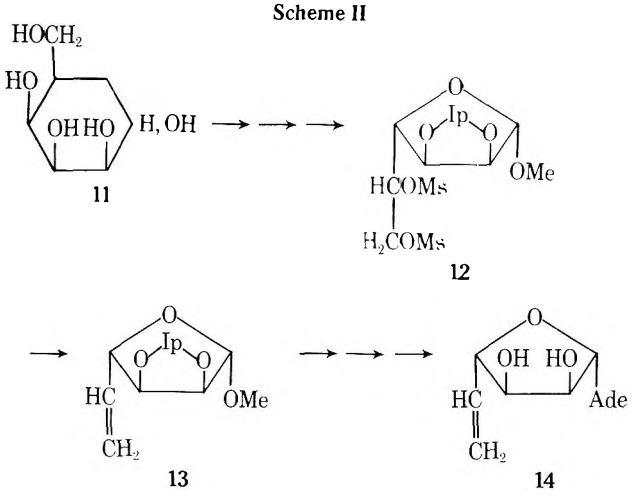
Scheme I



obtained from **4** with sodium iodide in boiling 2-butanone. The spectral data and optical rotation of **5**, which was a distillable liquid, compared favorably to the compound reported by Ryan et al.[7] The present synthesis has the distinct advantage that large quantities of **5** can be produced from D-glucose and purified by distillation without the problem of contaminating byproducts.

In order to prepare nucleoside **9**, it was necessary to exchange the blocking groups of **5** for ester groups. The isopropylidene group was removed in boiling methanol containing the acid form of an ion-exchange resin.[13] The hydroxyl groups were benzoylated, giving methyl 2,3-di-*O*-benzoyl-5,6-dideoxy-β-D-*ribo*-hex-5-enofuranoside (**6**), and acetolysis afforded the 1-*O*-acetate **7**. The benzoate groups precluded isomerization at C-2 of the sugar during the acetolysis reaction.[14] The sugar derivative **7** was condensed with 6-benzamidochloromercuripurine by the titanium tetrachloride method[5,15] and the blocking groups of the nucleoside **8** were removed in hot methanolic sodium methoxide. The crystalline product **9** was purified by chromatography on an ion-exchange column[16] and obtained in 44% yield from **7**. The elemental analysis and UV, IR, and NMR spectra indicated that **9** was an N-9 substituted adenine hexofuranosyl nucleoside. However, the H-1′ proton was obscured by overlapping of the multiplet from H-5′ so that no decision concerning the anomeric configuration could be made. It was expected that **9** would have the β-D configuration because of the directive effect of the benzoyl group at C-2 during the coupling reaction.[17] Since the optical rotation of **9** offered no basis for a decision, it was converted to the isopropylidene derivative **10** and the NMR spectrum recorded

Scheme II



Ade = adenyl

again. The anomeric proton was still not clearly defined; however, the $\Delta\delta$ value of the α- and γ-methyl groups of the isopropylidene group was 0.22. Imbach[18] has stated that values of $\Delta\delta > 0.18$, when recorded in Me_2SO-d_6, are indicative of the β-D configuration, which has been assigned to **9**.[19]

The starting sugar for the preparation of the enantiomeric nucleoside **14** was D-talose (**11**) (Scheme II). The preparation of methyl 2,3-*O*-isopropylidene-5,6-bis(*O*-methanesulfonyl)-α-D-talofuranoside (**12**) followed the preparation of the D-mannose isomer[10] more closely than the D-allose isomer **4** in that the intermediates were not isolated. Attempts were made to purify and crystallize methyl 2,3:5,6-di-*O*-isopropylidene-α-D-talofuranoside and methyl 2,3-*O*-isopropylidene-α-D-talofuranoside, but these substances did not crystallize and the purification process decreased yields. Therefore, the entire reaction sequence to **12** from **11** was performed without isolation of intermediates. Similar to the case of D-allose, the aqueous phase after selective hydrolysis was recycled one time and, following mesylation, a 60% total overall yield of **12** from D-talose was obtained.

Treatment of **12** with sodium iodide in 2-butanone gave methyl 5,6-dideoxy-2,3-*O*-isopropylidene-β-L-*ribo*-hex-5-enofuranoside (**13**). From this point on, the synthesis of **14** was achieved in the same manner as described for **9**.

Experimental Section[20]

D-Allose (1). To a 1-L Morton flask was added 10 g of sodium bicarbonate, 50 mL of water, and 1 g of ruthenium dioxide hydrate,[21] and the mixture was stirred magnetically. Sodium metaperiodate (5 g) was added and the insoluble black ruthenium dioxide was converted to the soluble yellow-orange ruthenium tetraoxide. Carbon tetrachloride (200 mL) was added followed by 50 g of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose,[22] which was added in small portions over 1 h. During this time a solution containing 55 g of sodium metaperiodate in 500 mL of water was added intermittently in small portions to the well-stirred mixture to maintain the yellow-orange color. After each addition of the sugar derivative the formation of black ruthenium dioxide could be observed around the dissolving crystals. After all of the sugar derivative and sodium metaperiodate solution had been added the orange solution was stirred until ruthenium dioxide was regenerated. Solid sodium metaperiodate was added in 3–5-g portions from time to time to regenerate the orange color until a total of 20 g had been added. TLC using 1:1 chloroform–ether indicated that the reaction was complete in 4–5 h. The mixture was treated with 50 mL of 2-propanol for 0.5 h, filtered through a pad of Celite-545, and the orange organic layer separated. The aqueous layer was extracted with chloroform (8 × 150 mL) and combined with the main organic layer, and the solvents were removed by evaporation, leaving a yellow crystalline mass. The reduction of 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofurano-3-ulose hydrate to 1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose (41.6 g, 83% yield from 1,2:5,6-di-*O*-isopropylidene-D-glucofuranose) and subsequent hydrolysis to obtain D-allose (95% yield) was conducted as described by Baker et al.[8]

Methyl 2,3:5,6-Di-*O*-isopropylidene-β-D-allofuranoside (2). A mixture containing 1 g (5.55 mmol) of D-allose (**1**), 5 mL of 2,2-dimethoxypropane, 3.3 mL of methanol, 3.3 mL of acetone, and 0.1 mL of concentrated hydrochloric acid was heated under reflux for 2 h. The mixture was cooled to room temperature and neutralized with 3 mL of saturated sodium bicarbonate solution. An additional 10 mL of water was added and enough methanol to dissolve the precipitate that formed. The organic solvents were evaporated and the product crystallized from the water. The crystals were filtered off, washed with water, and air dried: 0.838 g (55% yield). Recrystallization from methanol–water gave clear, colorless micaceous platelets: mp 66–66.5 °C; $[\alpha]^{25}_D$ −54.3° (*c* 1.36, chloroform) [lit.[12] mp 67–68 °C; $[\alpha]^{23}_D$ −54° (*c* 0.19, chloroform)].

Anal. Calcd for $C_{13}H_{22}O_6$: C, 56.92; H, 8.09. Found: C, 56.95; H, 8.13.

Methyl 2,3-*O*-Isopropylidene-β-D-allofuranoside (3). A mixture containing 22 g (0.122 mol) of D-allose, 110 mL of 2,2-dimethoxypropane, 73 mL of acetone, 73 mL of methanol, and 2.2 mL of concentrated hydrochloric acid was boiled under reflux for 2 h. The orange solution was cooled to room temperature and poured into 220 mL of water. The organic solvents were evaporated (30 °C), during which process crystals of **2** began forming. The amount of water was readjusted to 220 mL and 220 mL of methanol was added. The crystals dissolved, 5.5 mL of concentrated hydrochloric acid was added, and the solution was kept at room temperature for 3.5 h. The acid was neutralized with Amberlite IR-45 (OH^-) anion-exchange resin and the resin was removed by filtration and washed with 200 mL of 1:1 methanol–water. The filtrate was evaporated to about 125 mL of water and extracted with chloroform (4 × 70 mL), and the chloroform extracts were combined and dried. The solvent was evaporated and the residue crystallized from a mixture of ethyl acetate (20 mL) and petroleum ether (bp 30–60 °C, 60 mL) to afford 14.03 g of **3**. An additional 0.5 g was crystallized from the mother liquor for a 51% yield.

The original water layer was evaporated and the residue dried by coevaporation several times with absolute ethanol. The residue, which weighed 13.8 g, was treated with 69 mL of 2,2-dimethoxypropane, 46 mL of methanol, 46 mL of acetone, and 1.4 mL of concentrated hydrochloric acid, and boiled under reflux for 2 h. The rest of the procedure was the same as above except that neutralization of the acid was effected with saturated sodium bicarbonate solution. An additional 5.88 g of **3** was obtained for a total of 20.42 g (71%). These crystals were satisfactory for use in the next step.

In a separate experiment 1 g of **1** was converted to **3** in 51% yield and recrystallized from ethyl acetate–petroleum ether to obtain microcrystals; mp 100–100.5 °C; $[\alpha]^{25}_D$ −66.8° (*c* 1.37, methanol); IR (KBr) ν_{max} 3340 (OH), 1384 cm^{-1} (*gem*-dimethyl); NMR (acetone-d_6) δ 4.87 (br s, 1, OH), 4.75 (s, 1, H-1), 4.42 (d, 1, $J_{2,3}$ = 6 Hz, H-2), 4.02 (d, 1, $J_{2,3}$ = 6 Hz, H-3), 3.83–3.40 (m, 5, H-4, H-5, H-6a, H-6b, OH), 3.20 (s, 3, OMe) 1.33, 1.21 (both s, 6, *gem*-dimethyl). A previous paper[12] reported **3** as a syrup having $[\alpha]^{25}_D$ −43° (*c* 0.35, water).

Anal. Calcd for $C_{10}H_{18}O_6$: C, 51.27; H, 7.74. Found: C, 51.35; H, 7.73

Methyl 2,3-*O*-Isopropylidene-5,6-bis(*O*-methanesulfonyl)-β-D-allofuranoside (4). To a solution of **3** (20.4 g, 87 mmol) in 102 mL of dry pyridine, chilled in an ice bath, was added 31 mL of methanesulfonyl chloride dropwise. The mixture was stirred for 2 h at room temperature, chilled again, and 45 mL of water was added very slowly. Crystallization of the product began and after 1 h the contents of the flask was transferred to a beaker containing 1 L of water and stirred for 20 min. The crystals were filtered off, washed copiously with water, and air dried: 29.34 g (86% yield). This material was satisfactory for the next reaction. Recrystallization of a sample (1.46 g) from ethanol–water afforded 1.21 g of needles: mp 102–103 °C; $[\alpha]^{25}_D$ −25.9° (*c* 1.38, chloroform); IR (KBr) ν_{max} 1374 (*gem*-dimethyl), 1350, 1170 cm^{-1} (sulfonyl), no OH; NMR (acetone-d_6) δ 5.00–3.95 (series of unresolved, complex multiplets, 7 sugar protons), 3.33 (s, 3, OMe), 3.18, 3.12 (both s, 6, methanesulfonyl), 1.40, 1.27 (both s, 6, *gem*-dimethyl). The NMR spectrum very closely resembled that of other isomers of this type.

Anal. Calcd for $C_{12}H_{22}O_{10}S_2$: C, 36.91, H, 5.68; S, 16.43. Found: C, 36.93; H, 5.68; S, 16.42.

Methyl 5,6-Dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranoside (5). A mixture containing 29.4 g (75.5 mmol) of **4**, 83 g (0.55 mol) of sodium iodide, and 650 mL of 2-butanone was boiled under reflux for 39 h. The mixture was cooled to room temperature and filtered, and the solvent was evaporated. The liquid residue was

dissolved in 175 mL of chloroform, washed with 10% aqueous sodium thiosulfate solution (250 mL; then 2 × 175 mL) and water, (200 mL) and dried. After evaporation of the chloroform, the oil was dissolved in methanol and decolorized with activated charcoal.[23] The methanol was evaporated and the oil distilled to yield 13.14 g (87%): bp 79–80 °C (3.5 mmHg); $[\alpha]^{26}_D$ −61.0° (*c* 1.64, chloroform) [lit.[7] bp 104–105 °C (17 mmHg), $[\alpha]^{24}_D$ −57.9° (chloroform)]; IR (film) ν_{max} 3015, 2780 (=C-H stretching), 1682, 1635 (C=C), 1374 (d, *gem*-dimethyl), 992, 907 cm^{-1} (=CH bending); NMR (chloroform-*d*) 6.0–4.97 (complex m, 3, H-5, H-6a, H-6b), 4.90 (s, 1, H-1), 4.57 (m, 3, H-2, H-3, H-4), 3.25 (s, 3, OMe), 1.43, 1.27 (both s, 6, *gem*-dimethyl).

9-(5,6-Dideoxy-β-D-*ribo*-hex-5-enofuranosyl)adenine (9). To a solution containing 8 g (40 mmol) of **5** in 240 mL of methanol was added 80 g of Amberlite IR-120 (H^+) cation-exchange resin.[13,24] The well-stirred mixture was heated under reflux for 3.5 h, cooled to room temperature, and filtered by suction through a pad of Celite-545. The solids were washed with 200 mL of methanol, the methanol was evaporated, and a yellow syrup remained. The syrup was dissolved in 112 mL of dry pyridine, chilled in an ice bath, and 19 mL of benzoyl chloride was added, dropwise, to the stirring mixture. After 1 h the flask was stored at room temperature for 16 h, chilled again in an ice bath, and the contents treated with 7 mL of methanol[25] dropwise. After 0.5 h in the ice bath; the flask was kept at room temperature for 2.5 h, and then the contents was diluted with 100 mL of chloroform and transferred to a separatory funnel. The organic solution was washed with 250 mL of ice water, and the aqueous layer was back-extracted one time with 40 mL of chloroform. The chloroform solution was washed with 250 mL of saturated sodium bicarbonate solution and 250 mL of water and evaporated. The residue, which contained methyl benzoate, was suspended in 50 mL of 1:1 methanol–water and the solvents were evaporated. This process was repeated four times and removed all but traces of methyl benzoate. The syrupy residue was dried by coevaporation with absolute ethanol (4 × 50 mL) to afford 13.2 g (90% yield from **5**) of an orange syrup, methyl 2,3-di-*O*-benzoyl-5,6-dideoxy-β-D-*ribo*-hex-5-enofuranoside (**6**): NMR (chloroform-*d*) δ 8.07–7.00 (m, phenyl), 3.42 (s, OMe).

The entire sample (36 mmol) was dissolved in a mixture of glacial acetic acid (81 mL) and acetic anhydride (8.1 mL), chilled in an ice bath, and 3.8 mL of concentrated sulfuric acid was added dropwise. The mixture was kept at room temperature for 16 h, poured into 200 mL of ice, and the mixture was stirred until the ice melted. A gum had settled out, which was dissolved by stirring in 100 mL of chloroform, and the chloroform solution was separated in a separatory funnel. The aqueous layer was extracted with chloroform (2 × 50 mL) and the extracts were combined. The chloroform solution was washed with water (2 × 200 mL), saturated sodium bicarbonate solution (200 mL), and again with water (200 mL), and dried. Evaporation of the solvent and several coevaporations with benzene to remove traces of acetic acid afforded a colorless syrup, 14.34 g of 1-*O*-acetyl-2,3-di-*O*-benzoyl-5,6-dideoxy-D-*ribo*-hex-5-enofuranose (**7**): NMR (chloroform-*d*) δ 2.03 (acetyl), no methoxyl.

The sugar derivative **7** (14.3 g, 36 mmol), 21.4 g (45 mmol) of 6-benzamidochloromercuripurine, 21.4 g of Celite-545, and 1250 mL of 1,2-dichloroethane were set up to reflux and 250 mL of solvent was removed through a take-off adapter in order to eliminate traces of moisture. A solution containing 5.2 mL (47 mmol) of titanium tetrachloride in 200 mL of fresh, dry 1,2-dichloroethane was added and the mixture was refluxed for 22 h with efficient stirring and protected from moisture. The mixture was cooled to room temperature, treated with 700 mL of saturated sodium bicarbonate solution, stirred for 1.5 h, and filtered through a pad of Celite-545. The filter cake was washed with 250 mL of hot 1,2-dichloroethane, the filtrate was placed in a separatory funnel, and the organic layer separated. Evaporation of the solvent left a brown foam, which was dissolved in 200 mL of chloroform, and the solution was washed with 30% aqueous potassium iodide solution (2 × 200 mL) and saturated sodium chloride solution (300 mL). The chloroform solution was dried and evaporated, yielding a brown, foamy, stiff gum weighing 18.3 g. The gum was dissolved in 300 mL of methanol, 48 g of 1 N methanolic sodium methoxide was added, and the mixture was boiled under reflux for 1.5 h. When the solution was chilled, precipitation of a tan solid occurred, which was filtered off, washed with cold methanol, and air dried. This material (3.5 g) was dissolved in 50 mL of hot 30% aqueous methanol and placed on top of a column[26] (56 × 1.8 cm) of BioRad AG 1-X2 (200–400 mesh, OH^-). Fractions (19 mL) were collected, and at tube number 68 the solvent was changed to 60% aqueous methanol and 16-mL fractions were collected. The dark-colored material stayed at the top of the column and only a few very minor UV absorbing peaks were observed. The main UV peak was in tubes 53–134, which were pooled and the solvents evaporated. The product was crystallized from ethanol to give 2.679 g in two crops. Recrystallization from acetone afforded 2.616 g of white needles in two crops.

The original methanol filtrate was adjusted to neutral pH with Amberlite CG-120 (H^+) ion-exchange resin and the mixture was filtered through a pad of Celite. The methanol was evaporated and 50-mL portions of water were coevaporated three times to remove methyl benzoate as an azeotrope. The residue was dissolved in 50 mL of 30% aqueous methanol and placed on a fresh column (60 cm × 1.8 cm) of the same resin used above. Fractions (15 mL) were collected and the solvent changed to 60% aqueous methanol at tube number 88. The major UV peak corresponded to tubes 73–160. These were pooled, the solvents evaporated, and the residue was crystallized from ethanol in two crops, affording 1.850 g. Recrystallization from acetone gave 1.603 g of white needles in three crops, identical with the above product by melting point, mixture melting point, and IR spectrum. The total yield of **9** was 4.219 g (44% from **7**): mp 190–191 °C; $[\alpha]^{28}_D$ +5.4° (c 0.837, 1 N hydrochloric acid); UV max (pH 1) 256.5 (ε 15 025), (H_2O) 259 (ε 14 760), (pH 13) 259 nm (ε 15 180); UV min (pH 1) 230 (ε 5000), (H_2O) 227 (ε 2190), (pH 13) 231.5 (ε 3885); NMR (Me_2SO-d_6) δ 8.17, 8.03 (both s, 2, H-8, H-2). 7.13 (br s, 2, NH_2), 6.03–5.67 (m, 2, H-1′, H-5′), 5.53–4.93 (complex m, 4, 2′-OH, 3′-OH, H-6′a, H-6′b), 4.77–4.43 (m, 1, H-2′), 4.40–3.97 (complex m, 2, H-4′, H-3′).

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.60. Found: C, 50.38; H, 5.09; N, 26.73.

9-(5,6-Dideoxy-2,3-*O*-isopropylidene-β-D-*ribo*-hex-5-enofuranosyl)adenine (10). Nucleoside **9** (100 mg, 0.38 mmol) was suspended in a mixture containing 30 mL of acetone and 3 mL of 2,2-dimethoxypropane, and 0.64 g of *p*-toluenesulfonic acid monohydrate was added. After stirring for 4 h at room temperature, the orange solution was poured into a stirring solution of 1 g of sodium bicarbonate in 10 mL of water. The precipitate was removed by filtration, and the solvents were evaporated. The residue was triturated with 25 mL of chloroform, the mixture filtered, and the chloroform evaporated. The syrupy residue crystallized after standing for 2 days at room temperature. Recrystallization from ethanol afforded 53 mg (46% yield) of **10**: mp 182.5–183.5 °C with a wet appearance at 178 °C; NMR (Me_2SO-d_6) δ 8.18, 8.10 (both s, H-8, H-2), 7.23 (br s, NH_2), 1.55, 1.33 (both s, Δδ = 0.22, *gem*-dimethyl).

Anal. Calcd for $C_{14}H_{17}N_5O_3$: C, 55.47; H, 5.65; N, 23.09. Found: C, 55.20; H, 5.50; N, 22.84.

Methyl 2,3-*O*-Isopropylidene-5,6-bis(*O*-methanesulfonyl)-α-D-talofuranoside (12). D-Talose (**11**) was prepared from D-galactal[27] by the method of Bilik and Kučár.[28] A mixture containing 19.8 g (0.11 mol) of D-talose, 100 mL of 2,2-dimethoxypropane, 70 mL of acetone, 70 mL of methanol, and 2 mL of concentrated hydrochloric acid was boiled under reflux for 2 h, cooled, diluted with 200 mL of water, and the organic solvents evaporated below 30 °C. Methanol (200 mL) and 5 mL of concentrated hydrochloric acid were added and the mixture was kept at room temperature for 4 h. The pH was adjusted to neutrality with Amberlite IR-45 (OH^-) and the resin was removed by filtration and washed thoroughly with 1:1 methanol–water. The solvents were evaporated until about 200 mL of water remained. Continuous extraction of the water layer with ethyl acetate was carried out for 5 days.[29] Evaporation of the dried solution gave an orange syrup (17.34 g). The aqueous layer was recycled through this process as described for the D-allose isomer, and an additional 4.34 g of crude methyl 2,3-*O*-isopropylidene-α-D-talofuranoside was obtained. The two preparations were used separately in the following mesylation step.

To a solution containing the 17.34 g of syrup in 90 mL of dry pyridine, chilled in an ice bath, was added 24 mL of methanesulfonyl chloride dropwise. The reaction was allowed to proceed for 2 h at room temperature, the mixture was chilled again, and 40 mL of water was added very slowly. After 15 min of stirring the mixture was diluted with an additional 150 mL of water and extracted with chloroform (3 × 75 mL). The chloroform extracts were combined, washed with saturated sodium bicarbonate solution (2 × 175 mL) and water (175 mL), and dried, and the solvent was evaporated. Coevaporation with small portions of toluene gave a syrup which was crystallized from ethanol after seeding.[30] A yield of 20.48 g of white needles was obtained. Treatment of the 4.34-g sample of syrup with 6 mL of methanesulfonyl chloride in 25 mL of pyridine and similar processing afforded an additional 5.22 g of **12**, for a total yield of 25.70 g (60% from **11**): mp 74.5–75.5 °C; $[\alpha]^{25}_D$ +37.2° (c 1.20, chloroform); IR (KBr)ν_{max} 1384, 1360, 1346 (overlapping broad peaks, *gem*-dimethyl, sulfonyl), 1179 cm^{-1} (sulfonyl); NMR (chloroform-*d*) δ 5.10–3.90 (series of complex multiplets, 7 sugar protons), 3.37 (s, 3, OMe), 3.10, 3.05 (both s, 6, methanesulfonyl), 1.48, 1.32 (both s, 6, *gem*-dimethyl).

Anal. Calcd for $C_{12}H_{22}O_{10}S_2$: C, 36.91; H, 5.68; S, 16.43. Found: C, 37.00; H, 5.59; S, 16.45.

Methyl 5,6-Dideoxy-2,3-*O*-isopropylidene-β-L-*ribo*-hex-5-enofuranoside (13). Methyl 2,3-*O*-isopropylidene-5,6-di-*O*-methanesulfonyl-α-D-talofuranoside (**12**, 12.5 g, 32 mmol), 35 g of sodium iodide, and 275 mL of 2-butanone were heated under reflux for 26 h. The mixture was worked up in a similar manner as in the preparation of **5** to afford 4.33 g (67.5% yield) of a clear, colorless liquid after distillation: bp 85–87 °C (3 mmHg), $[\alpha]^{25}_{D}$ +61.0° (c 1.53, chloroform). The IR and NMR spectra of **13** were identical with **5**.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 59.92; H, 7.94.

9-(5,6-Dideoxy-β-L-*ribo*-hex-5-enofuranosyl)adenine (14). The preparation of **14** from **13** proceeded exactly as already described for the preparation of **9**. From 2.5 g of **13**, 4.89 g of methyl 2,3-di-*O*-benzoyl-5,6-dideoxy-β-L-*ribo*-hex-5-enofuranoside was obtained and this was acetolyzed to 1-*O*-acetyl-2,3-di-*O*-benzoyl-L-*ribo*-hex-5-enofuranose (4.16 g). Both of these compounds had NMR spectra which were virtually identical with their enantiomers. The 1-*O*-acetate (4.16 g, 10.5 mmol) was condensed with 6.2 g (13.1 mmol) of 6-benzamidochloromercuripurine in 450 mL of 1,2-dichloroethane as described for the synthesis of **9**. After workup, 4.48 g of tan foam was obtained. The blocking groups were removed with sodium methoxide, the methyl benzoate was removed as a water azeotrope, and the product was purified on a column[16] (33 × 2 cm) as described before.[31] The contents of the tubes containing the main UV peak were combined and crystallization from ethanol gave 1.201 g in two crops. Two recrystallizations from acetone yielded 0.998 g (36% from the 1-*O*-acetate) of needles, mp 191–191.5 °C. The sample required drying to 100 °C under high vacuum in a drying pistol (phosphorus pentaoxide) to remove traces of acetone and water. The IR spectrum of **14** was identical with **9**.

Anal. Calcd for $C_{11}H_{13}N_5O_3$: C, 50.18; H, 4.98; N, 26.60. Found: C, 49.79; H, 5.00; N, 26.46.

Registry No.—**1**, 2595-97-3; **2**, 28642-53-7; **3**, 28642-54-8; **4**, 65969-34-8; **5**, 29325-28-8; **6**, 65969-35-9; **7**, 65969-36-0; **8**, 66008-58-0; **9**, [65969-37-1; **10**, 65969-38-2; **11**, 2595-98-4; **12**, 65969-39-3; **13**, 65969-40-6; **14**, 65969-41-7; 1,2:5,6-di-*O*-isopropylidene-2-D-glucofuranose, 582-52-5; 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofurano-3-ulose, 2847-00-9; 6-benzamidochloromercuripurine, 17187-65-4; methyl 2,3-*O*-isopropylidene-α-D-talofuranoside, 65969-42-8; methyl 2,3-di-*O*-benzoyl-5,6-dideoxy-β-L-*ribo*-hex-5-enfuranoside, 65969-43-9; 1-*O*-acetyl-2,3-di-*O*-benzoyl-5,6-dideoxy-L-*ribo*-hex-5-enofuranose, 65969-44-0.

References and Notes

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(19) It should be noted that this method was worked out for ribofuranose nucleosides and may not be applicable here. For example, some discrepancies have been found when C-5′ has a substituent.[18]
(20) Elemental analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Mich., or by the Baron Consulting Co., Orange, Conn. Moist organic solutions were dried over anhydrous magnesium sulfate and evaporations were performed on a rotary evaporator under reduced pressure with a bath temperature of 40–45 °C unless specified otherwise. TLC was performed on silica gel G plates of 0.25-mm thickness, prepared with Desaga equipment. The NMR spectra were recorded on a Varian T-60A spectrometer with Me_4Si as the internal reference. IR and UV spectra were recorded on a Perkin-Elmer Model 21 spectrophotometer and a Beckman DK-2 spectrophotometer, respectively. Optical rotations were determined with a Rudolph polarimeter. A Kofler micro hot stage was used to determine melting points as corrected values.
(21) Ruthenium dioxide hydrate was purchased from Engelhard Industries, Newark, N.J. It was used without any special treatment or activation.
(22) 1,2:5,6-Di-*O*-isopropylidene-β-D-glucofuranose was purchased from Pfanstiehl Laboratories, Inc., Waukegan, Ill.
(23) If this step is omitted, the colored material will distill with **5**.
(24) The resin was suspended in methanol and after 15 min the solvent was decanted. This process was repeated three times before the resin was used.
(25) If water was used, a large amount of benzoic anhydride was formed. The latter could be removed by treatment with methanol–pyridine solution for several days to form methyl benzoate.
(26) It is advisable to use a jacketed column in order to apply heat, if necessary, because the nucleoside tends to crystallize during early stages of chromatography. A hot-air blower (hair drier) was found to be a useful alternative for heating just the upper regions of the column.
(27) D-Galactal was purchased from Raylo Chemical, Ltd., Edmonton, Alberta, Canada.
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(29) Extraction of the aqueous layer using a separatory funnel with either chloroform or ethyl acetate produced a hopeless emulsion. It was desirable not to add salts so that the sugar in the aqueous layer could be easily recycled through the reaction sequence.
(30) Seed crystals were originally obtained from a small-scale reaction by scratching the product in a mixture of methanol and water.
(31) No significant crystallization of the nucleoside in the methanolysis solution occurred in this case, therefore, only one column was necessary.

Diels–Alder Approach to Naphthocyclobutenes and Anthrocyclobutenes

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The [2 + 4] cycloaddition of benzyne with 1,2-dimethylenecyclobutane or 1-vinylcyclobutene leads to the formation of an adduct which can be dehydrogenated with DDQ to provide naphtho[*b*]cyclobutene or naphtho[*a*]cyclobutene, respectively. Similar reaction of 2,3-dehydronaphthalene with these same two dienes provides analogous cycloadducts which can then be oxidized to anthro[*a*]cyclobutene and anthro[*b*]cyclobutene. Pyrolysis of 1,4-dihydronaphtho[*b*]cyclobutene provides a ring-opened diene which can undergo further cycloaddition. Other oxidative routes to naphtho[*b*]cyclobutene are presented.

The preparation of annelated aromatic systems is often best accomplished by the utilization of synthetic techniques in which the fused ring portion of the molecule comprises one of the initial reacting partners. This species can then undergo cycloaddition or condensation reactions to build up the aromatic nucleus. We have demonstrated the utility of this ap-

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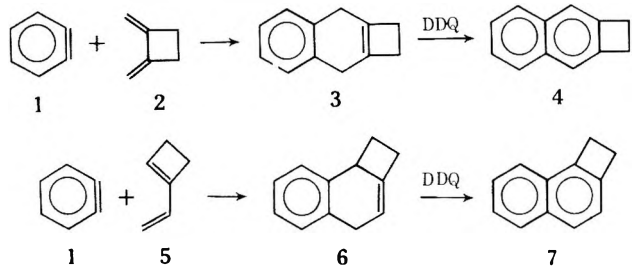
proach in the preparation of mono- and bisannelated benzenes[1] and pyridines.[2] When a Diels–Alder sequence is utilized to establish the molecular framework, the nature of the aromatic portion very often depends upon the dienophile which is employed. This paper will discuss how the [2 + 4] addition of 1,2-dimethylenecyclobutane and 1-vinylcyclobutene to a dehydroaromatic species can lead to the facile two-step preparation of cyclobutene-fused polynuclear aromatics.

The reaction of 1,2-dimethylenecyclobutane with excess benzyne (generated from anthranilic acid and isoamyl nitrite in tetrahydrofuran) in refluxing dichloromethane for 2 h resulted in a 25% yield of 1,4-dihydronaphtho[*b*]cyclobutene (**3**) after chromatography on silica gel: mp 69–70 °C; NMR ($CDCl_3$) δ 7.15 (s, 4 H, Ar**H**), 3.3 (s, 4 H, ArCH_2), and 2.6 (s, 4 H, cyclobutyl **H**). Treatment of **3** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene provides naphtho[*b*]cyclobutene in 81% yield, mp 85–86 °C (lit.[3] mp 86.5 °C). A similar Diels–Alder reaction between benzyne and 1-vinylcyclobutene provided a 25% yield of adduct **6** which showed a characteristic olefinic resonance at 5.5 ppm. This



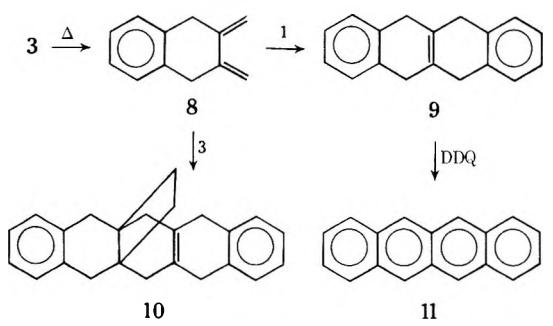
1 2 3 4

1 5 6 7

material was contaminated by an equivalent amount of a phenyl-substituted triene whose precise structure could not readily be determined. Treatment of the mixture with DDQ resulted in the disappearance of **6** and the formation of naphtho[*a*]cyclobutene (**7**) which was isolated in 35% yield by chromatography on silica gel.

Cava and co-workers have reported the synthesis of both naphtho[*a*]cyclobutene[4] (**7**) and naphtho[*b*]cyclobutene[3] (**4**) by the extrusion of sulfur dioxide from the corresponding dihydronaphthothiophene dioxides. This elimination is accomplished by a pyrolysis reaction and suffers the disadvantage of incorporating a good deal of steric strain in the final step. Our Diels–Alder approach to these two molecules incorporates the strain into the species undergoing cycloaddition, thereby enhancing reactivity through the release of steric strain. The final step involves the aromatization of a benzene ring and is thus driven by the resonance energy gained by the system.

Pyrolysis of **3** through a spiral glass tube heated to 300 °C (0.05 mm) provides the ring-opened diene **8**: mp 64 °C; NMR (CCl_4) δ 7.04 (s, 4 H, Ar**H**), 5.30 (m, 2 H, =CH_2), 4.88 (m, 2 H, =CH_2), and 3.50 (s, 4 H, ArCH_2). If this diene is allowed to react with a second equivalent of benzyne, 5,6,11,12-tetrahydronaphthacene (**9**) can be prepared: mp 160–165 °C; NMR (CCl_4) δ 7.1 (s, 8 H, Ar**H**) and 3.45 (s, 8 H, ArCH_2). Oxidation of **9** with DDQ afforded naphthacene which was identical with a commercial sample.

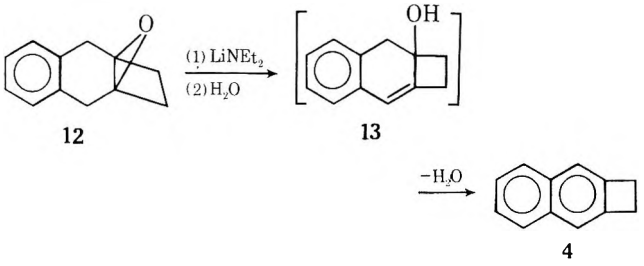


8 9

10 11

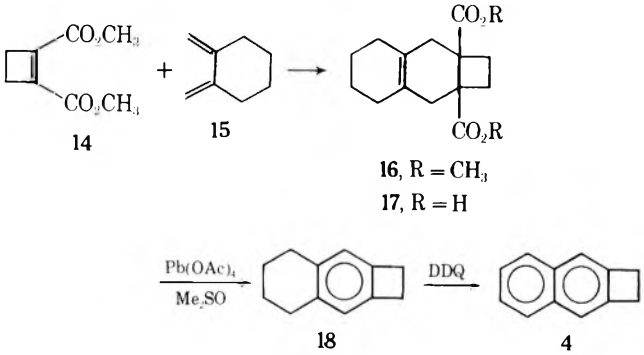
When the pyrolysis of **3** is carried out in a sealed tube at 200 °C, a dimer is formed in 70% yield as the result of diene **8** adding in a [2 + 4] fashion to its precursor **3**. Compound **10** (mp 119–121 °C) exhibited a parent ion at *m/e* 312 as well as a base peak at *m/e* 156 indicating that retro-Diels–Alder reaction is facile in the mass spectrometer. Cava has observed a similar dimer upon heating the analogous quinone to 200 °C.[5]

Oxidation of **3** with *m*-chloroperbenzoic acid results in the formation of the corresponding epoxide **12**. When this epoxide is treated with lithium diethylamide, the only product obtained is naphtho[*b*]cyclobutene. Abstraction of a benzylic proton accompanied by epoxide ring opening would lead to the formation of a tertiary allylic alkoxide which could dehydrate after hydrolysis or lose lithium hydroxide to aromatize directly.[6] The intermediate alcohol **13** was not observed.



12 13 4

Naphtho[*b*]cyclobutene may also be prepared by aromatization of the other six-membered ring. The synthesis of 5,6,7,8-tetrahydronaphtho[*b*]cyclobutene (**18**) was accomplished by a well-established cycloaddition route.[1] The addition of 1,2-dimethylenecyclohexane (**15**) to dimethyl 1,2-cyclobutenedicarboxylate (**14**) provides 64% of an adduct **16** which may be readily hydrolyzed to the corresponding diacid **17**. Bisdecarboxylation of this diacid and oxidation of the resulting 1,4-cyclohexadiene were accomplished by treatment with 2 equiv of lead tetraacetate in dimethyl sulfoxide. If **18** is then allowed to react with DDQ in benzene at room temperature for 16 h, smooth conversion to naphtho[*b*]cyclobutene occurs.



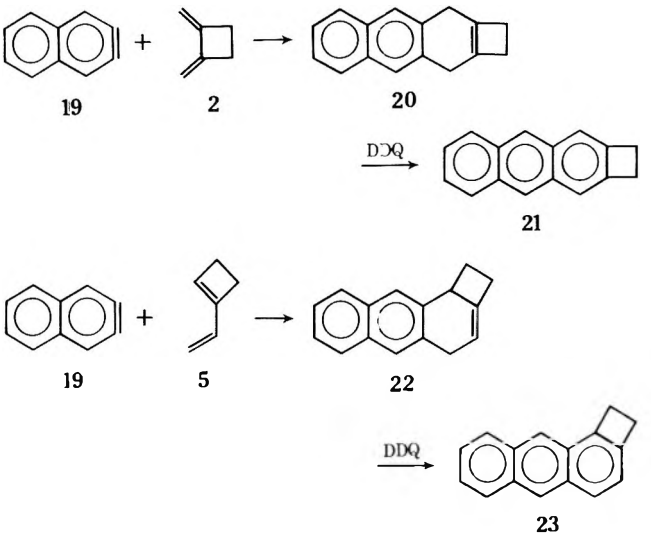
14 15

16, R = CH_3
17, R = H

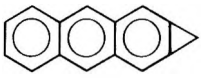
18 4

When 2,3-dehydronaphthalene (**19**) is substituted for benzyne in the cycloaddition reactions described above, the corresponding ring-fused 1,4-dihydroanthracenes may be obtained. Diazotization of 3-amino-2-naphthoic acid, followed by gentle pyrolysis, leads to the formation of **19**. Addition of 1,2-dimethylenecyclobutane to this species provides the adduct **20** which can then be aromatized by DDQ to anthro[*b*]-cyclobutene (**21**) in good yield. Reaction of 1-vinylcyclobutene with **19** provides a complex mixture from which **22** may be isolated by preparative gas chromatography. The NMR spectrum of this molecule is very similar to that of compound **6**. The DDQ promoted oxidation of **22** proceeds much more slowly than that of **20** but after 3 days at 45 °C conversion to **23** is complete. It has been noted in a number of related cases

that the position of ring fusion plays an important role in determining the rate of aromatization. These findings will be presented in a later paper.[7]



It is interesting to note that the cyclopropene-fused analogues of **21** and **23** are as yet unknown. Billups[8] and Garratt[9] have attempted preparation of anthro[*b*]cyclopropene **24** by



similar routes without success. Garratt has suggested that the apparent instability of this molecule might indicate a higher degree of bond fixation than in the corresponding naphtho[*b*]cyclopropene. For the present, it appears that the cyclobutene-fused anthracene derivatives which we have described here represent the outer limit of ring strain which will be tolerated by this polynuclear aromatic system.

Experimental Section

Dimethyl sulfoxide was distilled under vacuum from calcium hydride. Pyridine was distilled from barium oxide. Just prior to use, lead tetraacetate was recrystallized from acetic acid and protected from oxygen and light. DDQ was recrystallized from benzene/chloroform. Proton and carbon nuclear magnetic resonance spectra were obtained on a Varian Associates T-60 or XL-100 spectrometer and chemical shifts are reported in ppm downfield from Me_4Si. Infrared spectra were obtained on a Beckman IR-4250 spectrometer. Mass spectra were obtained by direct sample introduction into a Hewlett Packard 5933 A GC–mass spectrometer system. High-resolution mass spectral analyses were performed by Dr. R. Grigsby at the Department of Biochemistry and Biophysics, Texas A & M University, on a CEC21-110B double-focusing magnetic sector spectrometer at 70 eV. Exact masses were determined by peak matching. All melting points are uncorrected.

1,4-Dihydronaphtho[*b*]cyclobutene (3). Treatment of 9.5 g (0.07 mol) of anthranilic acid with 14 g (0.12 mol) of isoamyl nitrite in 50 mL of dry tetrahydrofuran at 20 °C for 1.5 h provided benzenediazonium 2-carboxylate as a tan precipitate.[10] This material was collected by filtration and combined with 100 mL of dichloromethane to which was added 2.2 g (0.028 mol) of 1,2-dimethylenecyclobutane.[11] The mixture was refluxed for 2 h until gas evolution had ceased. It was then cooled, washed three times with saturated sodium bicarbonate solution, and dried over magnesium sulfate. Filtration and evaporation of the solvent gave a yellow oil which was chromatographed on 35 g of silica gel, eluting with petroleum ether, to provide 1.10 g (25%) of 1,4-dihydronaptho[*b*]cyclobutene: mp 69–70 °C; NMR ($CDCl_3$) δ 7.15 (s, 4 H, Ar**H**), 3.3 (s, 4 H, ArCH_2), and 2.6 (s, 4 H, cyclobutyl protons); IR (KBr) 3070, 2945, 2910, 2885, 2830, 1495, 1430, 1286, 1175, and 737 cm^{-1}.

1,4-Dihydronaphtho[*a*]cyclobutene (6). Following the above procedure, 25 mmol of benzenediazonium 2-carboxylate was reacted with 1.0 g (12 mmol) of 1-vinylcyclobutene.[1c] Chromatography of the crude product on 10 g of silica gel, eluting with petroleum ether, provided 0.98 g (50%) of a colorless oil. Analysis of this material by VPC (10 ft × 1/8 in. 10% Carbowax 20 M on Chromosorb W 60/80 mesh at 112 °C and 30 mL/min) showed two equal area peaks with retention times of 9.7 and 16.5 min. Both of these peaks were isolated by preparative VPC. The first peak showed: NMR (CCl_4) δ 7.25 (broad s, 5 H, Ar**H**), 6.55 (m, 3 H), and 5.6–5.0 (overlapping m, 4 H); IR (thin film) 3100, 1498, 1452, 916, and 700 cm^{-1}. The IR did not correspond to 2-vinylnaphthalene and thus the material was considered to be an isomer of phenylhexatriene. Isolation of the second peak provided 1,4-dihydronaphtho[*a*]cyclobutene as a colorless oil: NMR (CCl_4) δ 6.98 (s, 4 H, Ar**H**), 5.5 (broad S, 1 H, = C**H**), 3.8 (broad m, 1 H), 3.2 (m, 2 H), 2.8–2.3 (m, 3 H), and 2.0 (m, 1 H); IR (thin film) 3025, 2985, 2870, 1486, 1457, 1433, 1215, 1005, and 816 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 156 (92, parent), 141 (92), 128 (100), and 115 (36).

Naphtho[*b*]cyclobutene (4). To a stirred solution of 0.29 g (1.3 mmol) of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in 25 mL of dry benzene was added 0.10 g (0.64 mmol) of **3**. The reaction mixture was stirred at room temperature for 1 h by which time the peak corresponding to **3** had disappeared by VPC. The mixture was filtered and the benzene was evaporated to give a black residue which was chromatographed on 10 g of silica gel, eluting with petroleum ether to provide 0.08 g (81%) of **4**: mp 85–86 °C; lit mp 86.5 °C;[3] NMR ($CDCl_3$) δ 7.5 (m, 6 H, Ar**H**) and 3.28 (s, 4 H, ArCH_2); IR (KBr) 3060, 2920, 870, and 740 cm^{-1}.

Naphtho[*a*]cyclobutene (7). To a stirred solution of 1.43 g (6.3 mmol) of DDQ in 50 mL of dry benzene was added 0.49 g of 50% pure **6** (1.57 mmol). The reaction mixture was refluxed for 30 min and filtered and the benzene was evaporated. The black residue was dissolved in petroleum ether and filtered and the solvent was evaporated to give 0.17 g of a yellow oil. This oil was first distilled in a Kugelrohr apparatus (bp 20–70 °C (0.1 mm)) and then chromatographed on 35 g of silica gel, eluting with petroleum ether, to afford 0.048 g (20%) of **7** as a colorless oil: NMR ($CDCl_3$) δ 7.45 (m, 6 H, Ar**H**) and 3.25 (m, 4 H, ArCH_2); IR (thin film) 3060, 2930, 1595, 1365, 810, 775, and 732 cm^{-1}.

2,3-Dimethylene-1,2,3,4,-tetrahydronaphthalene (8). A pyrolysis apparatus was constructed from a 12 in. long 1-in. diameter spiral of 0.25 in. (o.d.) Pyrex tubing. At the bottom end of this tube was attached a 15-mL round-bottom flask equipped with a side arm for the introduction of nitrogen. At the top of the tube was a trap cooled in a dry ice–acetone bath and connected to the vacuum line. The spiral tube was heated to 300–310 °C in a vertical tube furnace and evacuated to 0.05 mm. A 1.50-g (9.6 mmol) sample of 1,4-dihydronaphtho[*b*]cyclobutene (**3**) placed in the 15-mL flask was rapidly forced into the hot zone by heating with a microburner. After all the sample had evaporated from the pot, a slow bleed of nitrogen was continued until no further material collected in the cold trap. The pyrolyzed material (1.30 g) was collected and subjected to a second pyrolysis under the same conditions to ultimately yield 1.00 g (67%) of a white solid which NMR analysis showed to consist of a mixture of 30% of unreacted **3** and 70% of diene **8**. Pure **8**, mp 64 °C, was isolated by preparative VPC (6 ft × 0.25 in. 2% OV-101 on Chromosorb W 80/100 mesh at 100 °C and 30 mL/min): NMR (CCl_4) δ 7.04 (s, 4 H, Ar**H**), 5.3 (broad s, 2 H, =CH_2), 4.88 (broad s, 2 H, =CH_2), and 3.50 (s, 4 H, ArCH_2); IR (thin film) 3013, 2920, 2870, 2820, 1501, 1460, 1425, 888, and 743 cm^{-1}.

5,6,11,12-Tetrahydronaphthacene (9). A 0.10-g (0.64 mmol) sample of **3** was subjected to a double pyrolysis as described above. The crude pyrosylate was taken up in 20 mL of dichloromethane to which was added 1.28 mmol of benzenediazonium 2-carboxylate generated as described above. The mixture was refluxed for 2 h and cooled and the dichloromethane was removed under vacuum. The residue was chromatographed on 60 g of silica gel, eluting with petroleum ether, to yield 0.04 g (27%) of **9** as a white solid: mp 160–165 °C; NMR ($CDCl_3$) δ 7.1 (s, 8 H, Ar**H**) and 3.45 (s, 8 H, ArCH_2); IR (KBr) 2980, 2910, 1540, 1305, 1075, and 785 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 232 (60, parent), 229 (30), 217 (31), and 104 (100). Treatment of a small sample of **9** with DDQ in refluxing benzene resulted in the formation of a material which had an R_f identical to that of naphthacene.

Sealed Tube Pyrolysis of 3. In a small, heavy-wall tube was placed 0.10 g (0.64 mmol) of 1,4-dihydronaphtho[*b*]cyclobutene (**3**). The tube was sealed and heated to 200 °C for 8 h. After cooling, the resulting yellow oil was chromatographed on 35 g of silica gel, eluting with petroleum ether, to afford 0.04 g (40%) of adduct **10**: mp 133–134 °C;

NMR (CCl_4) δ 7.0 (8, H, ArH) and 3.2, 2.7, 2.05, 1.9 (overlapping m, 16 H); IR (KBr) 3060, 3020, 2930, 1500, 1490, 1440, and 750 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 312 (54, parent), 284 (4), 156 (100), 141 (74), 128 (36), and 114 (34).

1,4-Dihydronaphtho[*b*]cyclobutene Oxide (12). A solution of 0.20 g (1.28 mmol) of 1,4-dihydronaphtho[*b*]cyclobutene in 15 mL of dichloromethane under nitrogen was cooled in an ice bath. A solution of 0.30 g (1.47 mmol) of *m*-choroperbenzoic acid in 10 mL of dichloromethane was then slowly added. The reaction mixture was stirred for 1 hour and then allowed to warm to room temperature and stirred an additional 23 h. The organic phase was then washed with 10% sodium thiosulfate, 5% sodium bicarbonate, water, and saturated sodium chloride solution. Drying over magnesium sulfate and evaporation of the solvent provided 0.18 g (80%) of epoxide **12**: mp 94–95 °C; NMR ($CDCl_3$) δ 7.08 (s, 4 H, ArH), 3.27 (s, 4 H, $ArCH_2$), and 2.10 (s, 4 H, cyclobutyl **H**); IR (KBr) 2950, 2850, 1440, 1155, and 765 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 172 (58, parent), 144 (23), 130 (50), 129 (100), 128 (66), 116 (74), and 115 (79).

Reaction of 12 with Lithium Diethylamide. To a stirred, ice-cold mixture of 0.04 g (0.58 mmol) of diethylamine in 3 mL of anhydrous ether was added 0.3 mL of 2.4 M *n*-butyllithium in hexane. The solution was stirred for 10 min and 0.05 g (0.29 mmol) of epoxide **12** was added. The reaction mixture was stirred at 4 °C for 20 min and for an additional 2 h at room temperature. It was then poured into 30 mL of H_2O and extracted with ether. The ether extracts were dried over magnesium sulfate, filtered, and evaporated to provide a material which showed an NMR spectrum identical with that of naphtho[*b*]cyclobutene (**4**).

Dimethyl Tricyclo[8.2.0.0^{3,8}]dodec-3(8)-ene-1,10-dicarboxylate (16). In a heavy-wall glass tube were placed 1.75 g (0.0162 mol) of 1,2-dimethylenecyclohexane (**15**),[12] 0.05 g of hydroquinone, and 2.76 g (0.0162 mol) of dimethyl-1,2-cyclobutene dicarboxylate (**14**).[13] The tube was sealed and heated in an oil bath to 85 °C for 18 h. The tube was then cooled and opened and the crude product was purified on 100 g of 60/200 mesh silica gel, eluting with 1:5 ether/petroleum ether to provide 2.91 g (64%) of the Diels–Alder adduct: mp 64–66 °C: NMR (CCl_4) δ 3.63 (s, 6 H, CO_2CH_3) and 2.55–1.42 (m, 16 H); IR (KBr) 2910, 1720, 1440, 1330, 1280, 1265, 1220, 1100, and 1038 cm^{-1}.

Tricyclo[8.2.0.0^{3,8}]dodec-3(8)-ene-1,10-dicarboxylic Acid (17). To a solution of 2.90 g (0.0105 mol) of diester **16** in 40 mL of methanol was added a solution of 4.7 g (0.084 mol) of potassium hydroxide in 5 mL of water. The mixture was refluxed overnight, poured into 200 mL of saturated NaCl solution, and acidified with concentrated hydrochloric acid. The aqueous solution was extracted with ether and the extracts were dried over anhydrous sodium sulfate. Filtration, removal of solvent, and drying under vacuum provided 2.27 g (87%) of the corresponding dicarboxylic acid: mp 145–155 °C: NMR (Me_2SO-d_6) δ 2.6–1.4 (m, 16 H); IR (KBr) 3100 (6), 2940, 1734, 1405, 1295, 1240, 1178, 1150, and 1110 cm^{-1}.

5,6,7,8-Tetrahydronaphtho[*b*]cyclobutene (18). To a solution of 2.1 g (8.4 mmol) of diacid **17** and 3.3 g (42 mmol) of pyridine in 25 mL of dry dimethyl sulfoxide under nitrogen was added 8.2 g (18.5 mmol) of lead tetracetate. An exothermic reaction was observed with the evolution of gas. The reaction mixture was stirred at room temperature for 75 min and then poured into 125 mL of saturated NaCl solution and extracted five times with ether. The ether solution was washed first with cold, dilute hydrochloric acid and then with water, dried over anhydrous sodium sulfate, and filtered; the solvent was removed under vacuum to provide 0.52 g of a yellow liquid. This crude product was purified on 30 g of 60/200 mesh silica gel, eluting with 1:5 ether/petroleum ether to provide 0.343 g (26%) of pure hydrocarbon **18**: NMR (CCl_4) δ 6.45 (s, 2 H, ArH), 2.98 (s, 4 H), 2.60 (m, 4 H), and 1.62 (m, 4 H); IR (thin film) 3010, 2935, 2860, 2840, 1478, 918, and 864 cm^{-1}. Anal. Calcd for $C_{12}H_{14}$: *m/e* 158.1096. Found: *m/e* 158.1089.

DDQ Oxidation of 18. To a solution of 20 mg of 5,6,7,8-tetrahydronaphtho[*b*]cyclobutene (**18**) in 5 mL of dry benzene was added 50 mg of DDQ and the reaction mixture was stirred at room temperature for 10 h. The resulting yellow solution was passed through a small silica gel column, eluting with petroleum ether. Removal of the solvent gave a white solid, mp 78–80 °C, which showed an NMR spectrum identical to that of naphtho[*b*]cyclobutene (**4**).

1,4-Dihydroanthro[*b*]cyclobutene (20). In a 100-mL round-bottom flask were placed 0.5 g (2.7 mmol) of 3-amino-2-naphthoic acid,[14] 0.5 mL of concentrated HCl, 20 mL of tetrahydrofuran, and 0.63 g (5.4 mmol) of isoamyl nitrite. The mixture was stirred for 1 h and the resulting orange precipitate was collected by filtration and washed with dioxane (distilled from sodium). The wet precipitate was transferred to a 100-mL round-bottom flask to which was added 30 mL of dioxane, 0.2 mL of propylene oxide, and approximately 0.5 g (6.3 mmol) of 1,2-dimethylenecyclobutane. This mixture was rapidly heated to 100 °C in an oil bath and stirred for 1 h until no further gas evolution was observed. The red solution was cooled and filtered through 30 g of silica gel, washing with 200 mL of dichloromethane. The oil obtained by evaporation of solvent was taken up in petroleum ether and removed from a tarry precipitate. The petroleum ether was evaporated and the resulting yellow oil was chromatographed on 30 g of silica gel eluting with petroleum ether. A white solid (50 mg, 9% yield) was obtained which appeared to be 85% pure by NMR. This material was subjected to preparative TLC (SilicAR TLC-7GF) eluting with petroleum ether to provide 40 mg of **20**: mp 135–136 °C; NMR ($CDCl_3$) δ 7.8–7.2 (m, 4 H), 7.60 (d, 2 H, J = 2.5 Hz), 3.50 (broad s, 4 H, cyclobutenyl **H**), and 2.67 (broad s, 4 H, ArC**H**); IR (KBr) 3050, 2935, 2908, 2865, 2830, 868, and 746 cm^{-1}.

Anthro[*b*]cyclobutene (21). In a 5-mm NMR tube was placed 40 mg of **20** and 0.5 mL of carbon tetrachloride. To this solution was added 0.10 g of DDQ and the tube was heated in a water bath at 40 °C. The reaction was followed by NMR. After 16 h the peaks corresponding to **20** had completely disappeared while those corresponding to **21** had grown in. The solution was filtered through silica gel and the solvent was removed to provide a white solid: mp 245–247 °C; NMR ($CDCl_3$) δ 8.35 (s, 2 H, $H_{9,10}$), 7.95 (m, 2 H, $H_{5,8}$), 7.56 (s, 2 H, $H_{1,4}$), 7.33 (m, 2 H, $H_{6,7}$), and 3.38 (s, 4 H, $ArCH_3$); IR (KBr) 3060, 2965, 2935, 1415, 1290, 995, 902, and 740 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 204 (100, parent), 203 (42), 202 (41), 101 (46), 89 (18), and 88 (18). Anal. Calcd for $C_{16}H_{12}$: *m/e* 204.0939. Found: *m/e* 204.0932.

1,4-Dihydroanthro[*a*]cyclobutene (22). The same procedure as for **20** utilizing 0.5 g (2.7 mmol) of 3-amino-2-naphthoic acid[18] and 0.5 g (6.3 mmol) of 1-vinylcyclobutene[1c] was followed. After workup as outlined for **20** above there was obtained 30 mg (5.4%) of solid material, mp 98–101 °C, which was identified as **22** by its spectral properties: NMR ($CDCl_3$) δ 7.9–7.2 (m, 6 H, ArH), 5.67 (broad s, 1 H, =C**H**), 4.05 (broad s, 1 H, ArC**H**), 3.40 (broad s, 2 H, $ArCH_2$), and 3.0–2.0 (overlapping m, 4 H, cyclobutyl **H**); IR (KBr) 2955, 1659, 1562, 1510, 880, and 755 cm^{-1}.

Anthro[*a*]cyclobutene (23). A solution of 30 mg of **22** and 0.10 g of DDQ in 0.5 mL of $CDCl_3$ was placed in a 5-mm NMR tube. The tube was warmed to 45 °C in a water bath and the reaction was followed by NMR. After 3 days the upfield peaks corresponding to **22** had disappeared. The solution was filtered through silica gel, the solvent was evaporated, and the residue was purified by preparative TLC (SilicAR TLC-7GF) eluting with petroleum ether to provide 20 mg of **23**: mp 103–105 °C: NMR ($CDCl_3$) δ 8.42 and 8.25 (singlets, 2 H, H_9 and H_{10}), 8.1–7.7 (m, 3 H, H_4, H_5, H_8), 7.6–7.2 (m, 3 H, H_3, H_6, H_7), and 3.35 (m, 4 H, cyclobutyl **H**); IR (KBr) 2950, 2920, 1260, 1095, 900, and 795 cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 204 (100, parent), 203 (48), 202 (46), 101 (47), 100 (20), and 88 (20). Anal. Calcd for $C_{16}H_{12}$: *m/e* 204.0939. Found: *m/e* 204.0930.

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Registry No.—**2**, 14296-80-1; **3**, 65957-25-7; **4**, 6827-31-2; **5**, 58436-36-5; **6**, 65957-26-8; **7**, 32277-35-3; **8**, 65957-27-9; **9**, 65957-28-0; **10**, 65957-29-1; **12**, 65957-30-4; **14**, 1128-10-5; **15**, 2819-48-9; **16**, 65957-31-5; **17**, 65957-32-6; **18**, 65957-33-7; **20**, 65957-34-8; **21**, 65957-35-9; **22**, 65957-36-0; **23**, 65957-37-1; anthranilic acid, 118-92-3; benzenediazonium 2-carboxylate, 1608-42-0; phenylhexatriene isomer, 65957-24-6; 3-amino-2-napthoic acid, 5959-52-4; 3-diazonium 2-naphthoate, 30013-85-5.

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Reductive Coupling of Carbonyl Compounds to Olefins by Tungsten Hexachloride–Lithium Aluminum Hydride and Some Tungsten and Molybdenum Carbonyls

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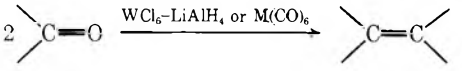
The WCl_6–$LiAlH_4$ system and some zerovalent metal carbonyls such as $W(CO)_6$, $W(CO)_5L$ (L = PPh_3, $NH_2C_6H_{11}$, $CPh(OCH_3)$, and Cl), and $Mo(CO)_6$ have been found to cause reductive coupling of carbonyl compounds. The reactivity of the WCl_6–$LiAlH_4$ system is almost the same as that of the WCl_6–BuLi system. The WCl_6–$LiAlH_4$ reagent is also capable of reducing epoxides to olefins. A mechanism involving a carbene–W complex is proposed for the carbonyl coupling.

The reductive coupling of carbonyl compounds by transition metal complexes is an important method for the formation of C–C bonds.[2] Sharpless et al. have reported that a new class of reagents derived from the interaction of tungsten(VI) hexachloride (WCl_6) and *n*-butyllithium (BuLi) causes coupling of carbonyl compounds.[3] We were interested in this tungsten-induced coupling for two reasons, because of its synthetic utility and because of its relationship to the significant olefin metathesis reaction caused by VIB group metals, especially tungsten.

We have found that the WCl_6–$LiAlH_4$ system and also hexacarbonyltungsten(0) ($W(CO)_6$) show similar reactivities to that of the WCl_6–BuLi system for coupling.



We have reported that these reagents are also effective for dehalogenative coupling of gem dihalides and related compounds.[4] In this paper we describe the reductive coupling of carbonyl compounds by tungsten compounds and hexacarbonylmolybdenum(0) and also the reductions of epoxides to olefins by tungsten compounds.[5]

Results and Discussion

WCl_6–$LiAlH_4$ System. The WCl_6–$LiAlH_4$-promoted coupling of carbonyl compounds was carried out using equimolar amounts of WCl_6 and $LiAlH_4$ and 0.5 equiv of the carbonyl compound in tetrahydrofuran (THF) under nitrogen atmosphere at room temperature. The reaction was rapid and complete within 1 h. The results are summarized in Table I. In contrast to the reaction with WCl_6–BuLi, it was important to use equimolar amounts of WCl_6 and $LiAlH_4$ to obtain optimum yield.[3] Substitution of other cocatalysts such as $NaAlH_4$, $NaBH_4$, LiH, CaH_2, Mg, or Zn or other solvent systems resulted in inferior yields (Tables II and III). As can be seen from Table I, aliphatic systems underwent coupling in poor yield. The reactivity of this reagent was almost the same

Table I. Coupling of Carbonyl Compounds by WCl_6–$LiAlH_4$ or $W(CO)_6$[a,d]

Carbonyl compd	Registry no.	Product	Yield, %[b] *E*	Yield, %[b] *Z*	Reagent[c]
Benzaldehyde	100-52-7	Stilbene	73	5	A
			21	21	B
p-Methoxybenzaldehyde	123-11-5	*p,p'*-Dimethoxystilbene	76	6	A
			39	24	B
p-Chlorobenzaldehyde	104-88-1	*p,p'*-Dichlorostilbene	63	2	A
			36	26	B
p-Methylbenzaldehyde	104-87-0	*p,p'*-Dimethylstilbene	57	3	A
			29	14	B
Benzophenone	119-61-9	Tetraphenylethylene	43		A
			3		B
Acetophenone	98-86-2	1,2-Dimethylstilbene	20	13	A
			3	4	B
Propionaldehyde	123-38-6	3-Hexene	18 (*E,Z*)		A
Cyclohexanone	108-94-1	Cyclohexylidenecyclohexane	55		A
			0.2		B

[a] Reaction was performed charging 0.8 mmol of WCl_6, 0.8 mmol of $LiAlH_4$, and 0.4 mmol of the carbonyl compound in 10 mL of THF (for reagent A) or CH_2Cl_2 (for reagent B) with stirring for 6 h at room temperature under nitrogen atmosphere. [b] Based on the starting carbonyl compound. [c] A, reagent WCl_6–$LiAlH_4$; B, reagent $W(CO)_6$. [d] Registry No.—WCl_6, 13283-01-7; $LiAlH_4$, 16853-85-3; $W(CO)_6$, 14040-11-0.

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Table II. Comparison of Cocatalysts for WCl_6-Induced Reductive Coupling of Benzaldehyde to Stilbene[a]

Cocatalyst	Stilbene yield, %	Cocatalyst	Stilbene yield, %
$LiAlH_4$	78	LiH	No
$NaAlH_4$	69	CaH_2	No
Zn	16	Mg	No
$NaBH_4$	No		

[a] Reaction was performed under the same conditions as Table I using THF as the solvent.

Table III. Comparison of Solvents for WCl_6–$LiAlH_4$-Induced Coupling of Benzaldehyde to Stilbene[a]

Solvent	Stilbene yield, %	Solvent	Stilbene yield, %
THF	78	Cyclohexane	Trace
Ethyl ether	23	Benzene	No
Dioxane	13	DMF	No
Acetonitrile	Trace	Pyridine	No
Nitromethane	Trace	Ethanol	No
Methylene chloride	Trace	Carbon tetrachloride	No

[a] Reaction was performed under the same conditions as Table I.

as that of the WCl_6–BuLi reagent.[3] The role of the cocatalyst $LiAlH_4$ can be thought to be that it reduces W(VI) to some lower valent species which is active for coupling since WCl_6 alone is not responsible for the reaction.[3] If this is the case, some zerovalent tungsten compounds such as $W(CO)_6$ should also be capable of the reaction. We have found that $W(CO)_6$ and $Mo(CO)_6$ cause the reductive coupling of carbonyl compounds (Tables I and IV). In Table IV, the solvent effect on the reaction of benzaldehyde with tungsten and molybdenum carbonyls is shown. From the table it is apparent that CH_2Cl_2 and *n*-pentane are the best for $W(CO)_6$ and $Mo(CO)_6$, respectively. But in the case of $W(CO)_6$, the solvent dependency is not so high as that of the WCl_6–$LiAlH_4$ system. Although the different solvent systems are suitable for these reagents, the order of reactivity appears to be WCl_6–$LiAlH_4$ $\simeq$ WCl_6–BuLi > $W(CO)_6$ $\simeq$ $Mo(CO)_6$.

In Table V are shown the reactivities of some zeorvalent tungsten carbonyls to coupling of benzaldehyde. The table shows that $W(CO)_6$ is the most active of the tested complexes and that addition of $AlCl_3$ to tetraethylammoniumpentacarbonyltungsten(0) chloride increases the yield, probably because $AlCl_3$ causes elimination of the chloride ligand, furnishing the coordinately unsaturated site. It is interesting that the carbene–W complex, methoxyphenylcarbenepentacarbonyltungsten(0), causes coupling in modest yield. Although these reagents are not capable of coupling aliphatic ketones in good yield, they still have some practical advantage over titanium-induced coupling since they are relatively stable to air. The reagents $MoCl_5$, $PdCl_2$, and $Pd(OAc)_2$ do not cause coupling under similar conditions.

Mechanism. Mechanisms involving pinacol type intermediates are suggested in the titanium-induced carbonyl coupling.[2] However, little is known about the tungsten-induced coupling of carbonyl compounds. We assume a carbene–W complex intermediate on the following bases: (i) When benzaldehyde was treated with the WCl_6–$LiAlH_4$–THF system in the presence of an enamine, 1-(2-methylpropenyl)-pyrrolidine, there was obtained 1-(2,2-dimethyl-3-phenylcyclopropyl)pyrrolidine (1), a cyclopropane,[6] in a 6.2% yield, together with 1.1% yield of stilbene.

Table IV. Comparison of Solvents for Coupling of Benzaldehyde to Stilbene by $W(CO)_6$ or $Mo(CO)_6$[a,b]

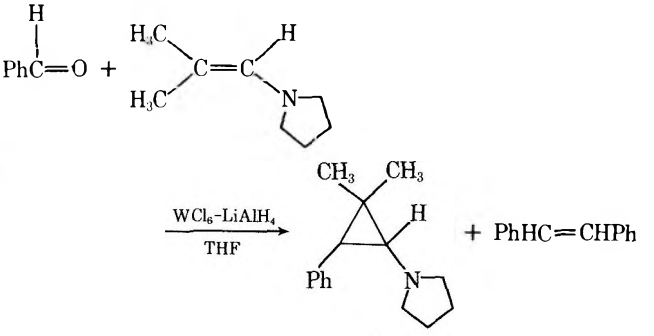
Solvent	Reagent and yield, % $W(CO)_6$	$Mo(CO)_6$
THF	21	10
Ether	14	39
Dioxane	20	13
Benzene	19	39
n-Pentane	17	41
Cyclohexane	20	38
Methylene chloride	42	5
CCl_4	27	No
Chlorobenzene	27	
Ethanol	10	No
Me_2SO	Trace	No
CH_3CN	1	No
Pyridine	No	No
Nitromethane	No	1

[a] Reaction conditions same as Table I. [b] Registry No.—$Mo(CO)_6$, 13939-06-5.

Table V. Coupling of Benzaldehyde by Tungsten(0) Carbonyls[a]

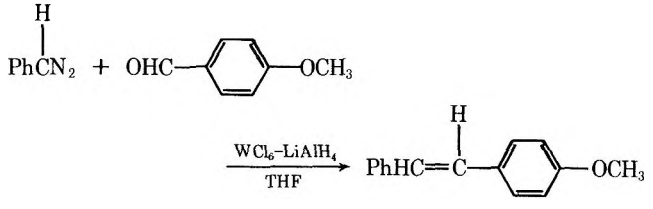
W complex	Registry no.	Stilbene yield, % *Z*	*E*
$W(CO)_6$		21	21
$W(CO)_5PPh_3$	15444-65-2	9	9
$W(CO)_5NH_2C_6H_{11}$	16969-84-9	7	8
$W(CO)_5{=}C(OCH_3)Ph$	37823-96-4	13	19
$[W(CO)_5Cl]NEt_4$	14780-97-3	4	27
$[W(CO)_5Cl]NEt_4$[b]			

[a] Reaction conditions same as Table I. [b] An equivalent amount of $AlCl_3$ was added.



1

(ii) When *p*-methoxybenzaldehyde was treated with phenyldiazomethane, a carbene precursor, in the WCl_6–$LiAlH_4$ system at room temperature, a 12% yield of *p*-methoxystilbene (2) was detected along with *p,p'*-dimethoxystilbene.



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These results i and ii are also observed with the $W(CO)_6$ reagent. (iii) Carbene–W complexes such as methoxyphenylcarbenepentacarbonyltungsten(0) cause carbonyl coupling in fair yield (Table V). (iv) NMR spectral studies have been performed to detect the carbene–W complex intermediate.

Table VI. Reduction of Epoxides by WCl_6–$LiAlH_4$[a]

Epoxide	Registry no.	Product	Yield, %[b] Z	Yield, %[b] E
Styrene oxide	96-09-3	Styrene	49	
(*Z*)-Stilbene oxide	1689-71-0	Stilbene	4	80
(*E*)-Stilbene oxide	1439-07-2	Stilbene	1	80
m,m'-Dichlorostilbene oxide (*E*–*Z* = 1:9)[c]		*m,m'*-Dichlorostilbene	12	88
1-Octene oxide	2984-50-1	1-Octene	75	
(*Z*)-2-Hexene oxide	6124-90-9	2-Hexene	23	29
(*E*)-2-Hexene oxide	6124-91-0	2-Hexene	20	36
Cyclohexene oxide	286-20-4	Cyclohexene	27	
Cyclooctene oxide	286-62-4	Cyclooctene	72	

[a] Reaction was performed charging 0.8 mmol of WCl_6, 0.8 mmol of $LiAlH_4$, and 0.8 mmol of the epoxide in 10 mL of THF with stirring for 6 h at room temperature under nitrogen atmosphere. [b] Based on the starting epoxide. [c] Registry No.—*m,m'*-dichlorostilbene oxide (*E* isomer), 65956-99-2; *m,m'*-dichlorostilbene oxide (*z* isomer), 65957-00-8.

Five minutes after the addition of benzaldehyde to a solution of WCl_6–$LiAlH_4$ in THF, a new peak at τ 1.20 appeared besides the aldehydic (τ 0.00) and phenyl protons (τ 2–3) of benzaldehyde, and this new peak disappeared after 15 min. We assume this new peak at τ 1.20 to be due to the α hydrogen of the carbene–W complex **3** since α protons of metal–carbene complexes have been reported to resonate over a relatively wide range such as τ $-7 \sim 8$.[7] Although these facts are inconclusive we would propose the following mechanism:

$$WCl_6 + \text{reductant} \longrightarrow WX \text{ (lower valent)}$$

$$PhC(H)=O + WX \longrightarrow XW(=O)-C(H)(Ph)$$

3

$$3 + PhC(H)=O \longrightarrow \text{metallocycle } \mathbf{4} \longrightarrow PhHC=CHPh + XWO_2$$

4

Recently Sharpless et al. have proposed a metallocycle intermediate such as **4** in the chromyl chloride oxidation of olefins.[8] The carbene formation from interaction of aldehydes and transition metal systems has also been reported.[9]

Reductions of Epoxides. Several transition-metal-induced reductions of epoxides are reported.[10] Sharpless et al. reported that the WCl_6–BuLi system is effective for the reduction of epoxides to olefins.[3] The WCl_6–$LiAlH_4$ system has been found to be as effective as the WCl_6–BuLi system for the reduction. The results are summarized in Table VI. Sharpless et al. have proposed a mechanism involving a metallocycle intermediate such as **4** for this epoxide reduction.[8]

In conclusion, it is shown that WCl_6–$LiAlH_4$ and $W(CO)_6$ reagents are capable of coupling of carbonyl compounds, gem dihalides, benzyl halides, and some alcohols[4] and reduction of epoxides to olefins.

Experimental Section

NMR spectra were obtained with a Japan Electron Optics JNM-4H-100 spectrometer using Me_4Si as an internal standard.

Materials. WCl_6 was purified by sublimation. 1-(2,2-Dimethylvinyl)pyrrolidine was prepared according to the literature.[11] Other starting materials were commercial grade. THF was refluxed and distilled from a dark purple solution of sodium benzophenone dianion under nitrogen. Other solvents were purified by the usual methods. $W(CO)_5PPh_3$ was prepared from $W(CO)_6$ and triphenylphosphine according to the literature.[12] Cyclohexylaminepentacarbonyltungsten(0) was prepared from $W(CO)_6$ and cyclohexylamine.[13] Methoxyphenylcarbenepentacarbonyltungsten(0)[14] and tetraammoniumpentacarbonyltungsten(0) chloride[15] were prepared according to the literature.

General Procedure for Coupling of Carbonyl Compounds by WCl_6–$LiAlH_4$. Into a flame-dried 50-mL centrifuge tube containing a magnetic stirring bar was added 10 mL of THF by syringe, and the tube was sealed with a No-Air stopper. After the tube had been flushed with nitrogen it was cooled to −78 °C and then WCl_6 (0.8 mmol) and $LiAlH_4$ (0.8 mmol) were added under nitrogen. The solution changed from green to dark brown. Then 0.4 mmol of the carbonyl compound was added by syringe and the mixture was stirred for 6 h at room temperature under nitrogen. The reaction mixture was quenched with 20% aqueous NaOH. The organic materials were extracted with ether. The combined ether layers were washed with water, dried over $MgSO_4$, filtered, and concentrated. The products were analyzed by GLC. The products were identified by mixture melting point, IR, NMR, and retention time comparison with authentic samples. The authentic *p,p'*-dichlorostilbene,[16] *p,p'*-dimethoxystilbene,[17] *p,p'*-dimethylstilbene,[17] cyclohexylidene cyclohexane,[18] and 1,2-dimethylstilbene[19] were prepared according to the procedures in the literature.

General Procedure for Coupling of Carbonyl Compounds by Metal Carbonyls. Into the same centrifuge tube as described above was added 10 mL of CH_2Cl_2 (in the case of $Mo(CO)_6$, *n*-pentane was the solvent) and tungsten carbonyl (0.4 mmol) and the tube was sealed with a No-Air stopper. After the tube had been flushed with nitrogen 0.2 mmol of the carbonyl compound was added by syringe. The mixture was stirred for 6 or 24 h at room temperature under nitrogen, then the tube was cooled to −78 °C and the precipitated metal complexes were removed by filtration. To the mother liquor was added ether and the ethereal layers were washed, dried with Na_2SO_4, and concentrated. The products were analyzed and isolated by GLC. Identities of the products were proved by the same procedures as above.

Trapping of Carbene Intermediate. Into a flame-dried 50-mL centrifuge tube containing a magnetic stirring bar and 40 mL of THF were added 3.2 mmol of WCl_6 and $LiAlH_4$ (equal amount) and the tube was sealed with a No-Air stopper. After the tube had been flushed with nitrogen, 3.2 mmol of benzaldehyde and 10 mL of 1-(2,2-dimethylvinyl)pyrrolidine were added. The mixture was allowed to warm to room temperature and stirred for 6 h at room temperature under nitrogen. After work-up as described above, the products were analyzed by GLC and shown to contain 1-(2,2-dimethyl-3-phenylcyclopropyl)pyrrolidine (**1**) and stilbene in 6.2 and 1.1% yields, respectively. The cyclopropane derivative **1** was identified by comparison with a sample of which preparation and physical properties were already described.[4]

General Procedure for Reduction of Epoxides by WCl_6–$LiAlH_4$. The epoxides were reduced in the same procedure described in the section of the coupling of carbonyl compounds by this reagent, charging 0.8 mmol of WCl_6, 0.8 mmol of $LiAlH_4$, and 0.8 mmol of the epoxide in 10 mL of THF with stirring for 6 h under nitrogen atmosphere. All the products formed were identified by comparison with authentic samples. The results are listed in Table VI.

Reaction of Phenyldiazomethane with p-Methoxybenzaldehyde in the Presence of WCl_6–$LiAlH_4$. Into a centrifuge tube containing a magnetic stirring bar, WCl_6 (0.8 mmol), $LiAlH_4$ (0.8 mmol), *p*-methoxybenzaldehyde (0.4 mmol), and THF (10 ml) was added an ethereal solution of phenyldiazomethane (0.6 mmol) prepared from oxidation of phenylhydrazone with HgO. The mixture was stirred until the solution changed from dark red to dark brown, and then the mixture was quenched with 20% aqueous NaOH. After work-up as usual, the residue was analyzed by GLC to give *p*-methoxystilbene[20] (12% yield based on phenyldiazomethane) and *p,p'*-dimethoxystilbene.[19]

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Oxidation of Long-Chain and Related Alcohols to Carbonyls by Dimethyl Sulfoxide "Activated" by Oxalyl Chloride[1]

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Dimethyl sulfoxide "activated" by oxalyl chloride at low temperatures in methylene chloride reacts rapidly with alcohols to give alkoxysulfonium salts, convertible to carbonyls in high to quantitative yields upon addition of triethylamine. Oxalyl chloride is the most efficient and generally useful Me_2SO "activator" thus far reported. The mild, high yield oxidation of long-chain saturated, unsaturated, acetylenic, and steroidal alcohols to carbonyls utilizing Me_2SO "activated" by oxalyl chloride is described.

Long-chain aldehydes (in masked form) are of importance in biological systems, such as plasmalogens, found in many organs of the body, e.g., heart, muscle, liver, kidney, pituitary gland, and cerebellum white and gray matter.[2] In the synthesis of plasmalogens, long-chain saturated and unsaturated aldehydes are necessary intermediates.

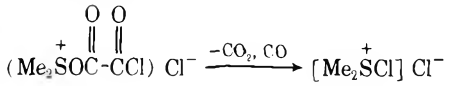
No satisfactory and universally applicable method for the preparation of long-chain carbonyls by the mild, selective oxidation of the corresponding long-chain saturated and unsaturated alcohols has been reported. Earlier work[3] involved the preparation of a sulfonate ester (mesylate or tosylate) of the alcohol followed by reaction with dimethyl sulfoxide (Me_2SO) at 160 °C for 5–10 min in the presence of sodium bicarbonate (yields 60–72%). The use of Me_2SO–acetic anhydride or Me_2SO–sodium bicarbonate at room temperature with the sulfonate esters was unsuccessful.

The oxidation of long-chain primary alcohols to aldehydes by the dipyridine–chromic anhydride complex was recently reported[4] but a sixfold excess of oxidant to alcohol is required. Yields are good, however, and range from 83–94%. No evidence (by infrared) of cis–trans isomerization of double bonds was observed in the preparation of mono-, di-, or triunsaturated aldehydes. Isomerization of double bonds is observed when more acidic oxidizing agents are employed.[5–8]

"Activated" Me_2SO has been used extensively by us to oxidize many classes of alcohols to carbonyls in excellent yields under mild conditions via the intermediate alkoxysulfonium salts.[9–11] In this paper we report our studies of "activated" Me_2SO as an oxidant for the mild, high-yield oxidation of long-chain saturated, unsaturated, acetylenic, and steroidal alcohols at low temperatures to carbonyls utilizing the newly discovered and most successful "activator" developed in our laboratory, namely, oxalyl chloride.[11] The results were compared with those obtained at room temperature with pyridinium chlorochromate[7] and pyridine–SO_3–Me_2SO,[12] two other well-known oxidants, and Me_2SO "activated" by trifluoroacetic anhydride (TFAA).[9,10]

Results and Discussion

Oxalyl chloride reacts violently and exothermically with Me_2SO at room temperature; therefore successful "activation" of Me_2SO by oxalyl chloride requires the use of low temperatures (−60 °C) to form intermediate **1**. The structure of intermediate **1** from oxalyl chloride and Me_2SO is unknown; intermediates **1a** and **1b** are both possible. Intermediate **1b**



1a **1b**

is the same as that reported by Corey and Kim for the low-temperature reaction of dimethyl sulfide with chlorine (Me_2S–Cl_2),[6] also a useful intermediate in alcohol oxidations.

The oxidation of long-chain saturated and unsaturated alcohols by Me_2SO "activated" by oxalyl chloride is summarized in Table I, acetylenic alcohols are summarized in Table II, and steroidal alcohols are summarized in Table III. The TFAA "activated" Me_2SO oxidation of several long-chain saturated alcohols is summarized in Table IV.

The oxalyl chloride "activated" Me_2SO oxidation of long-chain saturated alcohols to the corresponding aldehydes proceeds virtually quantitatively (Table I) and is limited only by the solubility of the alcohol in the solvent system

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Table I. Oxidation of Long-Chain Alcohols with Me_2SO–$(COCl)_2$[f]

Alcohol	Registry no.	Conditions[a]	Carbonyl yield, % 2,4-DNP	GLC >C=O	GLC >CHOH	Registry no. of >C=O deriv
1-Undecanol	112-42-5	A	99	100	0	112-44-7
1-Dodecanol	122-53-8	A	99	100	0	112-54-9
1-Dodecanol		D	98	98	0.2	
1-Tetradecanol	112-72-1	A	26	23	76	124-25-4
1-Tetradecanol		D	97	96	4	
1-Pentadecanol	629-76-5	A	25	24	75	2765-11-9
1-Pentadecanol		D	95	99	0.2	
1-Hexadecanol	36653-82-4	A (−35 °C)	79	80[b]	20[b]	629-80-1
1-Octadecanol	112-92-5	D	84	86[b]	4[b]	638-66-4
Oleyl (cis)	143-28-2	A	97	98[b]	2[b]	2423-10-1
Elaidyl (trans)	506-42-3	A	97	98[b]	2[b]	10009-79-7
Linoleyl	506-43-4	D	98	98[b]	1.9[b]	2941-61-9
Methyl ricinoleate	141-24-2	D	oil	79[b]	20[b]	3047-65-2
Citronellol	106-22-9	A	83	85	14	106-23-0
Geraniol	106-24-7	A	94	95	5	141-27-5
Farnesol	4602-84-0	D	88	92	8	19317-11-4
1,12-Dodecanediol	5675-51-4	A	98[c,d]	99[c,d]	1	38279-34-4
4-Hydroxystearic acid	2858-39-1	D	80[e]			
12-Hydroxystearic acid	106-14-9	D	75[e]			

[a] See Experimental Section. [b] Relative ratios. [c] Dialdehyde. [d] 1 molar equiv of Me_2SO–$(COCl)_2$ per hydroxy function. [e] Isolated keto acid. [f] Registry No.—Me_2SO, 67-68-5; $(COCl)_2$, 79-37-8.

Table II. Oxidation of Acetylenic Alcohols with DMSO–$(COCl)_2$, TEA, −60 °C

Alcohol	Registry no.	Carbonyl yield, % 2,4-DNP	GLC >C=O	GLC >CHOH
$HC{\equiv}C(CH_2)_2CH_2OH$	5390-04-5	99.6	99.8[a]	0.2
$CH_3C{\equiv}CCH_2C(OH)HCH_3$	19780-36-4			
$CH_3(CH_2)_3C{\equiv}CCH_2OH$	1002-36-4	79	98.3[b]	1.7
$CH_3(CH_2)_2C{\equiv}C(CH_2)_2OH$	14916-79-1			90
$CH_3(CH_2)_4C{\equiv}CCH_2OH$	20739-58-6	93	95[c]	5
$CH_3(CH_2)_4C(OH)HC{\equiv}CH$	818-72-4			

[a] Registry no. 18498-59-4. [b] Registry no. 1846-67-9. [c] Registry no. 1846-68-0.

Table III. Oxidation of Steroidal Alcohols with Me_2SO–$(COCl)_2$, TEA, −10 °C

Alcohol	Registry no.	Carbonyl yield, %[a]	Registry no.
Dihydrocholesterol (cholestanol)	80-97-7	96	566-88-1
Cholesterol (5-ene)	57-88-5	95	601-54-7
Stigmasterol (5,22-diene)	83-48-7	95	51529-12-5
11α-Hydroxyprogesterone	80-75-1	99	516-15-4
Testosterone	58-22-0	99	63-05-8

[a] Isolated carbonyl.

Table IV. Oxidation of Long-Chain Alcohols with Me_2SO–TFAA (Procedure C)

Alcohol	Base	Carbonyl yield, %, 2,4-DNP
1-Tetradecanol	TEA	72
	DIPEA	85
1-Pentadecanol	TEA	66
1-Octadecanol	DIPEA	84

(CH_2Cl_2–Me_2SO) at low temperatures. As the solubility decreases at the lower temperature (−60 °C) and with increasing chain length it is necessary to conduct the oxidation at −10 °C, the upper limit for the addition of the alcohol to **1**. High yields of carbonyls are obtained, however, when a 100% excess of oxalyl chloride "activated" Me_2SO is used to ensure that the alkoxysulfonium salt of the alcohol forms at −10 °C even though a considerable amount of intermediate **1** is sacrificed. The longest straight-chain alcohol examined was 1-octadecanol (C-18). The oxalyl chloride–Me_2SO route to carbonyls is superior to TFAA–Me_2SO (Table IV), even when diisopropylethylamine is used with the latter reagent.

The unsaturated lipid alcohols, oleyl (cis), elaidyl (trans), linoleyl (*cis,cis*-9,12-octadecadienol), and methyl ricinoleate, are converted to their corresponding carbonyls in high yield with no cis–trans isomerization of double bonds observed. The terpene alcohols, citronellol, and the two allylic alcohols, geraniol and farnesol, are also oxidized in good yields with no effect on the double bond systems.

The only diol examined gives an almost quantitative yield of dialdehyde when 1 equiv of "activated" Me_2SO per hydroxyl function is used (Table I).

Hydroxy acids can also be successfully oxidized to their corresponding keto acids (Table I).

Acetylenic Alcohols. Although the oxidation of unsaturated and allylic alcohols with the oxalyl chloride–Me_2SO reagent is very successful, oxidation of acetylenic alcohols is complex and the results are neither uniform nor understood (Table II). 1-Octyn-3-ol also fails to give any isolable carbonyl product when oxidized by TFAA–Me_2SO or pyridinium chlorochromate.[7]

Those acetylenic alcohols that can be successfully oxidized by our method can also be oxidized by other methods,[4,7] but

Table V. Oxidation of Long-Chain Alcohols by Pyridinium Chlorochromate[7] and Pyridine–SO_3–Me_2SO[12] at Room Temperature (25 °C)

Alcohol	Oxidant	Carbonyl yield, %
1-Tetradecanol	$Py{\cdot}SO_3{\cdot}Me_2SO$	42[a]
1-Tetradecanol	$PyHCrO_3{\cdot}Cl$	69
1-Octadecanol	$PyHCrO_3{\cdot}Cl$	85
Citronellol	$PyHCrO_3{\cdot}Cl$	82[b]
2-Octyn-1-ol	$PyHCrO_3{\cdot}Cl$	84[b]

[a] Recovered alcohol (58%). [b] Taken from ref 7.

not in as high yields. The acetylenic alcohols which fail to yield carbonyl by our oxidation procedure have not been reported to yield carbonyls by other methods.

Steroidal Alcohols (Table III). The oxidation of steroidal alcohols by Me_2SO–*N*,*N*-dicyclohexylcarbodiimide (Moffatt oxidation) has been examined extensively[14–16] and will not be discussed further. Oxalyl chloride–Me_2SO gives almost quantitative oxidation of cholesterol and stigma sterol without isomerization (5-en-3-one products). The absence of the 4-en-3-one isomers was confirmed by the absence of the α,β-unsaturated carbonyl band in the infrared spectrum of the products. Ergosterol gives a 90% yield of carbonyl products whose composition is not the same under three sets of presumably identical oxidation conditions. The 4,6-dien-3-one, 4,7-dien-3-one and 5,7-dien-3-one isomerization mixture is known to be light and moisture sensitive and extremely prone to isomerization. The 5,7-dien-3-one is very difficult to obtain regardless of the oxidation method. It has previously been reported in admixture with the 4,7-dien-3-one.[17] The oxalyl chloride–Me_2SO oxidation has been used by us[11] to oxidize β,γ-unsaturated alcohols to the corresponding β,γ-unsaturated carbonyls without isomerization to the α,β-unsaturated carbonyls.

Comparison of Oxidation Methods. We used pyridinium chlorochromate[7] ($PyHCrO_3{\cdot}Cl$) to oxidize 1-tetradecanol and 1-octadecanol for comparison with the oxalyl chloride–Me_2SO and TFAA–Me_2SO procedures. Unoxidized alcohol is not recovered in this procedure and yields of the carbonyls are comparable but somewhat lower than with oxalyl chloride–Me_2SO. The pyridinium chlorochromate reagent has the advantage of being operable at room temperature, however, but its versatility, scope, and limitations have not been totally explored.[7]

Pyridine–SO_3–Me_2SO[12] at room temperature was also used as an oxidant by us; it does not give as good yields of long-chain carbonyls as does oxalyl chloride–Me_2SO.

The results obtained in the oxidation of several long-chain alcohols by $PyHCrO_3{\cdot}Cl$ and Py–SO_3–Me_2SO are summarized in Table V.

Experimental Section

Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. IR spectra were obtained using a Pye Unicam SP1000 spectrometer. A Varian Aerograph Series 2100 gas chromatograph with a flame-ionization detector and a 4 ft × 0.125 in. column packed with 8% SE-30 on Chromosorb P was used in the analysis of oxidations of long-chain alcohols (C_8 or greater; N_2 was the carrier gas). Occasionally a 6 ft × 0.25 in. column packed with 10% FFAP on Chromosorb P in a Varian A-90 P-3 gas chromatograph with a thermal conductivity detector was used; He was the carrier gas. Me_2SO was distilled from calcium hydride under reduced pressure and the heart cut was stored over Linde Molecular Sieves Type 3A in a sealed brown bottle. Purest grades of alcohols were purchased and purified, if necessary; purity exceeded 98% in most cases. Oxalyl chloride and other acid halides for "activation" of Me_2SO were freshly distilled and stored over Linde Molecular Sieves Type 3A in sealed brown bottles under N_2. Trifluoroacetic anhydride, gold label, pyridinium chlorochromate, and pyridine–sulfur trioxide were used as received from Aldrich Chemical Co. Amines were distilled from calcium hydride or sodium, and the heart cuts were retained and stored over Linde Molecular Sieves Type 3A or sodium. Authentic samples of carbonyls were purchased. Methylene chloride was distilled from phosphorus pentoxide and stored over Linde Molecular Sieves Type 4A. Glassware was dried in an oven just before use. A sample of 1-pentyn-5-ol was generously supplied by Dr. Grant R. Krow, Temple University and a sample of linoleyl alcohol was generously supplied by Applied Science Laboratories, State College, Pa.

Oxidation of Alcohols to Carbonyls by Oxalyl Chloride–Me_2SO. Procedure A. General Procedure. A solution of CH_2Cl_2 (25 mL) and oxalyl chloride (1.0 mL, 11 mmol) was placed in a 100-mL four-neck round-bottom flask equipped with an overhead mechanical stirrer, a thermometer, a $CaSO_4$ drying tube, and two pressure-equalizing dropping funnels containing Me_2SO (1.7 mL, 22 mmol) dissolved in CH_2Cl_2 (5 mL) and the alcohol (10 mmol in 10 mL of CH_2Cl_2 or a minimum amount of CH_2Cl_2–Me_2SO to dissolve the alcohol), respectively. The Me_2SO was added to the stirred oxalyl chloride solution at −50 to −60 °C. The reaction mixture was stirred for 2 min and the alcohol was added within 5 min; stirring was continued for an additional 15 min. TEA (7.0 mL, 50 mmol) was added and the reaction mixture was stirred for 5 min and then allowed to warm to room temperature. Water (50 mL) was then added and the aqueous layer was reextracted with additional $CHCl_2$ (50 mL). The organic layers were combined, washed with saturated NaCl solution (100 mL), and dried over anhydrous $MgSO_4$. The filtered solution was concentrated in a rotary evaporator to 25 mL. A 5-mL solution was used for GLC analysis; a 10-mL portion was used for characterization of carbonyls as their 2,4-DNP derivatives. The remaining 10-mL portion was washed successively with dilute HCl (1%), water, dilute Na_2CO_3 (5%), and water and evaporated to dryness to give a slightly colored crude carbonyl which was frequently pure without further workup. IR and NMR spectra of the crude products were identical with those of authentic samples of the carbonyls. Melting points of crude derivatives agreed well with the literature values. In some cases, derivatives and carbonyls were recrystallized.

Procedure D. This procedure is identical to procedure A except (a) $(COCl)_2$ (2 mL, 22 mmol) and Me_2SO (3.4 mL, 48 mmol) were used and (b) the alcohol (10 mmol) was added at −10 °C and the reaction temperature was maintained for 15 min.

Oxidation of Alcohols to Carbonyls by TFAA–Me_2SO. This procedure has already been reported by us.[9,10]

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Resolution of Trishomocubanone: The Enantiomeric (D_3)-Trishomocubanes

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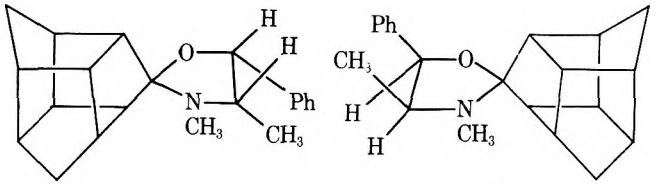
The resolution of trishomocubanone and the preparation of the enantiomeric (D_3)-trishomocubanes (pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane) are reported. Absolute configurations are assigned.

(D_3)-Trishomocubane is a saturated pentacyclic cage compound containing neither cyclobutane nor cyclopropane rings.[1] It is very probably the most stable member of the saturated set of compounds of formula $C_{11}H_{14}$.[2] The carbon skeleton is made up of fused five-membered rings and is intrinsically chiral. Its D_3 point group symmetry is exceedingly rare in organic compounds.[3] In complement to our initial synthesis of this system,[1c] we report now preparation of the enantiomeric (D_3)-trishomocubanes and assignment of absolute configuration. Our results agree nicely with those reached by other methods and published during the course of our work.[4]

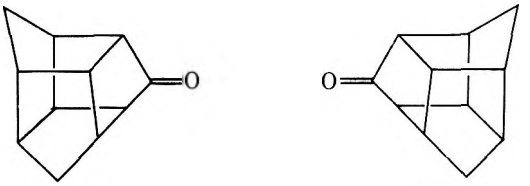
Racemic trishomocubanone (**1a,b**) is readily available by simple chemical transformations of the Diels–Alder adduct of cyclopentadiene to *p*-benzoquinone, as we have reported elsewhere.[1c] Reaction of the racemic ketone with *l*-ephedrine, available commercially, gives the mixture of isomers **2a,b** from which the individual diastereomers can be separated easily by fractional crystallization from methanol. The separation is monitored conveniently by ^{1}H NMR. The benzylic proton resonances of the isomers are cleanly resolved at 270 MHz: that of isomer mp 104–105 °C is at δ 5.08 ppm (d, J = 7 Hz); that of isomer mp 88–89 °C is at δ 5.20 ppm (d, J = 7 Hz). Other interesting differences in the ^{1}H NMR spectra of the diastereomers can be noted from the data in the Experimental Section.

Acid hydrolysis of the separated diastereomers **2a** and **2b** gives the enantiomeric ketones: **1a**, (−)-trishomocubanone,



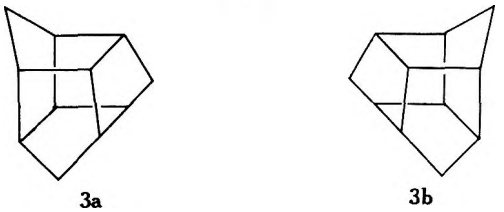
2a **2b**

l-ephedrine ⇕ water, acid



1a **1b**

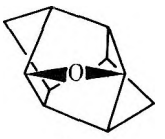
hydrazine, KOH, heat ↓



3a **3b**

mp 162–163 °C, $[\alpha]^{20}_D$ −98.8° (cyclohexane) from the higher melting diastereomer; and **1b**, (+)-trishomocubanone, mp 162–163 °C, $[\alpha]^{20}_D$ +98.8° from the lower melting diastereomer.

As has been shown,[5] the absolute configuration of polycyclic ketones can be derived from the sign of the CD curve for their n–π^* absorption by proper application of the octant rule. In the case at hand, examination of the "outer ring"[6] in a projection of **1a** in which the carbonyl group is held at the "point



1a

of twist"[7] leads to prediction of a positive Cotton effect for this enantiomer. As it turns out, negatively rotating trishomocubanone exhibits a positive CD absorption at 293 nm, [θ] +6.58 × 10^3, and is thus assigned absolute configuration **1a**, (3*S*)-trishomocubanone.[4]

Wolff–Kishner reduction of the enantiomeric trishomocubanones using standard Huang-Minlon conditions gives the corresponding hydrocarbons in excellent yield. Negatively rotating ketone **1a** gives (−)-(D_3)-trishomocubane (**3a**): mp 148–149 °C; $[\alpha]^{20}_D$ −162° (cyclohexane). Positively rotating ketone gives (+)-(D_3)-trishomocubane (**3b**): mp 148–149 °C; $[\alpha]^{20}_D$ +162°. Thus, (−)-(D_3)-trishomocubane is of absolute *S* configuration at position 3; the configuration at each of the other chiral centers follows by symmetry. Correspondingly, (+)-(D_3)-trishomocubane is 3*R*.

Experimental Section

^{1}H NMR spectra were recorded at 270 MHz of solutions in $CDCl_3$ and are referenced to internal tetramethylsilane. Melting points are not corrected. Optical rotations were taken for solutions in cyclohexane in a thermostated 1-dm cell using a Perkin-Elmer Model 141 digital polarimeter. Circular dichroism measurements were performed using a Cary Model 60 spectropolarimeter.

Preparation and Separation of 2a and 2b. Racemic trishomocubanone[1c] (pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecan-4-one, 430 mg) and *l*-ephedrine (Aldrich Chemical Co., 460 mg) were heated together for 72 h in benzene (25 mL) refluxing beneath a Dean–Stark trap. The solvent was then removed under vacuum on a rotary evaporator leaving a clear oil (810 mg) which was taken up in methanol. The diastereomers were obtained separate and pure by fractional crystallization. Two crops of the higher melting isomer **2a** (260 mg, 63%) were taken: clear cubes; mp 104–105 °C; ^{1}H NMR δ 7.3–7.1 (5 H), 5.08 (1 H, d, J = 7 Hz), 3.58 (1 H, p, J = 7 Hz), 2.62 (1 H, m), 2.53 (3 H, s), 2.50 (1 H, m), 2.34 (1 H, sym m), 2.3–2.1 (4 H, m), 2.0 (1 H, m), 1.48 (2 H, d, $J \sim 10$ Hz), 1.36 and 1.32 (1 H each, overlapping d, $J \sim 10$ Hz), 0.84 ppm (3 H, d, J = 7 Hz). Further concentration of the mother liquor gave isomer **2b** (200 mg, 49%): white needles; mp 88–89 °C; ^{1}H NMR δ 7.3–7.1 (5 H), 5.20 (1 H, d, J = 7 Hz), 3.64 (1 H, p, J = 7 Hz), 2.83 (1 H, m), 2.58 (3 H, s), 2.47 (1 H, m), 2.2–2.0 (6 H, m), 1.53 and 1.49 (1 H each, overlapping d, $J \sim 9$ Hz), 1.40 and 1.36 (1 H each, overlapping d, $J \sim 9$ Hz), 0.93 ppm (3 H, d, J = 7 Hz).

(−)- and (+)-Trishomocubanone. The high-melting diastereomer **2a** (230 mg) was dissolved in a mixture of benzene (5 mL), water (0.5 mL), and methanesulfonic acid (3 drops). The mixture was refluxed overnight. Water was added; the aqueous phase was separated and

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extracted three times with chloroform. The extract was combined with the original organic phase and concentrated in vacuo. The solid residue was sublimed (40 °C (0.5 Torr)) to give (−)-trishomocubanone, **1a** (98 mg, 81%), of good purity: mp 162–163 °C; α^{20}_D −1.211 ± 0.002°; $[\alpha]^{20}_D$ −98.8°; CD (*c* 0.0355, cyclohexane) $[\theta]$ 0 (340), +6.58 × 10^3 (293), 0 (240 nm); lit.[4] mp 159 °C, $[\alpha]^{20}_D$ −99.1°.

A similar procedure produced the enantiomeric ketone **1b**: mp 162–163 °C; α^{20}_D +0.355 ± 0.002°; $[\alpha]^{20}_D$ +98.8°; CD (C 0.0298, cyclohexane) $[\theta]$ 0 (330), −6.48 × 10^3 (293), 0 (240 nm).

(−)- and (+)-(D_3)-Trishomocubane. A mixture of resolved ketone **1a** (60 mg), hydrazine hydrate (85%, 1 mL), and triethylene glycol (2.5 mL) was refluxed for 10 min and then cooled. Potassium hydroxide pellets (200 mg) were added, and the mixture was heated vigorously. The clear distillate was collected until the pot residue charred. The distillate was extracted thoroughly with pentane. The extract was washed with dilute hydrochloric acid, followed by water, and then dried. The solvent was blown off in a slow stream of nitrogen. The white residue was sublimed (25 °C (80 Torr)) to give (−)-(D_3)-trishomocubane (**3a**, 48 mg, 88%): mp 148–149 °C; α^{20}_D −0.694 ± 0.002°; $[\alpha]^{20}_D$ −162°; lit.[4] mp 149 °C, $[\alpha]^{20}_D$ −164°.

Similarly, (+)-(D_3)-trishomocubane (**3b**) was obtained: mp 148–149 °C; α^{20}_D +0.571 ± 0.002°; $[\alpha]^{20}_D$ +162°.

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Registry No.—**1a**, 61473-76-5; **1b**, 61473-82-3; **2a**, 65957-38-2; **2b**, 66007-13-4; **3a**, 61473-77-6; **3b**, 61473-83-4; (±)-trishomocubanone, 66007-14-5; *l*-ephedrine, 299-42-3.

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Cyclophanes. 9. Dibenzo[*def,pqr*]tetraphenylene: A Benzoannulated Cyclooctatetraene Composed of Orthogonal Aromatic Systems[1]

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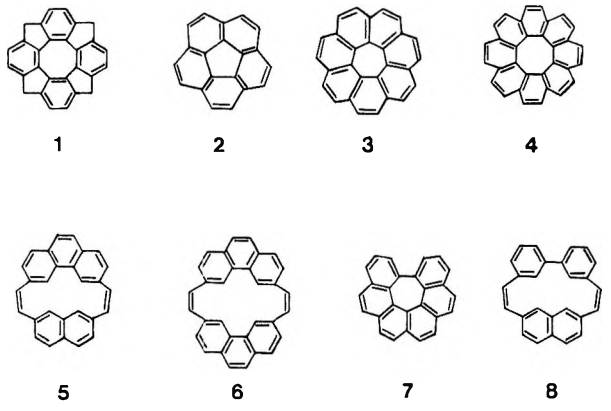
2,17-Dithia[3.3](3,3′)biphenylophane (**10**) was prepared from the coupling of 3,3′-bis(bromomethyl)biphenyl and 3,3′-bis(mercaptomethyl)biphenyl. Bridge contraction to generate the bis(methylthio) ether **14** and subsequent oxidation gave the disulfoxide **15** which undergoes thermal elimination of methylsulfenic acid to yield [2.2](3,3′)-biphenylophane-1,15-diene (**9**). Oxidative photocyclization of the diene **9** gave dibenzo[*def,pqr*]tetraphenylene (**13**), an analogue of [8]circulene. Raney nickel desulfurization of the disulfoxide **15** or thermal elimination of sulfur dioxide from the disulfone **12** produced the [2.2](3,3′)biphenylophane (**16**), which has a preferred anti geometry which is in contrast to the syn geometry of the corresponding diene **9**.

Recent investigations of the class of compounds known as circulenes[2] have provided information on the chemical and physical properties of fused aromatic macrocycles incorporating benzene, furan, and thiophen systems. Coronene or [6]circulene,[3] a tetraoxo[8]circulene,[4] a tetramethano-*o*-tetraphenylene **1**,[5] and several thia[7]circulenes[6] have provided the basis for these investigations. There is considerable interest in the fully carbocyclic aromatic molecules which are expected to be considerably more distorted from planarity than the abovementioned examples. Compounds in this category include corannulene or [5]circulene (**2**),[7] which has been shown by x-ray structure determination[8] to be bowl shaped, and the unreported higher homologs, [7]circulene (**3**) and [8]circulene (**4**). Unsuccessful attempts to synthesize these latter two compounds by the oxidative photochemical cyclization of the cyclophane dienes **5** and **6** have been recorded by ourselves[1] and others.[9] Unlike the bowl-shaped [5]circulene, [7]- and [8]circulene are expected, on the basis of molecular models, to have saddle-shaped geometries similar to that predicted for the hexa[7]circulene (**7**), which has been prepared from the corresponding cyclophane diene **8**.[10]



We wish to report the synthesis of [2.2](3,3′)biphenylophane-1,15-diene (**9**) from its corresponding dithiacyclophane **10** and the successful photochemical cyclization to give dibenzo[*def,pqr*]tetraphenylene (**13**), which may be regarded as a cyclooctatetraene composed of two orthogonal phenanthrylene moieties. Thulin and Wennerstrom[11] have recently reported the synthesis of the title compound **13** by an alternative, shorter, albeit lower yielding route.

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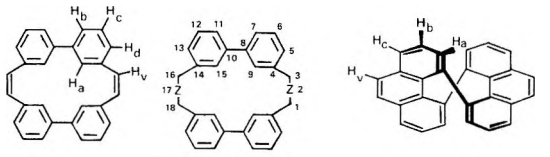
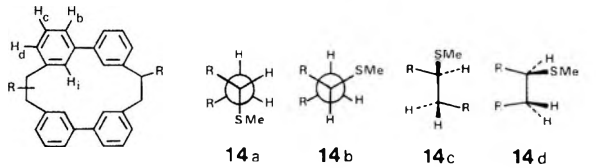


9 10 Z = S 11 Z = $\overset{+}{S}MeBF_4^-$ 12 Z = SO_2 13



14a 14b 14c 14d

14 R = SMe
15 R = SOMe
16 R = H

R = Biphenylyl

Results and Discussion

2,17-Dithia[3.3](3,3′)biphenylophane (**10**),[12] a compound having poor solubility properties, was prepared under high-dilution conditions by the addition with a mechanical syringe drive[13] of a solution of 3,3′-bis(bromomethyl)biphenyl[14] and 3,3′-bis(mercaptomethyl)biphenyl to a large volume of refluxing basic ethanol. Methylation of compound **10** with dimethoxycarbonium tetrafluoroborate[15] in dichloromethane gave a quantitative yield of the salt **11**, and on treatment with sodium hydride in tetrahydrofuran (Stevens rearrangement conditions), the salt **11** gave rise to the bridge contracted bis(methylthio) ether **14** in high yield, as a mixture of structural isomers and stereoisomers. The ^{13}C-NMR spectrum of **14** showed a singlet at δ 15.2 (SMe), lines at 44.4 and 44.7 (β-benzylic C), resonances at 54.0 and 54.6 (α-benzylic C), as well as aromatic resonance peaks at 125.1–140.8. These data are consistent with the presence of axial and equatorial isomers of the type **14a** and **14b** (showing only one bridge) in approximately equal distribution. This would imply a statistical distribution of the six possible structural isomers.

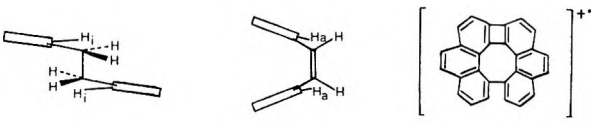
The ^1H-NMR spectrum of **14** showed four singlets at δ 2.04–2.08 (SMe), multiplets at 2.55–4.18 (benzylic H), broad singlets at 5.79–6.10 (internal aromatic protons H_i, 2 H) and a multiplet at 6.10–7.68 (aromatic H, 14 H). The presence of four separate methyl resonances, internal shielded protons, and the integral ratio of the aromatic protons suggests that compound **14** consists of approximately equal quantities of the syn and anti isomers **14c** and **14d**. The ^1H-NMR spectra of **14** remained unchanged up to a temperature of 178 °C indicating a conformational energy barrier ($\Delta G^{\ddagger}$) of at least 100 kJ between the syn and anti forms.

Although there are several established methods for the ring contraction of dithia[3.3]cyclophanes, it has been our experience that the success of a particular method is dependent on the nature of the cyclophane being investigated. An attempt to ring contract the cyclophane **10** under Wittig rearrangement conditions after the method of Boekelheide[16] (treatment with *n*-butyllithium followed by methyl iodide) was only partially successful and gave low yields of the desired product.

Oxidation of the cyclophane **14** with *m*-chloroperbenzoic acid at 0 °C gave the disulfoxide **15** in high yield, again as a mixture of structural isomers and stereoisomers which was confirmed by the ^{13}C-NMR and ^1H-NMR spectra of the product. The mass spectrum (30–70 eV) of the disulfoxide **15** showed no molecular ion. The ion of highest mass was observed at *m/e* 356 indicating a facile thermal loss of two sulfoxide functions.

Pyrolysis of the disulfoxide **15** at 300 °C (8×10^{-4} mm) gave a good yield of [2.2](3,3′)biphenylophane-1,15-diene (**9**). The ^1H-NMR spectrum of **9** showed the vinylic protons H_v as a singlet at δ 6.60 and the aromatic protons H_a–H_d as the expected group of multiplets at δ 6.6–7.6, and its ^{13}C-NMR spectrum showed the expected five singlets for the tertiary C's and two singlets for the quaternary C's. A mass spectrum of compound **9** exhibited a stepwise and facile loss of four mass units from the molecular ion to give presumably the radical cation of the dibenzotetraphenylene **13**.

[2.2](3,3′)Biphenylophane (**16**), a related compound with saturated C_2 bridging functions, was prepared in high yield by hydrogenolysis of the disulfoxide **15** with Raney nickel in refluxing ethanol. The cyclophane **16** was also prepared in low yield (<10%) by the pyrolysis (600 °C (8×10^{-4} mm)) of the disulfone **12**, in turn obtained from the oxidation of compound **10** with excess hydrogen peroxide. The yield of product from the pyrolysis reactions could be increased to 70% by effecting the reaction at 500 °C (100 mm), conditions which ensured that the thermal elimination reaction preceded sublimation of the disulfone. The ^1H NMR, ^{13}C NMR, and mass spectra confirmed the structure of the cyclophane **16**. In particular,



16a 9a a

its ^1H NMR spectrum showed resonances at δ 2.86 (methylene CH_2) and 5.96 (dt, J = 1.7 and 0.7 Hz; internal aromatic H_i) and a multiplet at 6.97–7.25 (aromatic H). This observed upfield shift of the internal protons indicated that the cyclophane **16** assumes a preferred anti geometry **16a**. In contrast, the ^1H-NMR spectrum of the diene **9** showed the equivalent "internal" protons, H_a, at δ 7.62 implying a syn geometry **9a**. Comparison of the UV absorption spectrum of the diene **9** (λ_{max} 213, 243, and 282 nm) with those of *cis*- and *trans*-stilbene also supports a cis configuration about the carbon–carbon double bonds and hence a syn geometry. Molecular models suggest that the syn geometry of the diene **9a** would be much less strained than the alternative anti form.

Irradiation of a solution of the diene **9** in cyclohexane with a mercury–quartz lamp in the presence of iodine as an oxidant afforded dibenzo[*def,pqr*]tetraphenylene (**13**) in an overall yield of 15% from the bis(mercaptomethyl)biphenyl precursor. The structure of **13** was confirmed by the usual spectral methods. In particular, the ^1H-NMR spectrum of **13**, a typical AMX spectrum, showed a doublet of doublets at δ 6.63 (J = 7.3 and 1.2 Hz) which were assigned to the H_a proton. We attribute this upfield shift of the H_a proton to the shielding of the opposite aromatic ring system, which has also been noted.[11] The two phenanthrene moieties in compound **13** are most probably orthogonal and such a structure is supported by simple molecular models. The UV absorption spectrum of **13** is similar to that of phenanthrene (Figure 1) but the spectrum shows a bathochromic shift of both the p band (295 to 317 nm) and the α band (345 to 361 nm), which is in accord with the proposed structure having a limited amount of interaction between the two constituent aromatic systems. The ^{13}C-NMR spectrum of **13** was consistent for an aromatic structure containing four tertiary and three quarternary C's. The mass spectrum of **13** showed a facile loss of two hydrogens from the molecular ion which we did not anticipate ($M^+ - 1$, 95%; $M^+ - 2$, 100% of the intensity of M^+). This may indicate the formation of a new C–C bond between two of the phenanthrene moieties to generate the radical cation a. The apparent stability of such a species in the gas phase is intriguing and we are pursuing the parent structure.

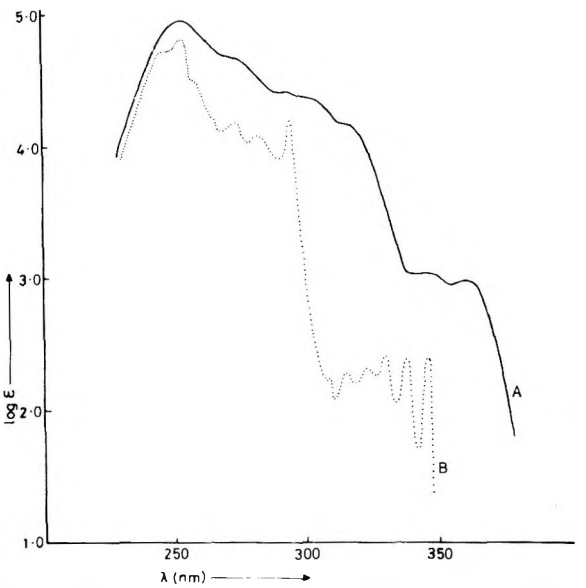


Figure 1. UV absorption spectra (C_6H_{12}) of: (A) dibenzo[*def*,*pqr*]-tetraphenylene (**13**) and (B) phenanthrene.

The successful photochemical closure of cyclophane dienes containing biphenyl moieties (e.g., **8** → **7**[10] and **9** → **13**) is in direct contrast to the lack of reactivity of cyclophanes **5** and **6** which contain phenanthrene units. This is probably due to the increased flexibility in the biphenyl which allows the cyclophane diene to attain the required transition state geometry for the photochemical ring closure and also decreases the strain due to nonplanarity in the final cyclized product. Although a considerable number of polycyclic aromatic compounds have been synthesized from the appropriate cyclophane dienes, it now appears that a synthetic pathway to [7]- and [8]circulene (**3** and **4**) employing the dienes of the type **5** and **6** as intermediates is unlikely to be successful.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 257 spectrophotometer. Mass spectra were determined with a JEOL JMS D-100 double-focusing spectrometer. Proton and carbon magnetic resonance spectra were obtained with a JEOL PS-100 PFT spectrometer operating at 100 and 25 MHz, respectively. Both proton and carbon chemical shifts (δ) are recorded in ppm from $SiMe_4$. Ultraviolet absorption spectra were recorded with a Varian Techtron 635 spectrometer. Microanalyses were carried out by the Australian Microanalytical Service, Melbourne.

(a) 3,3′-Bis(mercaptomethyl)biphenyl. 3,3′-Bis(bromomethyl)biphenyl[14] (10.0 g; 29.4 mmol) and thiourea (4.47 g; 58.8 mmol) were heated under reflux in water (50 mL) for 2 h. To the clear solution was added sodium hydroxide (2.35 g; 58.8 mmol) in water (10 mL) and heating was continued for another 2 h. The solution was cooled, acidified with concentrated hydrochloric acid, and extracted with ether. The ether extracts yielded 3,3′-bis(mercaptomethyl)-biphenyl (6.0 g, 81%) as white plates (EtOH): mp 54–55 °C; ^{1}H NMR ($CDCl_3$) δ 1.78 (t, J = 7.6 Hz, 2 H, exchanged with D_2O), 3.74 (d, J = 7.6 Hz, 4 H), and 7.23–7.50 (m, 6 H, aromatic H); ^{13}C NMR ($CDCl_3$) δ 29.0 (CH_2), 125.9, 126.9, 127.1, 129.1 (tertiary C), 141.3, 141.6 (lower intensity, quaternary C); mass spectrum (75 eV) $M^+ + 2$ at m/e 248 (7% rel intensity), $M^+ + 1$ 247 (10), M^+ 246.0537 (54) [$C_{14}H_{14}S_2$ requires 246.0537], and fragmentation ions at 215 (22), 214 (100), 180 (27), and 165 (22). Anal. Calcd for $C_{14}H_{14}S_2$: C, 68.24; H, 5.69; S, 26.05. Found: C, 67.94; H, 5.75; S, 25.7.

(b) 2,17-Dithia[3.3](3,3′)biphenylophane (10). 3,3′-Bis(bromomethyl)biphenyl (3.4 g; 10 mmol) and 3,3′-bis(mercaptomethyl)-biphenyl (2.46 g; 10 mmol) were dissolved in benzene (200 mL) and added dropwise to refluxing basic ethanol (NaOH, 0.88 g; 20 mmol dissolved in 2 L) with syringe drives over 7 h. After refluxing for a further 18 h, the solvents were evaporated and the residue was extracted with toluene. Chromatography on alumina with toluene at 100 °C (using a jacketed glass column) gave, as the single major product, 2,17-dithia[3.3](3,3′)biphenylophane (**10**) (3.4 g; 74%) as white prisms (toluene): mp 266–268 °C; mass spectrum (75 eV) $M^+ + 2$ at m/e 426 (14% rel intensity), $M^+ + 1$ 425 (24), M^+ 424.1318 (69%) [$C_{28}H_{24}S_2$ requires 424.1319], and fragmentation peaks at 243 (16), 212 (41), 211 (33), 183 (22), 182 (100), 181 (53), 180 (22), and 165 (43); ^{1}H NMR ($AsCl_3$) δ 3.7 (bs, 2 H), and 7.2–7.5 (m, 4 H); ^{13}C NMR ($AsCl_3$) δ 33.7 (benzylic C), 124.9, 126.0, 127.4, 128.6 (tertiary C), 136.6, 138.7 (quaternary C). Anal. Calcd for $C_{28}H_{24}S_2$: C, 79.26; H, 5.66; S, 15.09. Found: C, 79.32; H, 5.92; S, 14.8.

(c) Bis(methyl tetrafluoroborate) Salt (11) of Cyclophane (10). Cyclophane **10** (1.0 g, 2.36 mmol) in dry dichloromethane (100 mL) was treated with dimethoxycarbonium tetrafluoroborate[15] (1.0 g, excess) at room temperature with stirring for 18 h. Ethanol was added and the precipitated product was filtered, washed with dichloromethane, and dried to yield 2,17-bis(methylsulfonium)[3.3](3,3′)-biphenylophane (**11**) in quantitative yield as a white powder, mp > 300 °C (a phase change occurred at 185 °C). The product was used without further purification.

(d) Stevens Rearrangement of the Salt 11. The bis(methylsulfonium) salt **11** (1.3 g; 2.0 mmol) was suspended in dry THF (100 mL) with excess sodium hydride and the mixture was stirred under nitrogen at room temperature for 4 days. Water (100 mL) was carefully added and the mixture was extracted with chloroform. The combined extracts were washed, dried, and evaporated to yield a mixture of the structural isomers and stereoisomers of bis(methylthio)[2.2](3,3′)-biphenylophane (**14**) (630 mg, 67%) as a pale yellow glass: mp 82–92 °C; mass spectrum $M^+ + 2$ at m/e 454 (4% rel intensity) $M^+ + 1$ 453 (10), M^+ 452.1632 (27) [$C_{30}H_{28}S_2$ requires 452.1632], and major fragmentation peaks at 423 (9), 422 (20), 322 (29), 210 (38), 182 (62), 181 (62), 179 (43), 178 (62), 166 (43), and 165 (100); ^{1}H NMR ($CDCl_3$) δ 2.04–2.08 (four singlets, 3 H, Me), 2.55–4.18 (m, 3 H, benzylic H), 5.79–7.68 (m, 8 H, aromatic); ^{13}C NMR ($CDCl_3$) δ 15.2 (SMe), 44.4, 44.7 (β-benzylic C), 54.0, 54.6 (α-benzylic C), 124.7–140.9 (aromatic C). Anal. Calcd for $C_{30}H_{28}S_2$: C, 79.58; H, 6.25; S, 14.17. Found: C, 79.34; H, 6.19; S, 13.8.

(e) Bis(methylthio)[2.2](3,3′)biphenylophane *S*,*S*′-Dioxide (15). The cyclophane **14** (200 mg; 0.44 mmol) and *m*-chloroperbenzoic acid (153 mg; 0.88 mmol) were dissolved in chloroform (50 mL) at 0 °C and the solution was stirred for 18 h at room temperature. The solution was extracted with a phosphate/citric acid buffered solution (pH 7.6) and water, dried over anhydrous $MgSO_4$, and concentrated. Bis(methylthio)[2.2](3,3′)biphenylophane *S*,*S*′-dioxide (**15**) (190 mg, 89%) was obtained as a yellow glass: mp 173–175 °C; IR ($CHCl_3$) ν_{max} 1050 cm^{-1} (strong, sharp, S=O); ^{1}H NMR ($CDCl_3$) δ 2.43–2.83 (m, Me), 3.37–3.91 (m, benzylic H), 5.90–7.30 (m, aromatic); ^{13}C NMR ($CDCl_3$) 37.5 (m, Me and β-benzylic C), 72.9 (m, α-benzylic C), 125.0–142.4 (aromatic C); mass spectrum (10–75 eV) showed only fragmentation peaks at m/e 358 (11% rel intensity), 357 (42), 356 (100), 206 (33), 192 (83), 179 (24), 178 (65), 165 (38), and 152 (32). A satisfactory elemental analysis could not be obtained.

(f) [2.2](3,3′)Biphenylophane-1,15-diene (9). The disulfoxide **15** (170 mg; 0.35 mmol) was heated in a silica tube at 320 °C (8×10^{-4} mm). The product which sublimed to the cold portion of the tube was collected. Chromatography on alumina with cyclohexane gave a single major band which yielded [2.2](3,3′)biphenylophane-1,15-diene (**9**) (70 mg, 56%) as white needles (EtOH): mp 124–125 °C [lit.[11] mp 113–115 °C]; mass spectrum $M^+ + 2$ at m/e 358 (17% rel intensity), $M^+ + 1$ 357 (35), M^+ 356.1565 (91) [$C_{28}H_{20}$ requires 356.1565], and fragmentation ions at 355 (10), 354 (10), 353 (10), 352 (10), 351 (10), 350 (10), 208 (59), 193 (67), 182 (80), 179 (48), 178 (67), 168 (48), and 166 (100); ^{1}H NMR ($CDCl_3$) δ 6.6–7.6 (m); ^{13}C NMR ($CDCl_3$) δ 127.1, 127.9, 128.5, 128.9, 130.1 (tertiary C), 136.4, and 142.5 (lower intensity, quaternary C); UV (C_6H_{12}) λ_{max} 213 nm (log ϵ 4.74), 243 sh (4.51), and 282 sh (4.28). Anal. Calcd for $C_{28}H_{20}$: C, 94.34; H, 5.66. Found: C, 94.25; H, 5.87.

(g) Dibenzo[*def*,*pqr*]tetraphenylene (13). The cyclophane diene **9** (80 mg; 0.22 mmol) dissolved in spectroscopic grade cyclohexane (85 mL) with a small quantity of iodine was irradiated for 3.5 h with a Philips 125-W high-pressure mercury-quartz lamp in a water-cooled photochemical reactor. The solution was stirred during the irradiation and the course of the reaction was monitored by determining the UV–visible absorption spectra. The solvent was evaporated and the product was chromatographed on alumina with cyclohexane as eluent to yield dibenzo[*def*,*pqr*]tetraphenylene (**13**) (50 mg, 63%) as white prisms (EtOH): mp 258–260 °C [lit.[11] mp 262–263 °C]; mass spectrum (75 eV) $M^+ + 2$ at m/e 354 (5% rel intensity), $M^+ + 1$ 353 (36), M^+ 352.1258 (100) [$C_{28}H_{16}$ requires 352.1252] and fragmentation peaks at 351 (91), 350 (100), 175 (68), 173 (45); ^{1}H NMR ($CDCl_3$) δ 6.62 (dd, J = 7.3 and 1.2 Hz, H_a), 7.39 (t, overlapping doublets, J = 7.3 and 7.8 Hz, H_b), 7.66 (s, H_v), 7.79 (dd, J = 7.7 and 1.3 Hz, H_c); ^{13}C NMR

($CDCl_3$) δ 126.0, 126.2 (2 C), 130.9 (tertiary C), 131.2, 132.0, 142.2 (lower intensity, quaternary C); UV (C_6H_{12}) λ_{max} 254 nm (log ε 4.94), 273 sh (4.66), 294 sh (4.40), 304 sh (4.32), 317 sh (4.14), 346 sh (3.02), and 361 sh (2.96). Anal. Calcd for $C_{28}H_{16}$: C, 95.42, H, 4.58. Found: C, 94.84, H, 4.74.

(h) 2,17-Dithia[3.3](3,3')biphenylophane *S,S,S',S'*-Tetroxide (12). The dithiacyclophane **10** (100 mg; 0.23 mmol) was dissolved in toluene (100 mL) and acetic acid (20 mL) and brought to reflux. Hydrogen peroxide (30%, 5 mL, excess) was added dropwise and the mixture was heated under reflux for 18 h. The precipitate was filtered, washed with sodium bicarbonate (5% aqueous) and water, and dried to yield 2,17-dithia[3.3](3,3')biphenylophane *S,S,S',S'*-tetroxide (**12**) (90 mg, 84%) as white prisms: mp >300 °C; mass spectrum $M^+ + 2$ at *m/e* 490 (6% rel intensity), $M^+ + 1$ 489 (10), M^+ 488.1116 (24) [$C_{28}H_{24}S_2O_4$ requires 488.1116], and fragmentation ions at 360 (74), 194 (86), 181 (69), 180 (82), 179 (71), 178 (98), 167 (100), and 165 (94); IR (Nujol mull) ν_{max} 1120, 1320 cm^{-1} (strong, sharp, $-SO_2-$). Anal. Calcd for $C_{28}H_{24}S_2O_4$: C, 68.85; H, 4.92; S, 13.12. Found: C, 68.48; H, 4.89; S, 13.0.

(i) [2.2](3,3')Biphenylophane (16). (A) Freshly prepared W-2 Raney Nickel[17] (0.5 g) was added to a solution of the disulfoxide **15** (100 mg; 0.21 mmol) in ethanol (50 mL) and the mixture was heated under reflux for 3 h. The solution was filtered and concentrated; the residue was chromatographed on alumina to yield [2.2](3,3')biphenylophane (**16**) (50 mg, 67%) as white needles (C_6H_{12}): mp 174–176 °C; mass spectrum $M^+ + 2$ at *m/e* 362 (14% rel intensity), $M^+ + 1$ 361 (32), M^+ 360.1878 (100) [$C_{28}H_{24}$ requires 360.1878], and fragmentation peaks at 178 (23), 177 (36), 176 (23), 175 (27), 166 (27), and 164 (32); ^1H NMR ($CDCl_3$) δ 2.86 (s, 2 H), 5.95 (dt, J = 1.7 and 0.7 Hz, H_i), 6.97 (dt, J = 7 and 1.7 Hz, $H_{b/d}$), 7.13 (dt, J = 7 and 1.7 Hz, $H_{d/b}$), 7.15 (t, J = 7 Hz, H_c); ^{13}C NMR ($CDCl_3$) δ 38.6 (benzylic C), 124.6, 127.0, 128.5, 131.2 (tertiary C), 140.4, 141.3 (lower intensity, quaternary C). Anal. Calcd for $C_{28}H_{24}$: C, 93.33; H, 6.66. Found: C, 93.23; H, 6.59.

(B) The disulfone **12** (80 mg; 0.16 mmol) was heated at 500 °C (100 mm) in a silica tube using a tube-furnace and a slow stream of nitrogen. The product which sublimed was collected and chromatographed on alumina with cyclohexane to yield the cyclophane **16** (40 mg, 68%) identical in all respects to the sample described in (A).

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Registry No.—**9**, 66018-33-5; **10**, 66018-32-4; **11**, 66018-31-3; **12**, 66018-34-6; **13**, 63838-46-0; **14**, 66008-63-7; **15**, 66008-62-6; **16**, 24656-54-0; 3,3'-bis(mercaptamethyl)biphenyl, 66018-35-7; 3,3'-bis(bromomethyl)biphenyl, 24656-53-9; dimethoxycarbonium tetrafluoroborate, 18346-68-4.

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Gas-Phase Photolysis of 1,2,3-Thiadiazoles: Evidence for Thiirene Intermediates

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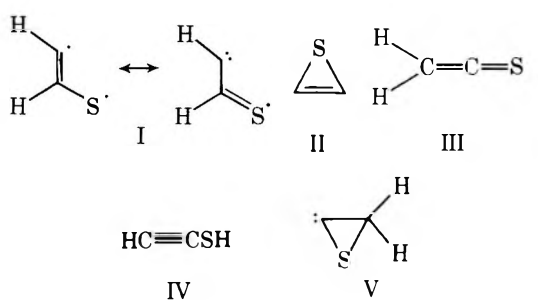
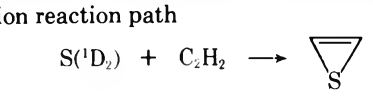
The gas-phase photolyses of 1,2,3-thiadiazole (VIa), 4-methyl-1,2,3-thiadiazole (VIb), and 5-methyl-1,2,3-thiadiazole (VIc) have been studied. Evidence for the formation of thiirene intermediates has been obtained by trapping experiments with hexafluoro-2-butyne. While VIa yields 2,3-bis(trifluoromethyl)thiophene, both isomers VIb and VIc yield only one and the same product, 5-methyl-2,3-bis(trifluoromethyl)thiophene, suggesting a common precursor, namely, methylthiirene.

The question of the existence of thiirenes, the family of unsaturated thiiranes, has only recently been considered. Thiirenes were first postulated as short-lived transients in the addition of $^1D_2$ sulfur atoms to alkynes[1] and in the case of acetylene the following isomeric C_2H_2S structures can be considered:



Flash photolysis experiments with kinetic mass spectrometry[2] have shown the presence of adducts having lifetimes from a tenth to several seconds, depending on the nature of the alkyne. Conventional photolysis of COS, a source of $S(^1D_2)$ atoms, in the presence of alkynes has been shown to yield thiophene, carbon disulfide, benzene, and a solid polymer as end products. The thiophene yield is highest from the $S(^1D_2) + CF_3C{\equiv}CCF_3$ reaction, which makes III, IV, and V unlikely precursors since forth and back migration of CF_3 would be required here and the migrational aptitude of CF_3 is lower than that of H or CH_3 in C_2H_2, $CH{\equiv}CCH_3$, or $CH_3C{\equiv}CCH_3$. Preference for thiirene II as the precursor, compared with thioformyl methylene I, was stated on the basis of preliminary semiempirical MO computations which indicated that the least motion reaction path



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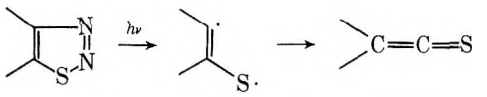
is spin and orbital symmetry allowed and energetically feasible.

1,2,3-Thiadiazoles VI appeared to be the most promising source of compounds for the generation of C_2H_2S isomers. The formation of thioketene in the thermal decomposition of 1,2,3-thiadiazoles has been detected in flash thermolysis,[3] by chemical scavenging experiments, e.g., the thermolysis of VI in ethylene glycol produces thiono esters,[4] and by means of photoelectron spectroscopy.[5] Attempts to trap thiirene II intermediates via complexation with diiron carbonyl catalyst have been unsuccessful,[6,7] but on the other hand two isomeric thioketocarbene I–$Fe_2(CO)_6$ complexes have been isolated[7] from 4,5-substituted VI, indicating the possibility of a common precursor, most probably thiirene II.

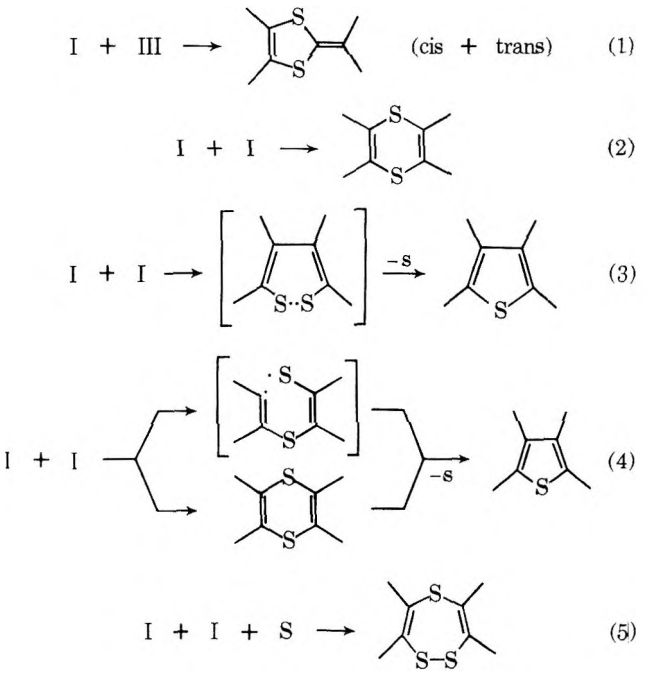
The first reported study of the photolysis of 1,2,3-thiadiazoles is that of Kirmse and Hörner in 1958[8] who described the formation of thiofulvenes upon irradiation of 1,2,3-thiadiazole and several of its derivatives via the reaction of diradical I with thioketene III, presumably formed from the rearrangement of II:



VI I III

Subsequently Huisgen[9] characterized diradical I as a 1,3-dipolarophile which adds preferentially across the C=S bond as compared to C=C or C=N bonds. Since then the photolysis of 1,2,3-thiadiazoles in benzene solution has been extensively studied by Zeller *et al.*[10] Thiofulvenes, thioanthrenes, thiophenes, and 1,2,5-trithiepins were identified as reaction products, formed via self- and cross-combination reactions of I and III (Scheme I). On the other hand, photolysis of VI using unfiltered (λ >290 nm) radiation in an argon matrix at 8 K generates ethynyl mercaptan as well as thioketene.[11] In addition, a photolabile intermediate, which was claimed[12] to be thiirene, is observed upon irradiation with (λ 300 nm) filtered light. Photolysis of matrix-isolated substituted thiadiazoles, however, does not generate ethynyl mercaptans, and when the exciting radiation is filtered (λ 265 nm) new IR spectra are observed which are consistent with the carriers being the corresponding thiirenes II.[13] It was also shown that

Scheme I



I + III → (cis + trans) (1)

I + I → (2)

I + I → (3)

I + I → (4)

I + I + S → (5)

Table I. Gas-Phase Photolysis of VIa, VIb, and VIc[a]

Thiadiazole	Alkyne, %	Methane, %	CS_2, %
VIa	12.6		1.8
VIb	14.4	5.0	3.6
VIc	16.1	4.8	4.8

[a] Percentages are given in terms of N_2.

thiirenes undergo secondary photolysis to yield thioketenes III.

The present study of the gas-phase photolysis of 1,2,3-thiadiazole (VIa), 4-methyl-1,2,3-thiadiazole (VIb), and 5-methyl-1,2,3-thiadiazole (VIc) was therefore undertaken under conditions similar to those used in the COS + acetylene studies in order to examine the effects of radical scavengers and to obtain further chemical evidence for the transient existence of thiirene.

Experimental Section

Apparatus. Standard high-vacuum techniques and apparatus were employed throughout the investigation. The light source was a medium-pressure, mercury arc, Hanovia Model 30620, equipped with a 7910 vycor filter. Photolyses were carried out in a 10 × 4.5 cm quartz cell.

A Varian Aerograph (90P) GC was used for preparation purposes. UV spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer and the NMR spectra were recorded on a Varian Associates Model HR-100 spectrometer using Me_4Si as internal standard. Values are given in τ units. Mass spectra were determined on a Metropolitan Vickers Model MS-2 at an ionization potential of 70 eV.

Materials. 1,2,3-Thiadiazole (VIa) was prepared according to Hurd and Mori[14] as a clear liquid: bp 50–52 °C (14 Torr); ^1H NMR (CCl_4) AB system centered at 1.2; UV $\lambda_{max}^{cyclohexane}$ (ε) 211 (4380), 249 (1460), 294 (195); mass spectrum, *m/e* 86 (11), 58 (100), 57 (19), 45 (6), 44 (6), 32 (9).

4-Methyl-1,2,3-thiadiazole (VIb) was similarly obtained from acetone: bp 57–58 °C (15 Torr); ^1H NMR (CCl_4) 1.8 (q, 1 H), 7.2 (d, 3 H); UV $\lambda_{max}^{cyclohexane}$ (ε) 213 (4820), 258 (1850), 290 (220); mass spectrum, *m/e* 100 (2), 72 (84), 71 (100), 57 (3), 45 (42).

5-Methyl-1,2,3-thiadiazole (VIc) was prepared according to the method of Schmidt *et al.*:[15] bp 65 °C (18 Torr); ^1H NMR (CCl_4) 1.65 (q, 1 H), 7.31 (d, 3 H); UV $\lambda_{max}^{cyclohexane}$ (ε) 217 (5300), 253 (2100), 293 (245); mass spectrum, *m/e* 100 (3), 72 (64), 71 (100), 69 (20), 57 (7), 45 (62).

Hexafluoro-2-butyne (Columbia) was purified by low-pressure vacuum distillation at −130 °C.

Procedure. 1,2,3-Thiadiazoles VIa, VIb, and VIc were introduced in excess into the quartz cell with or without known amounts of hexafluoro-2-butyne. The cell was then immersed in a water bath and kept at 60–65 °C throughout the photolysis (at this temperature the vapor pressures are approximately 21 Torr for VIa and 3 Torr for VIb and VIc) which was carried out for 2 h.

Non-condensable gases were measured in a gas buret and analyzed on a 10-ft medium-activity silica gel column. The alkyne products and CS_2 were recovered in separate distillations and also analyzed on the silica gel column. The remaining fraction condensable at −78 °C was found (10 ft 10% tricresyl phosphate on diatoport, 110 °C) to consist only of unreacted substrate.

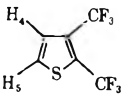
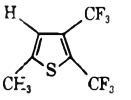
In experiments with added hexafluoro-2-butyne the butyne was distilled out of the reaction mixture and the remainder was analyzed on the tricresyl phosphate column.

Results

Photolysis of 1,2,3-thiadiazoles VIa, VIb, and VIc at λ >220 nm afforded, in addition to N_2, the corresponding alkyne[16] and CS_2; small amounts of methane were also formed from VIb and VIc. The results are summarized in Table I.

Photolysis of VIa in the presence of 200 Torr of hexafluoro-2-butyne afforded 2,3-bis(trifluoromethyl)thiophene (VIIa), identified by its mass (M^+· 220) and NMR spectra, Table II. The positions of protons H_4 and H_5 have been assigned by comparison with those of similarly disubstituted thiophenes.[17,18] Photolysis of either VIb or VIc under the same conditions afforded only 5-methyl-2,3-bis(trifluoromethyl)-

Table II. Photolysis of VIa, VIb, and VIc in the Presence of Hexafluoro-2-butyne

Thiadiazole	Registry no.	Thiophene	Registry no.	Yield,[a] %	NMR[b]	Mass spectrum
VIa	288-48-2		773-61-5	6.7	AB system with fine structure due to long-range coupling with CF_3: H_4 2.72, H_5 2.54 ($J_{4,5}$ 5.4 Hz)	220 (100), 201 (94), 151 (73), 69 (21), 57 (13), 45 (21)
VIb	18212-62-9		55162-36-2	12.3	3.07 (s, 1 H, with fine structure); 7.49 (s, 3 H)	234 (57), 233 (27), 215 (30), 165 (100), 69 (19), 45 (14)
VIc	50406-54-7			12.5		

[a] At 270 Torr pressure of $CF_3C{\equiv}CCF_3$. [b] In CCl_4 solution with Me_4Si as internal standard. Values are given in τ units.

Table III. Yield of 5-Methyl-2,3-bis(trifluoromethyl)thiophene as a Function of the Pressure of Hexafluoro-2-butyne

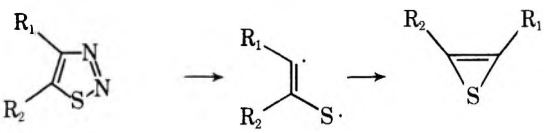
Pressure of C_4F_6, Torr	Yield of VIIb[a] From VIb	From VIc
270	12.3	12.5
600	20.8	30.5
900	23.1	34.0
1200	33.3	37.5

[a] In terms of N_2 produced.

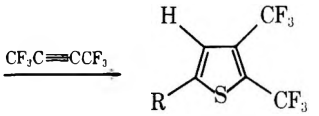
thiophene (VIIb). It was identified as the 5-methyl isomer from its mass spectrum (M^+· 234) and the NMR chemical shifts, Table II, by using the additivity rule and the available data for 2- and 3-methyl-substituted thiophenes.[17,18] Considering as basic values the chemical shift for H_4 and H_5 in VIIa, a methyl group in the 4 position would be expected to shift H_5 to τ 2.99 whereas a methyl group in the 5 position should shift H_4 to τ 3.09. The actual value of 3.07 clearly favors the latter. Similarly, the assignment of the methyl group in VIIb at τ 7.49 to the 5 position is reasonable compared to τ 7.59 for 2-methylthiophene and τ 7.80 for 3-methylthiophene. Moreover, decoupling experiments with VIIb, irradiating it in the methyl position, simplified the H multiplet into a quartet with a J value of 1.35 Hz, which is comparable to the one obtained for the long-range coupling between H_4 and fluorine in VIIa (J = 1.40 Hz). The results are summarized in Scheme II.

The yield of 5-methyl-2,3-bis(trifluoromethyl)thiophene is dependent on the pressure of hexafluoro-2-butyne and increases with increasing pressure as seen from the data in Table III. The highest yield obtained, 37.5% at 1200 Torr of pressure and still exhibiting a rising tendency, is comparable to the 50% yield of perfluorotetramethylthiophene obtained in the conventional photolysis of COS in the presence of hexafluorobutyne.[1]

Scheme II



VIa, R_1 = H; R_2 = H
VIb, R_1 = CH_3; R_2 = H
VIc, R_1 = H; R_2 = CH_3

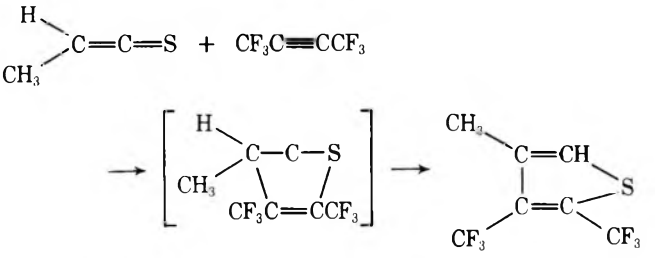


VIIa, R = H
VIIb, R = CH_3

Discussion

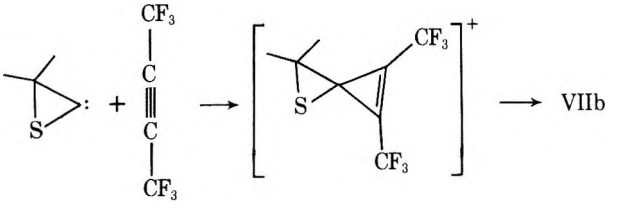
The completely analogous behavior of VIb and VIc suggests the intervention of a common intermediate which makes methyl substitution in either isomer indistinguishable. Diradical or carbene structure I can therefore definitely be ruled out. Acetylenethiol IV can also be ruled out on the ground that it has been shown[13] not to be formed in the matrix isolation photolysis of VIb and VIc.

Thioketenes would not be expected to react with acetylenes via 1,3 addition,

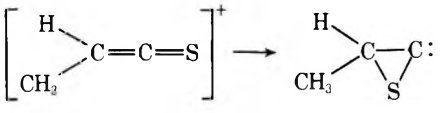


and if they did the 4-methyl-2,3-bis(trifluoromethyl)thiophene rather than the 5-methyl-2,3-bis(trifluoromethyl)-thiophene should be the predominant product on account of the greater migrational aptitude of the hydrogen atom compared with the methyl radical. Therefore thioketene can also be eliminated as the precursor of thiophene.

The cyclic carbene V may undergo a cycloaddition reaction with perfluorobutyne-2 to yield a chemically activated thiaspiropentene which may collapse to 5-methyl-2,3-bis(trifluoromethyl)thiophene.



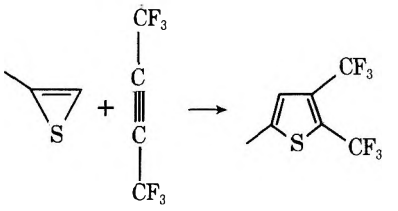
The intervention of the cyclic carbene formed presumably via the rearrangement of an excited thioketene,



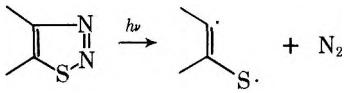
however, is not likely since the yield of thiophene from either the 4-methyl- or 5-methylthiadiazole is higher than from thiadiazole. Also, the yield of thiophene from the addition of singlet excited sulfur atom to the alkynes C_2H_2, C_3H_4, C_4H_6-2, and C_4F_6-2 is highest from the latter whereas the migrational aptitude varies in the order CF_3 < CH_3 < H. It can also be

pointed out that the IR spectra of the matrix isolated photolyzate of 1,2,3-thiadiazole and its 4-methyl, 5-methyl, 4-*tert*-butyl, 5-*tert*-butyl, 4-methyl-5-carboethoxy, 5-methyl-4-carboethoxy, and 4-trifluoromethyl derivatives did not indicate the presence of the cyclic carbene, V.[13]

Thus, the most likely precursor left for thiophene formation is the thiirene structure, and the formation of only the 5-methyl isomer appears to be a consequence of the combined electronic and steric effects of the methyl substituent and can be rationalized by addition of the alkyne to thiirene across the less hindered C-S side:



The enthalpy change of the reaction



VI I

can be estimated to be about 50–60 kcal/mol; photolysis at $\lambda > 220$ nm would therefore provide sufficient excess energy to form the singlet excited state of thioketocarbene which, according to recent MO calculations,[19] lies only 8.8 kcal/mol above its ground triplet state and also to form singlet thiirene which lies 15.5 kcal above the singlet state thioketocarbene. Thiirene would thus be formed on a singlet surface by analogy with the oxirene–ketocarbene rearrangement[20] which in the case of the sulfur system lies above the ground state triplet surface.

These results are in line with those obtained from the photolysis of matrix-isolated 1,2,3-thiadiazoles.[11-13] They provide chemical evidence for thiirene formation and do not contradict previous results on the solution photolysis of 1,2,3-thiadiazoles. On the contrary, matrix isolation photolysis studies have shown that thiirene rearranges to thioketene on photolysis.[13]

Acknowledgments. The authors thank the National Research Council of Canada for financial support and Dr. E. M. Lown for helpful assistance.

Registry No.—II ($R_1 = R_2$ H), 157-20-0; II ($R_1 = CH_3$; R_2 = H), 45345-86-6; hexafluoro-2-butyne, 692-50-2.

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Low-Temperature Matrix Isolation of Thiirenes

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Several thiirene molecules have been prepared by the argon matrix photolysis of 1,2,3-thiadiazoles at 8 K and identified by IR spectroscopy. Of the expected eight IR absorption bands of the parent thiirene molecule, seven have been located and a tentative assignment of them made. Thiirene, trifluoromethylthiirene, and benzothiirene are highly unstable, but electron-withdrawing substituents exert a marked stabilizing effect on the 4π-electron ring system: carboethoxymethylthiirene is stable up to at least 73 K.

The synthesis of thiirene, like that of the analogous three-membered heterocycles, oxirene and 2-azirene, presents a formidable challenge to the synthetic chemist since they belong to the 4n π-electron ring systems which defy Hückel's aromaticity rule. According to Breslow's postulate[1] these systems possess an antiaromatic character as manifested by their low thermodynamic stability. Indeed, detailed molecular orbital computations confirm this prediction and oxirene,[2] 2-azirene,[3] and thiirene[4] are all computed to be thermodynamically less stable than their acyclic isomers, the ketocarbenes, or 1-azirene. Coupled with their thermodynamic instability is the apparent kinetic instability of the ring system since the ab initio MO computed activation energy of the ring-opening reaction of oxirene is only 7 kcal/mol.[2] Although none of these species could be isolated until quite recently, there are several reports in the literature[5] providing indirect although compelling evidence for their transient existence as short-lived intermediates. The possibility of chemical trapping of thiirenes, from the gas-phase photolysis of 1,2,3-thiadiazoles, with hexafluoro-2-butyne to give the corresponding thiophene has also been demonstrated.[6] Photolysis of 1,2,3-thiadiazole in the presence of hexafluoro-2-butyne yields

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2,3-bis(trifluoromethyl)thiophene and the photolyses of 4-methyl- and 5-methyl-1,2,3-thiadiazoles both yield only one and the same thiophene, namely the 5-methylbis(trifluoromethyl) derivative. This suggests addition of the acetylene across the less hindered C–S side of the methylthiirene molecule.

In recent developments the low-temperature matrix isolation of thiirene, methylthiirene, and dimethylthiirene has been reported. Krantz et al.[7] in the argon matrix isolated photolyzate of 1,2,3-thiadiazole (1) ($\lambda > 290$ nm) at ~8 K have detected thioketene and ethynylthiol by IR spectroscopy. The 268-nm photolysis of 1 under otherwise identical conditions afforded an IR spectrum consisting of six bands (3207 (w), 3169 (m), 3166 (m), 1663 (w), 912 (m), and 563 (m) cm^{-1}) which have been attributed to thiirene. No assignment of the individual bands was attempted. The appearance of three absorptions in the C–H stretching region around 3100 cm^{-1} is inconsistent with the thiirene structure. The thiirene molecule should have nine normal modes of which the A_2 out-of-plane C–H bending should be IR inactive and consequently the spectrum should consist of eight absorptions, only two of which, the symmetric and asymmetric C–H stretchings, should lie in the 3100–3200-cm^{-1} region. The IR spectrum of the photolysis product of monodeuterio-1,2,3-thiadiazole reportedly shows three absorptions in the C–H stretching region and three in the C–D region, contrary to the expected single C–H and C–D stretchings.

Probably, the low intensity of the spectrum attributed to thiirene and its contamination with the intense spectra of thioketene, ethynylthiol, and possibly of unphotolyzed 1 made the analysis of the thiirene spectrum difficult and somewhat uncertain.

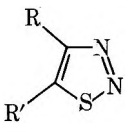
In the present article we wish to report the results of our studies on the matrix isolation photolysis of 1 and several of its derivatives which are relevant to the chemistry of thiirene.

Experimental Section

Apparatus. A cryostatic system Model LT-3-110 liquid helium transfer refrigerator with a WMX-1A shroud from Air Products and Chemicals Inc. was employed throughout the investigation. The shroud was equipped with two cesium iodide windows and two spectrosil windows. The cryostatic system was connected to a standard high-vacuum apparatus. The light source was a medium-pressure mercury arc, Hanovia Model 30620, equipped with either a 7910 Vycor filter or a 265 nm (or 215 nm) interference filter. Alternatively a 254-nm Hanovia low-pressure mercury resonance lamp was used.

A Varian Aerograph (90P) GC was employed for preparative purposes and a Hewlett Packard 5750 instrument for analysis. UV spectra were obtained on a Perkin-Elmer Model 202 spectrophotometer; preliminary IR spectra of matrix isolated species were recorded on a Beckman Acculab I spectrophotometer and final IR spectra on a Nicolet 7199 FT infrared spectrophotometer. Argon and xenon from Union Carbide (Linde Division) research grade were dried only before use. Commercial reagent grade chemicals were used without further purification.

1,2,3-Thiadiazole (1), benzothiadiazole (2), 4-trifluoromethyl-1,2,3-thiadiazole (3), and 4 methyl-5-carboethoxy- and 5 methyl-4-carboethoxy-1,2,3-thiadiazole (4 and 5, respectively) were prepared according to known procedures.[8–10]



1, R = H; R′ = H

2, R + R′ =

3, R = CF_3; R′ = H

4, R = CH_3; R′ = COOEt

5, R = COOEt; R′ = CH_3

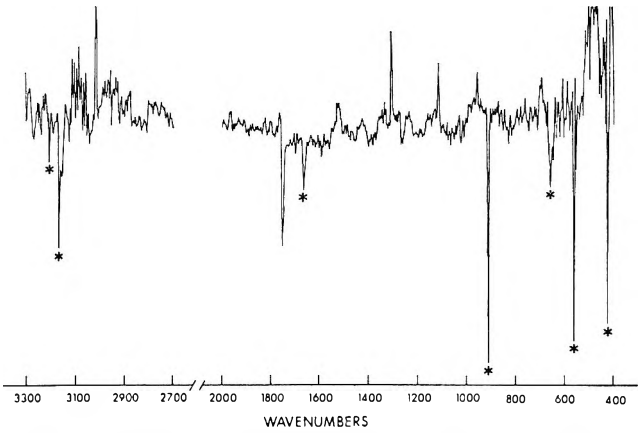


Figure 1. IR spectrum of the argon-matrix-isolated photolyzate of 1,2,3-thiadiazole at 8 K and with λ 215 nm as obtained after computed substraction of the thioketene, ethynylthiol, and remaining 1,2,3-thiadiazole spectra by a Nicolet 7199 FT-spectrophotometer. The asterisk indicates an assignment to thiirene.

Procedure. Samples with sufficient vapor pressure at room temperature (1 and 3) were introduced together with the host (argon or xenon) in a mixing reservoir and stirred constantly. The mixture was then directed to the cell and deposited on the plate (cesium iodide for IR studies and spectrosil for UV studies) that had been previously cooled at 8 K; guest to host ratios were less than 1:700. Alternatively, samples with low vapor pressure were placed in a finger trap close to the cell and warmed to 40–50 °C; they were then swept into the cell by a flow of argon. The irradiation was followed by IR or UV spectroscopy and was continued until the disappearance of the IR spectrum of the starting material.

Results and Discussion

The photolysis of **1**, isolated in an argon matrix at 8 K, at 265 nm yielded a product with an IR spectrum composed of intense absorptions due to thioketene and ethynylthiol and exhibiting certain weak absorption bands attributed by Krantz et al.[7] to thiirene. The 254-nm photolysis of **1** resulted in a similar IR spectrum as above; however, attempts to carry out the photolysis to completion resulted in the partial disappearance of the thioketene and thiirene spectra and in the appearance of the characteristic 1528-cm^{-1} absorption of CS_2.

The UV spectrum of the matrix-isolated photolyzate obtained from 1 upon photolysis at $\lambda > 210$ nm at 8 K featured a window at 215 nm where 1 also absorbs weakly. Irradiation of 1 was then carried out using a 215-nm interference filter under the same conditions used earlier. This resulted in a decrease in the rate of photolysis and, more significantly, in an appreciable increase in the IR absorption of the bands attributable to thiirene and ethynylthiol as compared to the absorption of thioketene. This enhancement in the spectral intensity made it possible to identify the bands which could be assigned to the thiirene molecule. On this basis, seven of the eight bands (3208 (w), 3170 (m), 1660, 912 (s), 660 (m), 563 (m), and 425 (m) cm^{-1}, Figure 1) expected for thiirene could be located and only two of these lie in the C–H stretching region. Based on the similarity between the fully optimized ab initio molecular orbital geometry of thiirene[4] and that of cyclopropene[11] and thiirane,[12] Table I, it is possible to make the following tentative assignments of the observed bands.

From the parallelism between the IR spectrum of cyclopropene and the one observed for thiirene, the missing band should be assigned to a C–H in-plane bending and would be expected to lie at ~1000 cm^{-1}. In fact, some weak absorption is present at 1010–1020 cm^{-1}, but its assignment at the moment is uncertain. IR studies of isotopic substituted thiirene, now in progress, will allow a more definitive assignment.

It was also observed that prolonged photolysis of the pri-

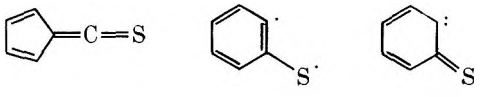
Table I. Tentative Assignment of the Observed Bands of Thiirene (cm^{-1})

	Thiirene	Reference compd
C—H stretch	3208	3124[a]
	3170	3158[a]
C=C stretch	1660	1656[a]
C—H in-plane bend		1010[a]
	912	905[a]
C—H out-of-plane bend	425	570[a]
Ring deformation	660	633[b]
	563	646[b]
	Geometry	
R(C=C)	1.270 Å[c]	1.300 Å[d]
R(CH)(vinyl)	1.074 Å[c]	1.070 Å[d]
α(C=CH)	149° 55'[c]	149° 18'[d]
R(CS)	1.810 Å[c]	1.819 Å[e]

[a] Cyclopropene, ref 13. [b] Thiirane, ref 14. [c] Calculated for thiirene, ref 4. [d] Cyclopropene, ref 11. [e] Thiirane, ref 12.

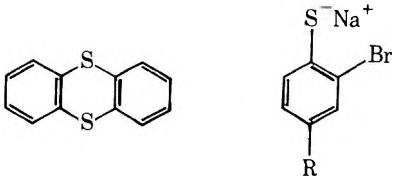
mary photolyzate resulted in a slow decrease in the intensity of the thioketene spectrum, accompanied by a slow increase in the spectrum of ethynylthiol, indicating that at this wavelength thioketene is converted to ethynylthiol without the formation of CS_2.

The effect of substituents was also investigated. The photolysis of benzothiadiazole (**2**) with 265-nm radiation resulted in the formation of the 1,3-butadienylenethioketene (**6**) and another species in low yield which exhibited IR absorptions at 1670 (w) (tentative), 1440 (m), 970 (w), 950 (m), 720 (s), 680 (m), and 670 (w) cm^{-1}, and which was converted to the thioketene on further irradiation with $\lambda > 210$ nm radiation, in a manner similar to that reported for the photolysis of **1** at 300 nm.[7] Thus, the spectrum is due either to benzothiirene or to the isomeric species **7** and/or **8**. On the other hand, pho-



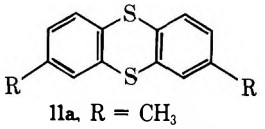
6 **7** **8**

tolysis of **2** in liquid benzene solution has been reported[15] to yield thianthrene (**9**) as the sole product, which is a clear indication of the stability of the intermediate diradical **7** or benzothiirene toward rearrangement. Moreover, thermolysis of sodium *o*-bromobenzenethiolate (**10a**) also yields thianthrene (**9**) and the 4-methyl derivative **10b** gives a 1:1 mixture of the thianthrenes **11a** and **12a**[16] which can only arise from

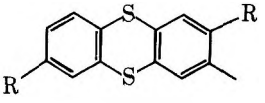


9

10a, R = H
b, R = CH_3



11a, R = CH_3
b, R = COOMe



12a, R = CH_3
b, R = COOMe

a benzothiirene intermediate. Similarly, a mixture of thianthrenes **11b** and **12b** has recently been reported in the thermolysis of 6-carbomethoxy-1,2,3-thiadiazole[17] and this provides additional evidence for the benzothiirene intermediate. Thus, the combined evidence would strongly suggest that the observed spectrum is that of benzothiirene.

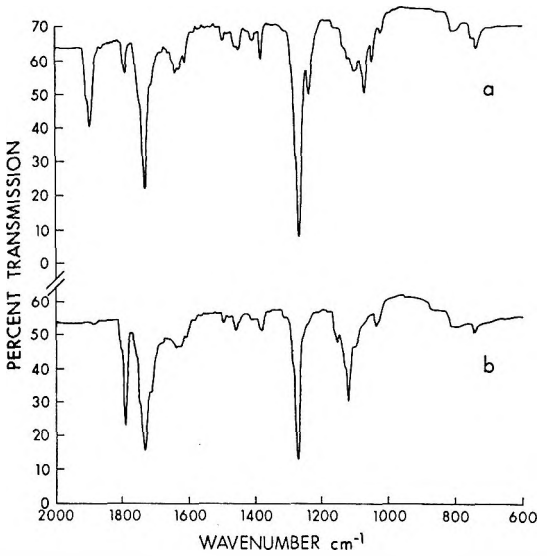
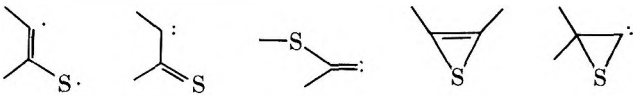


Figure 2. (a) IR spectrum of the argon-matrix-isolated photolyzate of 4-methyl-5-ethoxycarbonyl-1,2,3-thiadiazole at 8 K and with λ 265 nm. (b) IR spectrum of the above sample after irradiation with a Vycor filtered mercury arc.

The photolysis of 4-trifluoromethyl-1,2,3-thiadiazole (**3**) at 265 nm affords an intermediate in much higher yield than from any previously described thiadiazole to which we have assigned the absorptions 3210 (w), 1240 (s), 1190 (s), 1180 (s), and 720 (w) cm^{-1} and which is again converted to trifluoromethylthioketene upon further irradiation using a Vycor filter. In addition to this intermediate, trifluoromethylthioketene, 3,3,3-trifluoropropyne, and possibly $CF_3C{\equiv}CSH$ were observed.

A much clearer indication of the presence of thiirene was obtained in the photolysis of 4-methyl-5-carboethoxy and 5-methyl-4-carboethoxy-1,2,3-thiadiazole (**4** and **5**, respectively). Irradiation of either **4** or **5** using a 265-nm interference filter resulted in the appearance of a spectrum (Figure 2a) with significant absorptions at 3205 (vw), 3000 (w), 1875 (m), 1715 (s), 1440 (w), 1400 (w), 1370 (m), 1270 (s), 1070 (m), 1040 (m), 1020 (w), 760 (w), 730 (w), and 490 (w) cm^{-1}. Replacement of the 265-nm interference filter by a Vycor filter and continuation of the photolysis resulted in the disappearance of the intermediate spectrum and the appearance of the spectrum of thioketene (Figure 2b). This excludes diradical thioketocarbene intermediate, **13**, **14**, and **15**, leaving structures **16** and **17** as possible carriers.



13 **14** **15** **16** **17**

Photolysis, in this case, could also be carried out with the 265-nm source and complete disappearance of the IR spectrum of the starting material occurs without appreciable decomposition of the intermediate. No acetylene absorption was observed, indicating that substitution quenches the thiirene → acetylene rearrangement, and the low intensity of the characteristic 1785-cm^{-1} absorption of thioketene indicated the virtual absence of this species.

The presence of an absorption of 1875 cm^{-1} for a C=C stretching indicates an unusually large shift from the value of 1660 cm^{-1} for the parent compound; however, this again parallels the behavior of cyclopropenes, since similarly substituted cyclopropenes exhibit an absorption at 1840 cm^{-1} which was assigned to the C=C stretching.[18] Therefore, the spectrum obtained and reproduced in Figure 2a can be attributed only to the thiirene structure **16**.

The species responsible for the spectrum exhibits remarkable stability. Experiments carried out using a xenon matrix have shown that the spectrum persists up to at least 73 K, the softening point of the xenon matrix. This is a manifestation of the stabilizing effect of the electron-withdrawing substituents on the thiirene molecule which parallels the behavior of cyclobutadiene; similarly substituted cyclobutadiene has been reported[19] to be stable at room temperature.

In conclusion it may be stated that the IR spectrum consisting of seven bands that has been obtained in the argon matrix isolated photolyzate of 1 is consistent with the carrier being the thiirene molecule. The tentative assignment of the bands is based on analogous data reported for cyclopropene and thiirane.

The IR spectra of the matrix-isolated photolyzate of 4 and 5 are identical and bear close resemblance to the spectrum of the parent thiirene. The shifts in the C=C stretching frequencies of the photolyzates of 4 and 5 with respect to the parent thiirene are similar to those observed for cyclopropene and similarly substituted cyclopropenes. The spectrum is undoubtedly due to methylcarboethoxythiirene. The parallelism in the behavior of thiirene and cyclopropene also extends to their ring-opening reaction, leading respectively to methylacetylene[20] and ethynylthiol. The presence of alkyl substituents apparently hinders the rearrangement of thiirene. Substituents in general, and electron-withdrawing substituents in particular, endow the thiirene ring with an increased stability which manifests itself in an enhanced yield and persistence to higher temperatures on warming of the matrix.

Additional work in the area of thiirene formation and chemistry is presented in the accompanying paper.

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Registry No.—1, 288-48-2; 2, 273-77-8; 3, 65702-19-4; 4, 18212-20-9; 5, 29682-53-9; 6, 54191-78-5; thiirene, 157-20-0; benzothiirene, 65330-66-7; trifluoromethylthiirene, 65702-20-7; carboethoxymethylthiirene, 65702-21-8.

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Intra- and Intermolecular Photocycloadditions of Acetylenic Esters to Benzo[*b*]thiophenes

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Direct and sensitized irradiation of 2-(3-benzo[*b*]thienyl)ethyl but-2-ynoate (1) leads to an unrearranged intramolecular cycloaddition product, **2**, as primary photoproduct, which can rearrange to **3** on extended photolysis. An intramolecular cycloaddition product, **6**, has been obtained on sensitized irradiation of 2-(2-benzo[*b*]thienyl)ethyl but-2-ynoate (**5**), although a desulfurized naphthopyranone has been isolated as a major product. Reinvestigation of the photochemical cycloaddition of methyl phenylpropiolate to 2-methylbenzo[*b*]thiophene also shows the presence of small quantities of unrearranged photoproducts **14** and **15**. On sensitized and direct irradiation of (2-benzo[*b*]thienyl)alkyl phenylpropiolates **18** and **19**, only cycloadducts of the solvent benzene with the triple bond are observed. In the latter case, an intramolecular cycloaddition product, **23**, has been shown to be present. The mechanism of formation of the unrearranged products is discussed.

The photochemical addition of acetylenic esters to fused heteroaromatic compounds like benzo[*b*]thiophene,[1,2] benzo[*b*]furan,[3] and *N*-methylindole[4] has been investigated extensively in our laboratories. In general, these compounds give cyclobutenes, formed via $[{}_{\pi}2_s + {}_{\pi}2_s]$ addition of the acetylene to the 2,3 position of the heteroaromatic compound.[1-5] These cyclobutenes, however, are often not stable and undergo further photochemical[1-6] and/or thermal changes.[4,7] Thus, only rearranged cyclobutenes are found in the photoaddition of dimethyl acetylenedicarboxylate, methyl propiolate, and methyl phenylpropiolate to benzo[*b*]thiophene.[2]

Several important mechanistic questions present themselves in the relatively simple photoaddition of an alkyne ester to benzo[*b*]thiophene. Among these are which excited state

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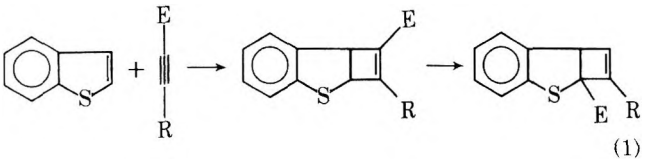
reacts and what intermediates are involved along the reaction coordinate (eq 1). In fact, in our first publications[1,2] on the



(1)

subject, none of the unrearranged adducts expected from [$_{\pi}2_s$ + $_{\pi}2_s$] addition was isolated or even observed. Thus, mechanisms involving either a concerted 1,2 addition or a concerted 1,3 addition could not be excluded.

Subsequent to our report[1] Sasse and co-workers[5] reported isolating an unrearranged adduct as a minor product from the addition of diphenylacetylene to benzo[*b*]thiophene. We subsequently argued[2] that this result was not germane since diphenylacetylene was likely the excited state in this addition.

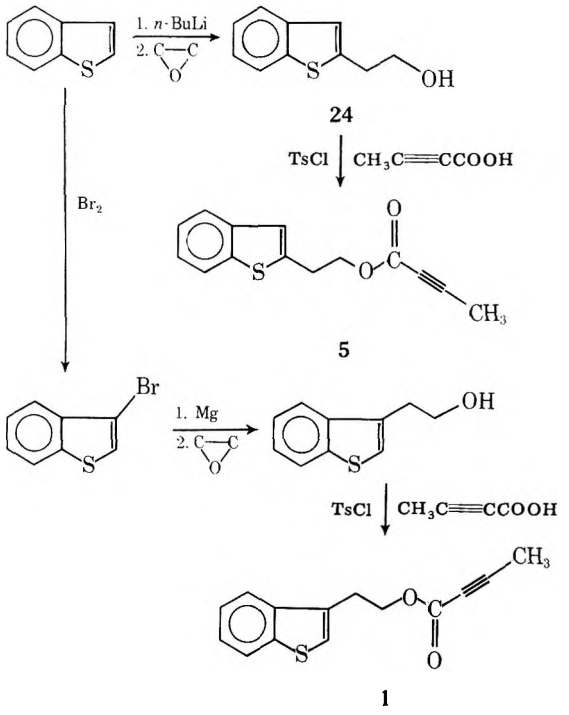
In order to gain more insight in the mechanistic aspects of these processes we have studied the photochemistry of several nonconjugated benzo[*b*]thienyl acetylenic esters. The results of these studies are described herein.

Results

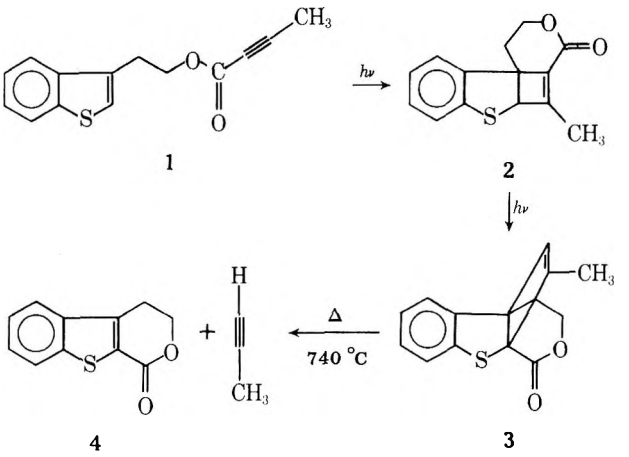
The most efficient, intramolecular cycloadditions are expected to occur on irradiation of benzo[*b*]thienyl acetylenic esters, which may form a six-membered ring fused to the cyclobutene moiety. 2-(3-Benzo[*b*]thienyl)ethyl but-2-ynoate (**1**) and 2-(2-benzo[*b*]thienyl)ethyl but-2-ynoate (**5**) were prepared from the appropriate benzo[*b*]thienylethanols and 2-butynoic acid according to the method of Brewster and Ciotti[8] (Scheme I).

Sensitized irradiation of **1** (2.15 × 10^{-3} M in nitrogen-degassed benzene) for 8 h resulted in formation of two monomeric photoproducts, **2** and **3**, in 2 and 42% yield, respectively (Scheme II). The major product, **3**, was found to be isomeric with **1**, and a molecular ion (*m/e* 244) confirmed its molecular weight. The base peak (*m/e* 204) included, as expected,[3] an ion from retrocleavage in a direction such that the benzo[*b*]thiophene nucleus remains intact. The IR spectrum contained an absorption at 1635 cm^{-1} (C=C),[3] and the NMR

Scheme I



Scheme II



spectrum was clearly consistent with structure **3**, including among others an allylic quartet (1 H) at δ 6.10, weakly coupled ($J \sim 1.6$ Hz) with a methyl doublet (3 H) at δ 1.86, and two multiplets centered at δ 2.28 (2 H) and 4.54 (2 H).

Chemical structure proof was derived from pyrolysis of **3** in the vapor phase at 740 °C (7 × 10^{-5} Torr). Ring opening to a benzo[*b*]thiepine, followed by desulfurization, is prohibited because of Bredt's rule. Cyclobutene cleavage occurred giving propyne and the olefinic fragment **4** instead. No reaction was observed at temperatures below 640 °C.

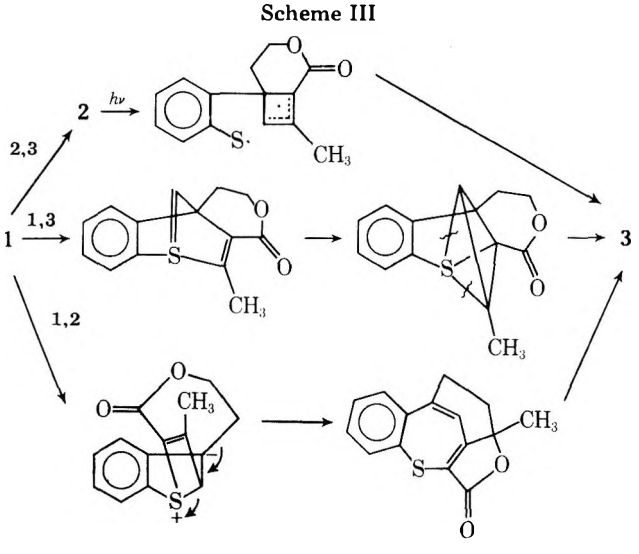
The minor product **2**, shown to be isomeric with **3**, revealed in its NMR spectrum a methyl doublet (3 H) at δ 2.03, weakly coupled ($J \sim 1.2$ Hz) with a methine doublet (1 H) at δ 4.42, proton H_1. Fine structure and chemical shift values are in good agreement with those of 6-methyl-substituted 2-thiabenzo[*b*]bicyclo[3.2.0]hepta-3,6-dienes.[2] Furthermore, compound **2** could be completely converted into **3** when irradiated at 300 nm. Under these conditions **3** appeared to be photostable.

Irradiation of methyl but-2-ynoate gives no cycloaddition product with benzene when irradiated at 350 nm with sensitizers like xanthen-9-one (E_T = 74.2 kcal mol^{-1}) or benzophenone (E_T = 68.5 kcal mol^{-1}), suggesting that the intramolecular cycloaddition of **1** proceeds from the excited state of the benzo[*b*]thiophene moiety.

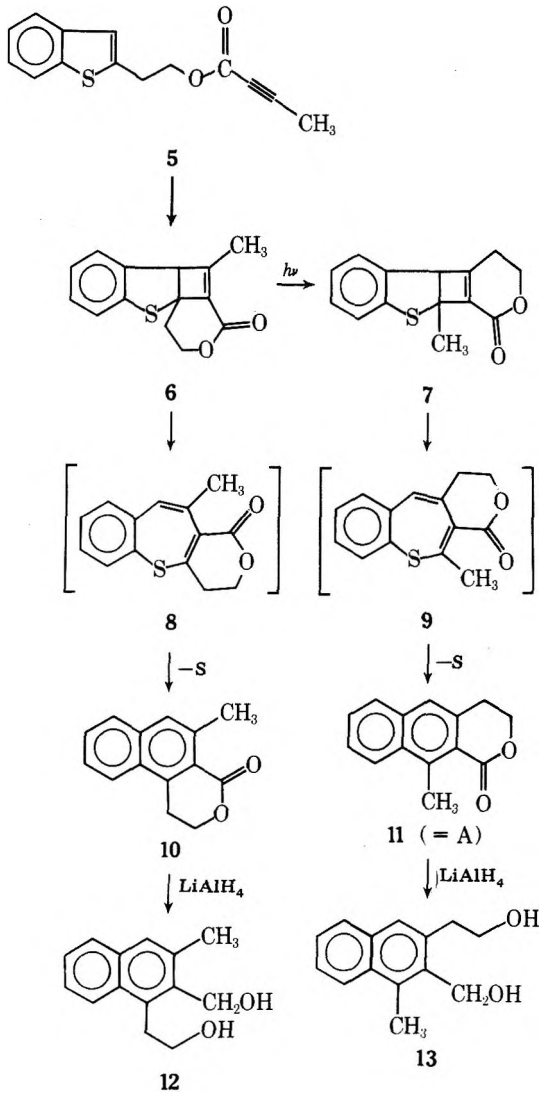
Theoretically the major product **3** can be formed via each of the reaction pathways outlined in Scheme III: a 2,3 addition, a concerted 1,2 addition, and a concerted 1,3 addition. For steric reasons the latter two pathways are unlikely. Formation of **3** via these pathways is also prohibited because it would proceed through highly strained intermediates.

We conclude that a 2,3 addition is operating, leading to the

Scheme III



Scheme IV



photolabile cyclobutene **2**, which is further converted, by a second light quantum, into **3**. In fact, compound **2** is the most likely precursor to **3**, since on irradiation of **1** under the same conditions as above but in the absence of sensitizer, at less than 10% conversion, the relative amount of **2** was substantially increased. As in similar systems,[2] the excited state of the benzo[b]thiophene seems highly polarized. This polarization would result in bond formation involving the acetylene carbon adjacent to the carboxy group rather than the carbon adjacent to the methyl group. This preferred mode of addition in **1*** leads to **2**.

2-(2-Benzo[b]thienyl)ethyl but-2-ynoate (**5**; 2.5×10^{-3} M), irradiated in benzene in the presence of acetophenone for 23 h, gave only one photoproduct, A, in 18% yield (Scheme IV). Compound A had a molecular ion peak at *m/e* 212, indicating the loss of sulfur during its formation. Peak matching confirmed the molecular formula $C_{14}H_{12}O_2$. Its IR spectrum contained a strong absorption at 1725 cm^{-1} (C=O). In the NMR spectrum compound A showed two two-proton triplets at δ 3.16 and 4.49, a deshielded methyl singlet at δ 3.07, and a one-proton low field multiplet, centered at δ 8.23. The latter two large downfield shifts are associated with the presence of a peri carbonyl group and alkyl group,[9a] respectively. The spectroscopic data are clearly consistent with either the naphthopyranone **10** or **11**.

More evidence for the presence of **10** or **11** was obtained by reduction of compound A with lithium aluminum hydride, leading to the diol **12** or **13**, with an NMR absorption of an upfield methyl group at δ 2.74 and with an aromatic fine structure pattern in good agreement with 1,2,3-trisubstituted naphthalene. From the relatively low chemical shift value at δ 2.74 it is most likely that **13** is the isolated naphthalene rather than **12**, since β-methylnaphthalenes ($\delta_{CH_3} \sim 2.3$–2.5) absorb about 0.2–0.3 ppm at higher field than α-methylnaphthalenes.[9b] Therefore, 9-methyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran-1-one (**11**) is the most likely structure for the isolated photoproduct A.

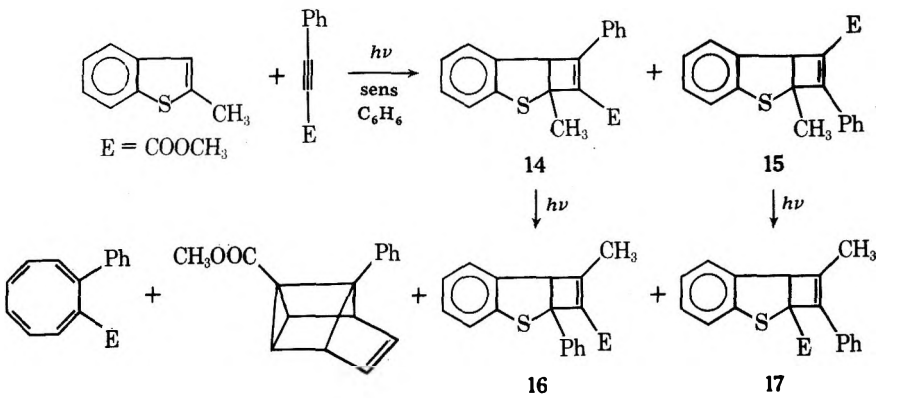
In one experiment at shorter irradiation time a fraction was also isolated which contains a second photoproduct B. Though compound B could not be separated from A, its most likely structure is the primary intramolecular cyclization product **6**. The NMR spectrum showed distinct signals at δ 2.05 (methyl doublet, $J \sim 1.5$ Hz) and a two-proton multiplet at δ 2.35 in agreement with that of **2** and **3**.

Based on the arguments as above, **6** is likely the initially formed photoproduct, and it rearranges to **7**. This rearrangement not only releases the strain at the quaternary carbon C_1, but also leads to an endocyclic conjugated double bond in **7**, which is expected to be thermodynamically more stable than the exocyclic one in **6**.[10] Compound **7** undergoes ring opening to the benzo[b]thiepine **9**. It is not surprising that **9** could not be detected, since it is known that benzo[b]thiepines easily lose sulfur and convert into the corresponding naphthalenes.[7] However, formation of **9** via a 1,2 addition cannot be completely ruled out.

In contrast to our earlier report,[2] sensitized irradiation of 2-methylbenzo[b]thiophene (8.3×10^{-3} M) and methyl phenylpropiolate in benzene for about 20 h at 350 nm resulted in the isolation of the unrearranged cyclobutenes **14** and **15** in 1 and 3% yields (Scheme V). Though these products are obviously minor, their presence is significant in that they represent the first such unrearranged adducts isolated from an intermolecular [$_\pi 2_s + {}_\pi 2_s$] addition of an alkyne ester to benzo[b]thiophene.

1-Carbomethoxy-8-phenylcyclooctatetra-1,3,5,7-ene and 4-carbomethoxy-5-phenyltetracyclo[3.3.0.0^{2,4}.0^{3,6}]oct-7-ene

Scheme V



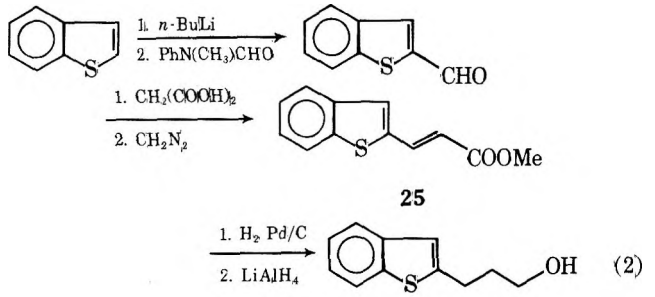
(mp 74–75 °C) were obtained as major products[12] in ~50% yield; the rearranged cyclobutenes **16** and **17** were isolated in 20 and 10% yields, respectively.

The predominant mass spectral fragmentation, *m/e* 210, is proof of the derived structure of the major cycloadduct **16**.[13] The NMR spectrum showed a methyl doublet at δ 2.10, weakly coupled ($J \sim 1.6$ Hz) with a methine quartet at δ 4.32. Compound **16** appeared to be photostable, and was shown to be formed from **14** upon irradiation at 300 nm. Chemical proof for the structure of **16** was derived from the thermal rearrangement at 240 °C. The corresponding 2-carbomethoxy-3-methyl-1-phenylnaphthalene, formed via a sulfur extrusion process,[2,6,14] did not show any absorption in its NMR spectrum below 8.0 ppm, which would be the case if the ester group would be in the 1 position of the formed naphthalene.

Though isomer **17** could only be obtained mixed with some **16**, there was spectroscopic evidence for its presence. The predominant peak at *m/e* 192 in its mass spectrum, completely absent in **16**, points to the loss of a $PhC{\equiv}CCH_3$ fragment. The NMR spectrum showed a weakly coupled doublet, δ 2.07, and quartet, δ 4.78, consistent with the methyl group and H_5, respectively. Compound **17** also appeared to be photostable, and was exclusively formed from **15** upon irradiation at 300 nm. Spectroscopic data of **14** and **15** are consistent with the assigned structures.

It cannot be excluded that the process producing the unrearranged product involves triplet state methyl phenylpropiolate, as has been shown to occur in the addition to benzene.[15] The huge difference in concentration of benzene vs. benzo[*b*]thiophene, however, would suggest a greater benzene adduct/benzo[*b*]thiophene adduct ratio than is found experimentally (1:1). Therefore, the process producing the cyclobutenes likely derives from an excited state of benzo[*b*]-thiophene.

In view of these results it became interesting to examine the photochemistry of (2-benzo[*b*]thienyl)alkyl phenylpropiolates, **18** and **19**. These compounds were prepared in good yield from the appropriate 2-benzo[*b*]thienyl alcohols and phenylpropiolyl chloride (eq 2 and 3).



(2)

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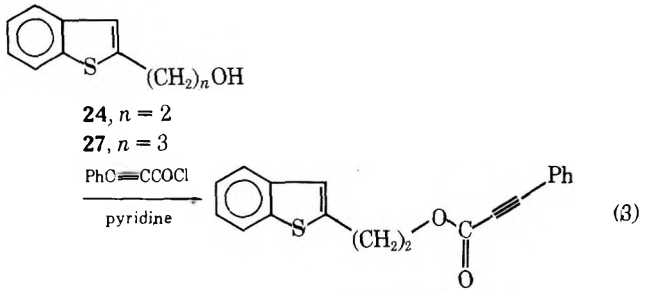
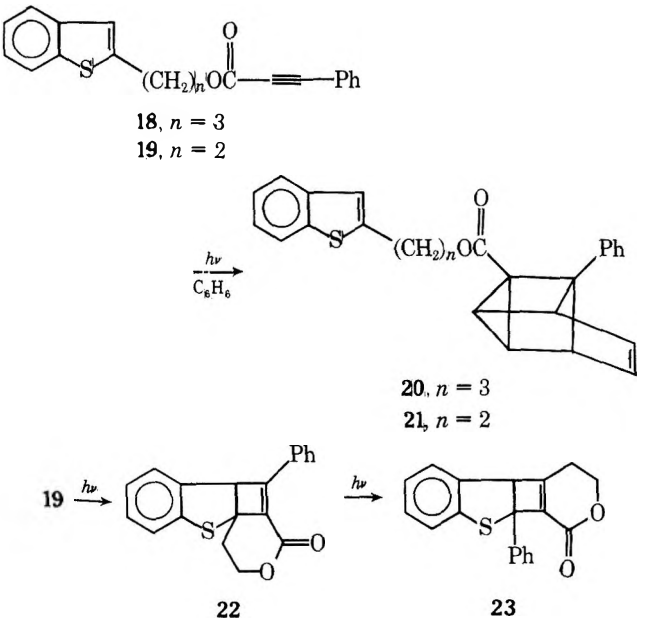


(3)

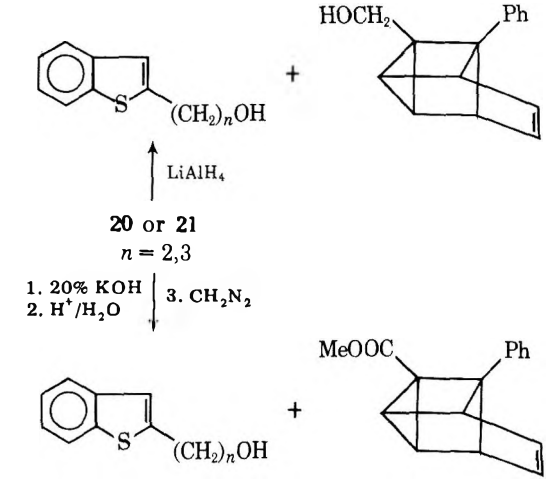
19, $n = 2$
18, $n = 3$

On sensitized and direct irradiation of 2×10^{-3} M benzene solutions of the esters **18** and **19**, the tetracyclo[3.3.0.0^{2,4}.0^{3,6}]oct-7-enes **20** and **21** could be isolated in 48 and 19% yield, respectively (Scheme VI). Structure proof was

Scheme VI



Scheme VII



based on reduction with lithium aluminum hydride to the known alcohols and by base-catalyzed hydrolysis followed by diazomethane esterification (Scheme VII). Apparently, the intermolecular addition of the triple bond to benzene[12] becomes more important than intramolecular cycloaddition. However, a monomeric compound was formed from **19** in a competitive side reaction. Its NMR spectrum revealed a broad singlet at δ 4.88 (1 H) and two two-proton triplets at δ 4.54 and 2.48. Though the spectral data do not clearly differentiate between **22** and **23**, we have assigned the structure **23** based on the efficient rearrangements which occur in analogous systems (e.g., **14** → **16**).

Discussion

Though the experiments do not completely rule out concerted 1,2 or 1,3 additions, which produce the rearranged adducts directly, the preponderance of evidence is not in their favor and these pathways are not necessary.

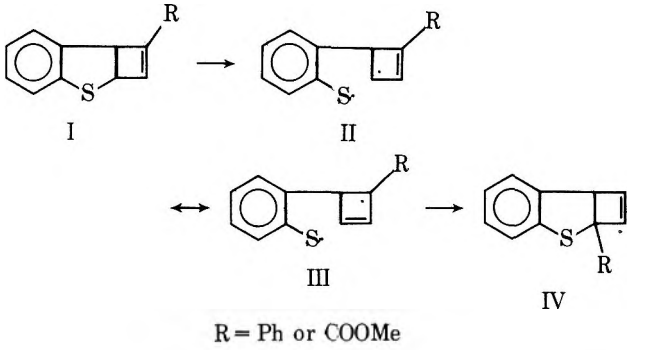
The results above, coupled with those published by us earlier, definitively prove that (i) the photocycloaddition of benzo[*b*]thiophene to acetylenic esters occurs from a triplet state of the heteroaromatic compound, (ii) unrearranged adducts form from this addition, though they are minor products, and (iii) these unrearranged adducts irreversibly and with great efficiency rearrange to the observed major products.

Consider the results: xanthone (E_T = 74.2 kcal mol^{-1}, λ_{max} 366 nm) sensitizes the intramolecular photoaddition of 1 forming 2. Though there is a sensitized addition of the separated reagents, benzo[b]thiophene and the alkyne ester, to one another under similar conditions, there is no addition of alkyne ester to benzene sensitized by xanthone under conditions where xanthone alone is absorbing the light. Since benzene is more reactive than benzo[b]thiophene toward the excited triplet state of another alkyne ester, methyl phenylpropiolate (E_T < 68 kcal mol^{-1}), one would expect the butynoate ester triplet to add to benzene if it was formed.

The photoaddition of diphenylacetylene (E_T = 62.5 kcal mol^{-1}) to benzo[b]thiophene likely occurs from the excited state of the diphenylacetylene, as has been argued by us earlier[2] and corroborated by Kuhn and Gollnick.[11] Benzophenone sensitizes the intermolecular addition of methyl phenylpropiolate to benzo[b]thiophene as well as to benzene. The triplet energy of methyl phenylpropiolate should therefore be lower than 68 kcal mol^{-1}, and the addition products to benzo[b]thiophene likely were derived from the triplet state of the alkyne ester.

Unrearranged adducts formed from the addition of excited benzo[b]thiophene to acetylenic ester have been isolated in every case reported in this paper, though they are minor products. These unrearranged adducts are all shown to rearrange with great efficiency to the observed major products. The reverse reaction, from major to minor product, does not occur under the same experimental conditions.

It remains to argue why the photorearrangement of I → IV is so facile. In essence the question is: why do compounds of the general structure I undergo facile (sensitized) rearrangement to IV?



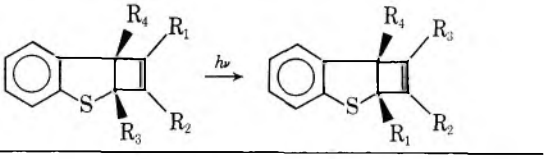
We would suggest that rearrangement of I → IV likely proceeds via rupture of the C_1–S bond to give a stabilized diradical (II ↔ III). The answer may lie in the higher electron density at the R-substituted carbon or the rapid ring closure of one or the other to cyclic products. Since the contribution of the resonance structure III when R = Ph is greater than that of II, and since polar contribution when R = COOMe would favor ring closure from III, the theory supports the experimental result.

Still another possible explanation can be seen by considering the photoadducts which exclusively rearrange (Table I).

In every case the double bond of the cyclobutene which eventually forms is less highly substituted with conjugated functional groups than the original photoproduct. The original adduct, in every case, likely has a lower triplet energy than the final product and the unrearranged product is a more efficient energy-transfer acceptor than the rearranged adduct. These results suggest therefore that the rearranged adduct is the energy sink in the system and that once it is formed there is no convenient photochemical pathway whereby it can be converted to other isomers.

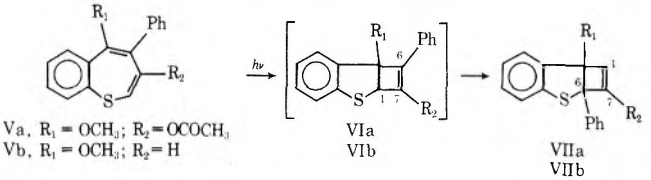
The cases of 6 and 7 present another interesting comparison: in this case alone are naphthalenes isolated from photo-

Table I. Photorearrangements of 2-Thiabenzo[b]bicyclo[3.2.0]hepta-3,6-dienes[a]



R_1	R_2	R_3	Ref
$COOCH_3$	$COOCH_3$	H or CH_3	1, 2, 6
$COOCH_3$	$COOCH_3$	$C(CH_3)_3$	*b*
$COOCH_3$	H	H or CH_3	2
$COOCH_3$	Ph	H or CH_3	2, *c*
e	CH_3	H	*c*
Ph	$COOCH_3$	H or CH_3	2, *c*
Ph	Ph	H	2, 5
Ph	$-C(=O)OCH_2CH_2-$		*c*
CH_3	$-C(=O)OCH_2CH_2-$		*c*
Ph	H	H	*d*

[a] R_4 = H unless otherwise indicated. [b] A. H. A. Tinnemans and D. C. Neckers, unpublished results. [c] This work. [d] Hofman and Meyer[16] reported that the photoisomerization of the benzo[b]thiepines Va,b gave the cyclobutenes VIa,b. The NMR spectral



data reported showed, among other peaks, a singlet at δ 5.7 for VIa and two "singlets" at δ 6.10 and 6.12 for VIb. However, since all known 2-thiabenzo[b]bicyclo[3.2.0]hepta-3,6-dienes[2,5,6] reveal in their NMR spectra vinylic absorptions at 5.9–6.8 and methine absorptions (H_1) at δ 4.05–4.75, it is more likely the isolated compounds were VIIa,b, in agreement with the expected rearrangement of VIa,b → VIIa,b under the reaction conditions used. [e] R_1R_4 = $-CH_2CH_2OC(=O)-$.

rearrangement. It is possible that these products ring open to benzo[b]thiepines rather than rearrange by biradical intermediates, thereby losing sulfur.

The results are, in our judgment, consistent with a mechanism involving two distinct photoprocesses:

benzo[b]thiophene (BT) + sensitizer* → BT*

BT* + alkyne → unrearranged adduct

unrearranged adduct + sens* → [unrearranged adduct]*

[unrearranged adduct]* → rearranged product

Based on the results, it is safe to predict that any benzo[b]thiophene will add to any alkyne, particularly electron-deficient ones, to give fused cyclobutenes which are rearranged and that 2-thiabenzo[b]bicyclo[3.2.0]hepta-3,6-dienes will likely rearrange to the isomer in which the double bond is less highly substituted.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded either in chloroform solution or in KBr disks using a Perkin-Elmer 337 infrared spectrophotometer. NMR spectra were recorded either on a Varian A-60 or CFT-20 spectrometer with deuteriochloroform as the solvent and tetramethylsilane as the internal reference. UV spectra were determined in methanol using a Beckman Acta MIV spectrophotometer. Mass spectra were obtained using a Varian MAT Model CH-7 mass spectrometer. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, Mich.

Photolysis experiments were carried out in a Rayonet RPR-100 reactor fitted with 300- or 350-nm fluorescence lamps. Otherwise, the photolyses were performed in a 400-mL Pyrex immersion well apparatus using a 450-W Hanovia medium-pressure mercury lamp.

Before the irradiation all samples were purged with nitrogen for at least 30 min.

2-(2-Benzo[*b*]thienyl)ethanol (24). Under a slight stream of dry nitrogen 181 mL of a 2.6 M solution of *n*-butyllithium in hexane was slowly added to a solution of 63 g (0.47 mol) of benzo[*b*]thiophene in 300 mL of anhydrous ether at 0–5 °C. The solution was warmed to reflux temperature and stirred for 1 h. The red solution was cooled to 0 °C and 21 g (0.48 mol) of ethylene oxide in 40 mL of cold ether was added to the reaction solution. Stirring was continued for an additional 1 h at 0 °C. The reaction was hydrolyzed with water, and the aqueous phase was extracted with ether. The etherea. extracts were combined, washed with water until neutral, dried, and concentrated. Crystallization from carbon tetrachloride gave 67 g of white plates, mp 68–78 °C. Recrystallization gave 64 g (76%) of analytically pure **24**: mp 77–78.5 °C (lit.[17] 79.5–80.5 °C); NMR δ 2.13 (s, 1 H, OH), 3.08 (asymm t, 2 H, CH_2), 3.89 (asymm t, 2 H, CH_2), 7.08 (br s, 1 H, H_3), 7.2–7.9 (m, 4 H, Ar). Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.65; S, 17.99. Found: C, 67.20; H, 5.56; S, 17.80.

2-(2-Benzo[b]thienyl)ethyl But-2-ynoate (5). A solution of 3.36 g (0.019 mol) of 2-(2-benzo[*b*]thienyl)ethanol (**24**) and 1.68 g (0.020 mol) of 2-butynoic acid[18] in 40 mL of anhydrous pyridine was cooled to 8 °C, and to this was slowly added a solution of 6.60 g (0.032 mol) of *p*-toluenesulfonyl chloride in 10 mL of pyridine. The reaction mixture was stirred at 15 °C for 2.5 h and then poured into water. After extraction with ether the organic layers were subsequently washed with 1 N hydrochloric acid solution, saturated sodium bicarbonate, and brine. After drying over magnesium sulfate, the solvent was removed and the residual oil was chromatographed over Florisil with benzene/petroleum ether (1:5) as eluent, yielding 3.5 g (76%) of **5**. The product was crystallized from methanol to give white needles: mp 41–42 °C; NMR δ 1.83 (s, 3 H, CH_3), 3.17 (t, 2 H, CH_2), 4.43 (t, 2 H, CH_2), 7.05 (br d, 1 H, H_3), 7.1–7.9 (m, 4 H, Ar); IR (KBr) 2235 cm^{-1} (C≡C); UV_{max} 257 nm (log ε 3.94), 288 sh (3.25). Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.82; H, 4.95; S, 13.12. Found: C, 68.88; H, 4.90; S, 13.17.

2-(3-Benzo[*b*]thienyl)ethyl But-2-ynoate (1). This compound was prepared in 83% yield according to the procedure described for **5**, starting with 5.04 g (0.028 mol) of 2-(3-benzo[*b*]thienyl)ethanol, prepared from the Grignard reagent of 3-bromobenzo[*b*]thiophene[19] and ethylene oxide according to Cagniant and Cagniant,[20] 2.52 g (0.030 mol) of 2-butynoic acid,[18] and 9.9 g (0.048 mol) of *p*-toluenesulfonyl chloride. The crude ester was crystallized from methanol to give **1** as very pale yellow needles: mp 53.5–54 °C; NMR δ 1.92 (s 3 H, CH_3), 3.17 (t, 2 H, CH_2), 4.44 (t, 2 H, CH_2), 7.18 (br s, 1 H, H_2), 7.2–8.0 (m, 4 H, Ar); IR (KBr) 2235 cm^{-1} (C≡C); UV_{max} 259 nm (log ε 3.68), 284–288 (3.35). Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.82; H, 4.95; S, 13.12. Found: C, 68.80; H, 4.94; S, 13.05.

Methyl *trans*-β-(2-Benzo[*b*]thienyl)acrylate (25). A solution of β-(2-benzo[*b*]thienyl)acrylic acid[21] in tetrahydrofuran was treated with an ethereal solution of diazomethane at 0 °C. The excess diazomethane was destroyed by carefully adding formic acid and the organic layer was washed with saturated sodium bicarbonate solution and subsequently with water until neutral. After drying ($MgSO_4$) the solvent was removed and the residual crude ester was crystallized from methanol, giving pale yellow needles: mp 122–123 °C; NMR δ 3.85 (s, 3 H, $COOCH_3$), 6.35 and 7.93 (AB, 2 H vinylic, J_{AB} = 15.5 Hz), 7.47 (br s, 1 H, H_3), 7.28–7.52 (m, 2 H, Ar), 7.63–7.95 (m, 2 H, Ar); UV_{max} 256 nm (log ε 3.77), 315 (4.50). Anal. Calcd for $C_{12}H_{10}O_2S$: C, 66.03; H, 4.62; S, 14.69. Found: C, 66.45; H, 4.52; S, 14.26.

Methyl β-(2-Benzo[*b*]thienyl)propionate (26). The unsaturated ester **25** (1.0 g) and 5% palladium on charcoal (0.15 g) in ethyl acetate (100 mL) were shaken with hydrogen overnight, at which time another small amount of catalyst (0.15 g) was added and the mixture was shaken with hydrogen until no vinylic hydrogens could be detected by NMR. The catalyst was filtered off and the solvent was removed under reduced pressure. The residue was crystallized from methanol, giving **26** as white plates: 88%; mp 70–71.5 °C; NMR δ 2.51–2.88 (m, 2 H, CH_2), 3.04–3.41 (m, 2 H, CH_2), 3.68 (s, 3 H, $COOCH_3$), 7.04 (br s, 1 H, H_3), 7.11–7.92 (m, 4 H, Ar). Anal. Calcd for $C_{12}H_{12}O_2S$: C, 65.43; H, 5.49; S, 14.55. Found: C, 65.36; H, 5.51; S, 14.33.

3-(2-Benzo[*b*]thienyl)propanol (27). Reduction of the ester **26** with lithium aluminum hydride in anhydrous ether gave the alcohol **27** in almost quantitative yield. The crude product was crystallized from carbon tetrachloride, giving **27** as white plates: mp 50–51.5 °C (lit.[22] 50 °C); NMR δ 1.92 (q, 2 H, CH_2), 2.70 (s, 1 H, OH), 2.96 (t, 2 H, CH_2), 3.66 (t, 2 H, CH_2), 7.01 (br s, 1 H, H_3), 7.06–7.92 (m, 4 H, Ar). Anal. Calcd for $C_{11}H_{12}OS$: C, 68.72; H, 6.29; S, 16.67. Found: C, 69.01; H, 6.25; S, 16.36.

3-(2-Benzo[*b*]thienyl)propyl Phenylpropiolate (18). To a stirred solution of freshly distilled phenylpropiolyl chloride[23] (3.62 g, 22 mmol) in 50 mL of benzene at 0 °C was added anhydrous pyridine (2.75 g, 34.8 mmol). Instantaneously a yellow precipitate was obtained which almost completely disappeared upon adding dropwise a solution of the above alcohol **27** (3.84 g, 20 mmol) in 30 mL of benzene. The resulting mixture was stirred for 2 h at 55 °C and kept overnight at room temperature. The reaction was poured into 200 mL of water. After extraction with benzene, the organic layers were respectively washed with a 1 N hydrochloric acid solution, saturated sodium bicarbonate, and water and dried over magnesium sulfate. The solvent was removed and the residual oil was chromatographed over Florisil (100–200 mesh) with carbon tetrachloride/benzene (4:1) as eluent. The white material eluted was crystallized from methanol, giving **18** as white needles in 85% yield: mp 73–75 °C; NMR δ 2.12 (q, 2 H, CH_2), 3.01 (t, 2 H, CH_2), 4.32 (t, 2 H, CH_2), 7.06 (br s, 1 H, H_3), 7.10–7.93 (m, 9 H, Ar); UV_{max} 257 nm (log ε 4.39). Anal. Calcd for $C_{20}H_{16}O_2S$: C, 74.97; H, 5.03; S, 10.00. Found: C, 74.63; H, 4.98; S, 9.87.

2-(2-Benzo[*b*]thienyl)ethyl Phenylpropiolate (19). Ester **19** was prepared according to the procedure described for **18**, starting with 3.0 g (0.018 mol) of phenylpropiolyl chloride,[23] 1.98 g (0.025 mol) of pyridine, and 2.70 g (0.015 mol) of 2-(2-benzo[*b*]thienyl)ethanol (**24**). After column chromatography the white material eluted was crystallized from methanol, giving **19** as white needles in 95% yield: mp 90–91.5 °C; NMR δ 3.30 (t, 2 H, CH_2), 4.53 (t, 2 H, CH_2), 7.14 (br s, 1 H, H_3), 7.20–7.95 (m, 9 H, Ar); UV_{max} 258 nm (log ε 4.39). Anal. Calcd for $C_{19}H_{14}O_2S$: C, 74.48; H, 4.60; S, 10.46. Found: C, 74.27; H, 4.55; S, 10.31.

Photolysis of 2-(3-Benzo[*b*]thienyl)ethyl But-2-ynoate (1). A solution of 210 mg (0.86 mmol) of **1** and about 24 mg (0.2 mmol) of acetophenone in 400 mL of benzene was irradiated in an immersion well apparatus for 8 h. After evaporation of the solvent the results of six consecutive runs were combined and purified by column chromatography over Florisil. With 250 mL of CCl_4 and 250 mL of CCl_4/CH_2Cl_2 (6:1) as eluent the acetophenone and 90 mg (7%) of the starting material was obtained. Further elution with CCl_4/CH_2Cl_2 mixtures of increasing ratio as eluent gave 470 mg of **3**. Finally, elution with CH_2Cl_2 gave a fraction which contained 52 mg of **3** and 28 mg of **2**. This fraction was further purified by TLC using C_6H_6/CH_2Cl_2 (1:1) as eluent to give 20 mg of almost pure **2**.

4a,9a-(1-Methyletheno)-1*H*-3,4-dihydro[1]benzothieno-[2,3-*c*]pyran-1-one (3): yield, 522 mg (42%); mp 97–98 °C (pale yellow plates from methanol); NMR δ 1.86 (d, 3 H, CH_3, $J \sim 1.6$ Hz), 2.17–2.38 (m, 2 H, CH_2), 4.43–4.64 (m, 2 H, CH_2), 6.10 (q, 1 H, H_{allyl}, $J \sim 1.6$ Hz), 7.19 (br s, 4 H, Ar); UV_{max} 247 nm (log ε 3.80), 285–287 (3.17); IR (KBr) 1635 cm^{-1} (C=C), 1720, 1725 (C=O); mass spectrum *m/e* (relative intensity) 244 (84), 204 (100), 184 (18), 174 (58), 146 (35). Anal. Calcd for $C_{14}H_{12}O_2S$: C, 68.82; H, 4.95; S, 13.12. Found: C, 68.79; H, 4.96; S, 13.06.

No reaction of **3** was observed upon irradiation of 175 mg of **3** and about 20 mg of acetophenone in 400 mL of benzene for 21 h in a Rayonet reactor with 300-nm lamps. No rearranged products could be detected by NMR analysis. The same result was obtained if no sensitizer was added.

6-Methyl-9-oxa-4-thia-2,3-benzotricyclo[5.4.0.0^{1,5}]undec-a-2,6-dien-8-one (2): 28 mg (2%); NMR δ 2.03 (d, 3 H, CH_3, $J \sim 1.2$ Hz), 2.42–2.63 (m, 2 H, CH_2), 4.40–4.88 (m, 2 H, CH_2), 4.42 (d, 1 H, methine, $J \sim 1.2$ Hz), 7.12 (br s, 4 H, Ar); mass spectrum *m/e* 244.

Upon irradiation of a solution of 20 mg of **2** in 15 mL of benzene for 5 h in a Rayonet reactor with 300-nm lamps, compound **2** was completely converted into the lactone **3**, as shown by NMR analysis.

A solution of 230 mg (0.94 mmol) of **1** in 400 mL of benzene was irradiated in an immersion well apparatus for 9 h. After evaporation of the solvent, the residue was passed through a Florisil column with CH_2Cl_2 as eluent in order to remove polymeric materials. NMR analysis of the eluate showed the presence of both **2** and **3** in about a 1:3 ratio at a <10% conversion.

Pyrolysis of 3 into 1*H*-3,4-Dihydro[1]benzothieno[2,3-*c*]-pyran-1-one (4). Pyrolysis of 148 mg of **3**, preheated to 120 °C, was conducted in the gas phase in a flow system by passing the vapor through a quartz tube packed with quartz chips at 720 °C (7×10^{-5} Torr). No reaction occurred below 640 °C. The resultant crude pyrolysate was collected at −195 °C, and almost pure **4** was scraped off the walls of the collector. NMR analysis of the crude pyrolysate revealed the presence of **4** (70%) and **3** (20%). Recrystallization from carbon tetrachloride gave white crystals of **4**: mp 172–173 °C; NMR δ 3.20 (t, 2 H, CH_2), 4.76 (t, 2 H, CH_2), 7.40–8.10 (m, 4 H, Ar); IR 1705 cm^{-1} (C=O), mass spectrum *m/e* (rel intensity) 204 (100), 174 (79), 146 (93). Anal. Calcd for $C_{11}H_8O_2S$: C, 64.68; H, 3.95; S, 15.70. Found: C, 64.40; H, 3.85; S, 15.61.

Photolysis of 2-(2-Benzo[*b*]thienyl)ethyl But-2-ynoate (5).

A solution of 250 mg (1.02 mmol) of **5** and 83 mg (0.69 mmol) of acetophenone in 400 mL of benzene was irradiated in an immersion well apparatus for 23 h. After evaporation of the solvent, the residue of three consecutive runs was passed through a Florisil column. Elution with CCl_4/CH_2Cl_2 (9:1) gave 76 mg (10%) of **5**, followed by the acetophenone. Further elution with CCl_4/CH_2Cl_2 (1:1), and finally with CCl_4/CH_2Cl_2 (1:3), gave 120 mg (15%) of crude **11** (**10**). Compound **11** (**10**) was further purified by TLC using ether/petroleum ether (1:4) as eluent. Analytically pure **11** (**10**) was obtained by crystallization from hexane: mp 98–101 °C; NMR δ 3.07 (s, 3 H, CH_3), 3.16 (t, 2 H, CH_2), 4.49 (t, 2 H, CH_2), 7.5–7.9 (m, 4 H, Ar), 8.16–8.30 (m, 1 H, Ar); IR (KBr) 1725 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 212 (100), 197 (16), 182 (51), 169 (22), 154 (38), 153 (41), 152 (29).

Reduction of **11** (**10**) with $LiAlH_4$ gave **13** (**12**): mp 103–105 °C; NMR δ 2.74 (s, 3 H, CH_3), 3.07 (t, 2 H, CH_2), 3.88 (t, 2 H, CH_2), 4.84 (s, 2 H, CH_2), two low-field one-proton multiplets in the aromatic region are present, centered at δ 8.01 and 7.74.

Photoaddition of Methyl Phenylpropiolate to 2-Methylbenzo[*b*]thiophene. Consecutively, six solutions of 512 mg (3.2 mmol) of methyl phenylpropiolate, 474 mg (3.21 mmol) of 2-methylbenzo[*b*]thiophene, and 105 mg (0.58 mmol) of benzophenone in 400 mL of benzene were irradiated in a Rayonet RPR-100 reactor fitted with 350-nm fluorescence lamps for 17–21 h. NMR analysis of the crude reaction mixtures revealed a conversion of 30–40% of the 2-methylbenzo[*b*]thiophene. After evaporation of the solvent the residues were combined and purified by column chromatography over Al_2O_3. With CCl_4 as eluent 1.65 g (58%) of 2-methylbenzo[*b*]thiophene was recovered. Further elution with CCl_4/CH_2Cl_2 mixtures of increasing ratio gave fractions of the photocycloaddition products. Each fraction was purified by TLC using ether/petroleum ether (1:19) as eluent. Thus, all four possible photocycloadducts of methyl phenylpropiolate to 2-methylbenzo[*b*]thiophene could be isolated. Unfortunately, the compounds **14**, **15**, and **17** could only be obtained mixed with some 1-carbomethoxy-8-phenylcyclooctatetraene.

7-Carbomethoxy-1-methyl-6-phenyl-2-thiabenzo[*b*]bicyclo[3.2.0]hepta-3,6-diene (14): yield ~1%; NMR δ 1.90 (s, 3 H, CH_3), 3.87 (s, 3 H, $COOCH_3$), 4.65 (s, 1 H, H_5, methine); mass spectrum *m/e* 308, 148 (100).

Upon irradiation of a solution of ~25 mg of **14** in 50 mL of benzene at 300 nm for 21 h, compound **16** was obtained, determined by NMR analysis.

6-Carbomethoxy-1-methyl-7-phenyl-2-thiabenzo[*b*]bicyclo[3.2.0]hepta-3,6-diene (15): yield ~3%; mixed with some **14**; NMR δ 1.94 (s, 3 H, CH_3), 3.84 (s, 3 H, $COOCH_3$), 4.42 (s, 1 H, H_5 methine); mass spectrum *m/e* 308, 148 (100).

Upon irradiation of a solution of ~25 mg of **15** in 50 mL of benzene at 300 nm for 22 h, compound **17** was obtained, determined by NMR analysis.

7-Carbomethoxy-6-methyl-1-phenyl-2-thiabenzo[*b*]bicyclo[3.2.0]hepta-3,6-diene (16): yield ~20%; mp 108–109 °C (from methanol); NMR δ 2.10 (d, 3 H, CH_3, $J \sim 1.4$ Hz), 3.80 (s, 3 H, $COOCH_3$), 4.32 (q, 1 H, H_5 methine, $J \sim 1.2$ Hz), 7.10–7.75 (m, 9 H, Ar); mass spectrum *m/e* (rel intensity) 308 (100), 276 (59, $M^+ - S$), 249 (73, $M^+ - COOCH_3$), 248 (70), 234 (64), 215 (57), 210 (61). Anal. Calcd for $C_{19}H_{16}O_2S$: C, 74.00; H, 5.23; S, 10.40. Found: C, 74.01; H, 5.23; S, 10.44.

Compound **16** appeared to be photostable on irradiation of a solution of 50 mg of **16** in 50 mL of benzene for 24 h at 300 nm. Also, no traces of the isomers **14**, **15**, or **17** could be detected when a solution of 50 mg of **16** in 50 mL of benzene was irradiated at 350 nm for 22 h in the presence of 50 mg of benzophenone.

1-Carbomethoxy-6-methyl-7-phenyl-2-thiabenzo[*b*]bicyclo[3.2.0]hepta-3,6-diene (17): yield ~10%; NMR δ 2.07 (d, 3 H, CH_3, $J = 1.4$ Hz), 3.78 (s, 3 H, $COOCH_3$), 4.78 (q, 1 H, H_5 methine, $J \sim 1.2$ Hz); mass spectrum showed major fragmentation peak at *m/e* 192.

Compound **17** appeared to be photostable on irradiation of a solution of **17** in benzene for 24 h at 300 nm. No isomers could be detected by TLC or NMR analysis.

Photolysis of 3-(2-Benzo[*b*]thienyl)propyl Phenylpropiolate (18). A solution of 250 mg (0.78 mmol) of **18** in 400 mL of benzene was irradiated in an immersion well apparatus for 20 h. After evaporation of the solvent the results of two consecutive runs were combined and purified by column chromatography over Florisil. With $CCl_4/CHCl_3$ (9:1) as eluent, 60 mg (14%) of **18** was obtained. Further elution with $CCl_4/CHCl_3$ (1:1) gave 298 mg (48%) of **3-(2-benzo[*b*]thienyl)propyl 5-phenyltetracyclo[3.3.0.$0^{2,4}$.$0^{3,6}$]oct-7-ene-4-carboxylate (20).** Further purification of **20** was done by TLC using benzene/$CHCl_3$ (1:1) as eluent: NMR δ 1.90 (m, 2 H, CH_2), 2.75 (t, 2 H, CH_2), 2.98 (t, 2 H, H′$_2$ and H′$_3$), 3.92 (m, 2 H, H′$_1$ and H′$_6$), 4.12 (t, 2 H, CH_2), 6.12 (t, 2 H, H′$_7$ and H′$_8$), 6.93 (br s, 1 H, H_3), 7.29–7.95 (m, 9 H, Ar) with a singlet (5 H, Ph) centered at δ 7.28. Anal. Calcd for $C_{26}H_{22}O_2S$: C, 78.36; H, 5.56; S, 8.04. Found: C, 78.40; H, 5.68; S, 7.85.

Chemical structure proof was obtained by reducing the ester **20** with lithium aluminum hydride, giving the alcohols **27** and 4-hydroxymethyl-5-phenyltetracyclo[3.3.0.$0^{2,4}$.$0^{3,6}$]oct-7-ene[12] with the same spectroscopic properties. The ester **20** (460 mg) was also saponified in a solution of 10 mL of 20% KOH solution and 50 mL of dioxane at 85 °C for 14 h. The reaction mixture was poured into water, neutralized, and extracted with ether. The combined ether extracts were dried and treated with an ethereal diazomethane solution. After workup as described for **25**, the residual oil was separated by TLC, using benzene/CH_2Cl_2 (1:1) as eluent. The top band showed the presence of methyl 5-phenyltetracyclo[3.3.0.$0^{2,4}$.$0^{3,6}$]oct-7-ene-4-carboxylate, contaminated with some 1-phenyl-8-carboxymethylcyclooctatetraene, which thermally arose during the saponification.[12]

Actually, the yield of **20** during the photolysis is much higher because addition products of 18 to **20** were also obtained. However, neither an intramolecular cycloadduct nor a cyclooctatetraene adduct could be detected.

The same result was observed when **18**, under the same conditions, was irradiated in the presence of 50 mg (0.41 mmol) of acetophenone.

Photolysis of 2-(2-Benzo[*b*]thienyl)ethyl Phenylpropiolate (19). A solution of 250 mg (0.82 mmol) of **19** in 400 mL of benzene was irradiated in an immersion well apparatus for 20 h. After evaporation of the solvent the results of two consecutive runs were combined and purified by column chromatography over Florisil. With CCl_4/CH_2Cl_2 mixtures of increasing ratio were eluted 105 mg (21%) of **19** and 120 mg (19%) of **21**. Further purification by TLC using benzene/$CHCl_3$ (1:1) as eluent gave pure **2-(2-benzo[*b*]thienyl)ethyl 5-phenyltetracyclo[3.3.0.$0^{2,4}$.$0^{3,6}$]oct-7-ene-4-carboxylate (21):** NMR δ 3.03 (t, 2 H, H′$_2$ and H$_3$′), 3.11 (m, 2 H, H′$_1$ and H′$_6$), 4.46 (t, 2 H, CH_2), 6.11 (t, 2 H, H′$_7$ and H′$_8$), 6.93 (br s, 1 H, H_3), 7.15–7.91 (m, 9 H, Ar) with a sharp singlet (5 H, pH) centered at δ 7.25. Anal. Calcd for $C_{25}H_{20}O_2S$: C, 78.10; H, 5.24; S, 8.34. Found: C, 78.11; H, 5.17; S, 8.17. Chemical degradation as described for **20** proved the assigned structure of **21**.

Further elution gave 76 mg (15%) of a monomeric compound [NMR δ 2.48 (t, 2 H, CH_2), 4.54 (t, 2 H, CH_2), 4.88 (br s, 1 H); mass spectrum *m/e* 306, 274] to which we assigned the structure of **23** (vide supra). A pure sample could not be obtained. In the fractions eluted with CH_2Cl_2 addition products of **19** to **21** were shown to be present.

Upon irradiation of **19** under the same conditions in the presence of 50 mg (0.41 mmol) of acetophenone, 250 mg (40%) of **21** was isolated in addition to 65 mg (13%) of starting material **19**. Furthermore, a trace of **23** could be detected besides dimeric compounds. No cyclooctatetraene adducts could be observed on irradiation with or without sensitizer.

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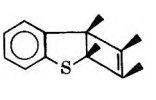
Registry No.—**1**, 65942-59-8; **2**, 65942-60-1; **3**, 65942-61-2; **4**, 65942-62-3; **5**, 65942-63-4; **6**, 65942-64-5; **7**, 65942-65-6; **11**, 65942-66-7; **13**, 65942-67-8; **14**, 65942-68-9; **15**, 65942-69-0; **16**, 31739-35-2; **17**, 31739-36-3; **18**, 56942-70-3; **19**, 65942-71-4; **20**, 65942-72-5; **21**, 65942-73-6; **23**, 65942-74-7; **24**, 30962-69-7; **25**, 65942-75-8; **26**, 65942-76-9; **27**, 31909-05-4; benzo[*b*]thiophene, 95-15-8; 2-butynoic acid, 590-93-2; 2-(3-benzo[*b*]thienyl)ethanol, 3133-87-7; β-(2-benzo[*b*]thienyl)acrylic acid, 25050-08-2; phenylpropiolyl chloride, 7299-58-3; methyl phenylpropiolate, 4891-38-7; 2-methylbenzo[*b*]-thiophene, 1195-14-8.

Supplementary Material Available: Full NMR data for all known compounds of the general structure



(2 pages). Ordering information is given on any current masthead page.

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Bis(trifluoromethyl)thioketene. 3. Further Cycloadditions

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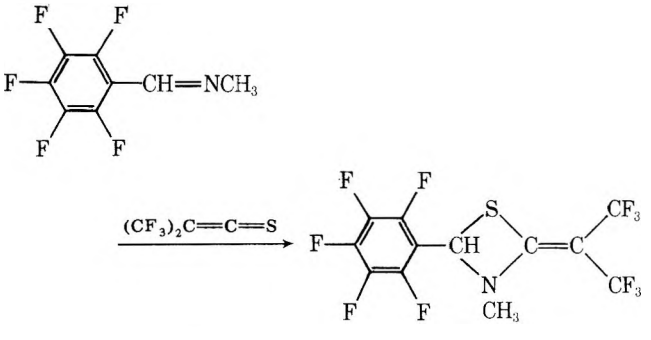
Bis(trifluoromethyl)thioketene cycloadds to Schiff bases to form thiazetidines and 1,3,5-dithiazines. Three moles of the thioketene adds to methyl isothiocyanate in a similar reaction. The thioketene adds to aryl azides to yield Δ^3-1,2,3,4-thiatriazolines which can be pyrolyzed to 2,1-benzisothiazoles. With phosphite esters, the thioketene forms phosphoranylidene-1,3-dithiolanes which hydrolyze to phosphonates. From certain methylbenzenes, substituted 1-phenethyl-3-hexafluoroisopropylidene-1,3-dithietanes are obtained. Novel heterocycles have been made by Diels–Alder reactions. Thiothiophthene forms adducts with 2 and 4 mol of the thioketene.

Previous articles have described the synthesis,[2a] cycloadditions,[2a] and acyclic derivatives[2b] of bis(trifluoromethyl)thioketene. The versatility of the thioketene as a reactant in a variety of cycloadditions is now further illustrated by its reaction with Schiff bases, aryl azides, phosphite esters, methylbenzenes, dienes, and thiothiophthene.

Cycloaddition to Schiff Bases. Both mono- and diadducts of bis(trifluoromethyl)thioketene with Schiff bases have been obtained. With *N*-(pentafluorobenzylidene)methylamine a 1,3-thiazetidine 1 is formed by a cycloaddition involving the thiocarbonyl group.

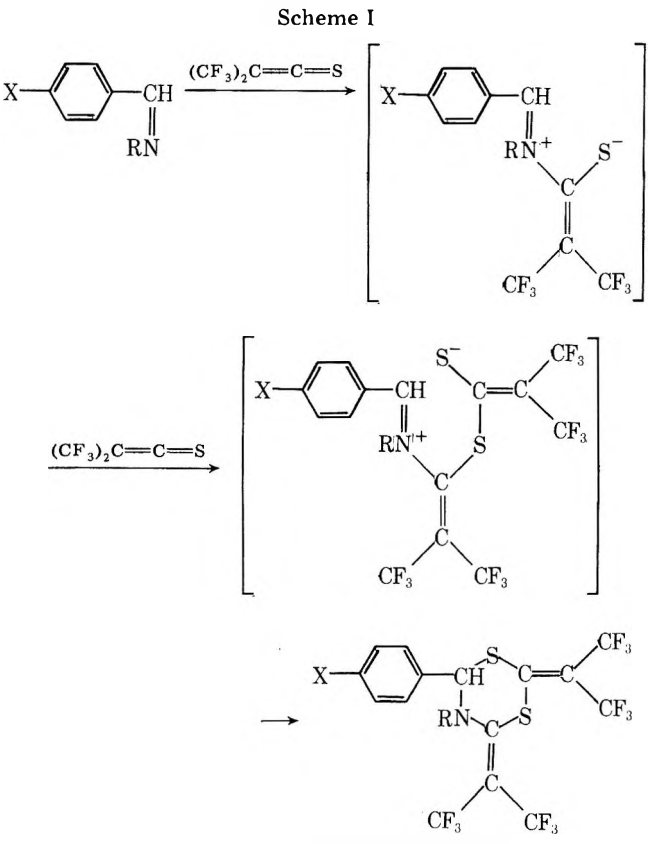


1

The structure was derived from IR and NMR data, with H–F and F–F couplings, as given in the Experimental Section. The mode of addition is analogous to the 1:1 reaction of the thioketene with carbodiimides to form 1,3-thiazetidines.[2a]

With ordinary arylideneamines, the reaction takes a different course and does not stop at the 1:1 stage even in the presence of excess Schiff base. Two molecules of the thioketene participate to form the 1,3,5-dithiazines **2** (Scheme I).

Scheme I



2a, X = H; R = CH_3
b, X = H; R = *i*-Pr
c, X = Cl; R = CH_3
d, X = O_2N; R = CH_3
e, X = CH_3O; R = *p*-$CH_3OC_6H_4$

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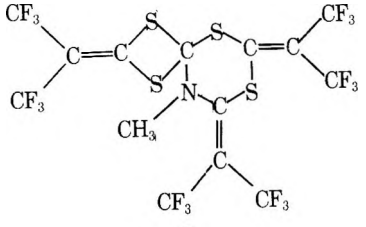
The mechanism is analogous to that proposed for the polymerization of the thioketene by Lewis bases,[2a] but here the process is terminated by cyclization.

Oxidation of **2a** with chromium trioxide in acetic acid yields $C_6H_5CON(CH_3)COCH(CF_3)_2$, prepared independently from *N*-methylbenzamide and $(CF_3)_2C{=}C{=}O$. This supports the sequence of atoms and substituents at positions 4, 5, and 6. The NMR analysis for **2a** is recorded in the Experimental Section.

The asymmetric carbon atom in the 6 position is reflected in the ^1H NMR spectrum for **2b**, which shows a quartet for the methyl groups in $(CH_3)_2CH$ rather than a doublet.

In contrast to bis(trifluoromethyl)thioketene, hindered thioketenes are reported mainly to add to Schiff bases to form thiolactams by 2 + 2 cycloaddition of C=C to C=N.[10] In some cases, thiazetidine formation took place followed by cycloreversion to a thione and a ketenimine.

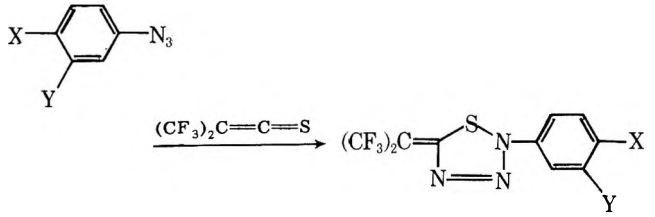
Addition to Methyl Isothiocyanate. Addition to aryl isothiocyanates to form 1,3-dithietanes was reported previously.[2a] With methyl isothiocyanate, three molecules of the thioketene add. The first step is probably analogous to the above reaction. The MeN=C double bond then functions as do the Schiff bases in the previous section because of the more basic nitrogen compared to ArN=C, and two more molecules of the thioketene add to form **3**.



3

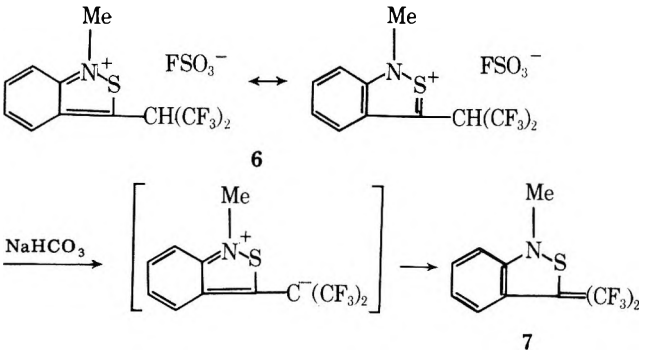
The $(CF_3)_2C{=}$ group on the left produces a singlet in the ^{19}F NMR spectrum as has been shown with many other 2-(hexafluoroisopropylidene)-1,3-dithietanes.[2a] The remaining four trifluoromethyl groups produce a spectrum identical, except for small shifts, with that of the 2:1 thioketene/Schiff base adducts described in the previous section. Thus, the two molecules have a common structural feature represented by the 1,3,5-dithiazine ring.

Addition to Aryl Azides. Aryl azides undergo 1,3-cycloaddition with bis(trifluoromethyl)thioketene to form yellow Δ^3-1,2,3,4-thiatriazolines **4a–e**. The ^{19}F NMR spectra show two quadruplets or an A_3B_3 pattern characteristic of $(CF_3)_2C{=}C$ attached to two different atoms, which indicates that addition to the thiocarbonyl group has occurred. The direction of addition is revealed by pyrolysis of the product to a 2,1-benzisothiazole, **5**. The 2,1-benzisothiazole structure is supported by NMR data and reductive desulfuration with Raney nickel in ethanol to 2-$EtNHC_6H_4CH_2CH(CF_3)_2$.[32] That the pyrolysis product was not 2-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]benzothiazole was demonstrated by the synthesis of this compound from 2-aminobenzenethiol and bis(trifluoromethyl)thioketene.



4a, X = H; Y = H
b, X = CH_3; Y = H
c, X = OMe; Y = H
d, X = Cl; Y = H
e, X = Cl; Y = Cl

Scheme II



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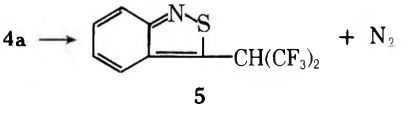
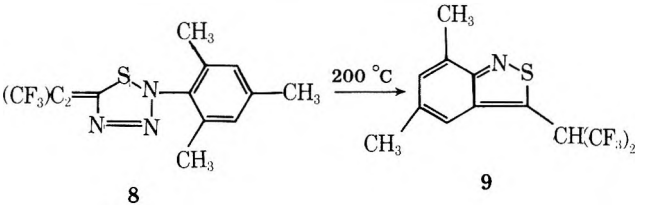


5

Methylation of **5** with methyl fluorosulfonate produces **6**. 2,1-Benzisothiazolium salts are known, but this one is converted to a substituted 1,3-dihydro-2,1-benzisothiazole (**7**) on treatment with base (Scheme II).

The pyrolysis was tried with a thiatriazoline (**8**) in which the ortho positions of the phenyl group were blocked by methyl groups. This, surprisingly, also gave a 2,1-benzisothiazole (**9**) with loss of the interfering methyl group. The loss of the methyl group is clearly shown by NMR. Since the yield was only 24%, the rest being tar, no clues to the mechanism were found.

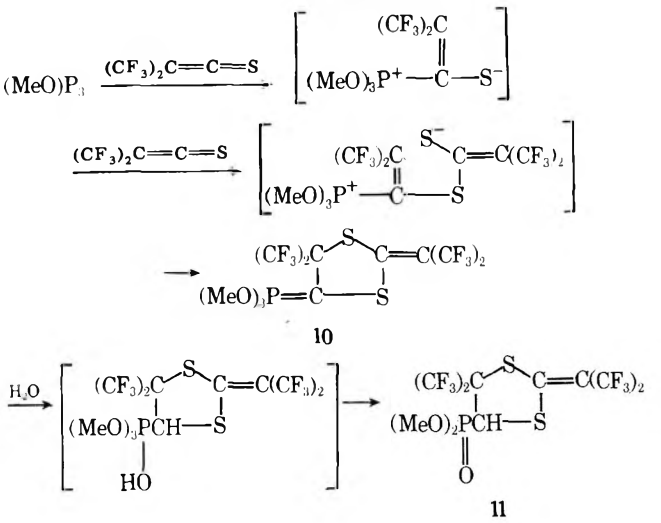


8 **9**

The formation of 1:1 $(CF_3)_2C{=}C{=}S$/azide adducts is accompanied by orange 2:1 adducts. These may also be formed by adding $(CF_3)_2C{=}C{=}S$ to the 1:1 adducts. The added molecule of $(CF_3)_2C{=}C{=}S$ produces a singlet in the NMR spectrum at a position for $(CF_3)_2$ attached to saturated carbon. The structure of the 2:1 adducts has not been established. In the mass spectrometer they break down to their components rather than providing definitive fragments.

Reaction with Phosphite Esters. Reaction of the thioketene with phosphite esters appeared to be a way to prepare a 1,4,2-dithiaphospholane, a ring system known only by a reference to it as an unstable intermediate in the reaction of chlorothioacetone with triethyl phosphite.[3] However, the cumulene structure of the thioketene made possible ring closure at a double bond, rather than at phosphorus, to form, with trimethyl phosphite, the water-sensitive phosphorus ylide **10** (Scheme III). Triphenyl phosphite also undergoes these reactions.

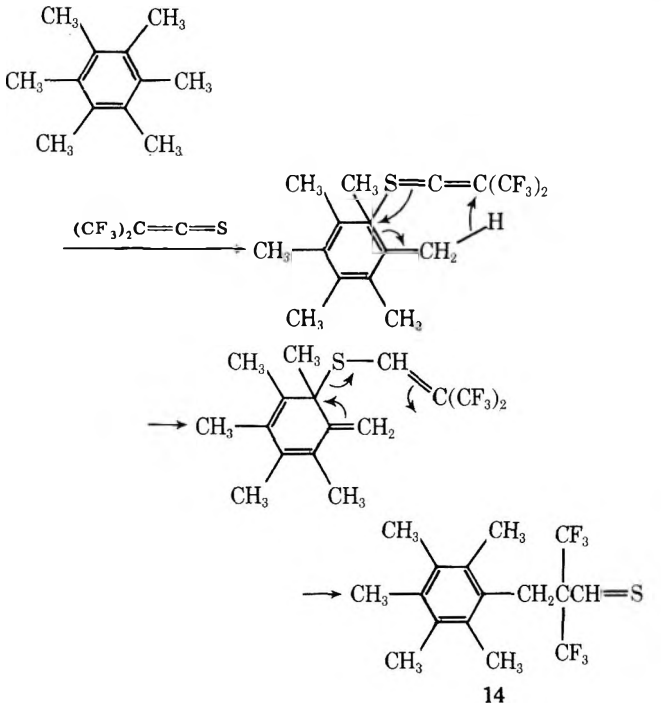
Scheme III



10

11

Scheme IV

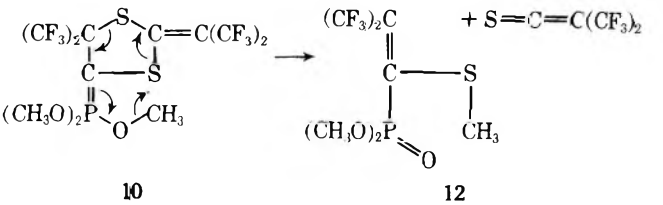


14

When **10** is exposed to moist air, one methyl group is removed and there results the phosphonate **11** (Scheme III), which is relatively stable to hydrolysis. This may result from hydrolysis of a methoxy group followed by a proton shift from oxygen to carbon, or addition of water to P=C followed by loss of methanol. The ^1H NMR spectrum shows typical couplings of 19 Hz for HCP and 11 Hz for HCOP. Residence of the proton on carbon is further substantiated by the fact that the CF_3 groups in the 5 position now appear as a pair of quadruplets in the ^{19}F spectrum because one is cis and one is trans to the proton.

When **10** is subjected to vacuum distillation, it decomposes to **12**.

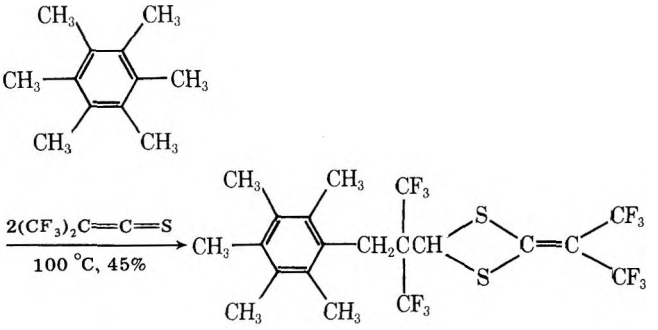
In contrast to the thioketene, hexafluorothioacetone and



10 12

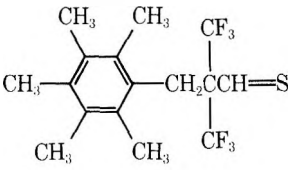
trimethyl phosphite form $(CF_3)_2C{=}P(OMe)_3$.[4] Thiofluorenone reacts in the same way,[4] while thiobenzophenone yields $(MeO)_3PS$, $Ph_2CHPO(OEt_2)$, $Ph_2CHSPO(OEt)_2$, and $Ph_2C{=}CPh_2$.[5] Thiocyclohexanone gives $(CH_2)_5C(SMe)PO(OMe)_2$ and $(CH_2)_5C(SH)PO(OMe)_2$.[6] Bis(trifluoromethyl)ketene and triethyl phosphite produce tetrakis(trifluoromethyl)allene.[7]

Addition to Methylbenzenes. Certain methylbenzenes add to the thioketene in an unusual reaction. With durene at 150 °C, a 54% yield of an analogous product was obtained, and with *p*-methylanisole at 150 °C the yield was 20%. Toluene and xylene were not reactive under these conditions.



13

The course of reaction might appear to be addition to C=C of the thioketene to form the intermediate thioaldehyde **14**,

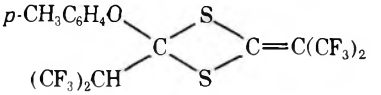


14

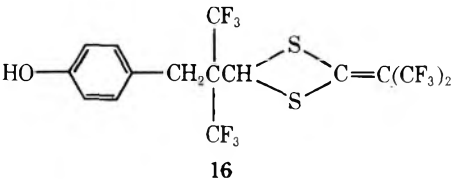
to which another molecule of the thioketene cycloadds to form the dithietane **13**. However, all other known reactions of the thioketene with organic compounds can be rationalized on the basis of addition to C=S. Hence, the following mechanism (Scheme IV) is proposed involving an initial ene reaction followed by rearrangement.[31] Ene reactions of the thioketene with aliphatic olefins have been amply demonstrated.[2b] Alkylbenzenes are known to undergo ene reactions with benzyne.[30]

A free-radical mechanism seems unlikely. The reaction proceeds just as well in the presence of the inhibitor 2,2-diphenyl-1-picrylhydrazyl, though the hydrazyl does not survive the heating period as such.

From the reaction of the thioketene with *p*-cresol at 100 °C, three compounds were isolated. The expected ester, *p*-$CH_3C_6H_4OCSCH(CF_3)_2$, was obtained in 35% yield. This added another mole of the thioketene to form the dithietane **15** (18%). Finally, a 1.7% yield of **16** was isolated, an analogue



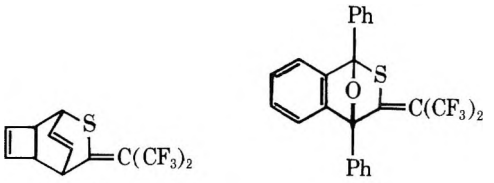
15



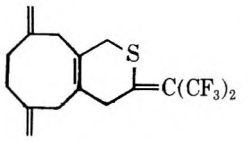
16

of the products obtained with the other methylbenzenes described above.

Diels–Alder Adducts. Diels–Alder adducts of the thioketene with 2,3-dimethylbutadiene[2a] and several cyclopentadienes[8,9] have been reported previously. The new heterocyclic ring systems **17**, **18**, and **19** have now been synthesized by reaction of the thioketene with cyclooctatetraene, 1,3-diphenylisobenzofuran, and 1,2,4.7-tetrakis(methylene)cyclooctane. Compound **17** represents the normal mode of Diels–Alder addition to cyclooctatetraene. Diels–Alder adducts have also been made from 6,6-diphenylfulvene, anthracene, pentamethyl-5-vinylcyclopentadiene, spiro[4.4]-nona-1,3-diene, butadiene, and 2,3-dichlorobutadiene. With 1,3-cyclohexadiene, both the Diels–Alder adduct **20** and the ene product **21** form.

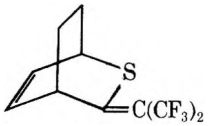


17 **18**

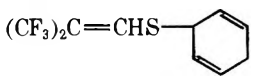


19

The cyclopentadiene adduct **22** has been progressively oxidized with *m*-chloroperbenzoic acid (Scheme V).



20, 54.5%



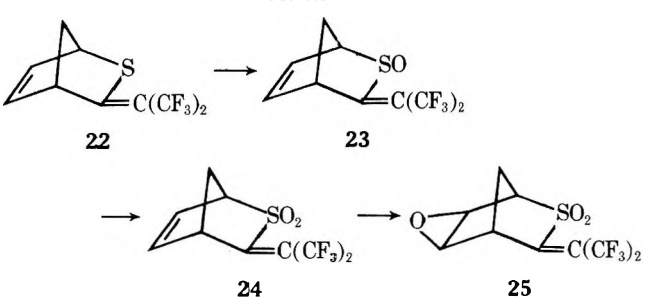
21, 45.5%

The sulfur atom does not interfere with catalytic hydrogenation. The cyclic double bond in **22** and the cyclobutene double bond in **17** have been reduced.

Thiothiophthene Adducts. Thiothiophthene has attracted interest since its structure was elucidated by X rays in 1958.[11,28] Bis(trifluoromethyl)thioketene (2 mol) reacts with thiothiophthene (2,5-dimethyl[1,2]dithiolo[1,5-*b*][1,2]dithiol-7-S^{IV}, **26**) to form a product with the same orange color as thiothiophthene. The ^{19}F NMR spectrum shows a doublet for $(CF_3)_2CH$ and a singlet for $(CF_3)_2C{=}C<$. This indicates thiothiophthene is acylated by the thioketene to form the intermediate **27** in Scheme VI, and that the second molecule of the thioketene cycloadds to the introduced, reactive thiocarbonyl group to form the dithietane **28**. The trithiapentalene system is not as reactive as a free thione group.[12] The reaction is comparable to the thioacylation of indole with the thioketene.[2b]

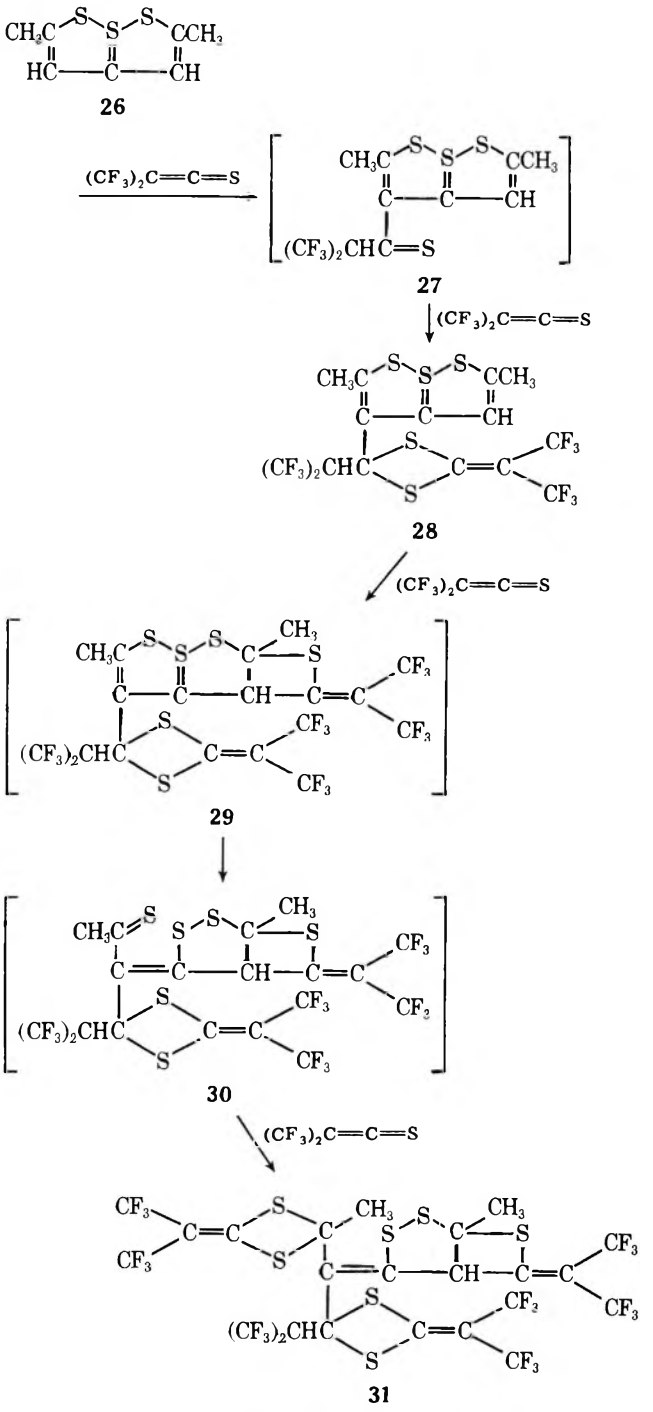
The compound **28** reacts with an additional 2 mol of the thioketene to form a white compound. The CH= absorption in the ^1H NMR spectrum is replaced by an upfield peak. This suggests thietane formation by cycloaddition of the thioketene to $-CH{=}C(CH_3)S-$ in the way the thioketene does to simple vinyl thioethers.[2a] Correlative to the shift of the proton peak is an A_3B_3 pattern at the proper shift for $(CF_3)_2C{=}$ in the ^{19}F spectrum. The addition would logically take place on the more electron-rich, less-hindered double bond not attached to the polyfluoro group to form the intermediate **29**. This cycloaddition disrupts the trithiapentalene system and bond rearrangement is postulated to take place to produce the intermediate conjugated thione **30**. The fourth molecule of the thioketene then reacts with the thiocarbonyl group of **30** to form another dithietane unit, which is indicated by an additional singlet at the proper shift in the ^{19}F NMR spectrum. A Raman spectrum band at 505 cm^{-1} is assigned to the disulfide link. Thus, **31** or its geometric isomer is proposed as the structure of the tetraadduct.

Scheme V



22 **23** **24** **25**

Scheme VI



26 **27** **28** **29** **30** **31**

Experimental Section

The ^1H NMR spectra were determined in Varian instruments using Me_4Si as internal reference. The ^{19}F NMR spectra were measured in a Varian A-56/60 instrument using CCl_2FCCl_2F as reference in a capillary placed in the sample tube. This standard is 3800 Hz (67.4 ppm) upfield from CCl_3F. The ^{13}C spectra, using Me_4Si as internal standard, and ^{31}P spectra, using H_3PO_4 in a capillary as reference, were taken on Bruker spectrometers. All downfield values are recorded as positive. A Perkin-Elmer Model 21 spectrometer was used for IR spectra. Raman spectra were taken on a Cary 81 laser spectrometer. Melting and boiling points are uncorrected.

For brevity, hexafluoroisopropylidene is used for $(CF_3)_2C=$ instead of the Chemical Abstracts name, 2,2,2-trifluoro-1-(trifluoromethyl)-ethylidene.

Addition to Schiff Bases. A. *N*-(Pentafluorobenzylidene)-methylamine. *N*-(Pentafluorobenzylidene)methylamine was prepared by stirring 6.5 g of pentafluorobenzaldehyde[13] with 10 mL of aqueous 40% methylamine solution for 16 h. A solid was filtered off and the liquid Schiff base in the filtrate was dissolved in dichloromethane, dried ($MgSO_4$), and distilled to give 2.98 g (43%); bp 55 °C (5 mm); $n^{25}D$ 1.4532; ^1H NMR ($CDCl_3$) 3.63 (s, CH_3), 8.41 ppm (m, CH).

Anal. Calcd for $C_8H_4F_5N$: C, 45.95; H, 1.93; N, 6.70. Found: C, 45.90; H, 2.30; N, 6.96.

To 1.05 g (0.005 mol) of the Schiff base in 10 mL of hexane was added 1.94 g (0.01 mol) of bis(trifluoromethyl)thioketene.[2a] The product precipitated and was filtered from the cooled mixture. Recrystallization from carbon tetrachloride–hexane gave 1.59 g (79%) of 2-(hexafluoroisopropylidene)-3-methyl-4-(pentafluorophenyl)-1,3-thiazetidine (**1**): mp 66.7–67.5 °C; IR 2967 (CH), 1631 (exocyclic C=C), 1515 cm^{-1} (aromatic C=C); ^1H NMR ($CDCl_3$) 2.82 (quadruplet, J = 2.6 Hz, CH_3), 6.21 ppm (s, broadened, CH); ^{19}F NMR 11.54 (quadruplet, J = 9.1 Hz, components split to doublets by CH, J = 1.2 Hz, with further splitting by CH_3, J = 0.5 Hz), 17.90 ppm (quadruplet, J = 9.1 Hz, components split to quadruplets by CH_3, J = 2.6 Hz, components split to doublets by CH, J = 1.3 Hz).

The two CF_3–CH_3 couplings, 0.5 and 2.6 Hz, support the structure given rather than the structure obtained by reverse addition. The two CF_3–CH couplings, 1.2 and 1.3 Hz, are consistent for a proton nearly symmetrically disposed with respect to the CF_3 groups.

Anal. Calcd for $C_{12}H_4F_{11}NS$: C, 35.74; H, 1.00; N, 3.48. Found: C, 35.97; H, 1.04; N, 3.51.

B. *N*-Benzylidenemethylamine. Bis(trifluoromethyl)thioketene (7.76 g, 0.04 mol) was slowly added to a stirred solution of 4.76 g (0.04 mol) of *N*-benzylidenemethylamine in 20 mL of petroleum ether cooled in ice. The product precipitated out and was filtered off (8.5 g). Recrystallization from carbon tetrachloride left 8.1 g (78%) of 2,4-bis(hexafluoroisopropylidene)-5,6-dihydro-5-methyl-6-phenyl-4*H*-1,3,5-dithiazine (**2a**): mp 162–162.8 °C; IR 3049 (=CH), 2941 (CH), 1575, 1548, 1502 cm^{-1} (C=C); ^1H NMR [$(CD_3)_2CO$] 2.65 (s, CH_3), 6.5 (s, CH), 7.1 ppm (Ph); ^{19}F NMR ($CDCl_3$) 9.30 (quadruplet, J = 8 Hz), 10.3 (quadruplet, J = 9 Hz), 11.4 and 13.5 ppm (ten-line patterns). Decoupling, which reduced the ten-line peaks to quadruplets, showed the 9.3-ppm peak to be coupled with 13.5 ppm and 10.3 ppm with 11.4 ppm. The latter two closely spaced peaks are assigned to $(CF_3)_2C=$ in the 2 position where the CF_3 groups are in a similar environment. The ten-line peaks result from F–F coupling (J = 4.5 Hz) between one CF_3 group in the 2 position with one in the 4 position. Coupling between CH_3 and one CF_3 is 1.3 Hz: ^{13}C NMR 40.7 (NCH_3), 70 (6-C in ring), 78, 93.9 [$(CF_3)_2C$], 116.4, 128.9 (CF_3), 152.4, 157.7 ppm (2- and 4-C in ring).

Anal. Calcd for $C_{16}H_9F_{12}NS_2$: C, 37.88; H, 1.79; S, 12.64. Found: C, 37.94; H, 1.90; S, 12.61.

C. *N*-Benzylideneisopropylamine. The adduct **2b** was prepared as above from *N*-benzylideneisopropylamine[14] in 52% yield: mp 138–139 °C; ^1H NMR ($CDCl_3$) 1.49 (d, J = 6.4 Hz, split to d's, J = 4.2 Hz, 2 CH_3), 4.38 (septuplet, CH), 5.93 (s, PhCH), 7.48 ppm (m, C_6H_5); ^{19}F NMR 10.13, 10.88 (quadruplets, 2 CF_3), 11.47, 14.94 ppm (m's, 2 CF_3).

Anal. Calcd for $C_{18}H_{13}F_{12}NS_2$: C, 40.47; H, 2.46; S, 11.98. Found: C, 40.35; H, 2.98; S, 12.00.

D. *N*-(4-Chlorobenzylidene)methylamine. The bis(trifluoromethyl)thioketene adduct **2c** of this Schiff base[15] was prepared as above in 60% yield: mp 143–144 °C; ^1H NMR (CCl_4) 3.03 (s, CH_3), 6.7 (s, CH), 7.65 ppm (4 H, aromatic).

Anal. Calcd for $C_{16}H_8ClF_{12}NS_2$: C, 35.47; H, 1.49; S, 11.84. Found: C, 35.10; H, 1.66; S, 11.80.

E. *N*-(4-Nitrobenzylidene)methylamine. Bis(trifluoromethyl)thioketene (3.88 g, 0.03 mol) was added to 1.64 g (0.01 mol) of *N*-(4-nitrobenzylidene)methylamine[16] in dichloromethane cooled in ice. The solvent was evaporated and the residue was recrystallized three times from carbon tetrachloride to give the adduct **2d**: mp 150–151 °C.

Anal. Calcd for $C_{16}H_8F_{12}N_2O_2S_2$: C, 34.80; H, 1.46; S, 11.61. Found: C, 34.88; H, 1.56; S, 11.63.

F. *N*-(4-Methoxybenzylidene)-4-methoxyaniline. To 2.41 g (0.01 mol) of the Schiff base[17] in 20 mL of dichloromethane was added 1.94 g (0.01 mol) of the thioketene. The solvent was removed and the crystals that slowly formed were washed with methanol to give 2.42 g of **2e**. Recrystallization from hexane left 1.94 g (62%): mp 122–123 °C; ^1H NMR ($CDCl_3$) 3.79 (s, CH_3), 3.82 (s, CH_3), 6.45 ppm (s, CH); ^{19}F NMR 8.50, 10.7 (quadruplets), 11.9, 13.1 ppm (m's).

Anal. Calcd for $C_{23}H_{15}F_{12}NO_2S_2$: C, 43.88; H, 2.40; S, 10.19. Found: C, 44.12; H, 2.56; S, 10.16.

Oxidation of 2a. To 5.07 g (0.01 mol) of **2a** in 100 mL of acetic acid was added 7 g (0.07 mol) of chromium trioxide with stirring. After the mixture became cool, it was poured into 500 mL of water and the solid was filtered off and dried. The product (2.3 g) was recrystallized twice from hexane to leave 1.35 g (43%) of *N*-methyl-*N*-[3,3,3-trifluoro(2-trifluoromethyl)]propionylbenzamide: mp 56–57.2 °C; IR 3012 (=CH), 1712, 1695 (C=O), 1600, 1580, 1493 cm^{-1} (aromatic C=C); ^1H NMR ($CDCl_3$) 3.29 (s, CH_3), 5.46 [septet, $(CF_3)_2CH$], 7.66 ppm (m, C_6H_5); ^{19}F NMR 3.68 ppm (d, J = 7.5 Hz).

Anal. Calcd for $C_{12}H_9F_6NO_2$: C, 46.01; H, 2.90; N, 4.47. Found: C, 45.73; H, 2.94; N, 4.43.

The oxidation product was synthesized independently by passing $(CF_3)_2C=C=O$[18] into a solution of *N*-methylbenzamide in dichloromethane: mp 57–58 °C; ^1H NMR identical with above.

Addition to Methyl Isothiocyanate. Methyl isothiocyanate (1.46 g, 0.02 mol) and 3.88 g (0.02 mol) of bis(trifluoromethyl)thioketene were mixed and occasionally cooled in ice. After 30 min the product was recrystallized from carbon tetrachloride to give 2.25 g (52%) of **3**; mp 121.5–122.5 °C; IR 2994, 2941 (CH), 1629, 1592, 1560 (C=C), 1433 cm^{-1} (NCH_3); ^1H NMR (CCl_4) 3.23 ppm (s, CH_3); ^{19}F NMR 7.94 (quadruplet, J = 8.7 Hz, components split to quadruplets by CH_3, J = 1.2 Hz), 8.92 [s, $(CF_3)_2C=$], 9.79 (quadruplet, J = 9.3 Hz), 11.1, 12.5 ppm (ten-line patterns). Decoupling showed the 7.94-ppm peak to be coupled with 12.5 ppm and 9.79 ppm with 11.1 ppm.

Anal. Calcd for $C_{14}H_3F_{18}NS_4$: C, 25.66; H, 0.46; S, 19.58; mol wt. 655. Found: C, 25.64; H, 0.67; S, 19.60; mol wt (ebullioscopic), 655 (in acetone), 696 (in $ClCH_2CH_2Cl$).

Addition to Aryl Azides. A. Phenyl Azide. To 17.5 g (0.147 mol) of phenyl azide[19] in 100 mL of petroleum ether was added 28.5 g (0.147 mol) of bis(trifluoromethyl)thioketene. The solution was allowed to stand for 6 days and 13.1 g of yellow crystals was filtered off. Recrystallization from methanol left 12.2 g (26.5%) of yellow 5-(hexafluoroisopropylidene)-2-phenyl-Δ^3-1,2,3,4-thiatriazoline (**4a**): mp 125–125.5 °C; IR 3115, 3040 (=CH), 1667 (w), 1590, 1565, 1497 (C=C), 769–714 cm^{-1} (monosubstituted phenyl); ^1H NMR ($CDCl_3$) 7.73 ppm (s, C_6H_5); ^{19}F NMR 10.20, 11.08 ppm [quadruplets, $(CF_3)_2C=C<$].

Anal. Calcd for $C_{10}H_5F_6N_3S$: C, 38.34; H, 1.61; S, 10.24. Found: C, 38.71; H, 1.85; S, 10.54.

The petroleum ether filtrate was allowed to evaporate at room temperature. The crystalline residue was rinsed with cold methanol to give 10.5 g of orange crystals. Recrystallization from methanol left 8.1 g (22%): mp 80–81 °C; IR 3077 (=CH), 1634 (shoulder), 1587, 1572, 1493 cm^{-1} (C=C); ^1H NMR (CCl_4) 7.6–8.2 ppm (broad, split band, C_6H_5); ^{19}F NMR 0.21 (s, 2 CF_3), 9.54, 9.98 ppm (quadruplets, $(CF_3)_2C=C<$]. This compound is the thioketene/azide 2:1 adduct. It was also made by adding $(CF_3)_2C=C=S$ to the 1:1 adduct above in dichloromethane.

Anal. Calcd for $C_{14}H_5F_{12}N_3S_2$: C, 33.16; H, 0.99; S, 12.34. Found: C, 33.59; H, 1.31; S, 12.59.

B. Addition to *p*-Tolyl Azide.[20] The reaction was carried out with *p*-tolyl azide[17] as described for phenyl azide to give 35% of yellow **4b**: mp 124.5–125 °C; ^1H NMR ($CDCl_3$) 2.41 (s, CH_3), 7.57 ppm (AA'BB', *p*-C_6H_4); ^{19}F NMR 9.66, 10.57 ppm [quadruplets, $(CF_3)_2C=C$].

Anal. Calcd for $C_{11}H_7F_6N_3S$: C, 40.43; H, 2.16; N, 12.86; S, 9.80. Found: C, 40.48; H, 2.31; N, 12.70; S, 9.72.

The orange 2:1 adduct (6%) melted at 77.5–78.5 °C; ^1H NMR ($CDCl_3$) 2.45 (s, CH_3), 7.55 ppm (AA'BB', *p*-C_6H_4).

Anal. Calcd for $C_{15}H_7F_{12}N_3S_2$: C, 34.56; H, 1.35; S, 12.30. Found: C, 34.81; H, 1.51; S, 12.51.

C. 4-Methoxyphenyl Azide. To 5.47 g (0.03 mol) of 4-methoxyphenyl azide[21,22] in 15 mL of hexane was added 5.82 g (0.03 mol) of bis(trifluoromethyl)thioketene. After 16 h, 5.82 g (57%) of yellow **4c** was filtered off. Recrystallization from methanol left 4.53 g: mp

113–113.7 °C; ^{19}F NMR (CCl_4) 10.21, 10.92 ppm [A_3B_3, $(CF_3)_2C{=}C$].

Anal. Calcd for $C_{11}H_7F_6N_3OS$: C, 38.48; H, 2.06; S, 9.34. Found: C, 38.81; H, 2.15; S, 9.15.

Evaporation of the hexane filtrate gave 0.44 g (5.5%) of the orange 2:1 adduct. Recrystallization from methanol left 0.27 g: mp 117.5–118 °C; ^{1}H NMR (CCl_4) 3.80 (s, CH_3), 7.32 ppm (aromatic AA'BB' pattern); ^{19}F NMR 0.25 (s, 2 CF_3), 8.42, 8.63 ppm [quadruplets, $(CF_3)_2C{=}C<$].

Anal. Calcd for $C_{15}H_7F_{12}N_3OS_2$: C, 33.52; H, 1.31; S, 11.93. Found: C, 33.81; H, 1.47; S, 11.29.

D. 4-Chlorophenyl Azide. A solution of 4.61 g (0.03 mol) of 4-chlorophenylazide[21,22] and 5.82 g (0.03 mol) of bis(trifluoromethyl)-thioketene in 8 mL of hexane was allowed to stand for 4 days and then filtered to give 3.6 g of a mixture of the 1:1 and 2:1 adducts. Recrystallization from hexane gave 1.5 g (14.4%) of yellow **4d**: mp 119–119.5 °C; ^{19}F NMR ($CHCl_3$) 10.25, 10.57 ppm [quadruplets, $(CF_3)_2C{=}C<$].

Anal. Calcd for $C_{10}H_4ClF_6N_3S$: C, 34.54; H, 1.16; S, 9.22. Found: C, 34,56; H, 1.26; S, 8.93.

The original filtrate and the recrystallization filtrate were combined and allowed to evaporate. The recovered crystals were recrystallized from methanol to give 2.01 g (25%) of the orange 2:1 adduct: mp 102.5–103 °C; ^{19}F NMR (CCl_4) 0.39 (s, 2 CF_3), 9.52, 9.89 ppm [quadruplets, $(CF_3)_2{=}C<$].

Anal. Calcd for $C_{14}H_4ClF_{12}N_3S_2$: C, 31.06; H, 0.75; S, 11.85. Found: C, 30.93; H, 0.94; S, 11.15.

E. 3,4-Dichlorophenyl Azide. A solution of 0.03 mol each of 3,4-dichlorophenyl azide (mp 32 °C) and bis(trifluoromethyl)thioketene in 13 mL of hexane was filtered after 4 days to give 0.46 g (4%) of yellow **4e**: mp 116.5–117 °C from methanol; ^{19}F NMR ($CDCl_3$) 10.25 ppm [A_3B_3 pattern]. At 0 °C this became quadruplets at 10.76 and 11.65 ppm [$(CF_3)_2C{=}C<$].

Anal. Calcd for $C_{10}H_3Cl_2F_6N_3S$: C, 31.40; H, 0.79; S, 8.38. Found: C, 31.73; H, 1.00; S, 8.27.

The solvent from the original hexane filtrate was allowed to evaporate, the residue was stirred with cold methanol, and 2.48 g (29%) of the orange 2:1 adduct was filtered off. Recrystallization from methanol left 1.75 g (20%): mp 96.5–97 °C; ^{19}F NMR (CCl_4) 0.62 (s, 2 CF_3), 9.75, 10.07 ppm [A_3B_3, $(CF_3)_2C{=}C<$].

Anal. Calcd for $C_{14}H_3Cl_2F_{12}N_3S_2$: C, 29.18; H, 0.52; S, 11.13. Found: C, 29.27; H, 0.66; S, 11.14.

F. 2,4,6-Trimethylphenyl Azide. A solution of 1.61 g (0.01 mol) of 2,4,6-trimethylphenyl azide[23] in 5 mL of hexane and 1.94 g (0.01 mol) of bis(trifluoromethyl)thioketene deposited 1.44 g (41%) of yellow 8 after 1 day: mp 126.7–127.2 °C from methanol; ^{1}H NMR ($CDCl_3$) 2.03 (s, 2,6-Me_2), 2.28 (s, 4-Me), 6.93 ppm (s, 3,5-H_2); ^{19}F NMR 10.28, 10.78 ppm [quadruplets, $(CF_3)_2C{=}C<$].

Anal. Calcd for $C_{13}H_{11}F_6N_3S$: C, 43.94; H, 3.12; N, 11.83; S, 9.02. Found: C, 43.69; H, 3.03; N, 11.85; S, 9.40.

Thermal Decomposition of Thiatriazolines. A. 3-[2,2,2-Trifluoro-1-(trifluoromethyl)ethyl]-2,1-benzisothiazole (5). A test tube was placed in an oil bath heated to 210 °C and **4a** (7 g) was added to the tube in portions, each of which decomposed with a puff. The product was cooled and recrystallized from hexane to give 4.7 g (75%) of silky, white needles of the 2,1-benzisothiazole: mp 73.5–74.5 °C; IR 3077 (=CH), 2941 (CH), 742 cm^{-1} (ortho-substituted aromatic); ^{1}H NMR (CCl_4) 5.08 ppm [septuplet, J = 8 Hz, $(CF_3)_2CH$]; ^{19}F NMR 1.06 ppm (d).

Anal. Calcd for $C_{10}H_5F_6NS$: C, 42.11; H, 1.77; S, 11.25; mol wt, 285. Found: C, 42.52; H, 1.83; S, 11.29; mol wt, 285 (mass spectrum).

B. 5-Methyl-3-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-2,1-benzoisothiazole.[20] Pyrolysis of **4b** was carried out at 180 °C as described for the phenyl compound. The product (48%) melted at 89.5–91.5 °C; ^{1}H NMR ($CDCl_3$) 2.48 (s, CH_3), 4.99 [septuplet, $(CF_3)_2CH$], 7.26–7.85 ppm (3 H, aromatic).

Anal. Calcd for $C_{11}H_7F_6NS$: C, 44.14; H, 2.36; S, 10.71. Found: C, 44.54; H, 2.57; S, 10.39.

C. 5,7-Dimethyl-3-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-2,1-benzoisothiazole. **8** (3.4 g) was decomposed at 200 °C as described above. The product was steam-distilled to give an oil which was collected with dichloromethane and dried ($MgSO_4$). Removal of the solvent left 1.6 g, mostly crystalline. Recrystallization from hexane left 0.72 g (24%) of the 2,1-benzoisothiazole **9**: mp 99–100 °C; IR 2924 (CH), 1634, 1541, 1517 cm^{-1} (C=C, C=N); ^{1}H NMR (CCl_4) 2.30 (s, Me), 2.55 (s, Me), 4.82 [septuplet, J = 8 Hz, $(CF_3)_2CH$], 6.94 (s, 6-H), 7.12 ppm (s, 4-H); ^{19}F NMR 1.08 ppm (d, J = 8 Hz).

Anal. Calcd for $C_{12}H_9F_6NS$: C, 46.01; H, 2.90; N, 4.47; S, 10.24. Found: C, 45.86; H, 2.72; N, 4.67; S, 10.60.

Desulfurization of 5. A mixture of 2.35 g of **5**, 85 mL of absolute alcohol, and 20 g of Raney nickel was refluxed for 15 h and then filtered. Hydrochloric acid (1 mL) was added and the solution was evaporated to a glass. The residue was taken up in 10% hydrochloric acid, filtered, and made alkaline with sodium carbonate. The product was extracted with ether which was dried ($MgSO_4$) and evaporated to leave 1.24 g of an oil. This was purified by GLC over silicone gum rubber SE-30 on Chromosorb WHP to yield a liquid fraction which is *N*-ethyl-2-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]aniline: NMR ($CDCl_3$) 1.28 (t, CH_3), 2.95 [d, J = 6 Hz, CH_2 of $CH_2CH(CF_3)_2$], ~3.1 (NH band buried under other peaks, removed by D_2O), 3.15 (q, CH_2 of Et), 3.26 [septuplet, $CH(CF_3)_2$], 6.5–7.35 ppm (m, C_6H_4).

Anal. Calcd for $C_{12}H_{13}F_6N$: N, 4.91. Found: N, 5.07.

Methylation of 5. **5** was warmed briefly with a 10% excess of methyl fluorosulfonate[27] (toxic) until the solid melted. Reaction took place and the fluorosulfonate salt crystallized. The excess methyl fluorosulfonate was pumped off to leave a 100% yield of the 2,1-benzisothiazolium fluorosulfonate **6**: ^{19}F NMR (H_2O) 2.3 ppm [d, J = 8 Hz, $(CF_3)_2CH$].

Anal. Calcd for $C_{11}H_8F_7NO_3S_2$: C, 33.08; H 2.02; N, 3.51. Found: C, 33.07; H, 2.44; N, 3.58.

The above salt was treated with sodium bicarbonate solution. The solid so formed was filtered off, dried, and taken up in hexane. 3-(Hexafluoroisopropylidene)-1,3-dihydro-1-methyl-2,1-benzisothiazole (**7**) was crystallized from the filtered solution in 26% yield: mp 79–81 °C; IR 3077 (=CH), 2950, 2841 (CH), 1608, 1567, 1513, 1488 (C=C), 741 cm^{-1} (ortho-substituted aromatic and CF_3); ^{1}H NMR ($CDCl_3$) 3.30 (s, CH_3), 6.85–8.15 ppm (m's, C_6H_4); ^{19}F NMR 11.90, 13.90 ppm (quadruplets).

Anal. Calcd for $C_{11}H_7F_6NS$: C, 44.14; H, 2.36; N, 4.68. Found: C, 44.28; H, 2.52; N, 4.46.

2-[2,2,2-Trifluoro-1-(trifluoromethyl)ethyl]benzothiazole. To 1.25 g (0.01 mol) of 2-aminobenzenethiol[27] in 10 mL of dichloromethane was added 1.94 g (0.01 mol) of bis(trifluoromethyl)thioketene. The solvent was then removed and the residue was heated in a test tube with a flame for 5 min. The product boiled at 230 °C. The product was extracted with hexane, treated with decolorizing carbon, and crystallized from the hexane to give 1.12 g (39%) of the benzothiazole: mp 101–103 °C; IR 3067 (w, =CH), 2907 (CH), 1600, 1572, 1558, 1504 cm^{-1} (C=C, C=N); ^{1}H NMR (CCl_4) 5.00 ppm [septet, $(CF_3)_2CH$]; ^{19}F NMR 2.30 ppm (d, J = 6 Hz).

Anal. Calcd for $C_{10}H_5F_6NS$: C, 42.11; H, 1.77; S, 11.25. Found: C, 42.33; H, 1.80; S, 11.23.

Reaction with Phosphites. A. Trimethyl Phosphite. Trimethyl phosphite (1.24 g, 0.01 mol) in 5 mL of dichloromethane was stirred and cooled in ice while 2.91 g (0.015 mol) of bis(trifluoromethyl)-thioketene was added dropwise. The volatiles, including thioketene dimer, were pulled off under oil pump vacuum at 25 ° C for 15 h. This left 2.35 g (59%) of a pale yellow oil, 5,5-bis(trifluoromethyl)-2-(hexafluoroisopropylidene)-4-(trimethoxyphosphoranylidene)-1,3-dithiolane (**10**): ^{1}H NMR ($CDCl_3$) 3.81 ppm (d, J_{HCOP} = 11.3 Hz); ^{19}F NMR 0.89 [d, $J_{F\text{-}P}$ = 1.3 Hz, 5-$(CF_3)_2$], 9.68 ppm [m, 2-$(CF_3)_2C{=}$]; ^{31}P NMR 38.7 ppm (eight peaks, outer two peaks not discernible, J = 11 Hz).

Anal. Calcd for $C_{11}H_9F_{12}O_3PS_2$: C, 25.79; H, 1.77; F, 44.51. Found: C, 26.13; H, 2.08; F, 44.34.

Vacuum distillation of the product decomposed it to dimethyl 3,3,3-trifluoro-1-methylthio-2-(trifluoromethyl)-1-propenephosphonate (**12**): bp 77 °C (0.7 mm); n^{25}D 1.4303; ^{1}H NMR ($CDCl_3$) 2.65 (s, CH_3), 3.90 ppm (d, J = 11.5 Hz, 2 CH_3O); ^{19}F NMR 7.35, 9.68 ppm (quadruplets); ^{31}P NMR 8.95 ppm (septuplet, J = 11 Hz); IR 1618 cm^{-1} (C=C).

Anal. Calcd for $C_7H_9F_6O_3PS$: C, 26.42; H, 2.85; S, 10.08. Found: C, 26.36; H, 2.90; S, 9.94.

In another run, 5.82 g (0.03 mol) of the thioketene was added to 3.72 g (0.03 mol) of trimethyl phosphite in 10 mL of pentane. The solvent was evaporated and the residue was allowed to stand in moist air. One methyl group was hydrolyzed off and the resulting product crystallized. Recrystallization from benzene gave 2.24 g (30%) of dimethyl 5,5-bis(trifluoromethyl)-2-(hexafluoroisopropylidene)-1,3-dithiolane-4-phosphonate (**11**): mp 100–101 °C; IR 2959, 2899 (CH), 1572 cm −1 (C=C); ^{1}H NMR ($CDCl_3$) 3.90 (d, J_{HCOP} = 11 Hz, 2 CH_3O), 4.70 ppm (d, J_{HCP} = 19 Hz, slowly removed by D_2O, CH); ^{31}P NMR 12.9 ppm (nine apparent peaks, d split to septuplets); ^{19}F NMR 1.67, 3.88 [quadruplets, 5-$(CF_3)_2$], 9.65 ppm [A_3B_3, 2-$(CF_3)_2C{=}$].

Anal. Calcd for $C_{10}H_7F_{12}O_3PS_2$: C, 24.10; H, 1.42; P, 6.20; S, 12.84. Found: C, 24.42; H, 1.66; P, 6.36; S, 12.67.

B. Triphenyl Phosphite. To 9.30 g (0.03 mol) of triphenyl phosphite was added 5.82 g (0.03 mol) of bis(trifluoromethyl)thioketene. The temperature was kept below 30 °C by cooling with ice. On standing in air, one phenyl group was hydrolyzed off and the resulting

product crystallized on scratching. The product was washed with cold hexane and recrystallized from hexane to give 5.8 g (62%) of diphenyl 5,5-bis(trifluoromethyl)-2-(hexafluoroisopropylidene)-1,3-dithiolane-4-phosphonate: mp 98–98.5 °C; IR 3067 (=CH), 1590, 1484 (aromatic C=C), 1565 cm −1 (exocyclic C=C); ^{1}H NMR (CCl_4) 4.78 ppm (d, J_{PCH} = 19 Hz); ^{19}F NMR 2.56, 4.47 [quadruplets, 5-$(CF_3)_2$], 9.95 ppm [A_3B_3, 2-$(CF_3)_2C$=].

Anal. Calcd for $C_{20}H_{11}F_{12}O_3PS_2$: C, 38.84; H, 1.81; F, 36.74; P, 5.03; S, 10.18. Found: C, 38.65; H, 1.78; F, 36.68; P, 4.87; S, 10.32.

Reaction with Methylbenzenes. A. Hexamethylbenzene. Hexamethylbenzene (4.87 g, 0.03 mol), 8 mL of benzene, and 6.40 g (0.033 mol) of bis(trifluoromethyl)thioketene were heated in a sealed glass tube at 100 °C for 15 h. The benzene was evaporated and the residue was heated at 100 °C and 1 mm to remove excess hexamethylbenzene by sublimation. The residue was recrystallized twice from methanol to give 4.04 g (45%) of 2-[1,1-bis(trifluoromethyl)-2-(pentamethylphenyl)ethyl]-4-(hexafluoroisopropylidene)-1,3-dithietane (**13**): mp 120–120.2 °C; ^{1}H NMR (CCl_4) 2.15 (s, 3,4,5-CH_3), 2.23 (s, 2,6-CH_3), 3.68 (s, CH_2), 4.98 ppm (broadened peak, CH); ^{19}F NMR 2.73 (s, 2 CF_3), 9.26 ppm [s, $(CF_3)_2C$=].

Anal. Calcd for $C_{20}H_{18}F_{12}S_2$: C, 43.63; H, 3.29; S, 11.65. Found: C, 44.00; H, 3.39; S, 11.56.

B. Durene. Durene (2.01 g, 0.015 mol) and 5.82 g (0.03 mol) of bis(trifluoromethyl)thioketene were sealed in a glass tube and heated at 150 °C for 6 h. The product crystallized on scratching and was allowed to stand in air for 3 days to permit durene and the thioketene dimer to sublime out. Recrystallization from methanol gave 4.24 g (54%) of 2-[1,1-bis(trifluoromethyl)-2-(2,4,5-trimethylphenyl)-ethyl]-4-(hexafluoroisopropylidene)-1,3-dithietane: mp 67–68 °C; IR 3012 (=CH), 2967, 2941, 2874 (CH), 1613 (exocyclic C=C), 1585, 1515 cm^{-1} (aromatic C=C); ^{1}H NMR (CCl_4) 2.20 (s, 4,5-CH_3), 2.30 (s, 2-CH_3), 3.58 (s, ch$_2$), 5.10 (s, CH), 6.31 (aromatic H), 6.60 ppm (aromatic H); ^{19}F NMR 2.39 (s, 2 CF_3), 9.57 ppm [s, $(CF_3)_2C$=].

Anal. Calcd for $C_{18}H_{14}F_{12}S_2$: C, 41.38: H, 2.70; S, 12.28. Found: C, 41.46; H, 2.92; S, 12.49.

C. *p*-Methylanisole. *p*-Methylanisole (4.88 g, 0.04 mol) and 7.76 g of bis(trifluoromethyl)thioketene were heated in a sealed glass tube at 150 °C for 8 h. The viscous product was distilled at 91–100 °C (0.05 mm). Seed crystals were obtained by cooling a portion in methanol in dry ice. The product was then seeded and the crystals were filtered from liquid. Recrystallization from methanol by cooling in dry ice gave 2.01 g (20%) in two crops of 2-[1,1-bis(trifluoromethyl)-2-(*p*-methoxyphenyl)ethyl]-4-(hexafluoroisopropylidene)-1,3-dithietane: mp 31.2–31.8 °C; IR 2950, 2849 (CH); 1613 (exocyclic C=C), 1515 (aromatic C=C), 1250 cm^{-1} (C=COC); ^{1}H NMR (CCl_4) 3.58 (s, CH_2), 3.78 (s, CH_3O), 5.13 (s, CH), 7.02 ppm (AA'BB', C_6H_4); ^{19}F NMR 2.54 (s, 2 CF_3), 9.72 ppm [$(CF_3)_2C$=].

Anal. Calcd for $C_{16}H_{10}F_{12}OS_2$: C, 37.65; H, 1.98; S, 12.57. Found: C, 37.99; H, 2.07; S, 12.73.

D. *p*-Cresol. Redistilled *p*-cresol (4.32 g, 0.04 mol) and 8.52 g (0.044 mol) of bis(trifluoromethyl)thioketene were heated in a sealed glass tube at 100 °C for 15 h. Combination of two runs and distillation gave a cut, bp 80–81 °C (7 mm), n^{25}_D 1.4444, 4.24 g (35%), which was *p*-tolyl 3,3,3-trifluoro-2-(trifluoromethyl)thiopropionate: ^{1}H NMR (neat) 1.78 (s, CH_3), 4.2 [septuplet, $(CF_3)_2CH$], 6.42 ppm (AA'BB', C_6H_4); ^{19}F NMR 1.29 ppm (d, J = 6 Hz).

Anal. Calcd for $C_{11}H_8F_6OS$: C, 43.71; H, 2.67; S, 10.61. Found: C, 43.87; H, 2.90; S, 10.59.

The distillation cut, bp 81–120 °C (7 mm), was partly crystalline. The crystals were filtered off and recrystallized from hexane to give 3.55 g (18%) of **15**: mp 76–77 °C; IR 3067 (=CH), 2944, 2941, 2882 (CH), 1623 (exocyclic C=C), 1511 (aromatic C=C), 842 cm^{-1} (*p*-aromatic); ^{1}H NMR (CCl_4) 2.31 (s, CH_3), 4.20 [septuplet, $(CF_3)_2CH$], 7.08 ppm (C_6H_4); ^{19}F NMR 6.27 [d, J = 7 Hz, $(CF_3)_2CH$], 8.87 ppm [s, $(CF_3)_2C$=].

Anal. Calcd for $C_{15}H_8F_{12}OS_2$: C, 36.29; H, 1.62; S, 12.91. Found: C, 36.84; H, 1.94; S, 12.58.

Finally, a dark distillation cut, bp 120–150 °C (7 mm), contained crystals which were filtered off and recrystallized from hexane to give 0.37 g (1.7%) of **16**: mp 102–104 °C; ^{1}H NMR (CCl_4) 3.6 (s, CH_2), 5.13 (s, CH), 5.64 (s, HO, exchanged with CF_3COOH), 6.9 ppm (AA'BB', C_6H_4); ^{19}F NMR 2.66 (s, 2 CF_3), 9.61 ppm [s, $(CF_3)_2C$=]. The compound dissolves in warm, dilute sodium hydroxide solution to give a surface active solution from which the compound can be reprecipitated with hydrochloric acid.

Anal. Calcd for $C_{15}H_8F_{12}OS_2$: C, 36.29; H, 1.62; S, 12.91. Found: C, 36.70; H, 1.68; S, 12.53.

Diels–Alder Reactions. A. Addition to Butadiene. Butadiene (10 g, 0.19 mol) was condensed into 50 mL of dichloromethane at −10 °C and 7.76 g of bis(trifluoromethyl)thioketene was added. The solution was allowed to stand 20 h at 0 °C while reaction slowly took place. Distillation gave 9.0 g (91%) of 6-(hexafluorisopropylidene)-5,6-dihydro-2*H*-thiopyran: bp 72–73 °C (8 mm); n^{25}_D 1.4439; IR 3077 cm^{-1} (=CH), 1642 (ring C=C), 1572 (exocyclic C=C); ^{1}H NMR (neat), 3.08, 3.17 (two peaks, 2 CH_2 groups), 6.06 ppm (center of nine peaks, CH=CH); ^{19}F NMR 9.79, 12.5 ppm (quadruplets).

Anal. Calcd for $C_8H_6F_6S$: C, 38.70; H, 2.44; S, 12.91. Found: C, 39.22; H, 2.71; S, 12.98.

B. Addition to 2,3-Dichlorobutadiene. 2,3-Dichlorobutadiene[24] (7.38 g, 0.06 mol) containing 100 ppm of phenothiazine and 11.64 g (0.06 mol) of bis(trifluoromethyl)thioketene were sealed in a glass tube and heated at 100 °C for 2 h. Distillation gave 13.7 g (72%) of 3,4-dichloro-6-(hexafluoroisopropylidene)-5,6-dihydro-2*H*-thiopyran: bp 64 °C (0.25 mm); n^{25}_D 1.4770; ^{1}H NMR (neat) 3.60 (s, CH_2S), 3.89 ppm (s, broader, CH_2); ^{19}F NMR 9.70, 12.60 ppm (quadruplets, former split to triplets).

Anal. Calcd for $C_8H_4Cl_2F_6S$: C, 30.30; H, 1.27; S, 10.11. Found: C, 30.69; H, 1.65; S, 10.23.

C. Addition to Pentamethyl-5-vinylcyclopentadiene. To 9.72 g (0.06 mol) of pentamethyl-5-vinylcyclopentadiene[25] was added 11.6 g (0.6 mol) of the thioketene in small portions with occasional cooling. Distillation gave 17.4 g (81%) of adducts: bp 76 °C (0.5 mm). These were isomers with the vinyl group syn and anti to the sulfur atom. Crystallization from methanol gave 8.5 g (36%) of a solid isomer of 3-(hexafluoroisopropylidene)-1,4,5,6,7-pentamethyl-7-vinyl-2-thiabicyclo[2,2.1]hept-5-ene:[6] mp 50–52 °C; IR 1656 (cyclic C=C), 1629 (vinyl C=C), 1563 cm^{-1} (exocyclic C=C); Raman 1665, 1637, 1567 cm^{-1}; ^{1}H NMR (CCl_4) 1.09 (s, 7-CH_3), 1.21 (1-CH_3), 4.85–6.85 ppm (m, CH_2=CH); ^{19}F NMR 9.65, 17.9 ppm (quadruplets, components of latter split to quadruplets, J = 2.6 Hz).

Anal. Calcd for $C_{16}H_{18}F_6S$: C, 53.93; H, 5.09; S, 9.00. Found: C, 53.77; H, 5.08; S, 9.12.

D. Addition to Spiro[4.4]nona-1,3-diene. To 6 g (0.05 mol) of spiro[4.4]nona-1,3-diene[26] in 15 mL of dichloromethane was added 9.7 (0.05 mol) of the thioketene in 10 mL of dichloromethane with cooling in ice. Distillation gave 12.8 g (83%) of 3-(hexafluoroisopropylidene)spiro(2-thiabicyclo[2.2.1]hept-5-ene-7,1′-cyclopentane): bp 65 °C (0.2 mm); n^{25}_D 1.4685; ^{1}H NMR (neat) 1.48 [s, $(CH_2)_4$], 3.84 (broadened peak, 1-H), 4.02 (m, 4-H), 6.02 (m, 5-H), 6.53 ppm (q, 6-H); ^{19}F NMR 8.13, 12.4 ppm (quadruplets).

Anal. Calcd for $C_{13}H_{12}F_6S$: C, 49.68; H, 3.85; S, 10.20. Found: C, 49.22; H, 3.68; S, 10.26.

E. Addition to 6,6-Diphenylfulvene. To 4.6 g (0.02 mol) of 6,6-diphenylfulvene[27] in 20 mL of hexane was added 3.88 g (0.02 mol) of the thioketene with occasional cooling. From the cooled mixture 7.18 g of product was filtered. Recrystallization from hexane left 6.22 g (73%) of 7-(diphenylmethylene)-3-(hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]hept-5-ene: mp 118.3–119 °C; IR 3049 cm^{-1} (=CH), 1621 [$(CF_3)_2C$=C], 1577, 1502 (aromatic C=C); H NMR ($CDCl_3$) 4.80 (broad m, bridgehead protons), 6.27 and 6.65 (m and quartet, CH=CH), 7.1 ppm (m, 10 aromatic protons); ^{19}F NMR 8.70, 12.6 ppm (quadruplets).

Anal. Calcd for $C_{22}H_{14}F_6S$: C, 62.26; H, 3.33; S, 7.56. Found: C, 62.56; H, 3.36; S, 7.66.

F. Addition to 1,3-Cyclohexadiene. 1,3-Cyclohexadiene (17 g, 0.21 mol) in 50 mL of dichloromethane was stirred and cooled in ice while 38.8 g (0.2 mol) of bis(trifluoromethyl)thioketene was added during 1 h at 10–20 °C. Distillation gave 49.6 g (91%) of product: bp 45–47 °C (0.6 mm); ^{19}F NMR (neat) 3.41, 6.33 (quadruplets, J = 6.4 Hz, former split to doublets, J = 1.5 Hz), 9.55, 13.2 ppm (quadruplets, J = 9.7 Hz). The low-field pair of quadruplets represent the Diels–Alder adduct (**20**, 54.5%) and high-field pair the ene product (45.5%), 3-[3,3,3-trifluoro-1-(trifluoromethyl)propenylthio]-1,4-cyclohexadiene (**21**). The presence of the latter was confirmed in the ^{1}H NMR spectrum by a quadruplet at 7.34 ppm, J = 1.3 Hz, for $(CF_3)_2C$=CH.[2b] Preparative GLC over polyfluoroalkyl pyromellitate on Gas Chrom R at 150 °C gave 22 g (40%) of the Diels–Alder adduct, 3-(hexafluoroisopropylidene)-2-thiabicyclo[2.2.2]oct-5-ene[6] (20). To remove color, the compound in dichloromethane was slurried with neutral Woelm alumina and redistilled: bp 78 °C (5 mm); n^{25}_D 1.4589; ^{1}H NMR (neat) 1.2–2.2 (m, CH_2CH_2), 3.78, 4.30 (complex doublets, bridgehead protons), 6.12, 6.58 ppm (t's, J = 8 Hz, components of former split to doublets, CH=CH); ^{19}F NMR 9.65, 13.2 ppm [quadruplets, $(CF_3)_2C$=C<]. The ene product did not emerge from the column as it was converted to tar.

Anal. Calcd for $C_{10}H_8F_6S$: C, 43.79; H, 2.94; S, 11.66. Found: C, 43.73; H, 2.96; S, 11.99.

G. Addition to Anthracene. Anthracene (0.89 g, 0.005 mol) was dissolved in 60 mL of benzene, 0.97 g (0.005 mol) of the thioketene was added, and the solution was allowed to stand for 18 h. The reaction

was not complete and the solution was refluxed for 2 h, after which the benzene was evaporated off. The residue was taken up in ether, filtered from 0.27 g of anthracene, and the solution was evaporated to leave 1.1 g (59%) of 12-(hexafluoroisopropylidene)-11-thia-9,10-dihydro-9,10-ethanoanthracene: mp 118.5–119 °C from methanol; ^{1}H NMR ($CDCl_3$) 5.40, 6.05 ppm (singlets, bridgehead protons), 7.2 (m, 8 aromatic protons); ^{19}F NMR 9.79, 14.9 ppm (quadruplets).

Anal. Calcd for $C_{18}H_{10}F_6S$: C, 58.08; H, 2.71; S, 8.61. Found: 57.95; H, 2.97; S, 8.50.

H. Addition to Cyclooctatetraene. Cyclooctatetraene (3.12 g, 0.03 mol) and 5.82 g (0.03 mol) of the thioketene were sealed in a glass tube and heated at 100 °C for 16 h. Recrystallization of the product from methanol gave 7.0 g (78%) of 4-(hexafluoroisopropylidene)-3-thiatricyclo[4.2.2.0^{2,5}]deca-7,9-diene[6] (**17**) in three crops: mp 49–50 °C; IR 3067 (=CH), 2941 (CH), 1575 cm^{-1} (exocyclic C=C); ^{1}H NMR (CCl_4) 2.85, 3.20 (t's, six-membered ring bridgehead protons), 3.9, 4.4 (broad m's, saturated cyclobutene protons), 6.07 (sharp peak, cyclobutene CH=CH), superimposed on this is a broader absorption corresponding to another =CH, 6.43 ppm (t, =CH); ^{19}F NMR 10.3, 13.8 ppm (quadruplets).

Anal. Calcd for $C_{12}H_8F_6S$: C, 48.23; H, 2.70; S, 10.75. Found: C, 48.16; H, 298; S, 10.62.

I. Addition to 1,3-Diphenylisobenzofuran. A solution of 5.4 g (0.02 mol) of 1,3-diphenylisobenzofuran[27] in 35 mL of dichloromethane was stirred and cooled in ice and 4.27 g (0.022 mol) of the thioketene was added dropwise. The solvent was allowed to evaporate. The crystalline product was unstable to heat and was recrystallized cold by dissolving in 7 mL of dichloromethane, adding 75 mL of hexane, and concentrating the solution under reduced pressure. This gave 7.7 g (83%) of 3,4-dihydro-1,4-diphenyl-3-(hexafluoroisopropylidene)-1,4-epoxy-1*H*-[2]benzothiopyran (**18**). The compound is dissociated to its components by heat, but if placed in a hot bath, a melting point of 123 °C is obtained: IR 3067 (=CH), 1600 (exocyclic C=C), 1497 cm^{-1} (aromatic C=C); ^{19}F NMR (CCl_4) 6.84, 13.9 ppm (quadruplets).

Anal. Calcd for $C_{24}H_{14}F_6OS$: C, 62.07; H, 3.04; S, 6.90. Found: C, 62.42; H, 3.24; S, 6.81.

J. Addition to 1,2,4,7-Tetrakis(methylene)cyclooctane. To 2.4 g (0.0015 mol) of the tetraene[29] in 5 mL of dichloromethane was added 2.91 g (0.015 mol) of the thioketene. After 1 h the product was distilled to give 2.63 g of 6,9-bis(methylene)-3-(hexafluoroisopropylidene)-3,4,5,6,7,8,9,10-octahydro-1*H*-cycloocta[c]thiopyran (**19**): bp 88 °C (0.025 mm); n^{25}D 1.4975; IR 3125 (=CH), 2941, 2865 (CH), 1647 (CH_2=C), 1577 [$(CF_3)_2C$=C], 894 cm^{-1} (CH_2=C); Raman 1665, 1635, 1560 cm^{-1}; ^{1}H NMR (CCl_4) 2.19 (s, 7,8-CH_2), 3.07 (s, 2 CH_2), 3.16 (s, 2 CH_2), 4.71 ppm (2 CH_2=); ^{19}F NMR 10.3, 13.5 (quadruplets, J = 11 Hz).

Anal. Calcd for $C_{16}H_{16}F_6S$; c, 54.23; H, 4.55; S, 9.05. Found: C, 54.52; H, 4.82; S, 9.21.

Reduction of Diels–Alder Adducts. A. Cyclopentadiene Adduct. A solution of 30 g of 3-(hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]hept-5-ene[8] (**22**) in 125 mL of ethanol containing 1.7 g of 5% palladium on carbon and 0.3 g of palladium black was subjected to hydrogenation at room temperature and 40 lb/in.^{2} hydrogen pressure. After 1 h the pressure drop had leveled off, and the solution was filtered and distilled to give 25.4 g (85%) of 3-(hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]heptane:[6] bp 70 °C (5 mm); n^{25}D 1.4442; ^{1}H NMR (neat) 1.1–2.0 (m, 6 H), 3.52 (s, bridgehead in 1 position), 3.74 ppm (s, broader, bridgehead in 4 position); ^{19}F NMR 8.69, 11.5 ppm (quadruplets, J = 8.5 Hz, latter split to doublets, J = 2 Hz).

Anal. Calcd for $C_9H_8F_6S$: C, 41.23; H, 3.07; S, 12.23. Found: C, 41.61; H, 3.10; S, 12.39.

B. Reduction of Cyclooctatetraene Adduct. A solution of 25.6 g of **17** in 100 mL of alcohol containing 0.1 g of platinum oxide was hydrogenated at room temperature and 40 lb/in.^{2} for 1 h. The solution was filtered and distilled in a simple still at 120 °C (5 mm) to remove colloidal platinum. The white crystals (25.2 g) were recrystallized from methanol to give 23.5 g (91%) of 4-(hexafluoroisopropylidene)-3-thiatricyclo[4.2.2.0^{2,5}]deca-9-ene[6] in four crops: mp 46–46.5 °C; IR 3086 (=CH), 3003, 2874, 2857 (CH), 1631 (shoulder, ring C=C), 1577 cm^{-1} (exocyclic C=C); Raman 1575 (exocyclic C=C), 1635 cm^{-1} (ring C=C); ^{1}H NMR (CCl_4) 1–3.1 (m, 6 H), 3.82, 4.22 (2 m, bridgeheads), 6.35, 6.76 ppm (2 t, CH=CH), the sharp peak for the starting compound at 6.07 ppm, attributed to cyclobutene CH=CH, is gone; ^{19}F NMR 10.5, 14.0 ppm (quadruplets).

Anal. Calcd for $C_{12}H_{10}F_6S$: C, 48.00; H, 3.36; S, 10.68. Found: C, 48.22; H, 3.16; S, 10.88.

3-(Hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]hept-5-ene 2-Oxide. To 26 g (0.1 mol) of 3-(hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]hept-5-ene[8] (**22**) dissolved in 50 mL of dichloromethane was added at 15–20 °C 20.4 g (0.1 mol) of 85% *m*-chloroperbenzoic acid dissolved in 225 mL of dichloromethane. The solution was then washed with 5% sodium bicarbonate solution and dried (Na_2SO_4). The solvent was boiled off, finally under vacuum. The product was recrystallized from methanol by cooling in dry ice to give 10.2 g in two crops (38%) of the sulfoxide[9] **23**: mp 46–49 °C; IR 3077 (=CH), 2950 (CH), 1647 (exocyclic C=C), 1567 (ring C=C), 1042 cm^{-1} (SO); ^{1}H NMR (CCl_4) 2.65 (AB, bridge CH_2), 4.22, 4.32 (singlets, bridgeheads), 6.12 ppm (m, CH=CH); ^{19}F NMR 7.89, 9.70 ppm (quadruplets).

Anal. Calcd for C_9H_6OS: C, 39.14; H, 2.19; S, 11.61. Found: C, 39.31; H, 1.96; S, 11.58.

6-(Hexafluoroisopropylidene)-3,7-oxathiatricyclo[3.2.1.0^{2,4}]-octane 7,7-Dioxide. 3-Hexafluoroisopropylidene-2-thiabicyclo-[2.2.1]hept-5-ene 2,2-dioxide[8] (**24**, 21.4 g, 0.073 mol) was added to 16.4 g (0.081 mol) of 85% *m*-chloroperbenzoic acid in 150 mL of 1,2-dichloroethane and heated on a steam bath for 16 h. The solution was then washed with 5% aqueous sodium hydroxide, dried (Na_2SO_4), and evaporated. The residue was recrystallized from methanol to give 14.7 g (65%) of the epoxide **25**: mp 135–137 °C; IR 3086 (epoxide ring CH), 2994 (CH), 1675 cm^{-1} (C=C); ^{1}H NMR ($CDCl_3$) 2.17 (m, CH_2), 3.6–4.1 ppm (m, 4 H).

Anal. Calcd for $C_9H_6F_6O_3S$: C, 35.07; H, 1.96; S, 10.40. Found: C, 35.23; H, 1.89; S, 10.33.

Addition to Thiothiophthene. To 2.82 g (0.015 mol) of thiothiophthen[28] (**26**) dissolved in 150 mL of dichloromethane was added 5.82 g (0.03 mol) of bis(trifluoromethyl)thioketene and the solution was allowed to stand for 20 h. Not all of the thiothiophthene had reacted and 1.94 g (0.01 mol) more of the thioketene was added. After 2 h the solvent was evaporated and the crystalline residue was washed with cold hexane to leave 5.6 g of product. Recrystallization from hexane left 5.0 g (58%) of deep orange **28**: mp 151–152 °C; IR 2985, 2857 (CH), 1613 [$(CF_3)_2C$=C], 1504 cm^{-1} (C=C); Raman, sample decomposed in laser beam; ^{1}H NMR (CCl_4) 2.77 (s, CH_3), 2.86 (s, CH_3), 4.48 [septuplet, $(CF_3)_2CH$], 7.3 ppm (s, =CH); ^{19}F NMR 4.49 [d, J = 7 Hz, $(CF_3)_2CH$], 9.84 ppm [s, $(CF_3)_2C$=].

Anal. Calcd for $C_{15}H_8F_{12}S_5$: C, 31.24; H, 1.40; S, 27.80. Found: C, 31.43; H, 1.50; S, 27.87.

To 1.15 g (0.002 mol) of the above compound in 10 mL of dichloromethane was added 1 g (0.0052 mol) of bis(trifluoromethyl)thioketene and the solution was allowed to stand for 16 h. Then 1 g more of the thioketene was added and the solution was let stand for 24 h. The solvent was evaporated and the residue was recrystallized from nitromethane to give 1.19 g (77%) of white **31**: mp 134–135 °C; IR 2994, 2941, (CH), 1603 [$(CF_3)_2C$=], 1558 cm^{-1} (C=C); Raman 1610 [$(CF_3)_2C$=C], 1565 (C=C), 505 cm^{-1} (S-S); ^{1}H NMR (CCl_4) 2.24 (s, CH_3), 2.55 (s, CH_3), 5.03 [septuplet, $CH(CF_3)_2$], 5.70 ppm (s, CH); ^{19}F NMR 3.03 [d, J = 6 Hz, $(CF_3)_2CH$], 9.73 [s, $(CF_3)_2C$=CS_2], 9.84 [s, $(CF_3)_3C$=CS_2], 9.66 ppm [A_3B_3, $(CF_3)_2C$=].

Anal. Calcd for $C_{23}H_8F_{24}S_7$: C, 28.63; H, 0.84; S, 23.27; mol wt, 965. Found: C, 28.80; H, 1.16; S, 23.28; mol wt, 970 (in $CHCl_3$ by vapor pressure osmometer).

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Registry No.—**1**, 66172-18-7; **2a**, 66172-19-8; **2b**, 66172-20-1; **2c**, 66172-21-2; **2d**, 66172-22-3; **2e**, 66172-23-4; **3**, 66172-24-5; **4a**, 66172-25-6; **4b**, 66172,26-7; **4c**, 66172-27-8; **4d**, 66172-28-9; **4e**, 66172-29-0; **5**, 66172-30-3; **6**, 66172-32-5; **7**, 66172-33-6; **8**, 66172-34-7; **9**, 66172-35-8; **10**, 66172-36-9; **11**, 66172-37-0; **12**, 66172-38-1; **13**, 66172-08-5; **15**, 66172-09-6; **16**, 66172-10-9; **17**, 24515-53-7; **18**, 24515-66-0; **19**, 66172-11-0; **20**, 35012-33-0; **21**, 66172-12-1; **22**, 35012,32-9; **23**, 35012-39-6; **24**, 35012-38-5; **25**, 66172-13-2; **26**, 2080-35-5; **28**, 66172-14-3; **31**, 66172-15-4; *N*-(pentafluorobenzylidene)methylamine, 62454-76-6; pentafluorobenzaldehyde, 653-37-2; methylamine, 74-89-5; bis(trifluoromethyl)thioketene, 7445-60-5; *N*-benzylidenemethylamine, 622-29-7; *N*-benzylideneisopropylamine, 6852-56-8; *N*-(4-chlorobenzylidene)methylamine, 13114-22-2; *N*-(4-nitrobenzylidene)methylamine, 877-80-5; *N*-(4-methoxybenzylidene)-4-methoxyaniline, 1749-08-2; *N*-methyl-*N*-[3,3,3-trifluoro(2-trifluoromethyl)]propionylbenzamide, 51254-13-8; $(CF_3)_2C$=C=O, 684-22-0; *N*-methylbenzamide, 613-93-4; methyl isothiocyanate, 556-61-6; phenyl azide, 622-37-7; *p*-tolyl azide, 2101-86-2; 4-

methoxyphenyl azide, 2101-87-3; 4-chlorophenyl azide, 3296-05-7; 3,4-dichlorophenyl azide, 66172-16-5; 2,4,6-trimethylphenyl azide, 14213-00-4; 5-methyl-3-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-2,1-benzisothiazole, 66172-17-6; *N*-ethyl-2-[3,3,3-trifluoro-2-(trifluoromethyl)propyl]aniline, 66172-00-7; methyl fluorosulfonate, 421-20-5; 2-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]benzothiazole, 66172-01-8; 2-aminobenzenethiol, 137-07-5; trimethyl phosphite, 121-45-9; triphenyl phosphite, 101-02-0; diphenyl 5,5-bis(trifluoromethyl)-2-(hexafluoroisopropylidene)-1,3-dithiolane-4-phosphonate, 66172-02-9; hexamethylbenzene, 87-85-4; durene, 95-93-2; 2-[1,1-bis(trifluoromethyl)-2-(2,4,5-trimethylphenyl)ethyl]-4-(hexafluoroisopropylidene)-1,3-dithietane, 66172-03-0; *p*-methylanisole, 104-93-8; 2-[1,1-bis(trifluoromethyl)-2-(*p*-methoxyphenyl)ethyl]-4-(hexafluoroisopropylidene)-1,3-dithietane, 66172-04-1; *p*-cresol, 106-44-5; *p*-tolyl 3,3,3-trifluoro-2-(trifluoromethyl)thiopropionate, 66172-05-2; butadiene, 106-99-0; 6-(hexafluoroisopropylidene)-5,6-dihydro-2*H*-thiopyran, 24515-61-5; 2,3-dichlorobutadiene, 1653-19-6; 3,4-dichloro-6-(hexafluoroisopropylidene)-5,6-dihydro-2*H*-thiopyran, 66172-06-3; pentamethyl-5-vinylcyclopentadiene, 20145-47-5; 3-(hexafluoroisopropylidene)-1,4,5,6,7-pentamethyl-7-vinyl-2-thiabicyclo[2.2.1]hept-5-ene, 35012-44-3; spiro[4.4]nona-1,3-diene, 766-29-0; 3-(hexafluoroisopropylidene)spiro[2-thiabicyclo[2.2.1]hept-5-ene-7,1′-cyclopentene, 35012-45-4; 6,6-diphenylfulvene, 2175-90-8; 7-(diphenylmethylene)-3-(hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]hept-5-ene, 24515-65-9; 1,3-cyclohexadiene, 592-57-4; anthracene, 120-12-7; 12-(hexafluoroisopropylidene)-11-thia-9,10-dihydro-9,10-ethanoanthracene, 24515-64-8; cyclooctatetraene, 629-20-9; 1,3-diphenylisobenzofuran, 5471-63-6; 1,2,4,7-tetrakis(methylene)cyclooctane, 35061-75-7; 3-(hexafluoroisopropylidene)-2-thiabicyclo[2.2.1]heptane, 35012-42-1; 4-(hexafluoroisopropylidene)-3-thiatricyclo-[4.2.2.0^{2,5}]deca-9-ene, 66172-07-4.

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Intramolecular Addition of Aryl Azides to the Azo Group. 2.[1] Synthesis and Properties of Benz[*cd*]indazole *N*-Arylimines

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Thermal and photochemical decomposition of 8-azido-1-arylazonaphthalenes results in intramolecular addition to the azo group to give previously unknown benz[*cd*]indazole *N*-arylimines in good yields by 1,5-cyclization. Only in one case 1,6-cyclization leading to a 2-arylnaphtho[1,8-*de*]triazine has also been observed. Chemical and spectroscopic properties of all *N*-imines are in accord with the proposed structures containing the stable 1,3-dipolar azimine system. Formation of products is discussed in terms of a possible concerted process not involving nitrene intermediates.

In a previous paper[1] we have reported what appears to be the first definite example of addition of aryl azides to the azo group leading to the formation of azimines, 1,3-dipolar valence tautomers of unknown triaziridines, presumably through the intermediacy of nitrenes. Photochemical decomposition of a number of 2-azido-2′-arylazobiphenyls (**1**, Ar = aryl) was in fact found to afford benzo[c]cinnoline *N*-arylimines (**2**) as major products as well as minor amounts of 4-arylazocarbazoles (**3**), 2-amino-2-arylazobiphenyls (**4**), and benzo[c]cinnoline (**5**).

These results prompted us to prepare a series of 1-azido-8-arylazonaphthalenes (**6**) and to investigate their thermal and photochemical decomposition in the hope that analogous intramolecular additions of the azido group (or nitrene) to the peri azo group would lead to the formation of 2-arylnaphtho[1,8-*de*]triazines (**7**) and/or benz[*cd*]indazole *N*-

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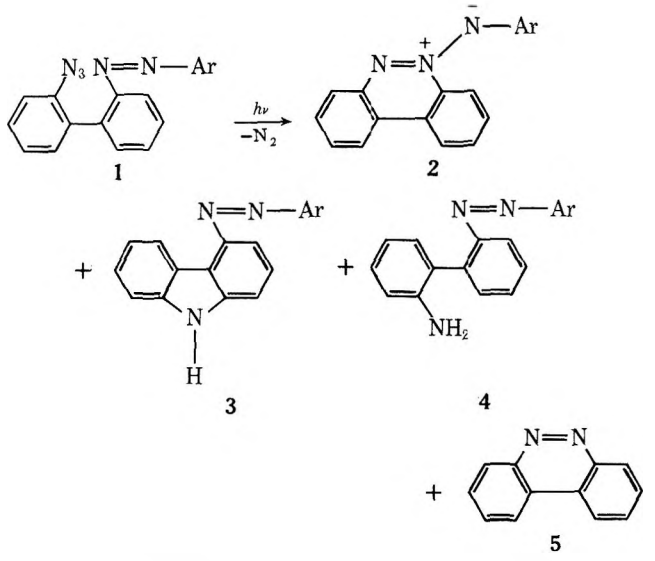
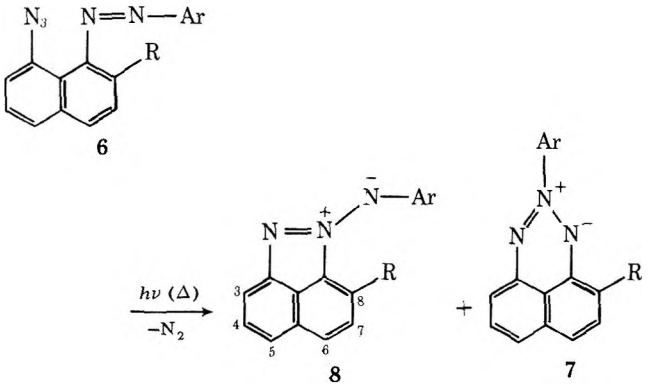


arylimines (8) by 1,6- or 1,5-cyclization, respectively. Reactions of peri-substituted 1-naphthyl azides are known[2,3b] and the stereochemistry appears to be favorable for intramolecular reaction in these cases.

Whereas several 2-substituted naphtho[1,8-*de*]triazines [7, Ar = alkyl or aryl; R = H] have been reported[4] and have been shown to be formed by alkylation and arylation of the 1*H*-naphtho[1,8-*de*]triazine,[4] benz[*cd*]indazoles *N*-arylimines (8) (if formed at all) would provide the first examples of the as yet unknown benz[*cd*]indazoles *N*-imines [8, Ar = H, alkyl, or aryl; R = H], which appear to be particularly interesting as members of heterocyclic *N*-imines[5,6] containing the rare 1,3-dipolar azimine function.[7,8] Moreover, benz[*cd*]indazole *N*-arylimines (8) would be representatives of the benz[*cd*]-indazole system whose synthesis has not as yet succeeded in spite of several attempts performed.[2,3] Although several of its dihydro derivatives are known,[3] so far the only authenticated examples of the benz[*cd*]indazole system are offered by the mono-[2] and di-*N*-oxide.[2]

Azides **6a–c** were obtained by diazotization of the readily available 1-amino-8-azidonaphthalene,[9] coupling of the diazonium salt with phenol or 1- and 2-naphthol, and methylation. Azides **6d–f** were prepared by coupling of the appropriate aryldiazonium chloride with 8-azido-2-naphthol and subsequent methylation of the coupling products with methyl iodide–silver oxide. Attempted preparation of 8-azido-1-arylazonaphthalenes (**6**) by condensation of 1-amino-8-azidonaphthalene with aryl nitroso compounds was unsuccessful.

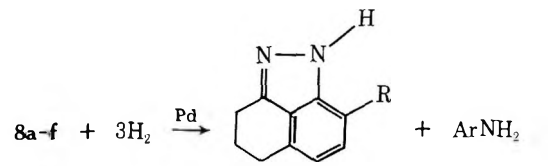


a, R = H; Ar = 4-$OCH_3C_6H_4$
b, R = H; Ar = 2-OCH_3-1-naphthyl
c, R = H; Ar = 4-OCH_3-1-naphthyl
d, R = OCH_3; Ar = Ph
e, R = OCH_3; Ar = 4-$CH_3C_6H_4$
f, R = OCH_3; Ar = 2-PhC_6H_4

Photolysis of azides **6a–f** with a 100-W high-pressure mercury lamp in benzene solution for 24–36 h (until TLC showed complete decomposition of starting material) led to the isolation of the stable, red-violet benz[*cd*]indazole *N*-arylimines (**8a–f**) in 70–85% yields together with minor unidentified colored products and some polymeric material. No evidence of formation of 2-arylnaphtho[1,8-*de*]triazines (**7**) was found in any cases examined except for photolysis of azide **6b** which afforded the blue 2-(2-methoxy-1-naphthyl)naphtho[1,8-*de*]triazine (**7b**) albeit in very low yield (5%).

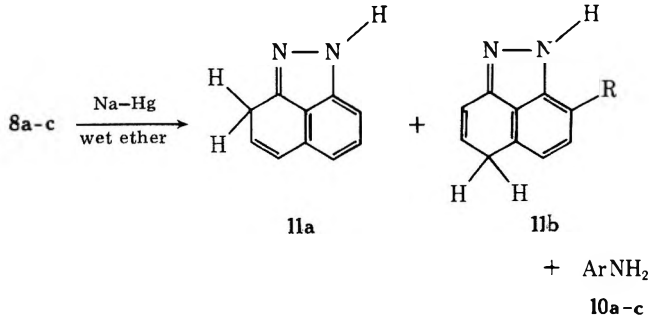
Thermolysis of azides **6a–f** took place readily in refluxing toluene (2–3 h) and was found to lead substantially to the same results as obtained from photolysis, *N*-imines **8** being isolated in comparable yields and no evidence of triazines **7** being obtained in any cases. The only exception was furnished by thermolysis of azide **6b** which gave only tars. Since control experiments (see later) showed azimine **8b** to be not capable of surviving the reaction conditions needed to bring about thermal decomposition of azide **6b**, whereas triazine **7b** was found to be quite stable, formation of **7b** in photolysis of **6b** and its absence in the corresponding thermolysis appeared to be possibly indicative of a photochemical rearrangement of *N*-imine **8b** to the valence tautomeric triazine **7b**. In order to check this point we effected irradiation of *N*-imine **8b** for the same time as employed in photochemical decomposition of azide **6b**, but TLC showed *N*-imine **8b** to be quite unaffected. However, when triazine **7b** was irradiated under the same conditions slow rearrangement to **8b** was observed, ca. 20% conversion taking place after the same irradiation time as employed to effect decomposition of azide **6b**. It thus appears that *N*-imine **8b** is a photoisomer of triazine **7b**. Since triazines **7a,c–f** could not be isolated from photolysis of the corresponding azides **6** their photochemical formation (and their possible conversion to *N*-imines **8a,c–f**) remains an open question, but it appears that photochemical rearrangement of 2-substituted naphthotriazines is not a general process since 2-methylnaphthotriazine (**7**, Ar = CH_3; R = H)[10] and 2-(2-nitropheny)naphthotriazine (**7**, Ar = $2NO_2C_6H_4$; R = H)[11] were found to be quite stable on irradiation for several days. On the other hand our observation that 2-methylnaphthotriazine (**7**, Ar = CH_3; R = H), 2-(2-nitrophenyl)naphthotriazine (**7**, Ar = 2-$NO_2C_6H_4$; R = H), and triazine **7b** are all thermally stable at least up to 180 °C (together with previous relevant findings[4,8c]) and the results obtained from thermolysis of all azides **6a–f** would lead to the conclusion that triazines **7** are not formed from thermolysis of **6**, since they would be expected to be quite stable and isolable in such conditions.

Catalytic hydrogenation of *N*-imines (**8a–f**) led to 1,3,4,5-tetrahydrobenz[*cd*]indazoles[2] **9a** and **9b**, respectively, and the corresponding arylamines **10a–f**. Attempts to stop the reactions at an uptake of 1 or 2 molar equiv of hydrogen gave complex mixtures consisting of starting material, dihydrobenzindazoles (**11**), tetrahydrobenzindazole (**9a** or **9b**), and arylamine (**10**). These findings are in agreement with previous reports[2] of the catalytic reduction of benzindazole *N*-oxide and its 3-methoxy derivative, which afforded tetrahydro-



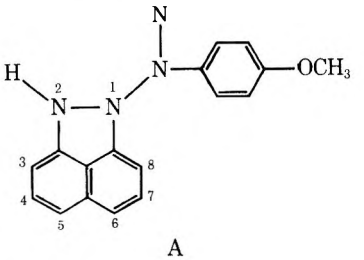
benzindazoles **9a** and **9b**, respectively, in fairly good yields, and with similar N–N reductive cleavage reported for other azimines.[7b,12]

Treatment of *N*-imines **8a–c** with sodium amalgam in wet ether also led to reductive cleavage of the exocyclic N–N bonds with formation of a mixture of 1,3- and 1,5-dihydrobenzindazole, **11a** and **11b**, and arylamines, **10a–c**. Similar behavior was shown by benzindazole *N*-oxide which was found to furnish dihydrobenzindazole **11a** and **11b** under the same reductive conditions.[2]

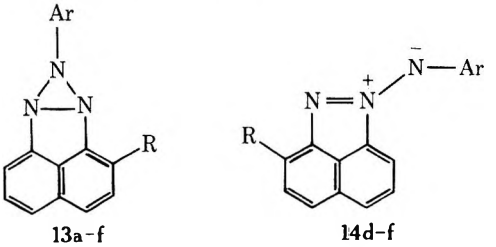


N-Imines **8a–f** were insoluble in concentrated hydrochloric acid and were unchanged by it; however, when hydrogen chloride was passed into a methylene chloride solution of benz[*cd*]indazole *N*-(4-methoxyphenyl)imine (**8a**) and the precipitate formed was filtered off and treated with an aqueous solution of sodium carbonate, TLC showed that starting azimine **8a** had been largely converted in a reddish product. Chromatography led to the isolation of this compound, **12**, whose elemental analysis and parent ion in the mass spectrum were consistent with the molecular formula $C_{17}H_{14}ClN_3O$, thus pointing to a product deriving from hydrogen chloride addition to azimine **8a**. The mass spectrum of product **12** showed, in addition to the parent ion at *m/e* 311, predominant fragment ions at *m/e* 189 ($C_{10}H_6ClN_2^+$) and 123 ($C_7H_9NO^+$), clearly indicating that the chloride ion had entered the benzindazole ring of **8a**. The NMR spectrum consisted, in the aromatic region, of a two-proton AB quartet, with J_{AB} values of 8.2 Hz unmistakably ortho, superimposed on an AA′ BB′ and an ABX pattern. Finally the IR spectrum showed two sharp NH stretching absorptions at 3460 and 3320 cm^{-1}. All these data suggest a 1,2-dihydrobenzindazole structure such as A, with the halogen atom to be placed at positions 3, 5, 6, or 8.

Unfortunately a definite choice cannot be made between positions 3, 8 or 5, 6 for the chlorosubstituent on the basis of the observed J_{AB} values of 8.2 Hz since the available data for coupling constants for 1,8-disubstituted naphthalenes[2,13] (including some with a 1,8 bridge) would lead to expect $J_{3,4}$ and $J_{7,8}$ values of ca. 6.7–8.2 Hz and comparable values of ca. 7.8–8.6 Hz for $J_{4,5}$ and $J_{6,7}$.



A



However, a structure of type A, in which the halogen atom is placed either at the 3 or 5 position, seems to be possibly preferable for compound **12** to account for its preference to exist in a 1,2-dihydrobenzindazole form, whereas all known dihydrobenzindazoles[3] appear to exist in the 1,3- and 1,5-tautomeric forms. A slight stabilization of the ring nearer to the 2-nitrogen by the substituent in positions 3 or 5 might offer a possible explanation. Formation of product **12** can be most reasonably accounted for by a nucleophilic attack by chloride ion on azimine **8a** protonated at the imino nitrogen and subsequent prototropy induced by base. Qualitative experiments performed with the other *N*-imines **8b–f** showed hydrogen chloride addition to be a general process.

The UV spectra of *N*-imines **8a–f** showed intense absorption in the visible region between 500 and 600 nm as expected for dipolar compounds having easily polarizable valence electrons,[4,5] thus providing strong evidence (apart from lack of precedent) contrary to alternative unlikely triaziridine structures **13a–f**. Moreover their UV spectra showed similarity with that of benz[*cd*]indazole *N*-oxide[2] with its long wavelength absorptions shifted to notably longer wavelength.

NMR data are also in accord with the proposed structures **8**. In fact the NMR spectrum of **8a** showed a complex pattern of six protons in the aromatic region consisting of two overlapping ABC systems (the interpretation of which was not performed) which are in agreement with an unsymmetrical benzindazole ring. On the other hand the aromatic region of NMR spectra of compounds **8d–f** showed the low field half of the AB quartet, expected from the protons ortho and meta to the methoxy group, always to fall at lower field than any other benzindazole hydrogens. This pattern is consistent with structures **8d–f** if it is granted the reasonable assumption that protons 6–8 in the ring nearer to the arylimino group should be deshielded more than protons 3–5. Such assumption, which is consistent with previous reports[2] of NMR investigation of benzindazole *N*-oxide, would lead to exclude alternative tautomeric azimine structures **14d–f**.

Mass spectra of *N*-imines **8a–c** showed, in addition to the parent ion, characteristic ($M^+ - 1$) ions which were also observed in benzo[c]cinnoline *N*-arylimines[1] (**2**), together with predominant peaks due to loss of the methoxy fragment from the molecular ion and to N–N bond cleavage of the parent ion affording $ArNH_2^+$, $ArNH^+$, and ArN^+ fragments and fragments corresponding to loss of nitrogen from benzindazole ions. *N*-Imines **8d–f** showed an analogous fragmentation pattern, the only noticeable difference being that peaks at *m/e* 185 and 184, apparently deriving by loss of the arylimino fragment from the parent ion, were clearly more abundant in these cases. The corresponding ions at *m/e* 155 and 154 were almost absent in the mass spectra of *N*-imines **8a–c**.

As for the blue triazine **7b**, its structure was promptly assigned on the basis of spectroscopic and chemical evidence. Its mass spectrum showed the molecular ion as the base peak, its UV spectrum was as expected for a 2-substituted naphthotriazine,[10,11] and its NMR spectrum showed the two high-field aromatic protons (δ 5.8–6.0) characteristic of the 4-hydrogen atoms of the 2-substituted naphthotriazine system.[10,8c] Finally chemical proof came from its ready hydrogenolysis which resulted, as expected,[10] in the formation of 1,8-diaminonaphthalene and 2-methoxy-1-naphthylamine.

In principle benz[*cd*]indazole *N*-arylimines (**8a–f**) could undergo thermal or photochemical fragmentation to benzindazole (or 3-methoxybenzindazole, respectively) and a formal aryl nitrene fragment.[5,6]

On heating in refluxing toluene all *N*-imines **8** were found to be stable for several hours, with the exception of *N*-imine **8b** which was shown to be completely destroyed after 1 h in refluxing toluene and after several hours in boiling benzene. In refluxing *o*-dichlorobenzene (in the absence and in the

presence of suitable compounds expected to be able to trap either benzindazole or 1,8-dehydronaphthalene which might be formed by spontaneous decomposition of benzindazole), azimines 8 exhibited rapid decomposition with formation of tarry products and traces of arylamines **10**. These findings did not provide much diagnostic evidence for fragmentation of *N*-imines 8. However, formation of arylamines **10** only in trace amounts and in particular the absence of carbazole in the pyrolysis of **8f** would at least indicate that nitrene fragments are practically not formed in these cases in analogy with what is observed with benzocinnoline *N*-arylimines.[1,7b]

On UV irradiation all *N*-imines 8 were found to be largely unchanged for a few days, slow decomposition (to tars) being noticed with further increasing irradiation time. In the presence of acetophenone their decomposition took place readily (24 h) affording traces of arylamines **10** (no trace of carbazole from **8f**) and intractable material. As from pyrolysis we did not manage to detect or intercept either benzindazole or 1,8-dehydronaphthalene from suitable trapping experiments.

The results obtained from photochemical and thermal decomposition of 8-azido-1-arylazonaphthalenes (**6**) provide a new definite example of formation of azimines by intramolecular addition of aryl azides to the azo group in addition to that previously offered by 2-azido-2-arylazobiphenyls[1] (**1**). However, in contrast with results obtained from decomposition of these latter azides which appeared to provide evidence in favor of a nitrene mechanism in the formation of benzo[*c*]cinnoline *N*-arylimines (**2**), decomposition of azides **6** is more likely to lead to products 8 without the actual intermediacy of nitrenes. A concerted cyclization mechanism, in which the peri-azo group provides anchimeric assistance for the elimination of nitrogen, is much more plausible, at least in thermolysis, to account for the absence of other products expected from nitrene intermediates and, more significantly, for the low reaction temperatures. In fact azides **6a–f** were found to decompose smoothly at 110 ° whereas 1-azidonaphthalenes have been reported to decompose above 150 °C.[3b,14] Steric destabilization of the azido group by the peri-arylazo substituent might be an explanation alternative to that involving concerted cyclization for the decomposition temperatures of 8-azido-1-arylazonaphthalenes (**6**), but this possibility appears to be ruled out by previous findings[3b] that decomposition temperatures of 1-azidonaphthalenes are not affected by peri substituents, even if bulky, unless intramolecular catalysis is involved. As for photochemical decomposition of azides **6**, the only evidence against a nitrene mechanism is based on the following findings: (a) yields of *N*-imines 8 are comparable to those obtained from thermolysis, (b) absence of other products diagnostic for the intermediacy of nitrenes, (c) irradiation at 254, 300, and 350 nm (in the last case in the presence and in the absence of acetophenone) does not produce any detectable change.

Finally we wish to point out that thermal and photochemical decomposition of 8-azido-1-arylazonaphthalenes (**6**) represents a general synthetic route to benz[*cd*]indazole *N*-arylimines (8), which do not appear to be otherwise accessible at the moment; studies are in progress to further explore the chemical reactivity of these interesting compounds.

Experimental Section

All melting points are uncorrected. UV spectra are for solutions in ethanol and IR and NMR spectra for solutions in carbon disulfide unless otherwise stated. 1-Amino-7-naphthol was a commercial product; 1-amino-8-azidonaphthalene was prepared as described in the literature.[9] Reaction products such as aniline, *p*-anisidine, *p*-toluidine, and 2-aminobiphenyl were characterized by spectral comparison with authentic commercial samples.

8-Azido-2-naphthol. A suspension of 1-amino-7-naphthol (2 g) in 8 mL of concentrated hydrochloric acid and 70 mL of water was cooled to 0–5 °C and diazotized with a solution of 0.9 g of sodium nitrite in 10 mL of water. After standing for 15 min, the resulting solution was treated with 0.9 g of sodium azide in water (10 mL), stirred for 1 h at 0–5 °C, and then extracted with ether. The dried extracts were evaporated and the residue was chromatographed on silica gel. Elution with 5% ether–pentane afforded 1.3 g (57%) of 8-azido-2-naphthol: mp 127–129 °C; IR ν_{max} 3580 (OH) and 2100 cm^{-1} (N_3); mass spectrum *m/e* 185 (M^+) and 157 ($M^+ - N_2$). Anal. Calcd for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.81; H, 3.86; N, 22.74.

Preparation of 8-Azido-2-hydroxy-1-arylazonaphthalenes (6: R = OH; Ar = Ph, 4-$CH_3C_6H_4$, 2-PhC_6H_4). The preparation of these compounds was accomplished by coupling of the appropriate aryldiazonium chloride with 8-azido-2-naphthol by means of the following general procedure.

8-Azido-2-hydroxy-1-phenylazonaphthalene (6: R = OH; Ar = Ph). Aniline (3.6 g) was dissolved in 120 mL of water containing 12 mL of concentrated hydrochloric acid and diazotized with 3 g of sodium nitrite at 0 °C. The diazonium salt solution was filtered into a stirred solution of 8-azido-2-naphthol (7.4 g) in 400 mL of water containing 4.8 g of sodium hydroxide. After stirring 1 h, the reaction mixture was acidified and the bright red solid was filtered and washed with water. The crude material was purified through a silica gel column to give 8-azido-2-hydroxy-1-phenylazonaphthalene (6, R = OH; Ar = Ph) (10.4 g, 93%): mp 115–116 °C dec; IR ν_{max} 2080 cm^{-1} (N_3); mass spectrum *m/e* 289 (M^+). Anal. Calcd for $C_{16}H_{11}N_5O$: C, 66.43; H, 3.81; N, 24.22. Found: C, 66.34; H, 3.85; N, 24.35.

8-Azido-2-hydroxy-1-(4-tolylazo)naphthalene (6, R = OH; Ar = 4-$CH_3C_6H_4$) was obtained in 91% yield as bright red plates: mp 118–120 °C dec; IR ($CHCl_3$) ν_{max} 2110 and 2090 (N_3) cm^{-1}; mass spectrum *m/e* 303 (M^+). Anal. Calcd for $C_{17}H_{13}N_5O$: C, 67.32; H, 4.32; N, 23.09. Found: C, 67.42; H, 4.28; N, 22.98.

8-Azido-2-hydroxy-1-(2-biphenylylazo)naphthalene (6, R = OH; Ar = 2-PhC_6H_4) was obtained in 89% yield as dark red plates: mp 101–103 °C dec; IR ν_{max} 2080 cm^{-1} (N_3); mass spectrum *m/e* 365 (M^+). Anal. Calcd for $C_{22}H_{15}N_5O$: C, 72.31; H, 4.14; N, 19.17. Found: C, 73.02; H, 4.21; N, 19.33.

Synthesis of 8-Azido-2-methoxy-1-arylazonaphthalenes (6d–f). Azides **6d–f** were prepared from the corresponding hydroxy derivatives by methylation with methyl iodide–silver oxide in dimethylformamide at room temperature. The following procedure is representative.

8-Azido-2-methoxy-1-phenylazonaphthalene (6d). To a stirred mixture of 8-azido-2-hydroxy-1-phenylazonaphthalene (6, R = OH; Ar = Ph) (5.5 g) in dry dimethylformamide (DMF) (400 mL) was added silver oxide (5.5 g) and after 15 min methyl iodide (10 mL). Stirring was continued at room temperature until TLC showed complete absence of the starting material (24–30 h), then the reaction mixture was poured into water and extracted with methylene chloride. The extracts were washed with water and evaporated to give an oily residue which was chromatographed on silica gel. Elution with 10% ether–pentane afforded 8-azido-2-methoxy-1-phenylazonaphthalene (**8d**) (3.5 g, 61%) as dark red needles: mp 96–98 °C dec; IR ν_{max} 2835 (OCH_3) and 2090 cm^{-1} (N_3); mass spectrum *m/e* 303 (M^+) and 275 ($M^+ - N_2$). Anal. Calcd for $C_{17}H_{13}N_5O$: C, 67.32; H, 4.32; N, 23.09. Found: C, 67.45; H, 4.37; N, 23.35.

8-Azido-2-methoxy-1-(4-tolylazo)naphthalene (6e) was obtained in 55% yield as dark red needles: mp 101–103 °C dec: IR ν_{max} 2830 (OCH_3) and 2095 cm^{-1} (N_3); mass spectrum *m/e* 317 (M^+) and 289 ($M^+ - N_2$). Anal. Calcd for $C_{18}H_{15}N_5O$: C, 68.12; H, 4.76; N, 22.07. Found: C, 68.14; H, 4.73; N, 21.45.

8-Azido-2-methoxy-1-(2-biphenylylazo)naphthalene (6f) was obtained in 30% yield as a dark red, thick oil which did not solidify: IR ν_{max} 2835 (OCH_3) and 2095 cm^{-1} (N_3); mass spectrum *m/e* 379 (M^+) and 351 ($M^+ - N_2$). Anal. Calcd for $C_{23}H_{17}N_5O$: C, 72.8; H, 4.51; N, 18.46. Found: C, 73.15; H, 4.53; N, 18.38.

Synthesis of 8-Azido-1-arylazonaphthalenes (6a–c). These compounds were prepared by coupling of the diazonium chloride of 1-amino-8-azidonaphthalene with phenol, 1- and 2-naphthol, and subsequent methylation of the crude coupling product either with methyl iodide–silver oxide in DMF or with methyl iodide–potassium carbonate in dry acetone.

8-Azido-1-(4-methoxyphenylazo)naphthalene (6a). 1-Amino-8-azidonaphthalene (1.85 g) was suspended in a solution of concentrated hydrochloric acid (3 mL) and water (30 mL) and diazotized at 0 °C by dropwise addition of sodium nitrite (0.75 g) in water (10 mL). After the addition was complete, the diazonium salt solution was filtered dropwise into an ice-cold solution of 0.95 g of phenol in 100 mL of water containing 1.2 g of sodium hydroxide. After standing 1 h the mixture was acidified and the red precipitate was filtered off

and washed several times with water. The crude product (1.5 g) was directly methylated without further purification.

Methylation was accomplished by stirring it in a solution of dry acetone (50 mL) and methyl iodide (3 mL), containing 2 g of potassium carbonate. Stirring was effected at room temperature for 24 h, after which time the mixture was filtered and the filtrate was evaporated. The dark oily residue was chromatographed on alumina (20% benzene–pentane as eluant) to give 8-azido-1-(4-methoxyphenylazo)naphthalene (6a) (0.6 g) as dark red needles: mp 78–80 °C dec; IR ν_{max} 2840 (OCH_3) and 2100 cm^{-1} (N_3); mass spectrum *m/e* 303 (M^+) and 275 ($M^+ - N_2$). Anal. Calcd for $C_{17}H_{13}N_5O$: C, 67.32; H, 4.32; N, 23.09. Found: C, 67.55; H, 4.31; N, 22.89.

8-Azido-4'-methoxy-1,1'-azonaphthalene (6c). The above procedure, starting from 1.85 g of 1-amino-8-azidonaphthalene and 1.45 g of 1-naphthol, gave 1.8 g of azide **6c** as dark red needles; mp 130–132 °C dec; IR ν_{max} 2840 (OCH_3) and 2095 cm^{-1} (N_3); mass spectrum *m/e* 353 (M^+) and 325 ($M^+ - N_2$). Anal. Calcd for $C_{21}H_{15}N_5O$: C, 71.40; H, 4.25; N, 19.82. Found: C, 70.98; H, 4.53; N, 19.35.

8-Azido-2'-methoxy-1,1'-azonaphthalene (6b). Coupling of 2-naphthol (2.8 g) with the diazonium chloride of 1-amino-8-azidonaphthalene (from 3.6 g of amine) led to 6.5 g of crude azo compound which was methylated with methyl iodide–silver oxide in DMF to afford 5.5 g of azide 6b as dark red needles: mp 106–108 °C dec; IR ν_{max} 2840 (OCH_3) and 2090 cm^{-1} (N_3); mass spectrum *m/e* 353 (M^+) and 325 ($M^+ - N_2$). Anal. Found: C, 70.90; H, 4.18; N, 19.27.

Photolysis of 8-Azido-1-arylazonaphthalenes (6a–f). General Procedure. Stirred solutions of azides **6a–f** (1 g) in 400 mL of benzene were purged with nitrogen for 1 h and then irradiated at room temperature with a 100-W high-pressure mercury lamp. The progress of the reactions was monitored by TLC and irradiation was stopped after TLC showed absence of starting material (24–36 h). The excess solvent was distilled off and the residue was chromatographed on silica gel.

Photolysis of 8-Azido-1-(4-methoxyphenyl)naphthalene (6a). Chromatography with 5% ether–pentane afforded trace amounts of unreacted azide. Further elution with 10% ether–pentane gave benz[*cd*]indazole *N*-(4-methoxyphenyl)imine (**8a,** 82%) as dark red-violet needles: mp 139–140 °C (from pentane–benzene); IR ν_{max} 2840 (OCH_3), 1260, 1240, 1150, 1060 cm^{-1}; NMR δ 3.60 (OCH_3), 6.3 (2 H, d, J = 8.8 Hz), 6.43–7.3 (6 H, m), and 7.7 (2 H, d, J = 8.8 Hz); mass spectrum *m/e* 275 (M^+), 274, 260, 244, 232, 204, 140, 126, 123, 121, 106, 78; UV λ_{max} 293, 302, 352, 531, 554 nm (log ϵ 4.32, 4.25, 3.98, 4.39, 4.35). Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 73.98; H, 4.81; N, 14.98. Elution with ether afforded a violet product which was not identified.

Photolysis of 8-Azido-2'-methoxy-1,1'-azonaphthalene (6b). Chromatography (benzene–petroleum 2:3 as eluant) gave (1) trace amounts of unreacted azide, (2) 2-(2-methoxy-1-naphthyl)naphtho[1,8-*de*]triazine (**7b**), (3) benz[*cd*]indazole *N*-(2-methoxy-1-naphthyl)imine, and (4) a mixture of unidentified colored products. **7b** (5%) appeared as dark blue needles: mp 238–240 °C; NMR ($CDCl_3$) δ 3.78 (OCH_3), 5.8–6.0 (2 H, dd), and 6.32–7.7 (10 H, m); mass spectrum *m/e* 325 (M^+), 310, 294, 266, 254, 241, 168, 155; UV λ_{max} 341, 356, 584, 633, 693 nm (log ϵ 4.10, 4.15, 2.93, 2.90, 2.71). Anal. Calcd for $C_{21}H_{15}N_3O$: C, 77.52; H, 4.64; N, 12.91. Found: C, 77.65; H, 4.61; N, 12.97.

Hydrogenation of **7b** in methylene chloride with palladium–charcoal (10%) at room temperature and atmospheric pressure led to 1,8-diaminonaphthalene and 1-amino-2-methoxynaphthalene,[15] whose R_f's (SiO_2 and Al_2O_3) were identical to those of authentic compounds.

Benz[*cd*]indazole N-(2-methoxy-1-naphthyl)imine (**8b,** 85%) appeared as dark violet needles, which softened without melting at ca. 170 °C and then were converted to unmelting tarry material: IR ν_{max} 2840 (OCH_3), 1370, 1275, 1255, 1168, 1100, 1070 cm^{-1}; NMR δ 3.75 (OCH_3) and 6.9–7.9 (12 H, m); mass spectrum *m/e* 325 (M^+), 324, 294, 173, 158, 130, 126; UV λ_{max} 265, 326, 521 nm (log ϵ 4.27, 3.91, 3.99). Anal. Found: C, 77.54; H, 4.66; N, 12.78.

Photolysis of 8-Azido-4'-methoxy-1,1'-azonaphthalene (6c). Chromatography (25% benzene–pentane) afforded (1) traces of unreacted azide, (2) violet oily product not identified, and (3) benz[*cd*]-indazole *N*-(4-methoxy-1-naphthyl)imine (**8c,** 75%) as dark violet needles, which were converted to tar on heating without melting: IR ν_{max} 2835, 1360, 1325, 1092, 1070 cm^{-1}; mass spectrum *m/e* 325 (M^+), 324, 310, 294, 173, 171, 158, 130, 126; UV λ_{max} 279, 299, 364, 556, 597 nm (log ϵ 4.19, 4.23, 3.92, 4.47, 4.52). Anal. Found: C, 77.34; H, 4.68; N, 12.84.

Photolysis of 8-Azido-2-methoxy-1-phenylazonaphthalene (6d). Chromatography (5% ether–pentane) gave (1) traces of unreacted azide, (2) violet oily product not identified, and (3) 8-methoxybenz[*cd*]indazole *N*-phenylimine (**8d,** 70%) as red-violet needles: mp 111–112 °C (from benzene–pentane); IR ν_{max} 2840 (OCH_3), 1280, 1060 cm^{-1}; NMR δ 4.08 (OCH_3), 6.98–7.45 (7 H, m), 7.7 (1 H, d, J = 8.6 Hz), and 8.1–8.35 (2 H, m); mass spectrum *m/e* 275, 274, 260, 185, 184, 126, 77; UV λ_{max} 295, 305, 348, 498, 526, 560 nm (log ϵ 4.27, 4.20, 3.83, 4.18, 4.20, 4.02). Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.76; N, 15.26. Found: C, 74.10; 4.78; N, 14.96.

Photolysis of 8-Azido-2-methoxy-1-(4-tolylazo)naphthalene (6e). Chromatography (5% ether–pentane) gave (1) traces of unreacted azide, (2) a mixture of colored products, and (3) 8-methoxybenz[*cd*]indazole *N*-(4-tolyl)imine (**8e,** 70%) as bright red-violet needles: mp 150–152 °C (from benzene–pentane); IR ν_{max} 2840 (OCH_3), 1280, 1060 cm^{-1}; NMR δ 2.37 (CH_3), 4.1 (OCH_3), 6.95–7.4 (6 H, m), 7.73 (1 H, d, J = 8.6 Hz), and 8.16 (2 H, d, J = 8.7 Hz); mass spectrum *m/e* 289 (M^+), 288, 274, 260, 259, 185, 184, 126, 107, 106, 91; UV λ_{max} 295, 308, 349, 500, 527, 562 nm (log ϵ 4.33, 4.26, 3.91, 4.22, 4.31, 4.15). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.73; H, 5.22; N, 14.52. Found: C, 74.04; H, 5.20; N, 14.34.

Photolysis of 8-Azido-2-methoxy-1-(2-biphenylylazo)naphthalene (6f). Chromatography (10% ether–pentane) afforded (1) traces of unreacted azide, (2) a mixture of colored products, and (3) 8-methoxybenz[*cd*]indazole *N*-(2-biphenylyl)imine (**8f**) (72%) as bright red-violet plates: mp 141–143 °C; IR ν_{max} 2830 (OCH_3), 1280, 1055 cm^{-1}; NMR δ 3.95 (OCH_3), 7.06 (1 H, d, J = 8 Hz), 7.15–7.60 (11 H, m), 7.71 (1 H, d, J = 8 Hz), and 8.75–8.9 (1 H, m); mass spectrum *m/e* 351 (M^+), 350, 336, 184, 169, 168, 167, 166, 126; UV λ_{max} 298, 308, 505, 534, 574 nm (log ϵ 4.34, 4.23, 4.13, 4.15, 3.93). Anal. Calcd for $C_{23}H_{17}N_3O$: C, 78.61; H, 4.88; N, 11.96. Found: C, 78.27; H, 4.90; N, 11.77.

Thermolysis of 8-Azido-1-arylazonaphthalenes (6a–f). General Procedure. Solutions of azides **6a–f** (1 g) were refluxed in toluene (40 mL) until TLC showed that no starting material was left (1–2 h). Solvent was distilled off under reduced pressure and the residue was chromatographed as described above for the corresponding photolyses.

Azide **6a** gave benz[*cd*]indazole *N*-(4-methoxyphenyl)imine (**8a**) in 80% yield; azide **6c** afforded benz[*cd*]indazole *N*-(4-methoxy-1-naphthyl)imine (**8c**) in 77% yield; azide **6d** furnished 8-methoxybenz[*cd*]indazole *N*-phenylimine (**8d**) in 55% yield (this reaction was accompanied by much tarring); azide **6e** gave 8-methoxybenz[*cd*]-indazole *N*-(4-tolyl)imine (**8e**) in 70% yield. Decomposition of azide **6f** was not carried out on a preparative scale; however, the reaction performed on a qualitative scale was shown by TLC to follow the general trend, i.e., considerable formation of the corresponding *N*-imine (**8f**) and some tarring.

Thermolysis of azide **6b** did not furnish any isolable material but led to formation of a great amount of tars. Qualitative experiments showed initial formation of benz[*cd*]indazole *N*-(2-methoxy-1-naphthyl)imine (**8b**) (but not of triazine **7b**) and subsequent decomposition to tars. When decomposition of azide **6b** was carried out in boiling benzene formation of *N*-imine **8b** became more evident, but yield of isolable product appeared to be still too poor for the reaction to have a synthetic utility.

Hydrogenation of Benz[*cd*]indazole *N*-Arylimines (8a–f). The following procedure is typical of that used in the hydrogenation of *N*-imines **8a–f.**

Hydrogenation of Benz[*cd*]indazole *N*-(4-Methoxyphenyl)-imine (8a). The *N*-imine **8a** (500 mg) was dissolved in 50 mL of methylene chloride and hydrogenated at room temperature and atmospheric pressure using palladium–charcoal (10%, 100 mg) as catalyst. Hydrogenation led to the uptake of ca. 3 molar equiv of hydrogen in 0.5 h. After removal of the catalyst and the excess solvent the residue was chromatographed on silica gel.

Elution with 5% ether–pentane furnished *p*-anisidine (**10a,** 56%).

Elution with ether gave 1,3,4,5-tetrahydrobenz[*cd*]indazole (**9a,** 46%), mp 120–121 °C (lit.[2] mp 120–121 °C), identical in all respects with a sample prepared by hydrogenation of benzindazole *N*-oxide:[2] IR (CCl_4) 3490 cm^{-1} (NH); mass spectrum *m/e* 158 (M^+) and 157.

Hydrogenation of *N*-(2-Methoxy-1-naphthyl)imine (8b) gave 1-amino-2-methoxynaphthalene (**10b,** 77%), mp and mmp 53–54 °C (lit.[15] 54 °C) and IR spectrum identical with that of an authentic specimen, and 1,3,4,5-tetrahydrobenzindazole (**9a,** 60%).

Hydrogenation of *N*-(4-Methoxy-1-naphthyl)imine (8c) gave 1-amino-4-methoxynaphthalene (**10c,** 66%), mp and mmp 38–40 °C (lit.[16] 39–40 °C) and IR spectrum identical with that of an authentic specimen, and 1,3,4,5-tetrahydrobenzindazole (**9a,** 59%).

Hydrogenation of 8-Methoxybenz[*cd*]indazole *N*-Phenylimine (8d) furnished aniline (**10d,** 40%) and 8-methoxy-1,3,4,5-tetrahydrobenzindazole (**9b,** 38%), mp and mmp 121–122 °C (lit.[2]

164–166 °C), identical in all respects with a specimen prepared by hydrogenation of 3-methoxybenzindazole *N*-oxide as described by Alder and co-workers,[2] who reported for the compound **9b** a melting point 164–166 °C; in our hands the same compound (**9b**) had mp 121–122 °C: IR (CCl_4) 3495 (NH) and 2840 cm^{-1} (OCH_3); NMR ($CDCl_3$) δ 2.12 (2 H), 2.87 (2 H), 2.99 (2 H), 3.9 (OCH_3), 6.63 (1 H, d, J = 7.5 Hz), and 6.7 (1 H, d, J = 7.5 Hz); mass spectrum m/e 188 (M^+), 187, 173; UV δ_{max} 258, 266, 297 (log ϵ 3.67, 3.65, 3.73).

Hydrogenation of 8-Methoxybenz[*cd*]indazole *N*-(4-Tolyl)-imine (8e) afforded *p*-toluidine (**10e**, 45%) and 8-methoxy-1,3,4,5-tetrahydrobenzindazole (**9b**, 36%).

Hydrogenation of 8-Methoxybenz[*cd*]indazole *N*-(2-Biphenylyl)imine (8f) gave 8-aminobiphenyl (**10f**, 75%) and 8-methoxy-1,3,4,5-tetrahydrobenzindazole (**9b**, 40%).

Reduction of Benz[*cd*]indazole *N*-Arylimines (8a–c) with Sodium Amalgam in Wet Ether. The following procedure is typical of that employed in reduction of *N*-imines **8a–c**.

Reduction of Benz[cd]indazole *N*-(4-Methoxyphenyl)imine (8a). Compound **8a** (500 mg) was dissolved in diethyl ether saturated with water (100 mL) and treated with 1.2% sodium amalgam (12 g). After stirring 3 h and further addition of sodium amalgam (6 g), the reaction mixture was allowed to stand for 10 h. The solution was decanted, dried, and evaporated to give a dark oily residue which was chromatographed on silica gel. Elution with 10% ether–pentane afforded *p*-anisidine (**10a**, 68%); elution with 50% ether–pentane gave a mixture of 1,3- and 1,5-dihydrobenzindazole, **11a** and **11b** (54%), mp 152–156 °C after sublimation. The IR, NMR, and UV spectra of this mixture were practically identical with those of a mixture of **11a** and **11b** obtained by reduction of benz[cd]indazole *N*-oxide as described by Alder and co-workers:[2] IR ($CHCl_3$) 3475 cm^{-1} (NH); mass spectrum m/e 156 (M^+), 155.

Reduction of Benz[*cd*]indazole *N*-(2-Methoxy-1-naphthyl)-imine (8b) afforded 1-amino-2-methoxynaphthalene (**10b**, 88%) and a mixture of **11a** and **11b** (55%).

Reduction of Benz[*cd*]indazole *N*-(4-Methoxy-1-naphthyl)-imine (8c) led to 1-amino-4-methoxynaphthalene (**10c**, 70%) and to a mixture of **11a** and **11b** (50%).

Treatment of Benz[*cd*]indazole *N*-(4-Methoxyphenyl)imine (8a) with Acid. Hydrogen chloride was passed into a solution of *N*-imine **8a** (500 mg) in methylene chloride (15 mL) to give an orange-red precipitate which was filtered off, washed several times with methylene chloride, and then treated with 10% aqueous sodium carbonate. Extraction with methylene chloride and chromatography on silica gel using 5% ether–pentane as eluant gave trace amounts of starting imine **8a** and then 450 mg (80%) of compound **12** as reddish-brown needles: mp 144–146 °C; IR ν_{max} 3460 (NH), 3320 (NH), and 2825 cm^{-1} (OCH_3); NMR δ 3.87 (OCH_3), 6.67 (1 H, d, J = 8.2 Hz), 7.01 (2 H, d, J = 8.9 Hz), 7.24–7.36 (5 H, m), and 8.36 (1 H, dd); mass spectrum m/e 311 (M^+), 189, 123, 108; UV λ_{max} 295, 354, 476 nm (log ϵ 4.07, 4.41, 3.73). Anal. Calcd for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.53; Cl, 11.37; N, 13.48. Found: C, 65.65; H, 4.48; Cl, 11.43; N, 13.24.

Experiments to Determine Photosensitivity of Benz[*cd*]indazole *N*-Arylimines (8a–f). Solutions of *N*-imines **8a–f** in benzene (or cylcohexane) were irradiated for 3–6 days, after which time TLC showed **8a–f** to be largely unchanged, decomposition to tars having occurred to a very small extent. When irradiations were conducted at 350 nm in the presence of acetophenone as sensitizer (threefold molar excess) complete decomposition of *N*-imines **8a–f** took place in ca. 24 h, traces of arylamines **10a–f** and much tarry material being observed. Finally sensitized irradiations of *N*-imines **8a–f** in the presence of excess diethyl acetylendicarboxylate, methyl propiolate, or dimethyl azodicarboxylate did not lead to formation of identifiable products.

Pyrolyses of Benz[*cd*]indazole *N*-Arylimines (8a–f). All *N*-imines **8a–f** were found to be largely unchanged in refluxing toluene for several hours with the exception of *N*-imine **8b** which smoothly decomposed to tars and traces of 1-amino-2-methoxynaphthalene. The *N*-imine **8b** could be completely decomposed also in boiling benzene in ca. 24 h. Pyrolyses of *N*-imines **8** in refluxing *o*-dichlorobenzene (or decalin) brought about their rapid decomposition which was complete in 20–30 min to afford arylamines **10** in trace amounts (TLC) and much tarry material. No evidence of carbazole nor of azo-2-biphenyl could be obtained from pyrolysis of *N*-imine **8f**. Finally pyrolyses of *N*-imines **8** in DMF (at 150 °C, sealed tube) in the presence of a tenfold excess of diethyl acetylenedicarboxylate, vinyl acetate, or tetraphenylcyclopentadienone did not furnish any isolable product.

Control Experiments to Determine Thermal and Photochemical Sensitivity of 2-(2-Methoxy-1-naphthyl)-naphtho[1,8-*de*]triazine (7b). Triazine **7b** was found to be quite stable in refluxing toluene for 1 week and largely unchanged after refluxing in *o*-dichlorobenzene for 1 day. Irradiation of **7b** in benzene solution for 36 h led to its partial conversion to *N*-imine **8b**.

Chromatography on silica gel indicated that ca. 20% conversion had occurred. Rearrangement of **7b** to **8b** appeared to increase slowly with increasing irradiation time and after 1 week's irradiation triazine **7b** was still noticeably present.

No evidence of any rearrangement could be obtained from 1 week's irradiation of 2-methylnaphthotriazine[10] (**7**, R = H; Ar = CH_3) and 2-(2-nitrophenyl)naphthotriazine[11] (**7**, R = H; Ar = 2-$NO_2C_6H_4$). These two latter compounds were also recovered largely unchanged after refluxing in *o*-dichlorobenzene for 1 day.

Acknowledgment. The authors thank CNR for a research grant.

Registry No.—**6** (R = OH; Ar = Ph), 65832-01-1; **6** (R = OH; Ar = 4-$CH_3C_6H_4$), 65832-02-2; **6** (R = OH; Ar = 2-PhC_6H_4), 65832-03-3; **6a**, 65832-04-4; **6b**, 65832-05-5; **6c**, 65832-06-6; **6d**, 65832-07-7; **6e**, 65832-08-8; **6f**, 65898-26-2; **7b**, 65832-09-9; **8a**, 65898-25-1; **8b**, 65832-10-2; **8c**, 65832-11-3; **8d**, 65832-12-4; **8e**, 65832-13-5; **8f**, 65832-14-6; **9a**, 65832-15-7; **9b**, 26574-20-9; **10a**, 104-94-9; **10b**, 2246-42-6; **10c**, 16430-99-2; **10d**, 62-53-3; **10e**, 106-49-0; **10f**, 90-41-5; **11a**, 25262-27-5; **11b**, 25262-26-4; **12**, 65832-27-1; 8-azido-2-naphthol, 36519-80-9; 1-amino-7-naphthol, 118-46-7; phenyldiazonium chloride, 100-34-5; *p*-tolyldiazonium chloride, 2028-84-4; 2-biphenylyldiazonium chloride, 52500-12-6; 1-amino-8-azidonaphthanene, 2112-98-3; 8-azido-1-naphthyldiazonium chloride, 65832-16-8; phenol, 108-95-2; 1-naphthol, 90-15-3; 2-naphthol, 135-19-3.

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Brominations of Some 1,2,4-Triazine 2-Oxides

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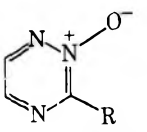
Some unique brominations of 1,2,4-triazine 2-oxides are described. It was found that 6-brominated, deoxygenated 6-brominated, and deoxygenated products are obtained, depending upon the reaction conditions. Mechanisms for these transformations are suggested, and supportive evidence for these is offered.

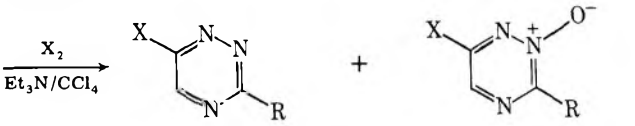
We have recently described the selective N-1 and N-2 oxidations of several 1,2,4-triazine derivatives[1] as well as some interesting transformations of these *N*-oxides.[2] As a continuation of our studies involving these systems, we now wish to report some unique brominations of some 1,2,4-triazine 2-oxides.

Treatment of 3-dimethylamino- (**1**) and 3-monomethylamino-1,2,4-triazine 2-oxides (**2**) with bromine and triethylamine gave, in each case, two products. In the former instance the minor component was found to be identical in all respects with the known[2] 6-bromo-3-dimethylamino-1,2,4-triazine (**3a**). As added proof of identity, this compound was treated with sodium methoxide, and the product thus obtained was compared with and found to be identical with authentic 6-methoxy-3-dimethylamino-1,2,4-triazine (**7**).[2]

The mass spectra of the main components (**4a** and **6a**) of the bromination reactions indicated that the *N*-oxide moiety had been retained. Both ^1H and ^{13}C NMR spectroscopy proved to be inconclusive as to the position of bromination since only small chemical shift differences are involved between H-5 and H-6 as well as C-5 and C-6. An x-ray analysis of the monobromo-3-monomethylamino-1,2,4-triazine 2-oxide (**6a**) clearly indicates that the bromine is substituted at position 6 (see Figure 1 of supplementary material).



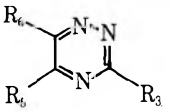
1, R = $N(CH_3)_2$
2, R = $NHCH_3$



3a, R = $N(CH_3)_2$; X = Br **4a**, R = $N(CH_3)_2$; X = Br
b, R = $N(CH_3)_2$; X = Cl **b**, R = $N(CH_3)_2$; X = Cl
5a, R = $NHCH_3$; X = Br **6a**, R = $NHCH_3$; X = Br
b, R = $NHCH_3$; X = Cl **b**, R = $NHCH_3$; X = Cl

When this reaction was carried out on 3-amino-1,2,4-triazine 2-oxide (**8**), only one product, 6-bromo-3-amino-1,2,4-triazine 2-oxide (**9a**) (cf. Table I), was obtained.

Table I. Analytical Data for Some 6-Halo-1,2,4-triazines and Their 2-Oxides



Compd	Molecular formula	Substituents R_3	R_5	R_6	NMR shifts,[a] δ R_3	R_5	Mp,[b] °C	Analysis C Calcd (Found)	H Calcd (Found)	N Calcd (Found)
4a	$C_5H_7N_4OBr$	$N(CH_3)_2$	H	Br	3.26	7.82	131–132.5	27.42 (27.62)	3.22 (3.24)	25.88 (25.47)
6a	$C_4H_5N_4OBr$	$NHCH_3$	H	Br	3.15 (d)	7.80	146–147	23.43 (23.66)	2.63 (2.48)	27.33 (27.20)
4b	$C_5H_7N_4OCl$	$N(CH_3)_2$	H	Cl	3.28	7.87	93–96	34.39 (34.64)	4.04 (4.09)	32.10 (31.97)
6b	$C_4H_5N_4OCl$	$NHCH_3$	H	Cl	3.18 (d)	7.83	95–97	29.91 (30.21)	3.14 (3.19)	34.90 (35.03)
9a	$C_3H_3N_4OBr$	NH_2	H	Br	8.50	8.40	138–139	18.86 (19.12)	1.58 (1.63)	29.43 (29.16)
9b	$C_3H_3N_4OCl$	NH_2	H	Cl	8.54	8.36	147–148.5	24.59 (24.79)	2.06 (2.15)	38.24 (38.01)
5b	$C_4H_5N_4Cl$	$NHCH_3$	H	Cl	3.12 (d)	8.16	84–85	33.23 (33.09)	3.48 (3.64)	38.76 (38.57)
3b	$C_5H_7N_4Cl$	$N(CH_3)_2$	H	Cl	3.28	8.12	55–57	37.86 (37.94)	4.44 (4.35)	35.33 (35.16)
14	$C_7H_9N_4ClO$	NC_4H_8O	H	Cl	3.88	8.18	68.5–70	41.90 (42.11)	4.52 (4.60)	27.93 (27.69)
15	$C_8H_{11}N_4Cl$	NC_5H_{10}	H	Cl	3.85 1.71	8.10	140	48.36 (48.10)	5.58 (5.61)	28.2 (27.9)
5a	$C_4H_5N_4Br$	$NHCH_3$	H	Br	3.10 (d)	8.28	70–72	25.41 (25.20)	2.66 (2.69)	29.64 (29.78)

[a] NMR spectra were taken in $CDCl_3$. [b] Melting points were taken on a Thomas-Hoover melting point apparatus.

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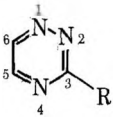
Table II. Product Distribution in the Bromination of Some 1,2,4-Triazine 2-Oxides[a]



Compd	Substituent	Reactant	Yield, % (6-halotriazine)	Yield, % (6-halo 2-oxide)
1	$N(CH_3)_2$	$Et_3N/Br_2/CCl_4$	28 (**3a**)	65 (**4a**)
		$K_2CO_3/Br_2/CCl_4$	7 (**3a**)	70 (**4a**)
		NBS/CH_2Cl_2	13 (**3a**)	67 (**4a**)
		$Et_3N/Cl_2/CCl_4$	5 (**3b**)	40 (**4b**)
2	$NHCH_3$	$Et_3N/Br_2/CCl_4$	5 (**5a**)	75 (**6a**)
		$K_2CO_3/Br_2/CCl_4$	5 (**5a**)	80 (**6a**)
		NBS/CH_2Cl_2		70 (**6a**)
		$Et_3N/Cl_2/CCl_4$	6 (**5b**)	78 (**6b**)
8	NH_2	$K_2CO_3/Br_2/CH_2Cl_2/CH_3CN$		50 (**9a**)
		$K_2CO_3/Br_2/CH_2Cl_2/CH_3CN$		72 (**9b**)
11	OCH_3	$Et_3N/Br_2/CHCl_3$		
10	SCH_3	$Et_3N/Br_2/CHCl_3$		

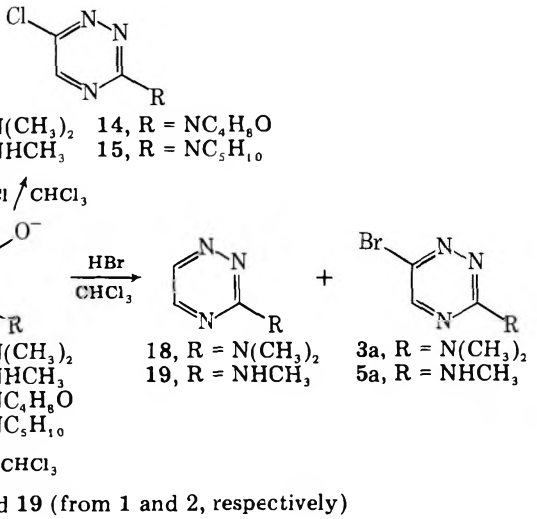
[a] Registry no.: **1**, 61178-04-9; **2**, 63197-00-2; **3a**, 63197-14-8; **3b**, 65914-96-7; **4a**, 65914-99-0; **4b**, 65915-00-6; **5a**, 65914-97-8; **5b**, 65914-98-9; **6a**, 65915-01-7; **6b**, 65915-02-8; **8**, 61177-95-5; **9a**, 65915-03-9; **9b**, 65915-04-0; **10**, 63197-03-5; **11**, 61178-03-8.

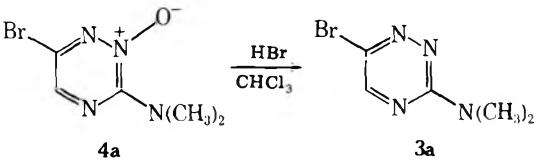
These halogenations were also carried out with chlorine and other halogenating agents. The conditions and yields of products are given in Table II. Under these same conditions, 3-methylthio- (**10**) and 3-methoxy-1,2,4-triazine 2-oxides (**11**) do not react.

The formation of the deoxygenated products in these bromination reactions along with our previous report on the deoxygenative alkoxylation of these *N*-oxides[2] led us to examine their reactivity toward the halogen acids in aprotic solvents. Upon treatment of 3-dimethylamino- (**1**), 3-monomethylamino- (**2**), 3-morpholino- (**12**), or 3-piperidino-1,2,4-triazine 2-oxides (**13**) with dry HCl gas in chloroform (cf. Scheme I), only one major product was obtained in each case. The mass spectra of these compounds showed that the products had lost the *N*-oxide function, while the ^1H NMR spectra clearly indicate that we are dealing with 6-chloro-3-substituted-1,2,4-triazines (**3b, 5b, 14,** and **15**). The reaction was also attempted with 3-amino- (**8**), 3-methoxy- (**11**) 3-chloro- (**16**), and 3-methylthio-1,2,4-triazine 2-oxides (**10**) under similar conditions. The starting materials were recovered in all of these instances.

In order to determine if the deoxygenated products observed in the bromination reaction arise from the presence of hydrobromic acid in the reaction mixture, 6-bromo-3-dimethylamino-1,2,4-triazine 2-oxide (**4a**) was treated with HBr in chloroform. The product obtained proved to be 6-bromo-3-dimethylamino-1,2,4-triazine (**3a**), identical with an authentic sample.

Scheme I





When 3-dimethylamino- (**1**) and 3-monomethylamino-1,2,4-triazine 2-oxides (**2**) were treated with gaseous HBr in chloroform (cf. Scheme I), two products were obtained in each case. Comparison of their ^1H NMR spectra clearly shows them to be 3-dimethylamino- (**18**) and 6-bromo-3-dimethylamino-1,2,4-triazines (**3a**) and 3-monomethylamino- (**19**) and 6-bromo-3-monomethylamino-1,2,4-triazines (**5a**), respectively.

As in the reactions with HCl, 3-amino- (**8**), 3-methoxy- (**11**), 3-methylthio- (**10**), and 3-bromo-1,2,4-triazine 2-oxides (**20**) do not react under similar conditions.

Treatment of 3-dimethylamino- (**1**) and 3-monomethylamino-1,2,4-triazine 2-oxides (**2**) with hydrogen iodide gives good yields of 3-dimethylamino- (**18**) and 3-monomethylamino-1,2,4-triazines (**19**) (cf. Scheme I).

In order to determine if it is necessary to have the halogen present as an acid, and not simply as an anion, 3-dimethylamino-1,2,4-triazine 2-oxide (**1**) was treated with potassium bromide in the presence of 18-crown-6. The starting material was recovered quantitatively.

In previous work we reported the bromination of some 1,2,4-triazine 1-oxide derivatives. In these reactions, no deoxygenated products were obtained. When 3-methoxy- (**21**), 3-monomethylamino- (**22**), and 3-dimethylamino-1,2,4-triazine 1-oxides (**23**) are treated with hydrochloric or hydrobromic acid in chloroform, no brominated or deoxygenated products are observed.

Mechanistic Considerations. In proposing a mechanism for both electrophilic and deoxygenative bromination of the 1,2,4-triazine 2-oxides, several factors need to be considered. The first of these is the electron-donating ability, as exemplified by Hammet substituent constants, of the 3 substituent. Table III lists the various 3 substituents, their Hammet substituent constants,[3] and whether or not they undergo elec-

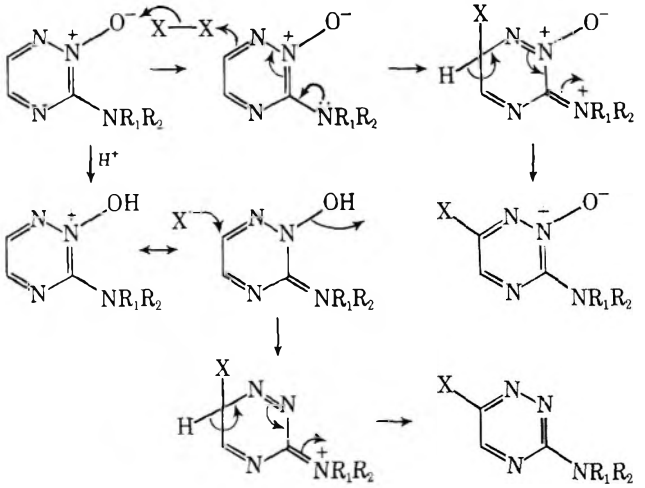
Table III. Hammet Substituent Constants

Substituent	σ_{para}[a]	Electrophilic bromination	Deoxygenative bromination
$N(CH_3)_2$	−0.600	Reacts	Reacts
$NHCH_3$	−0.592	Reacts	Reacts
NH_2	−0.660	Reacts	No reaction
SCH_3	−0.047	No reaction	No reaction
Cl	+0.227	No reaction	No reaction
Br	+0.232	No reaction	No reaction

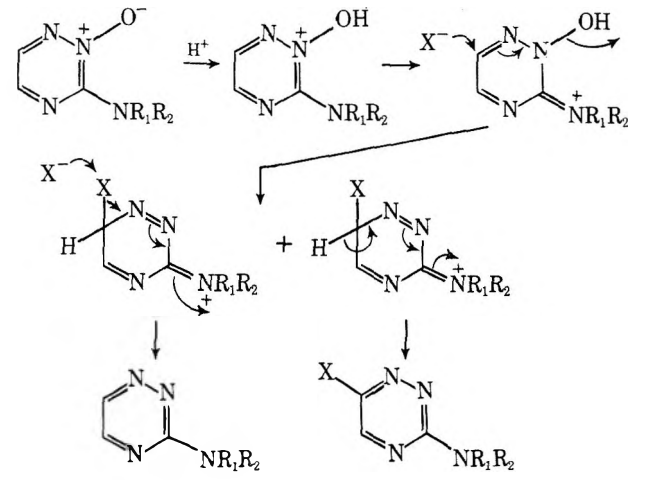
[a]Taken from ref 3.

trophilic or deoxygenative bromination. Except for the 3-amino derivative 8, only those groups that donate their electrons very efficiently (high negative σ_{para}'s) react under the conditions used in these brominations. Secondly, treatment of 6-bromo-3-dimethylamino-1,2,4-triazine 2-oxide (**4a**) with hydrobromic acid gave only the deoxygenated derivative. Thirdly, treatment of 3-dimethylamino-1,2,4-triazine 2-oxide (1) with Br^- gave no brominated or deoxygenated products. Fourthly, when the reactions were run with hydroiodic acid under a nitrogen atmosphere, the presence of iodine was indicated (starch–iodine tests). Finally, none of the 1,2,4-triazine 1-oxides give deoxygenated products.

On the basis of this evidence, the following two mechanistic pathways can be suggested. (1) For the products arising from electrophilic bromination conditions, the mechanism is straightforward. As the reaction proceeds, small amounts of



hydrobromic acid are built up, and the possibility of protonation of the *N*-oxide becomes feasible. This allows the molecule to be attacked by bromide, with subsequent loss of the elements of water. The small amounts of deoxygenated product formed can be attributed to the hydrobromic acid formed under the reaction conditions.



(2) For the deoxygenative bromination of the 1,2,4-triazine 2-oxides, a similar mechanism may be suggested. One would expect that the attack of halogen anion on the ring substituted halogen would be dependent upon the polarizability of the halogen. This is, in fact, born out since chloride anion does not react in this manner while bromide anion gives both products and iodide anion gives exclusively the product arising via this path.

In summary, the 1,2,4-triazine 2-oxides undergo some rather unique transformations. They are subject to electrophilic bromination, deoxygenation bromination, and deoxygenation. These transformations provide synthetic routes to many substituted 1,2,4-triazines and their 2-oxides. Further studies of the synthetic utility of these reactions in this and related ring systems are in progress.

Experimental Section

Mass spectra were recorded with a Hitachi Perkin-Elmer RMU-6M instrument of all new compounds. Their molecular ions and fragmentation patterns are consistent with the indicated structures. A Varian HA-100 instrument was used to record ^1H NMR spectra. Melting points are corrected. Elemental analyses were performed by Atlantic Microlabs, Inc., Atlanta, Ga., and the Analytical Services Laboratory, Department of Chemistry, University of Alabama.

Reaction of 3-Dimethylamino-1,2,4-triazine 2-Oxide (1) and 3-Monomethylamino-1,2,4-triazine 2-Oxide (2). (a) In the Presence of Et_3N: To a solution of 140 mg (1 mmol) of 3-dimethylamino-1,2,4-triazine 2-oxide (1) dissolved in 30 mL of CCl_4 was added 320 mg (2 mmol) of Br_2. The solution was stirred at room temperature for 5 min, and 151 mg (1.5 mmol) of Et_3N was added. Stirring was continued for 2 h, after which time TLC showed no starting material. The solvent was removed in vacuo. The residue was chromatographed on silica gel (grade III) with $CHCl_3$ as eluent. The resulting component mixture was separated by thick-layer chromatography with 50:50 $CHCl_3/C_6H_6$ as eluent to give 142 mg (65%) of 6-bromo-3-dimethylamino-1,2,4-triazine 2-oxide (**4a**) and 28 mg (14%) of 6-bromo-3-dimethylamino-1,2,4-triazine (**3a**), which was compared with an authentic sample.

In the case of 3-monomethylamino-1,2,4-triazine 2-oxide (**2**), 153 mg (75%) of 6-bromo-3-monomethylamino-1,2,4-triazine 2-oxide (**6a**) and 10 mg (5%) of 6-bromo-3-monomethylamino-1,2,4-triazine (**5a**) were obtained.

(b) In the Presence of K_2CO_3: To a solution of 500 mg (3.6 mmol) of 3-dimethylamino-1,2,4-triazine 2-oxide (1) in 75 mL of dry CCl_4 was added 1.14 g (7.1 mmol) of Br_2 and 1 g (7.1 mmol) of K_2CO_3. The resulting suspension was stirred for 2 h and the solvent removed in vacuo. The reside was passed through 25 g of alumina (grade III) with $CHCl_3$. The main yellow component was further separated as above to give 511 mg (70%) of 6-bromo-3-dimethylamino-1,2,4-triazine 2-oxide (**4a**) and 51 mg (7%) of 6-bromo-3-dimethylamino-1,2,4-triazine (**3a**).

In the case of 3-monomethylamino-1,2,4-triazine 2-oxide (**2**), 590 mg (80%) of 6-bromo-3-monomethylamino-1,2,4-triazine 2-oxide (**6a**) and 34 mg (5%) of 6-bromo-3-monomethylamino-1,2,4-triazine (**5a**) were obtained.

(c) Thru the Action of NBS: To a solution of 100 mg (0.7 mmol) of 3-dimethylamino-1,2,4-triazine 2-oxide (1) in 40 mL of CH_2Cl_2 was added 248 mg (1.4 mmol) of NBS. The solution was stirred for 48 h, after which time the solvent was removed in vacuo. The residue was passed through 25 g of alumina (grade III) with $CHCl_3$. The yellow material was further purified as above, yielding 102 mg of (67%) 6-bromo-3-dimethylamino-1,2,4-triazine 2-oxide (**4a**) and 18 mg (13%) of 6-bromo-3-dimethylamino-1,2,4-triazine (**3a**).

In the case of 3-monomethylamino-1,2,4-triazine 2-oxide (**2**), 153 mg (70%) of 6-bromo-3-monomethylamino-1,2,4-triazine 2-oxide (**6a**) was obtained only.

Treatment of 3-Dimethylamino-1,2,4-triazine 2-Oxide (1) with Cl_2 and Et_3N. To a solution of 199 mg (28 mmol) of Cl_2 in 150 mL of $CHCl_3$ was added 200 mg (1.4 mmol) of 3-dimethylamino-1,2,4-triazine 2-oxide along with 250 mg (2.5 mmol) of Et_3N. The mixture was stirred for 1 h and the solvent removed in vacuo. The residue was chromatographed by dry column chromatography on alumina (grade III) using 50:50 $CHCl_3/C_6H_6$ as eluent. The products were then sublimed at 0.05 Torr (45 °C) to yield 200 mg (40%) of 6-chloro-3-dimethylamino-1,2,4-triazine 2-oxide (**4b**) and 20 mg (4.5%) of 6-chloro-3-dimethylamino-1,2,4-triazone (**3b**).

In the case of 3-monomethylamino-1,2,4-triazine 2-oxide (**2**), 200 mg (78%) of 6-chloro-3-monomethylamino-1,2,4-triazine 2-oxide (**6b**)

and 15 mg (6%) of 6-chloro-3-monomethylamino-1,2,4-triazine (**5b**) were obtained.

Preparation of 6-Bromo-3-amino-1,2,4-triazine 2-Oxide (9a). To a solution of 222 mg (1.9 mmol) of 3-amino-1,2,4-triazine 2-oxide (**8**) dissolved in 100 mL of $CHCl_2$ and 40 mL of CH_3CN was added 704 mg (4.4 mmol) of Br_2, and the solution was stirred for 0.5 h. A 420-mg (4.9 mmol) amount of $NaHCO_3$ was then added, and stirring was continued for 1 h. The resulting mixture was filtered and the solvent evaporated. The residue was purified by thick-layer chromatography using silica (grade III) with CH_3CN as eluent to give 182 mg (50%) of 6-bromo-3-amino-1,2,4-triazine 2-oxide (**9a**).

The reaction was also carried out using Cl_2, and 200 mg (72%) of 6-chloro-3-amino-1,2,4-triazine 2-oxide (**9b**) was obtained.

Attempted Reaction of 3-Dimethylamino-1,2,4-triazine 2-Oxide (1) with KBr in the Presence of 18-Crown-6. To a dry 100-mL round-bottom flask containing 30 mL of dry benzene, 268 mg (1.4 mmol) of 18-crown-6, and 166 mg (1.4 mmol) of KBr was added 100 mg (0.7 mmol) of 3-dimethylamino-1,2,4-triazine 2-oxide (**1**) dissolved in 20 mL of benzene. The reaction mixture was refluxed for 4 days, after which time TLC showed only the presence of starting materials.

The above reaction was also attempted using 3-monomethylamino-1,2,4-triazine 2-oxide (**2**). Again, after 4 days at reflux, TLC showed no evidence of products.

Attempted Reaction of 3-Methylthio-1,2,4-triazine 2-Oxide (10) with Br_2 and Et_3N. To a solution of 100 mg (0.6 mmol) of 3-methylthio-1,2,4-triazine 2-oxide (**10**) in 20 mL of $CHCl_3$ was added 112 mg (0.6 mmol) of Br_2 in 5 mL of $CHCl_3$ and 60 mg (0.6 mmol) of Et_3N. The resulting solution was first stirred at room temperature for 24 h and then warmed gently for 16 h. The solution was evaporated and the residue chromatographed on alumina (grade III) with $CHCl_3$ as eluent to give 75 mg (75%) of 3-methylthio-1,2,4-triazine 2-oxide (**10**).

Attempted Reaction of 3-Methoxy-1,2,4-triazine 2-Oxide (11) with Br_2 and Et_3N. To a solution of 50 mg (0.39 mmol) of 3-methoxy-1,2,4-triazine 2-oxide (**11**) in 15 mL of $CHCl_3$ was added 112 mg (0.6 mmol) of Br_2 in 5 mL of $CHCl_3$ and 39 mg (0.39 mmol) of Et_3N. The resulting solution was stirred for 24 h and then warmed gently on a hot plate for 2 h. The solvent was evaporated and the residue purified by thick-layer chromatography on silica (grade III) with $CHCl_3$ as eluent to give 30 mg (60%) of 3-methoxy-1,2,4-triazine 2-oxide (**11**).

Conversion of 6-Bromo-3-dimethylamino-1,2,4-triazine (3a) to 6-Methoxy-3-dimethylamino-1,2,4-triazine (7). To a solution of 600 mg (27 mmol) of 6-bromo-3-dimethylamino-1,2,4-triazine (**3a**) in 20 mL of dry CH_3OH was added dropwise a solution of 136 mg (5.9 mmol) of Na in 10 mL of dry CH_3OH. The reaction mixture was refluxed for 4 h and then quenched with dry ice. The solvent was removed in vacuo and the residue chromatographed on alumina (grade III) to give 261 mg (70%) of 6-methoxy-3-dimethylamino-1,2,4-triazine (**7**).

Reaction of 6-Bromo-3-dimethylamino-1,2,4-triazine 2-Oxide (4a) with HBr. Into a solution of 100 mg (0.46 mmol) of 6-bromo-3-dimethylamino-1,2,4-triazine 2-oxide (**4a**) in 100 mL of $CHCl_3$ was bubbled dry HBr gas. The resulting solution was stirred overnight. Excess Na_2CO_3 was added, and stirring was continued for an additional hour. The mixture was then filtered and the solvent evaporated. The residue was purified by thick-layer chromatography on silica (grade III) using $CHCl_3$. The main component was sublimed at 0.05 Torr (60 °C) to give 66 mg (70%) of 6-bromo-3-dimethylamino-1,2,4-triazine (**3a**).

Reaction of 3-Monomethylamino-1,2,4-triazine 2-Oxide (2) with HCl. Into a solution of 100 mg (0.79 mmol) of 3-monomethylamino-1,2,4-triazine 2-oxide (**2**) in 75 mL of $CHCl_3$ was bubbled dry HCl gas. The reaction mixture was stirred for 16 h, and excess Na_2CO_3 was added. The mixture was stirred for an additional 4 h and filtered, and the solvent was removed to give a yellow solid. This was sublimed at a 0.05 Torr (60 °C) to yield 97 mg (85%) of 6-chloro-3-monomethylamino-1,2,4-triazine (**5b**).

The reaction was also carried out using 3-dimethylamino-1,2,4-triazine 2-oxide (**1**), 3-morpholino-1,2,4-triazine 2-oxide (**12**), and 3-piperidino-1,2,4-triazine 2-oxide, giving 180 mg (64%) of 6-chloro-3-dimethylamino-1,2,4-triazine (**3b**), 80 mg (80%) of 6-chloro-3-morpholino-1,2,4-triazine (**14**), and 50 mg (50%) of 6-chloro-3-piperidino-1,2,4-triazine (**15**), respectively.

Reaction of 3-Monomethylamino-1,2,4-triazine 2-Oxide (2) with HBr. Into a solution of 140 mg (1.1 mmol) of **2** in 75 mL of $CHCl_3$ was bubbled dry HBr gas. The solution became cloudy, and stirring was continued overnight. Excess $NaHCO_3$ was added, the mixture was stirred for 3 h and filtered, and the solvent was evaporated. The residue was chromatographed on silica (grade III) with $CHCl_3$ as eluent to give 39 mg (25%) of 6-bromo-3-monomethylamino-1,2,4-triazine (**5a**) and 78 mg (64%) of 3-monomethylamino-1,2,4-triazine (**19**).

The reaction was also carried out using 3-dimethylamino-1,2,4-triazine 2-oxide (**1**), and 124 mg (41%) of 6-bromo-3-dimethylamino-1,2,4-triazine (**3a**) and 118 mg (50%) of 3-dimethylamino-1,2,4-triazine (**18**) were obtained.

Reaction of 3-Monomethylamino-1,2,4-triazine 2-Oxide (2) with HI. Into a solution of 250 mg (1.9 mmol) of 3-monomethylamino-1,2,4-triazine 2-oxide (**2**) in 75 mL of dry $CHCl_3$ was bubbled dry HI gas. The reaction mixture was kept under static dry oxygen-free N_2 gas and stirred overnight at room temperature. Excess Na_2CO_3 was added, and stirring was continued for an additional 4 h. The mixture was filtered and a portion of the filtrate tested with freshly prepared starch solution. The presence of I_2 was indicated by the blue color. The remainder of the filtrate was evaporated and the residue chromatographed on silica (grade III) with $CHCl_3$ as eluent to give 175 mg (79%) of 3-monomethylamino-1,2,4-triazine (**19**).

The reaction was also carried out with 3-dimethylamino-1,2,4-triazine 2-oxide (**1**), and 175 mg (80%) of 3-dimethylamino-1,2,4-triazine (**18**) was obtained.

Attempted Reaction of 3-Chloro-1,2,4-triazine 2-Oxide (17) with HCl. Into a solution of 300 mg (2.5 mmol) of 3-chloro-1,2,4-triazine 2-oxide (**17**) in 30 mL of $CHCl_3$ was bubbled dry HCl gas. The resulting solution was stirred overnight. Excess Na_2CO_3 was added, and the mixture was stirred for an additional hour. The mixture was then filtered and the solvent evaporated to give 291 mg (97%) of 3-chloro-1,2,4-triazine 2-oxide (**17**).

Attempted Reaction of 3-Bromo-1,2,4-triazine 2-Oxide (20) with HBr. Into a solution of 300 mg (1.7 mmol) of 3-bromo-1,2,4-triazine 2-oxide (**20**) in 30 mL of $CHCl_3$ was bubbled dry HBr gas. The resulting solution was stirred overnight. Excess Na_2CO_3 was added, and the mixture was stirred for an additional hour. The mixture was filtered and the solvent evaporated to give 276 mg (92%) of 3-bromo-1,2,4-triazine 2-oxide (**20**).

Attempted Reaction of 3-Methylthio-1,2,4-triazine 2-Oxide (10) with HCl or HBr. Into a solution of 100 mg (0.6 mmol) of 3-methylthio-1,2,4-triazine 2-oxide (**10**) in 75 mL of $CHCl_3$ was bubbled dry HCl gas. The resulting solution was stirred overnight. Excess Na_2CO_3 was added, and stirring was continued for an additional 4 h. The mixture was filtered and the solvent removed to give 90 mg (90%) of 3-methylthio-1,2,4-triazine 2-oxide (**10**).

In the reaction with HBr, 95 mg (95%) of the starting material was recovered.

Attempted Reaction of 3-Methoxy-1,2,4-triazine 2-Oxide (11) with HCl for HBr. Into a solution of 100 mg (0.79 mmol) of 3-methoxy-1,2,4-triazine 2-oxide dissolved in 75 mL of $CHCl_3$ was bubbled dry HCl gas. The solution was stirred overnight. Excess Na_2CO_3 was added, and stirring was continued for an additional 4 h. The mixture was filtered and the solvent removed to give 75 mg (75%) of 3-methoxy-1,2,4-triazine 2-oxide (**11**).

The reaction was also carried out in the presence of HBr, and again, only starting material was recovered (92%).

Attempted Reaction of 3-Methoxy-1,2,4-triazine 1-Oxide (21) with HCl or HBr. Into a solution of 300 mg (2.4 mmol) of 3-methoxy-1,2,4-triazine 1-oxide (**21**) in 75 mL of $CHCl_3$ was bubbled dry HCl gas. The solution was stirred overnight and then extracted with 50 mL of saturated Na_2CO_3. The water layer was further extracted with $CHCl_3$ (2 × 100 mL), and the combined extracts were dried over Na_2CO_3. After filtration and evaporation of the solvent, 268 mg (89%) of 3-methoxy-1,2,4-triazine 1-oxide (**21**) was recovered.

The reaction was also carried out with 3-monomethylamino- (**22**) and 3-dimethylamino-1,2,4-triazine 1-oxides (**23**) with both HCl and HBr. In all cases, only starting material was recovered (81–93%).

Registry No.—**7**, 63197-02-4; **12**, 61178-05-0; **13**, 61178-06-1; **14**, 65915-05-1; **15**, 65915-06-2; **16**, 61178-03-8; **18**, 63197-03-5; **19**, 53300-17-7; **20**, 65915-07-3; **21**, 61178-02-7; **22**, 27531-67-5; **23**, 63197-06-8; **24**, 61178-07-2; **25**, 61202-85-5.

Supplementary Material Available: Tables I–III and Figure 1 of x-ray crystallographic data (4 pages). Ordering information is given on any current masthead page.

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α-Phosphoryl Sulfoxides. 4. Pummerer Rearrangements of α-Phosphoryl Sulfoxides and Asymmetric Induction in the Transfer of Chirality from Sulfur to Carbon[1]

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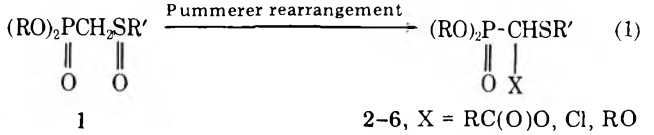
α-Phosphoryl sulfoxides (1) undergo the Pummerer rearrangement, providing an entry into various α-substituted α-phosphirylmethyl methyl(aryl) sulfides. Acetic and trifluoroacetic anhydrides convert α-phosphoryl sulfoxides (1) to the corresponding α-acetoxy- and α-trifluoroacetoxy-α-phosphorylmethyl sulfides. The reaction of sulfoxides I with benzoyl chloride affords α-chloro-α-phosphorylmethyl sulfides. A new method is also described for the synthesis of the *O,S*-thioacetals of formyl phosphonates which involves reaction of sulfoxides 1 with alcohols in the presence of iodine. Reaction of optically active dimethylphosphorylmethyl *p*-tolyl sulfoxide with acetic anhydride was found to result in asymmetric induction at the α-carbon atom in the corresponding α-acetoxy sulfide formed.

The reaction between acid anhydrides and sulfoxides bearing at least one α hydrogen, first discovered by Pummerer,[3] leads to the formation of α-acyloxy sulfides. This and related reactions have attracted considerable attention both from synthetic and mechanistic points of view.[4] It is now commonly accepted that the Pummerer reaction is a complex process which consists of three main steps (Scheme I), i.e., the formation of the acyloxysulfonium salt (A) and then sulfonium ylide (B) which in the last step undergoes the rearrangement to give the final reaction products.

The migration of the acyloxy group from sulfur to the α-carbon atom may occur inter- or intramolecularly depending on the structural effects in the starting sulfoxide.



(1)

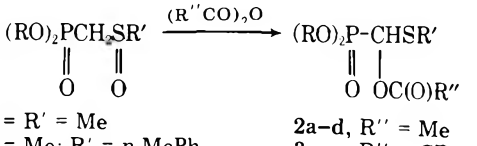
1 2–6, X = RC(O)O, Cl, RO

As part of a continuing study of α-phosphoryl sulfoxides (1), which recently became readily available in racemic[5] and optically active forms,[6] we have investigated their various Pummerer-type reactions. Generally, the Pummerer rearrangement of α-phosphoryl sulfoxides (1) results in the formation of α-substituted α-phosphorylmethyl sulfides. Since the latter compounds possess a relatively acidic hydrogen linked to the phosphonate carbon atom they may be utilized further as intermediates in the Horner PO–olefination reaction.[7]

In this paper we present details of several synthetically useful Pummerer-type reactions of α-phosphoryl sulfoxides as well as describe a new example of asymmetric induction in the reaction between optically active dimethylphosphorylmethyl *p*-tolyl sulfoxide and acetic anhydride.

Results and Discussion

Reaction of Racemic and Optically Active α-Phosphoryl Sulfoxides (1) with Carboxylic Acid Anhydrides. First the classical Pummerer reaction of α-phosphoryl sulfoxides (1) with carboxylic acid anhydrides was investigated (eq 2). These reactions, which were performed in refluxing



(2)

1a, R = R′ = Me
b, R = Me; R′ = *p*-MePh
c, R = Et; R′ = Me
d, R = Et; R′ = Ph

2a–d, R″ = Me
3a–c, R″ = CF_3

acetic anhydride, occurred quantitatively in 2–3 h as determined by a periodic assay of the ^{31}P-NMR spectra. The analytically pure α-acetoxy-α-phosphorylmethyl methyl(aryl) sulfides (2) were isolated by distillation or column chromatography on silica gel.

With the more reactive trifluoroacetic anhydride[9] the Pummerer reaction of 1 was complete after 15 min at −78 °C. The resulting α-trifluoroacetoxy-α-phosphorylmethyl methyl(aryl) sulfides (3) were isolated by distillation with the exception of sulfide **3b** which was purified by column chromatography. Physical properties for compounds **2** and **3** are summarized in Table I.[8]

The conversion of sulfoxides into α-acyloxy sulfides is especially interesting from the stereochemical point of view since the chirality at sulfur in transferred to the α carbon. Therefore, the generation of an optically active α-carbon center can be expected when an optically active sulfoxide is used as starting material. Allenmark[10] was the first who observed such asymmetric induction in the reaction of optically active *o*-carboxyphenyl benzyl sulfoxide with acetic anhydride

Scheme I

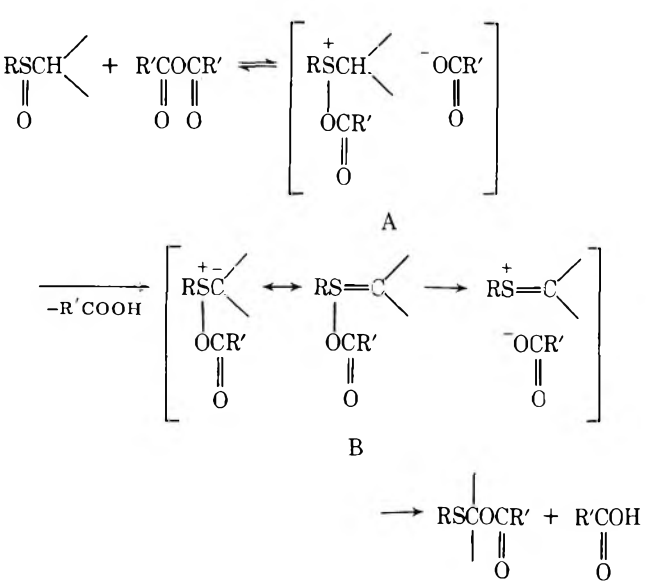


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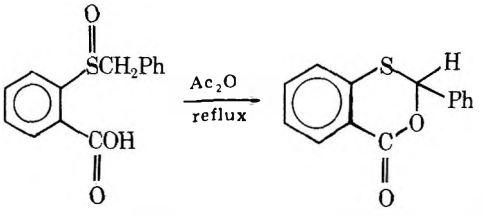
Table I. Preparation and Properties of α-Substituted α-Phosphorylmethyl Sulfides

No.	Product Structure	Registry no.	Reaction conditions Temp (°C)/time	Yield[a] %	n_D (°C) bp (°C)/Torr	^{31}P NMR ($CDCl_3/H_3PO_4$)[b]
2a	$(MeO)_2P(O)CH(OAc)SMe$	65915-08-4	120/2 h	90	1.4700 (26)	+16.4
2b	$(MeO)_2P(O)CH(OAc)STol$	65956-51-6	120/3 h	84	1.5420 (21)	+16.7
2c	$(EtO)_2P(O)CH(OAc)SMe$	65915-09-5	120/2 h	86	1.4570 (23) 85/0.1	+14.3
2d	$(EtO)_2P(O)CH(OAc)SPh$	65956-52-7	120/3 h	88	1.5130 (26)	+14.0
3a	$(MeO)_2P(O)CH(OCOCF_3)SMe$	65915-10-8	−78/15 min	74	1.4050 (22) 62/1.5	+13.9
3b	$(MeO)_2P(O)CH(OCOCF_3)STol$	65915-11-9	−78/15 min	72	1.4663 (23)	+13.7
3c	$(EtO)_2P(O)CH(OCOCF_3)SMe$	65915-12-0	−78/15 min	76	1.3925 (22) 65/0.4	+11.4
4a	$(MeO)_2P(O)CH(Cl)SMe$	65915-13-1	rt[c]/5 h	84	1.4960 (23) 81/0.01	+16.2
4c	$(EtO)_2P(O)CH(Cl)SMe$	65915-14-2	rt[c]/5 h	90	1.4850 (23) 88/0.01	+14.3
4d	$(EtO)_2P(O)CH(Cl)SPh$	65915-15-3	rt[c]/5 h	82	1.5330 (24)	+14.6
6a	$(MeO)_2P(O)CCl_2SMe$	65915-16-4	0/2 h	90	1.5040 (25)	+9.8
6c	$(EtO)_2P(O)CCl_2SMe$	28975-75-9	0/2 h	92	1.4931 (25)	+7.7
6d	$(EtO)_2P(O)CCl_2SPh$	65915-17-5	0/2 h	88	1.5410 (25)	+8.1
7a	$(MeO)_2P(O)CH(OMe)SMe$	65915-18-6	Reflux/2 h	70	1.4652 (22) 58/0.1	+18.0
7b	$(MeO)_2P(O)CH(OMe)STol$	65915-19-7	Reflux/7 h	65	1.5335 (22)	+17.5
7c	$(EtO)_2P(O)CH(OMe)SMe$	65915-20-0	Reflux/1.5 h	82	1.4622 (24) 64/0.1	+16.5
7d	$(EtO)_2P(O)CH(OMe)SPh$	65956-98-1	Reflux/4 h	68	1.5250 (20) 125–8/0.05	+15.0
8c	$(EtO)_2P(O)CH(OEt)SMe$	65915-21-1	Reflux/15 min	73	1.4570 (24) 103–5/1.5	+16.1
8d	$(EtO)_2P(O)CH(OEt)SPh$	65915-22-2	Reflux/50 min	78	1.5270 (20) 138–142/0.02	+16.0

[a] Isolated yield of purified product. Satisfactory analytical data (±0.4% for C, H, P) were reported for all new compounds listed in the table. [b] In this paper the new convention of positive ^{31}P-NMR signals to low field from H_3PO_4 is used. [c] Room temperature.

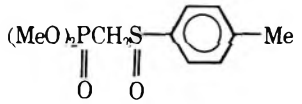
to give the cyclic optically active product, 3,1-benzoxathian-4-one (eq 3).



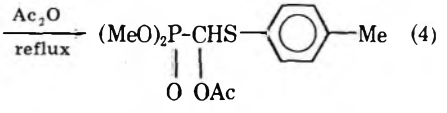
(3)

$[\alpha]_{589}$ +451° $[\alpha]_{589}$ +17.3° (ee 11.2%)

Since optically active dimethylphosphorylmethyl *p*-tolyl sulfoxide (**1b**) has become readily available,[6] it was of interest to investigate its Pummerer rearrangement in the hope of observing a new example of asymmetric induction in the transfer of chirality from sulfur to α carbon. In fact treatment of sulfoxide **1b**, $[\alpha]_{589}$ + 144°, with excess acetic anhydride at 120 °C for 2 h afforded optically active α-acetoxy-α-(dimethylphosphoryl)methyl p-tolyl sulfide (**2b**) having $[\alpha]_{589}$ −4° (eq 4). This value of optical rotation corresponds to 24%



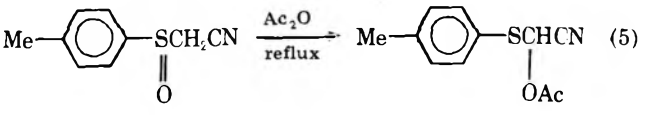
1b, $[\alpha]_{589}$ +144°



(4)

2b, $[\alpha]_{589}$ −4° (ee 24%)

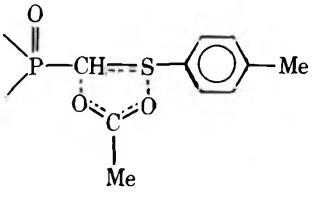
of optical purity at the chiral carbon center in **2b** as determined by means of ^1H-NMR spectroscopy using the chiral lanthanide shift reagent, tris[3-(trifluoromethylhydroxymethylene)-*d*-camphorato]europium.[11] The best separation of enantiomeric resonances of **2b** was observed for the methine proton which permitted accurate integration and determination of the enantiomeric purity. After this work was completed Oae and Numata[12] reported asymmetric induction in the Pummerer reaction of optically active α-cyanomethyl *p*-tolyl sulfoxide (eq 5).



(5)

$[\alpha]_{589}$ +252° $[\alpha]_{589}$ +26.8° (ee 29%)

It should be noted that the methylene group of **1b** is highly activated because of the presence of the highly electron withdrawing phosphoryl and sulfinyl groups. Therefore, it is reasonable to assume that proton removal should be fast and reversible,[13] whereas the 1,2 shift of the acetoxy group is likely to be rate determining (Scheme I). The observation of substantial asymmetric induction strongly suggests that acetoxy

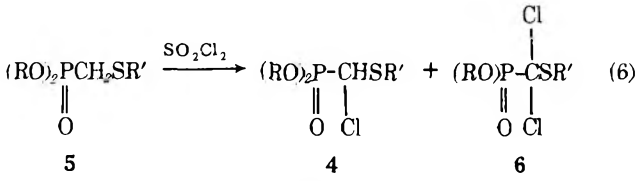


C

migration occurs to a large extent by an intramolecular process presumably via a five-membered cyclic transition state such as C. Additional studies regarding the mechanism of the Pummerer reaction using asymmetric substrates are under way.

Reaction of α-Phosphoryl Sulfoxides (1) with Acid Chlorides. *We next investigated the reaction of sulfoxides* 1 with acid chlorides which have also been used to initiate Pummerer rearrangements. In this case α-chloro-α-phosphorylmethyl methyl(aryl) sulfides (4) should result. It is worth pointing out that these compounds are potential precursors of the corresponding α-phosphoryl carbanions or carbenes.

A synthesis of α-chloro sulfides (4) by direct chlorination of α-phosphoryl sulfides (5) by means of sulfuryl chloride was reported by Gross et al.[14] (eq 6). However, careful examination

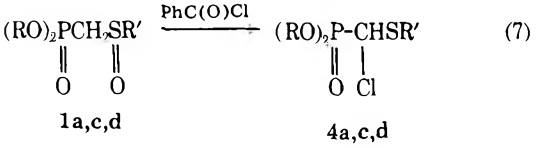


(6)

5 4 6

of this process using ^{31}P-NMR spectroscopy revealed that, although 4 clearly predominates, there is always formed a mixture of monochlorosulfide 4 and dichloro sulfide 6.

Our preliminary attempts to convert α-phosphoryl sulfoxides (1) into the corresponding sulfides 4 by means of acetyl chloride or thionyl chloride were only partly successful since the formation of dichloro sulfides 6 was also observed. For example, reaction of sulfoxide 1c with acetyl chloride afforded *a mixture containing 90% 4c and 10% 6c while thionyl chloride* gave 87% 4c and 13% 6c. On the other hand, benzoyl chloride, which is less reactive than acetyl chloride, leads to quantitative formation of the desired α-chloro-α-phosphorylmethyl sulfides (4) as shown by the ^{31}P-NMR spectroscopy (eq 7). The

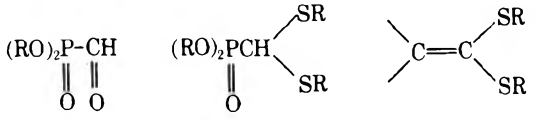


(7)

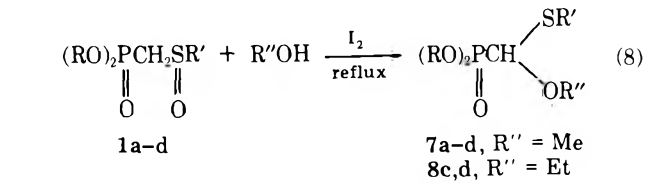
1a,c,d 4a,c,d

results are collected in Table I. For comparison purpose, we also prepared the dichloro sulfides 6 from α-phosphoryl sulfides (5) and 2 mol of sulfuryl chloride.

Synthesis of *O,S*-Thioacetals of Formyl Phosphonates. In a previous paper[15] devoted to α-phosphoryl-substituted organosulfur compounds we described simple methods for the preparation of the *S,S*-thioacetals of formyl phosphonates and their conversion[16] under Horner–Wittig reaction conditions into the corresponding ketene thioacetals which are key intermediates in a wide variety of organic syntheses.



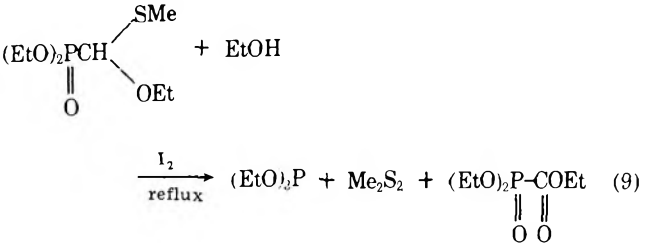
We now wish to report an efficient general synthesis of the *O,S*-thioacetals of formyl phosphonates, which represent a new class of compounds derived from formyl phosphonates. In contrast to the parent formyl phosphonates, which are practically unknown, these compounds are chemically stable and can be easily obtained by the Pummerer-type reaction between α-phosphoryl sulfoxides (1) and alcohols in the presence of iodine (eq 8). This reaction was based on the analogous reaction of β-keto sulfoxides which results, however, in the formation of α-keto acetals.[17]



(8)

1a–d 7a–d, R″ = Me; 8c,d, R″ = Et

Usually, these rearrangements were carried out under reflux in an excess of alcohol using equimolar amounts of iodine. All the reactions have been optimized with regard to yield and purity by ^{31}P-NMR spectroscopy. Results are summarized in Table I. Maintaining optimum reaction times was important since prolonged heating resulted in the formation of various by-products such as trialkyl phosphates, disulfides, dialkyl alkoxycarbonylphosphonates and the *O,O*-acetals or *S,S*-thioacetals of formyl phosphonates. These by-products undoubtedly arise from the further transformations of the *O,S*-thioacetals 7 and 8 under the reaction conditions. As an example, thioacetal 8c has been found to give triethyl phosphate, dimethyl disulfide, and diethyl ethoxycarbonylphosphonate[18] when refluxed in ethanol in the presence of iodine (eq 9).



(9)

Finally, it should be noted that the structures of all compounds synthesized in the present work have been confirmed by ^{1}H-, ^{13}C-, and ^{31}P-NMR spectroscopy. In a majority of cases we observed in the ^{1}H- and ^{13}C-NMR spectra magnetic nonequivalence of the P-methoxy groups due to the presence of the chirality center on the α-carbon atom. The most characteristic coupling constants $^{2}J_{CH-P}$ and $^{1}J_{^{13}C-P}$ are in the range 10–12.5 Hz and 162–188 Hz, respectively. Appropriate spectral data are given in Table II.

Experimental Section

All boiling points are uncorrected. Solvents and commercial reagents were distilled and dried by conventional methods before use. ^{1}H-NMR spectra were recorded at 60 MHz with a R 12 B Perkin-Elmer spectrometer. *^{31}P- and ^{13}C-NMR* spectra were obtained on a Jeol FX-60 F.T. spectrometer with external 85% H_3PO_4 and internal Me_4Si as standards. Column chromatography was carried out on silica gel Meck 100–200 mesh. Optical activity measurements were made with a Perkin-Elmer 241MC photopolarimeter in acetone solution.

Reaction of α-Phosphoryl Sulfoxide (1 with Acetic Anhydride. General Procedure. Sulfoxide 1 (0.01 mol) was dissolved in 10 mL of acetic anhydride and refluxed for 2–3 h at 120 °C. After removal of acetic anhydride and acetic acid under reduced pressure the crude product 2 obtained in 100% yield was purified by distillation or column chromatography.

Reaction of α-Phosphoryl Sulfoxide (1) with Trifuloroacetic Anhydride. General Procedure. Sulfoxide 1 (0.05 mol) and trifluoroacetic anhydride (3 mL) were mixed at −78 °C. The reaction mixture was stirred at this temperature for 15 min. The temperature was *then raised to 20 °C and the resulting mixture* was evaporated to give crude 3 in quantiative yield. An analytically pure sample of 3 was obtained by distillation or column chromatography.

Reaction of Optically Active Dimethylphosphorylmethyl *p*-Tolyl Sulfoxide (1b) with Acetic Anhdyride. A mixture of sulfoxide 1b 0.26 g, 0.001 mol), $[\alpha]_{589}$ +144° (97% ee), and acetic anhydride (1 mL) was refluxed for 2 h at 120 °C. Removal of excess acetic anhydride and acetic acid afforded the crude product 2b which was chromatographed [benzene/acetone, 20:1] to give the analtyically pure α-acetoxy-α-dimethylphosphorylmethyl *p*-tolyl sulfide (2b); 0.22 g (73%); $[\alpha]_{589}$ −4° (*c* 3.5, acetone); n^{23}_{D} 1.5230; $\delta_{^{31}P}$ +16.7. Anal. Calcd for $C_{12}H_{17}O_5PS$: C, 47.25; H, 5.62; P, 10.7. Found: C, 47.36; H, 5.63; P, 10.18.

Reaction of α-Phosphoryl Sulfoxide (1) with Benzoyl Chloride. General Procedure. Sulfoxide 1 (0.01 mol) and benzoyl chloride (5 mL) were stirred at room temperature for 5 h. An excess of benzoyl chloride was removed in vacuo and the residue was chromatographed to give chloro sulfide **4**.

Synthesis of α,α-Dichloro-α-phosphorylmethyl Alkyl(aryl) Sulfide (6). General Procedure. α-Phosphoryl sulfoxide (**6**) (0.01 mol) in methylene chloride (25 mL) was treated with sulfuryl chloride (0.022 mol) at 0 °C for 2 h. The solvent and hydrogen chloride were evaporated to give the crude dichloro sulfide (**6**) which was isolated by distillation.

Synthesis of *O,S*-Thioacetals of Formyl Phosphonates 7 and 8. General Procedure. α-Phosphoryl sulfoxide (**1**) (0.01 mol) was refluxed in an excess of alcohol in the presence of equimolar amounts of iodine. The optimal reaction time, as given in Table I, was estimated by ^{31}P NMR. After the reaction was complete excess alcohol was removed and chloroform was added. The organic solution was washed with thiosulfate solution followed by water, dried, and evaporated. The residue was fractionated or chromatographed to afford pure thioacetal **7** or **8**.

Registry No.—**1a**, 65915-23-3; **1b**, 63231-19-6; (+)-**1b**, 63231-19-6; **1c**, 65915-24-4; **1d**, 65915-25-5; (−)-**2b**, 65915-26-6; **5a**, 25508-32-1; **5c**, 28460-01-7; **5d**, 38066-16-9.

Supplementary Material Available: Table II including full ^1H- and ^{13}C-NMR data of **2**–**7** (4 pages). Ordering information is given on any current masthead page.

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(2) On leave of absence from the Institute of Organic Chemistry, Academy of Sciences of the German Democratic Republic, Berlin-Adlershof.
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(17) T. L. Moore, *J. Org. Chem.*, **32**, 2786 (1967).
(18) This product was identical with that prepared from triethyl phosphite and ethyl chlorocarbonate by the Arbuzov reaction, $\delta_{^{31}P}$ −5.1 ppm.

Intramolecular Nonphenol Oxidative Coupling of Phenethylisoquinolines

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Received December 7, 1977

Anodic and chemical oxidative coupling of homolaudanosine (**6a**) in TFA–TFAA gave homoglaucine (**9a**) in moderate yield. Oxidative coupling of *N*-acyl nonphenolic phenethyltetrahydroisoquinolines **6c,e,f** using VOF_3–TFA–TFAA yielded homoproerythrinadienones **8a,c** as the primary products, in contrast to the results of oxidative coupling reactions of nonphenolic benzyltetrahydroisoquinoline precursors which yield morphinandienones as the primary products. Furthermore, the homoproerythrinadienone-type intermediates (e.g., **19**) and homoneospirenedienone-type intermediates (e.g., **20**) were shown to be in equilibrium in the reaction medium, and both spirodienone intermediates rearranged to homoaporphines. Thus the oxidative coupling of nonphenolic phenethyltetrahydroisoquinolines with VOF_3–TFA–TFAA provides an efficient synthetic route to homoproerythrinadienones, homoneospirenedienones, and homoaporphines. Diaryl derivatives such as **11a,b** were also obtained as byproducts, which could be transformed to dibenz[*d,f*]azecine (**14a**).

Intramolecular phenol oxidative coupling reactions as a mode of carbon–carbon bond formation hold a prominent position in the biosynthesis of many classes of natural products.[3–5] However, the synthetic potential of these reactions has been limited due to the low yields and the complex mixtures of products usually encountered when the coupling step is carried out in the laboratory.[6,7] Recent reports[8–16] have demonstrated that intramolecular nonphenol oxidative coupling reactions hold promise as effective synthetic methods for the preparation of certain alkaloids and other polycyclic compounds. The first practical synthesis of this type involved electrooxidative coupling of nonphenolic benzylisoquinolines to morphinandienones.[8–11] Chemical intramolecular coupling of nonphenolic benzylisoquinolines using vanadium oxytrifluoride (VOF_3) in trifluoroacetic acid (TFA) also proceeded via morphinandienone intermediates[13–15] to give aporphines and some other spirodienone products. The present paper describes, in detail, studies[17] on the intramolecular oxidative coupling of nonphenolic phenethyltetrahydroisoquinoline derivatives which represent efficient syntheses of homoproerythrinadienones, homoneospirenedienones, homoaporphines, and dibenz[*d,f*]azecine precursors.

On the basis of the results of oxidative couplings of nonphenolic benzyltetrahydroisoquinolines,[8,13,14] it seemed reasonable to assume that anodic coupling of nonphenolic phenethyltetrahydroisoquinolines would yield homomorphinandienones, and VOF_3–TFA oxidations would give homoaporphines and homoneospirenedienones (Scheme I). Thus, homolaudanosine (**6a**) seemed a reasonable starting material for initial studies. Preparation of homolaudanosine

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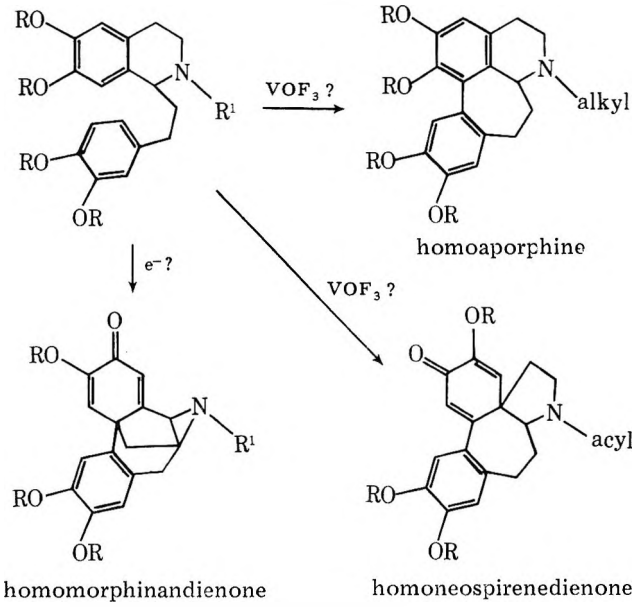
Scheme I[a]



[a] R = alkyl or benzyl; R¹ = alkyl or acyl.

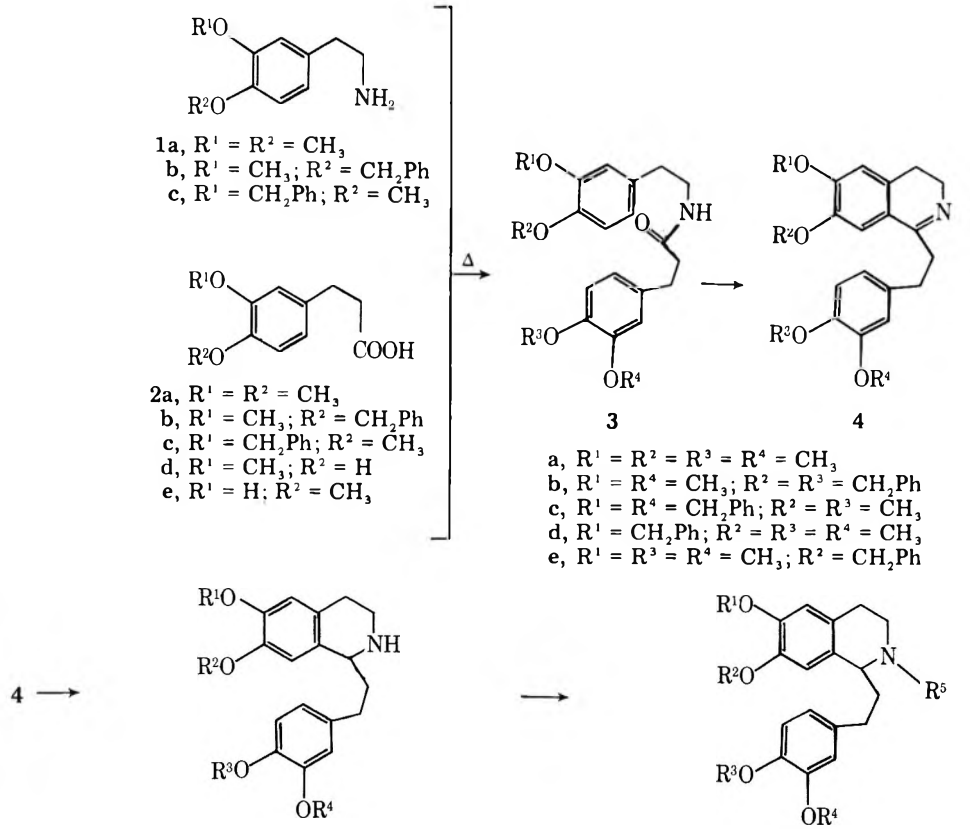
(6a) and other phenethyltetrahydroisoquinoline derivatives 6b–i was achieved by the route shown in Scheme II.

Anodic oxidation of homolaudanosine (6a), under the reaction conditions which yield *O*-methylflavinantine from laudanosine in 94% yield,[15] did not yield any isolable product. However, anodic oxidation of 6a in a mixture of trifluoroacetic acid (TFA) and trifluoroacetic anhydride (TFAA) containing tetraethylammonium tetrafluoroborate as the supporting electrolyte at a constant potential of 1.3 V gave homoaporphine 9a in 34% yield. The structure of the homoaporphine 9a was assigned on the basis of its physical and spectral data and confirmed by an unambiguous synthesis.

Phenol oxidation of 6b had previously been reported by several groups[18–21] to give a mixture of homoproaporphines 10a and 10b in yields of <40%. However, when 6b was oxidized with VOF_3–TFA–TFAA at −10 °C, homoproaporphine 10a and 10b were obtained in 38 and 30% yield, respectively. Treatment of homoproaporphine 10a with boron trifluoride etherate in CH_2Cl_2 afforded diphenolic homoaporphine[22] 9b (87%), which, upon methylation with diazomethane, gave the tetramethoxyhomoaporphine 9a in 70% yield as the hydrochloride salt, identical with the product obtained by anodic oxidation of 6a.

Vanadium oxytrifluoride oxidation of a solution of homolaudanosine (6a) in a mixture of CH_2Cl_2, TFA, TFAA, and fluorosulfonic acid (FSO_2OH) also gave homoaporphine 9a in 40% yield. FSO_2OH was used to ensure complete protonation of the nitrogen, since oxidation of 6a in the absence of FSO_2OH yielded a dimer as indicated by mass spectrometry and the NMR spectrum.

Scheme II



1a, $R^1 = R^2 = CH_3$
b, $R^1 = CH_3$; $R^2 = CH_2Ph$
c, $R^1 = CH_2Ph$; $R^2 = CH_3$

2a, $R^1 = R^2 = CH_3$
b, $R^1 = CH_3$; $R^2 = CH_2Ph$
c, $R^1 = CH_2Ph$; $R^2 = CH_3$
d, $R^1 = CH_3$; $R^2 = H$
e, $R^1 = H$; $R^2 = CH_3$

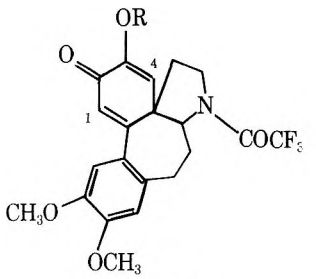
3

4

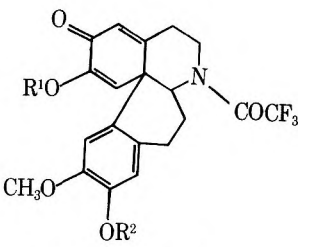
a, $R^1 = R^2 = R^3 = R^4 = CH_3$
b, $R^1 = R^4 = CH_3$; $R^2 = R^3 = CH_2Ph$
c, $R^1 = R^4 = CH_2Ph$; $R^2 = R^3 = CH_3$
d, $R^1 = CH_2Ph$; $R^2 = R^3 = R^4 = CH_3$
e, $R^1 = R^3 = R^4 = CH_3$; $R^2 = CH_2Ph$

5a, $R^1 = R^2 = R^3 = R^4 = CH_3$
b, $R^1 = R^4 = CH_3$; $R^2 = R^3 = CH_2Ph$
c, $R^1 = R^4 = CH_2Ph$; $R^2 = R^3 = CH_3$
d, $R^1 = CH_2Ph$; $R^2 = R^3 = R^4 = CH_3$
e, $R^1 = R^3 = R^4 = CH_3$; $R^2 = CH_2Ph$

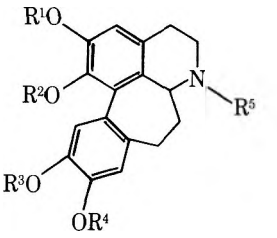
6a, $R^1 = R^2 = R^3 = R^4 = R^5 = CH_3$
b, $R^1 = R^4 = R^5 = CH_3$; $R^2 = R^3 = H$
c, $R^1 = R^2 = R^3 = R^4 = CH_3$; $R^5 = COCF_3$
d, $R^1 = R^4 = H$; $R^2 = R^3 = CH_3$; $R^5 = COCF_3$
e, $R^1 = CH_2Ph$; $R^2 = R^3 = R^4 = CH_3$; $R^5 = COCF_3$
f, $R^1 = R^3 = R^4 = CH_3$; $R^2 = CH_2Ph$; $R^5 = COCF_3$
g, $R^1 = R^4 = R^5 = CH_3$; $R^2 = R^3 = CH_2Ph$
h, $R^1 = R^4 = CH_2Ph$; $R^2 = R^3 = CH_3$; $R^5 = COCF_3$
i, $R^1 = R^2 = R^3 = R^4 = CH_3$; $R^5 = COOC_2H_5$



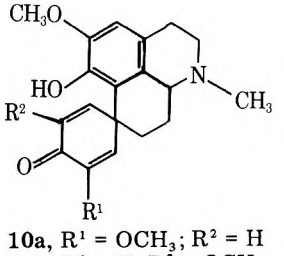
7a, R = CH_3
b, R = CH_2Ph



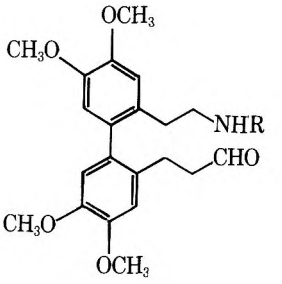
8a, $R^1 = R^2 = CH_3$
b, $R^1 = CH_3$; $R^2 = H$
c, $R^1 = CH_2Ph$; $R^2 = CH_3$



9a, $R^1 = R^2 = R^3 = R^4 = R^5 = CH_3$
b, $R^1 = R^4 = R^5 = CH_3$; $R^2 = R^3 = H$
c, $R^1 = R^2 = R^3 = R^4 = CH_3$; $R^5 = COCF_3$
d, $R^1 = R^4 = H$; $R^2 = R^3 = CH_3$; $R^5 = COCF_3$



10a, $R^1 = OCH_3$; $R^2 = H$
b, $R^1 = H$; $R^2 = OCH_3$



11a, R = $COCF_3$
b, R = $COOC_2H_5$

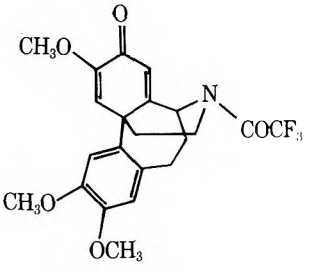


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Table I. Calculation of the Chemical Shifts of the C-1 and C-4 Protons of 7a[23]

For the C-1 proton:
δ(C=CH) = 5.28 + 1.06 (*gem*-C=O, conjugated)
+ 0.37 (cis aromatic) − 0.30 (trans alkyl ring)
= δ 6.41

For the C-4 proton:
δ (C=CH) = 5.28 + 0.95 (*trans*-C=O, conjugated)
+ 0.71 (geminal alkyl ring) − 1.06 (*cis*-OMe)
= δ 5.88

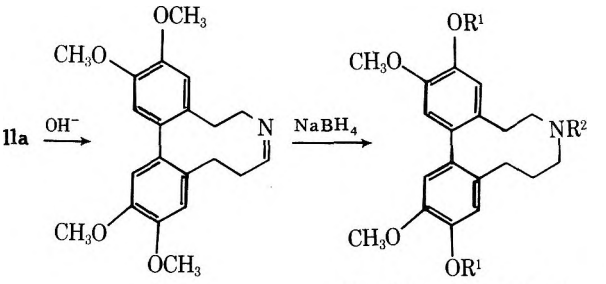
To study the effect of acylation of nitrogen, *N*-trifluoroacetylhomonorlaudanosine (**6c**) was prepared from tetrahydroisoquinoline **5a.** Treatment of (±)-*N*-trifluoroacetylhomonorlaudanosine (**6c**) with VOF_3–TFA–TFAA followed by aqueous workup gave homoneospirenedienone **7a** (64%), homoproerythrinadienone **8a** (5%), homoaporphine **9c** (2%), and aldehyde–amide **11a** (22%), respectively.

Homoneospirenedienone **7a** was assigned a molecular formula of $C_{22}H_{22}NO_5F_3$ on the basis of microanalysis and mass spectrometry (M^+ at *m/e* 437). The infrared spectrum showed typical dienone absorptions at 1690, 1653, and 1640 cm^{-1}, and the ultraviolet spectrum indicated a conjugated β-arylcyclohexadienone system in the structure. The NMR spectrum of **7a** in $CDCl_3$ showed peaks at δ 6.66 (s, 2 H, Ar**H**), 6.49 (s, 1 H, C-1 H), 5.75 (s, 1 H, C-4 H), 3.89, 3.87, and 3.72 (all s, 9 H, 3-OCH_3). The signals for the C-1 and C-4 protons were assigned in accordance with a calculation (Table I) of the expected chemical shifts by the method of Pascual, Meier, and Simon,[23] neglecting possible solvent and ring strain effects.

Mass spectrometry (M^+ at *m/e* 437) and microanalysis confirmed the formula $C_{22}H_{22}NO_5F_3$ for homoproerythrinadienone **8a.** The spectral data indicated that the structure was either **8a** or **12.** Therefore structure **8a** was confirmed by an unambiguous synthesis.

Marino has recently reported the oxidation of the diphenolic phenethyltetrahydroisoquinoline **6d** with vanadium oxytrichloride ($VOCl_3$) in CH_2Cl_2 to give homoproerythrinadienone **8b** in 35% yield. However, when **6d** was oxidized with VOF_3, homoproerythrinadienone **8b** was obtained in 78% yield. O-Methylation of **8b** with diazomethane then gave the homoproerythrinadienone **8a,** identical with a sample obtained by VOF_3 oxidation of **6c.**

Scheme III



13

14a, $R^1 = CH_3$; $R^2 = H$
b, $R^1 = R^2 = H$
c, $R^1 = R^2 = CH_3$

The structure of homoaporphine **9c** was assigned on the basis of its physical and spectral data. This structure was confirmed by conversion to homoaporphine **9a** via hydrolysis of the amide function with 1 N methanolic sodium hydroxide followed by N-methylation (formaldehyde–$NaBH_4$). The *N*-methyltetramethoxyhomoaporphine **9a** thus obtained was identical with a sample obtained by electrooxidation of homolaudanosine (**6a**).

Aldehyde–amide **11a** was also characterized on the basis of its physical and, particularly, its spectral data, and the structure of **11a** was further supported by the following transformation (Scheme III).

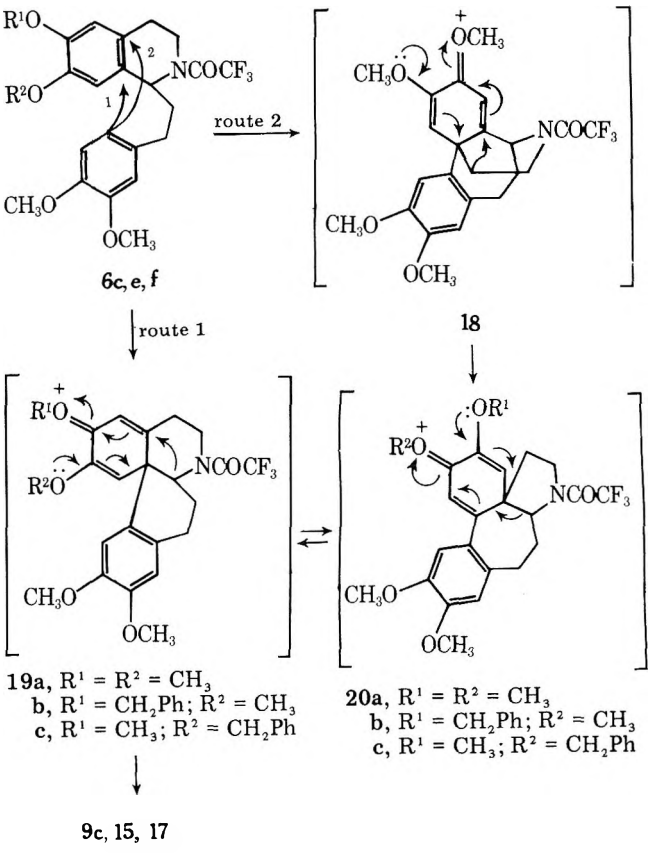
Treatment of **11a** with 1 N methanolic sodium hydroxide at room temperature resulted in hydrolysis of the amide and formation of the imine **13,** which was reduced with $NaBH_4$ to give tetramethoxydibenzazecine **14a.** The homoproerythrinadienone **8b** prepared previously was converted into diphenolic dibenzazecine **14b** by the procedure of Marino and Samanen.[25] Subsequent methylation of **14b** with diazomethane gave the tetramethoxydibenzazecine **14a,** identical with the product obtained from **11a,** along with some N-methylated product (**14c**).

In contrast to the acid-catalyzed rearrangement of proerythrinadienones to neospirenedienones,[26] homoproerythrinadienones rearrange to homoaporphines on treatment with boron trifluoride etherate.[24] Thus, treatment of 8a with boron trifluoride etherate in CH_2Cl_2 at room temperature for 24 h afforded homoaporphine **15** which, upon methylation with diazomethane, gave the tetramethoxyhomoaporphine **9c**, identical with the homoaporphine obtained by VOF_3 oxidation of *N*-trifluoroacetylhomonorlaudanosine (**6c**).

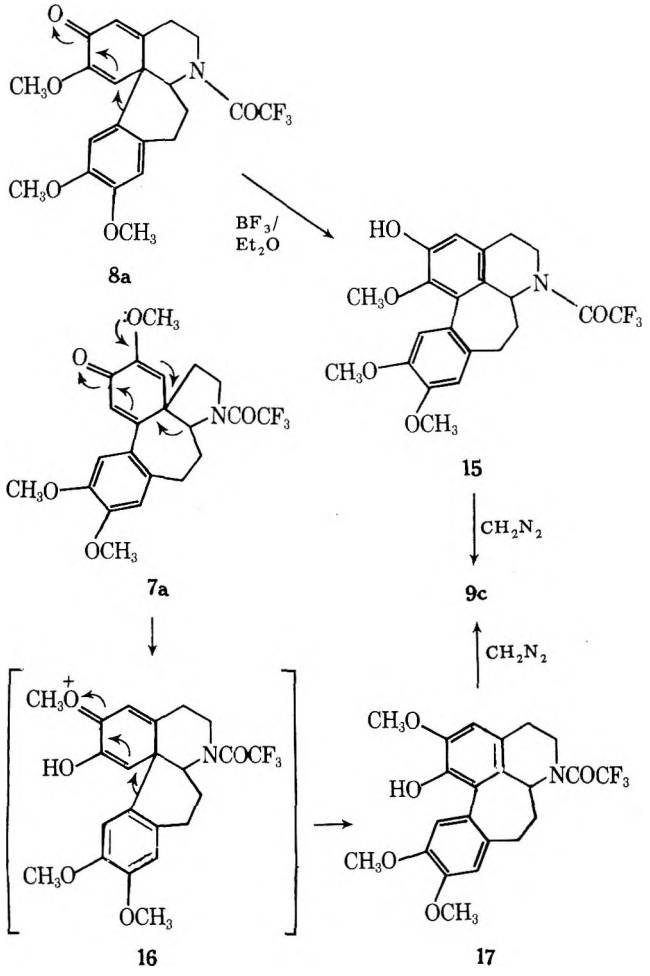
Interestingly, the homoneospirenedienone **7a** also rearranged to a monophenolic homoaporphine upon treatment with boron trifluoride etherate. The monophenolic homoaporphine product was different from homoaporphine **15** yet, upon methylation with diazomethane, gave the same tetramethoxyhomoaporphine **9c** as obtained by methylation of **15**, indicating that the structure of this monophenolic homoaporphine must be **17**. The formation of **17** from **7a** may be rationalized if homoneospirenedienone **7a** first rearranged to a homoproerythrinadienone-type intermediate **16**, which then rearranged to the homoaporphine **17** (Scheme IV).

Homoneospirenedienone **7a** could not be formed directly by oxidative coupling from *N*-trifluoroacetylhomonorlaudanosine (**6c**). Rather, the formation of **7a** must result from the rearrangement of either a homoproerythrinadienone-type intermediate (route 1, Scheme V) as in the acid-catalyzed rearrangement of proerythrinadienones to neospirenedienones,[26] or a homomorphinandienone-type intermediate (route 2, Scheme V) as in the conversions of (±)-*N*-acylnorlaudanosines to (±)-*N*-acylmorphinandienones and thence to (±)-*N*-acylneospirenedienones in nonphenol oxidative coupling of benzyltetrahydroisoquinolines.[14]

Scheme V



Scheme IV



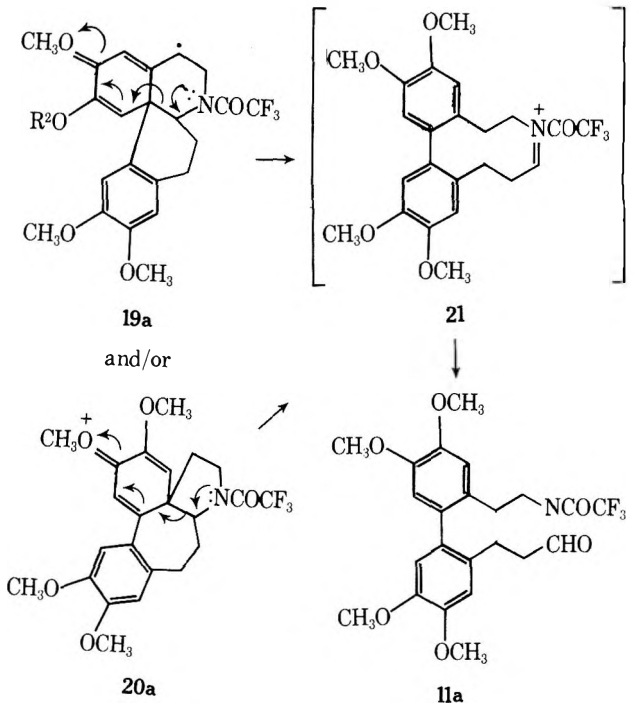
Evidence for determining the operative carbon rearrangement was obtained by oxidation of 6- and 7-benzyloxyphenethyltetrahydroisoquinolines **6e** and **6f**, respectively. Oxidation of **6e** with VOF_3 yielded homoproerythrinadienone **8a** (50%) and homoneospirenedienone **7b** (42%), the benzyloxy analogue of homoneospirenedienone **7a**. Oxidation of **6f** yielded homoneospirenedienone **7a** (60%), identical with the product obtained by oxidation of **6c**, and homoproerythrinadienone **8c** (3%), the benzyloxy analogue of homoproerythrinadienone **8a**.

Formation of **7b** via oxidation of **6e** and **7a** via oxidation of **6f** confirms that rearrangement of **6c**, **6e**, and **6f** to form homoneospirenedienones **7a** and **7b** takes place via homoproerythrinadienone-type intermediates **19a**, **19b**, and **19c**, respectively. If a homomorphinandienone intermediate had been involved, **6e** would have given **7a** and **6f** would have afforded **7b**.

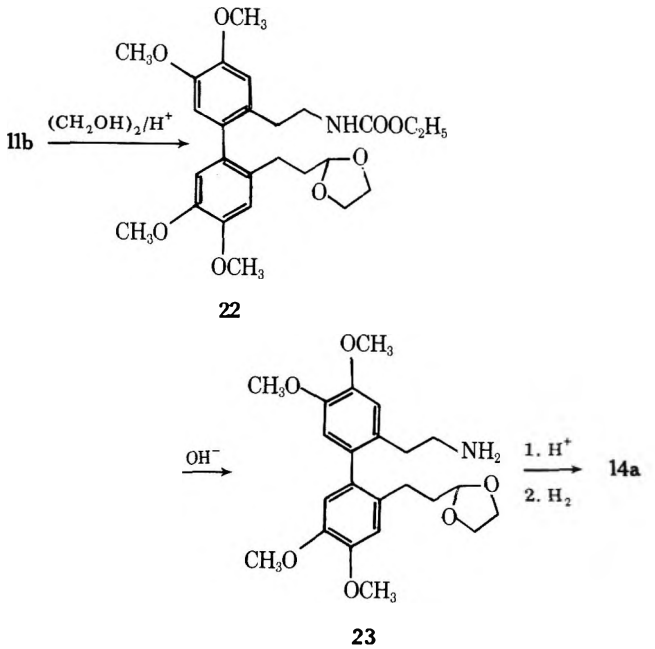
The formation of homoneospirenedienone **7a** via homoproerythrinadienone-type intermediate **19a**, and the demonstrated facile acid-catalyzed rearrangement of homoproerythrinadienone **8a** and homoneospirenedienone **7a** to homoaporphines **15** and **17**, respectively, suggested that homoproerythrinadienone-type intermediates (e.g., **19**) and homoneospirenedienone-type intermediates (e.g., **20**) exist in equilibrium in the reaction medium. In the oxidation of **6e**, cleavage of the benzyl group from the homoproerythrinadienone-type intermediate (**19b**) should shift the equilibrium toward the homoproerythrinadienone-type intermediate (**19b**), and, after a certain period of time, homoproerythrinadienone **8a** would be isolated as the major product. In the oxidation of **6f** cleavage of the benzyl group from **19c** should shift the equilibrium toward homoneospirenedienone-type intermediate **20c** and homoneospirenedienone **7a** would be the major product.

Indeed, when 6-benzyloxyphenethylisoquinoline **6e** was oxidized with VOF_3 and the reaction worked up after 1 h and

Scheme VI



Scheme VII



25 min, homoproerythrinadienone **8a** was obtained in 71% yield. Oxidation of 7-benzyloxyphenethyltetrahydroisoquinoline **6f** with VOF_3 and workup after 1 h afforded homoneospirenedienone **7a** in 65% yield. This evidence thus supports the proposed equilibrium of homoproerythrinadienone-type and homoneospirenedienone-type intermediates in the reaction mixture.

The equilibrium of homoproerythrinadienone-type and homoneospirenedienone-type intermediates and the demonstrated facile acid-catalyzed rearrangement of homoproerythrinadienone **8a** and homoneospirenedienone **7a** to 1,2,10,11-tetrasubstituted homoaporphines **15** and **17**, respectively, suggested that homoaporphines might be obtained directly from phenethyltetrahydroisoquinolines if enough time were allowed for rearrangement of the intermediates formed. Indeed, phenethyltetrahydroisoquinolines **6c**, **6e**, and **6f** gave homoaporphines **9c** (84%), **15** (80%), and **17** (67.5%), respectively, upon oxidation with VOF_3 for 3, 24, and 24 h, respectively. The difference in the reaction times can be rationalized on the basis of the difference in the rates of rearrangement of the corresponding homoproerythrinadienone-type and/or homoneospirenedienone-type intermediates. In the case of **6c**, the methoxonium ions **19a** and **20a** rearrange to homoaporphine **9e**, whereas in the case of **6e** and **6f**, cleavage of the benzyl group from intermediates **19b** and **20c** results in the formation of homoproerythrinadienone **8a** and homoneospirenedienone **7a**, which, as demonstrated earlier, undergo acid-catalyzed rearrangement to homoaporphines **15** and **17** in 24 h at room temperature.

Oxidation of **6c** with VOF_3–TFA–TFAA over 3 h resulted in the formation of only homoaporphine **9c** (84%) and no aldehyde–amide **11a**. Thus, **11a** could not be formed via direct oxidative coupling but must have resulted from rearrangement of intermediate(s) **19a** and/or **20a** during the workup procedure (Scheme VI). This requires the participation of the amide function which would be unexpected due to the strong withdrawing property of the acyl moiety.

If the proposed mechanism is correct, oxidation of *N*-carbethoxyhomonorlaudanosine (**6i**) should give a high yield of aldehyde–urethane **11b** because the nitrogen will retain a higher electron density. Consequently, *N*-carbethoxyhomonorlaudanosine (**6i**) was prepared by treatment of **5a** with ethyl chloroformate and pyridine, and oxidized with VOF_3 according to the procedure described earlier. Aldehyde–urethane **11b** was obtained in 62% yield, thus supporting the proposed mechanism.

The structure of aldehyde–urethane **11b** was confirmed by heating **11b** under reflux with ethylene glycol and *p*-toluenesulfonic acid using a Dean–Stark trap for azeotropic removal of water to give ketal **22** (Scheme VII). Heating ketal **22** with 20% aqueous sodium hydroxide then gave amine **23**. Hydrolysis of amine **23** with 5% aqueous HCl gave imine **13**, which was catalytically reduced to tetramethoxydibenzazecine (**14a**), identical in melting point, mixture melting point, NMR, TLC, IR, and mass spectrum with the product obtained from aldehyde–amide **11a**.

Experimental Section

General. Melting points were determined on a Mettler FP2 melting point apparatus and are uncorrected. UV and IR spectra were determined on Beckman DK-2A and Perkin-Elmer 337 spectrophotometers, respectively. NMR spectra were recorded on a JEOL PS-100p FT NMR spectrometer interfaced to a Texas Instruments JEOL 980A computer with Me_4Si as the internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E and AEI MS-902 spectrometers. All thin-layer chromatography was carried out on commercially prepared plates (E. M. Laboratories); silica gel 60 F-254 plates (2, 0.5, or 0.25 mm thickness 20 × 20 cm) were used for preparative TLC. Visualization of the alkaloids was performed by means of ultraviolet light and/or by spraying the entire analytical plate, or the edges of the preparative plate, with an aqueous solution of iodoplatinic acid reagent (1.0 g in 250 mL of water containing 15 g of potassium iodide). Microanalyses were carried out by Atlantic Microlab, Inc., Atlanta, Ga. Column chromatography was carried out on silica gel 60 (70–230 mesh ASTM) obtained from E. M. Laboratories. Anhydrous sodium sulfate was used as the drying agent exclusively. The phenethyltetrahydroisoquinolines **6a–i** were prepared by standard methods,[32,33] i.e., condensation of phenethylamines and acids to the corresponding amides followed by Bischler–Napieralski cyclization, $NaBH_4$ reduction, N-acylation, N-methylation, or N-carbethoxylation, and subsequent debenzylation by hydrogenolysis where required. Anodic oxidations were conducted in a three compartment cell (which separated the anode, cathode, and reference electrode solutions by glass frits) in conjunction with a Princeton Applied Model 376 potentiostat. The anode was a platinum mesh and a stainless steel spatula served as the cathode. The anode compartment had an ap-

proximate 120 mL volume in which the solution was agitated by means of a magnetic stir bar. A 0.1 N $AgNO_3$ solution in acetonitrile in contact with an Ag wire served as the reference.

3-Benzyloxy-4-methoxyphenylpropionic Acid (2c). A mixture of 24.0 g (122 mmol) of 3-hydroxy-4-methoxyphenylpropionic acid,[30] 10.6 g of sodium hydroxide, and 50 mL of methanol was heated until a clear solution was obtained. Following the addition of 30.0 mL of benzyl chloride, the solution was heated at 72 °C for 3 h, then 5.3 g of sodium hydroxide dissolved in 5.3 mL of water was added and the solution heated at reflux for an additional 6 h. The methanol was distilled off and the residue suspended in 300 mL of water, acidified with 6 N HCl, and extracted with $CHCl_3$. The $CHCl_3$ solution was washed with brine, dried, and evaporated to a semisolid residue. Crystallization from ethanol gave 22.0 g (62%) of **2c:** mp 120–122 °C; NMR ($CDCl_3$) δ 9.5 (br s, 1 H, COO**H**), 7.35 (s, 5 H, Ar**H**), 6.75 (s, 3 H, Ar**H**), 5.10 (s, 2 H, OCH_2), 3.83 (s, 3 H, OCH_3), 2.7 (m, 4 H, CH_2); mass spectrum *m/e* 286 (M^+), 195 ($M^+ - PhCH_2$).

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.31; H, 6.34. Found: C, 71.38; H, 6.37.

***N*-(3-Benzyloxy-4-methoxyphenethyl)-3-benzyloxy-4-methoxyphenylpropionamide (3c).** From 21.85 g (85 mmol) of 3-benzyloxy-4-methoxyphenethylamine[29] and 24.05 g (85 mmol) of **2c** there was obtained 39.0 g (88%) of **3c:** NMR ($CDCl_3$) δ 7.34 (m, 10 H, Ar**H**), 6.72 (m, 6 H, Ar**H**), 5.10 (s, 4 H, OCH_2), 3.85 and 3.84 (both s, 6 H, OCH_3), 3.3–2.3 (m, 8 H, CH_2).

Anal. Calcd for $C_{33}H_{35}NO_5$: C, 75.40; H, 6.71; N, 2.67. Found: C, 75.28; H, 6.77; N, 2.61.

***N*-(3-Benzyloxy-4-methoxyphenethyl)-3-(3,4-dimethoxyphenyl)propionamide (3d).** From 7.45 g (29 mmol) of 3-benzyloxy-4-methoxyphenethylamine[29] and 6.1 g (29 mmol) of 3,4-dimethoxyphenylpropionic acid (**2a**) there was obtained 11.0 g (84%) of **3d** as colorless crystals: mp 88.3–89.8 °C (ether); NMR ($CDCl_3$) δ 7.35 (m, 5 H, Ar**H**), 6.71 (m, 6 H, ArH), 5.11 (s, 2 H, OCH_2), 3.86 (s, 3 H, OCH_3), 3.84 (s, 6 H, OCH_3), 2.35 (t, 2 H, $COCH_2CH_2$, *J* = 7.5 Hz), 2.64 (t, 2 H, CH_2CH_2NH, *J* = 7.0 Hz), 2.88 (t, 2 H, $COCH_2CH_2$, *J* = 7.5 Hz), 3.38 (t, 2 H, CH_2CH_2NH, *J* = 7.0 Hz).

Anal. Calcd for $C_{27}H_{31}NO_5 \cdot \frac{1}{2}H_2O$: C, 70.72; H, 7.03; N, 3.05. Found: C, 70.70; H, 6.98; N, 2.92.

1-(3-Benzyloxy-4-methoxyphenethyl)-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline (4c). From 39.0 g (74.5 mmol) of **3c** and 10.0 mL of $POCl_3$ in 800 mL of toluene there was obtained, after heating at 100 °C for 1 h and usual workup, 32.3 g (80%) of **4c:** mp 113–115 °C (ethyl acetate); NMR ($CDCl_3$) δ 7.38 (m, 10 H, Ar**H**), 6.95 and 6.71 (both s, 2 H, Ar**H**), 6.81 (s, 3 H, Ar**H**), 5.17 and 5.1 (both s, 4 H, OCH_2), 3.86 (s, 6 H, OCH_3), 2.89 (s, 4 H, CH_2), 3.6 (t, 2 H, CH_2, *J* = 7 Hz), 2.53 (t, 2 H, CH_2, *J* = 7 Hz).

Anal. Calcd for $C_{33}H_{33}NO_4$: C, 78.08; H, 6.55; N, 2.76. Found: C, 77.95; H, 6.50; N, 2.72.

1-(3,4-Dimethoxyphenethyl)-6-benzyloxy-7-methoxy-3,4-dihydroisoquinoline (4d). From 8.03 g (17.9 mmol) of **3d** and 18 mL of $POCl_3$ in 130 mL of toluene there was obtained, after heating at 110 °C for 1 h and usual workup, 6.56 g (78.6%) of **4d** as the hydrochloride salt: mp 173.8–174.7 °C (ethanol–ether); IR ($CHCl_3$) 1645 (C=N) cm^{-1}; NMR ($CDCl_3$) δ 7.40 (s, 5 H, Ar**H**), 7.09, 6.88, 6.82 (each s, 3 H, ArH), 6.70 (s, 2 H, ArH), 5.26 (s, 2 H, OCH_2), 3.90, 3.87, 3.82 (all s, 9 H, OCH_3), 3.7–2.81 (m, 8 H, CH_2).

Anal. Calcd for $C_{27}H_{29}NO_4 \cdot HCl$: C, 69.29; H, 6.46; N, 2.99. Found: C, 69.23; H, 6.60; N, 2.97.

1-(3,4-Dimethoxyphenethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (5a). From 6.2 g (17.5 mmol) of 1-(3,4-dimethoxyphenethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline[27] (**4a**) by $NaBH_4$ reduction in methanol there was obtained 6.0 g (98%) of **5a** as the hydrochloride salt: mp 186.7–187.7 °C; NMR ($CDCl_3$) δ 6.95 (s, 1 H, Ar**H**), 6.78 (br s, 2 H, Ar**H**), 6.49 and 6.48 (both s, 2 H, Ar**H**), 4.33 (hump, 1 H, NH), 3.85 (s, 9 H, OCH_3), and 3.81 (s, 3 H, OCH_3).

Anal. Calcd for $C_{21}H_{27}NO_4 \cdot HCl$: C, 64.19; H, 7.18; N, 3.56. Found: C, 64.02; H, 7.20; N, 3.53.

1-(3-Benzyloxy-4-methoxyphenethyl)-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (5c). From 29.0 g (57.2 mmol) of **4c** by $NaBH_4$ reduction in methanol there was obtained 30.0 g of the crude product. Treatment with methanolic HCl gave 27.0 g (87%) of **5c** as the hydrochloride salt: mp 186.5–188 °C; NMR ($CDCl_3$) δ 7.38 (m, 10 H, Ar**H**), 6.98 (s, 1 H, Ar**H**), 6.78 (s, 2 H, Ar**H**), 6.58, 6.45 (both s, 2 H, ArH), 5.09 and 5.08 (both s, 4 H, OCH_2), 3.82 and 3.78 (both s, 6 H, OCH_3), 3.5–2.3 (m, 8 H, CH_2).

Anal. Calcd for $C_{33}H_{35}NO_4 \cdot HCl$: C, 72.58; H, 6.65; N, 2.56. Found: C, 72.61; H, 6.47; N, 2.56.

1-(3,4-Dimethoxyphenethyl)-6-benzyloxy-7-methoxy-1,2,3,4-tetrahydroisoquinoline (5d). From 6.42 g (13.8 mmol) of the hydrochloride salt of **4d** by $NaBH_4$ reduction in methanol there was obtained 6.0 g of a yellow oil. Treatment with methanolic HCl gave 6.05 g (94%) of **5d** as the hydrochloride salt: mp 132.6–133.7 °C; NMR ($CDCl_3$) δ 7.39 (br s, 5 H, $PhCH_2$), 6.95 (s, 1 H, ArH), 6.77 (s, 2 H, Ar**H**), 6.62, 6.50 (both s, 2 H, ArH), 5.10 (s, 2 H, OCH_2), 3.84 (s, 6 H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.25–2.4 (m, 8 H, CH_2).

Anal. Calcd for $C_{27}H_{31}NO_4 \cdot HCl$: C, 68.99; H, 6.86; N, 2.98. Found: C, 68.84; H, 6.82; N, 2.96.

1-(3,4-Dimethoxyphenethyl)-7-benzyloxy-6-methoxy-1,2,3,4-tetrahydroisoquinoline (5e). From 3.71 g (8.6 mmol) of 1-(3,4-dimethoxyphenethyl)-7-benzyloxy-6-methoxy-3,4-dihydroisoquinoline[31] (**4e**) by $NaBH_4$ reduction in methanol there was obtained 3.5 g of a brown oil. Treatment with methanolic HCl and crystallization from methanol–ether gave 3.12 g (77%) of **5e** as the hydrochloride salt: mp 183.4–184.4 °C; NMR ($CDCl_3$) δ 7.35 (m, 5 H, ArH), 6.90 (s, 1 H, ArH), 6.73 (s, 2 H, ArH), 6.60, 6.49 (both s, 2 H, ArH), 5.08 (s, 2 H, OCH_2). 3.86 (s, 3 H, OCH_3), 3.84 (s, 6 H, OCH_3), 3.5–2.3 (m, 8 H, CH_2).

Anal. Calcd for $C_{27}H_{31}NO_4 \cdot HCl$: C, 68.99; H, 6.86; N, 2.98. Found: C, 68.85; H, 6.81; N, 2.96.

***N*-Trifluoroacetylhomonorlaudanosine (6c).** From 8.93 g (25 mmol) of **5a,** 7.5 mL of TFAA, and 1.00 mL of pyridine in 25 mL of CH_2Cl_2 there was obtained, after stirring at room temperature for 4 h and usual workup, 9.00 g of the crude product. Crystallization from ethanol gave 8.75 g (77%) of **6c:** mp 89–90 °C; UV λ_{max}(EtOH) (log ε) 228 (sh, 4.30), 282 (3.84), 286 (sh, 3.83) nm; IR (KBr) 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.77 (s, 3 H, ArH), 6.59 and 6.53 (both s, 2 H, ArH), 5.56 (t, 1 H, CH, *J* = 7 Hz), 3.87 (s, 3 H, OCH_3), 3.85 (s, 6 H, OCH_3), 3.83 (s, 3 H, OCH_3), 3.85–2.20 (m, 8 H, CH_2); mass spectrum *m/e* 453 (M^+), 288.

Anal. Calcd for $C_{23}H_{26}NO_5F_3$: C, 60.92; H, 5.78; N, 3.09. Found: C, 60.91; H, 5.88; N, 3.13.

1-(3-Hydroxy-4-methoxyphenethyl)-6-hydroxy-7-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (6d). From 6.16 g (12 mmol) of **5c,** 7.5 mL of TFAA, and 1.0 mL of pyridine in 70 mL of CH_2Cl_2 there was obtained, after stirring at room temperature for 4 h and usual workup, 7.0 g of **6h** as a colorless foam. Hydrogenolysis of **6h** over 1.5 g of 10% Pd/C at atmosphere temperature and pressure of hydrogen gave, after crystallization from ether, 3.9 g (76%) of **6d:** mp 131.5–132.2 °C (lit.[24] 129–130 °C); NMR ($CDCl_3$) δ 6.73 (br s, 3 H, Ar**H**), 6.65 and 6.52 (both s, 2 H, Ar**H**), 5.62 (s, 2 H, OH), 3.84 (s, 6 H, OCH_3); mass spectrum *m/e* 425 (M^+), 274.

1-(3,4-Dimethoxyphenethyl)-6-benzyloxy-7-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (6e). From 4.6 g (10.6 mmol) of **5d,** 7.5 mL of TFAA, and 1.0 mL of pyridine in 70 mL of CH_2Cl_2 there was obtained, after stirring at room temperature for 4 h and usual workup, 5.45 g (97%) of **6e** as colorless foam: IR ($CHCl_3$) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.38 (m, 5 H, ArH), 6.77 (br s, 3 H, ArH), 6.61, 6.56 (s, 2 H, ArH), 5.57 (t, 1 H, CH, *J* = 7 Hz), 5.10 (s, 2 H, OCH_2), 3.95, 3.94, 3.93 (each s, 9 H, OCH_3), 3.8–2.5 (m, 8 H, CH_2).

1-(3,4-Dimethoxyphenethyl)-7-benzyloxy-6-methoxy-*N*-trifluoroacetyl-1,2,3,4-tetrahydroisoquinoline (6f). From 2.68 g (6.2 mmol) of **5e,** 3.75 mL of TFAA, and 0.5 mL of pyridine in 30 mL of CH_2Cl_2 there was obtained, after stirring at room temperature for 4 h and workup, 3.0 g (94%) of **6f:** mp 115.7–117 °C (methanol); IR ($CHCl_3$) 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.35 (m, 5 H, $PhCh_2O$), 6.76, 6.55 (both s, 2 H, ArH), 6.70 (S= 2 H, ArH), 5.45 (t, 1 H, CH, *J* = 8 Hz), 5.09 (s, 2 H, OCH_2), 3.87 (s, 3 H, OCH_3), 3.85 (s, 6 H, OCH_3), 3.5–2.5 (m, 8 H, CH_2).

Anal. Calcd for $C_{29}H_{30}NO_5F_3$: C, 65.77; H. 5.71; N, 2.65. Found: C, 65.72; H, 5.62; N, 2.65.

***N*-Carbethoxyhomonorlaudanosine (6i).** From 2.3 g (6.4 mmol) of **5a,** 1.2 mL of ethyl chloroformate, and 0.6 mL of pyridine in 45 mL of CH_2Cl_2 there was obtained, after stirring at room temperature for 4 h and usual workup, 2.5 g (94%) of **6i** as a colorless oil: IR ($CHCl_3$) 1680 cm^{-1} (C=O); NMR ($CDCl_3$) δ 6.78 (s, 3 H, ArH), 6.59 and 6.56 (both s, 2 H, ArH), 5.13 (mound, 1 H, CH), 4.19 (q, 2 H, $COOCH_2CH_3$, *J* = 7.1 Hz), 3.87 (s, 3 H, OCH_3), 3.85 (s, 9 H, OCH_3), 3.25–2.10 (m, 8 H, CH_2), 1.29 (t, 3 H, $COOCH_2CH_3$, *J* = 7.1 Hz); mass spectrum *m/e* 429 (M^+), 264.

Anodic Oxidation of Homolaudanosine (6a). Homolaudanosine perchlorate[27] (300 mg; 0.636 mmol) was added to the anode compartment containing 120 mL of a mixture of TFA–TFAA (20:1 by weight). Tetraethylammonium tetrafluoroborate (3.0 g) was added as a background electrolyte to the anode and to the cathode (1.0 g) compartments. The electrolysis was carried out at a constant potential of 1.3 V for 130 min. The anodic solution was evaporated to an oil; water was added and the solution made alkaline with 58% ammonium hydroxide. At this point there were two layers, one aqueous and the other a heavy syrupy red liquid. Addition of 50 mL of benzene to this

Table II. Oxidation of Phenethyltetrahydroisoquinolines with VOF_3 in CH_2Cl_2–(TFA–TFAA)

Substrate	Registry No.	Temp, °C	Time	Products	Registry No.	Yield, %
6a		−10	40 min	**9a**		40
6b	56114-05-7	−10	6 min	**10a**		38
				10b		30
6c	61659-99-2	−10	10 min	**9c**	61660-02-4	2
				11a	61660-03-5	22
				7a	61660-01-3	64
				8a	61660-00-2	5
6c		−10 → 30	3 h	**9c**		84
6d	65899-32-3	−10	5 min	**8b**	52418-69-6	78
6e	61660-07-9	−10	10 min	**8a**		50
				7b	61660-09-1	42
		−10 → 30[a]	15 h	**8a**		71
		−10 → 30[a]	24 h	**15**	61660-04-6	80
6f	61660-08-0	−10	10 min	**7a**		60
				8c	61660-10-4	3
		−10 → 30[a]	1 h	**7a**		65
		−10 → 30[a]	24 h	**17**	61659-92-5	67.5
6i	65899-33-4	−10	10 min	**11b**	65899-34-5	60

[a] The reaction mixture was slowly allowed to attain room temperature (30 °C).

resulted in three layers with benzene being at the top. Successive extraction with benzene, followed by drying and evaporation of the combined benzene extracts, gave a pale yellow oil which was chromatographed on four 0.5-mm preparative silica gel plates using 5% methanol in chloroform as eluent. The major band was collected to give 110 mg of a slightly yellow glass which was dissolved in methanolic HCl and evaporated to dryness, and the residue was crystallized from methanol–ether giving 90.0 mg of the homoaporphine **9a** as the hydrochloride salt: mp 242–244 °C dec; UV λ_{max}(EtOH) (log ϵ) 266 (4.11), 289 (3.95); NMR ($CDCl_3$) δ 7.05 (s, 1 H, C-12 H), 6.77 (s, 1 H, ArH), 6.74 (s, 1 H, ArH), 3.94, 3.93, 3.87, and 3.48 (all s, 12 H, OCH_3), 2.75 (s, 3 H, NCH_3); mass spectrum *m/e* 369 (M^+), 354, 338.

Anal. Calcd for $C_{22}H_{28}NO_4Cl \cdot \frac{1}{2} \cdot CH_3OH$: C, 64.04; H, 7.16; N, 3.32. Found: C, 64.22; H, 7.06; N, 3.42.

VOF_3 Oxidation. General Procedure. In a typical oxidation 0.25–1.0 mmol of the substrate [0.05 M solution in CH_2Cl_2 containing 20% TFA–TFAA (20:1 by weight)] was treated with 2.5 molar equiv of VOF_3 [dissolved in a minimum volume of 1:1 solution of ethyl acetate and TFA–TFAA (20:1 by weight)] at −10 °C (ice–salt bath) and the resulting dark red (in case of nonphenolic substrates) or dark blue (in case of phenolic substrates) solution was stirred for various lengths of time (see Table II). The reaction was quenched with 10% citric acid solution and the pH adjusted to ~7.5 with 58% NH_4OH. The solution was extracted with CH_2Cl_2 and the extract washed with brine, dried, and evaporated under reduced pressure to give the crude product.

VOF_3 Oxidation of Homolaudanosine (6a). Oxidation of 118 mg (0.25 mmol) of homolaudanosine perchlorate[27] (**6a**) in the presence of 0.1 mL of FSO_2OH gave 120 mg of a dark brown residue. Preparative TLC ($CHCl_3$–5% methanol) and crystallization from methanol–ether yielded 41 mg (40%) of **9a** as the hydrochloride salt: mp 243–245 °C. The melting point, mixture melting point, TLC, UV, NMR, and MS were identical with those of a sample prepared by anodic oxidation of **6a**.

VOF_3 Oxidation of 1-(4-hydroxy-3-methoxyphenethyl)-7-hydroxy-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (6b). Oxidation of 297.0 mg (0.78 mmol) of **6b**[19] gave 218 mg of a pale yellow gum. Preparative TLC ($CHCl_3$–12% methanol) yielded 218 mg of a yellow gum which was crystallized from benzene to give 100.5 mg (38%) of **10a**. A sample was purified by crystallization from acetonitrile–ether: mp transition at 150–153 °C, melts at 193–194 °C dec (lit.[19] 193–195 °C); NMR ($CDCl_3$) δ 6.84 (q, 1 H, H_B, J_{AB} = 2.5 Hz, J_{BX} = 10 Hz), 6.66 (s, 1 H, ArH), 6.34 (d, 1 H, H_X, J_{BX} = 10 Hz), 6.08 (d, 1 H, H_A, J_{AB} = 2.5 Hz), 3.85 (s, 3 H, OCH_3 aromatic), 3.58 (s, 3 H, OCH_3 olefinic), 2.42 (s, 3 H, NCH_3), 2.0–4.0 (m, 9 H, CH, CH_2).

The mother liquor was evaporated and then crystallized from benzene–hexane (1:2) to give 80.0 mg (30%) of **10b**: mp 198–200 °C (lit.[28] mp 202 °C dec); NMR ($CDCl_3$) δ 6.99 (q, 1 H, H_B, J_{AB} = 2.6 Hz, J_{BX} = 10 Hz), 6.54 (s, 1 H, ArH), 6.25 (d, 1 H, H_X, J_{BX} = 10 Hz), 5.81 (d, 1 H, H_A, J_{AB} = 2.6 Hz), 3.8 (s, 3 H, OCH_3 aromatic), 3.64 (s, 3 H, OCH_3 olefinic), 2.4 (s, 3 H, NCH_3), 1.5–3.5 (m, 9 H, CH, CH_2).

VOF_3 Oxidation of (±)-*N*-Trifluoroacetylhomonorlaudanosine (6c). Oxidation of 227.0 mg (0.5 mmol) of **6c** yielded 270 mg of a yellow glass. Separation of the mixture by preparative TLC (ether–2% acetone) afforded 4 mg (2%) of homoaporphine **9c**, 51 mg (22%) of the aldehyde–amide **11a**, 10 mg (5%) of dienone **8a**, and 140 mg (64%) of the dienone **7a**.

Homoaporphine **9c**: mp 167–169 °C (ether); UV λ_{max}(EtOH) (log ϵ) 267 (4.07), 289 (3.98) nm; IR (KBr) 1690 cm^{-1} (C=O); NMR ($CDCl_3$) δ 7.05 (s, 1 H, C-12 H), 6.78, 6.68 (both s, 2 H, ArH), 3.95, 3.90, 3.85, and 3.45 (all s, 12 H, OCH_3), 3.1–2.3 (m, 8 H, CH_2); mass spectrum *m/e* 451 (M^+), 420 ($M^+ - OCH_3$).

Anal. Calcd for $C_{23}H_{24}NO_5F_3$: C, 61.19; H, 5.36; N, 3.10. Found: C, 60.92; H, 5.45; N, 2.94.

Aldehyde–amide **11a**: mp 143–144 °C (ether); UV λ_{max}(EtOH) (log ϵ) 285 (3.84), 235 (sh, 4.25); mass spectrum *m/e* 469 (M^+), 298.

Anal. Calcd for $C_{23}H_{26}NO_6F_3$: C, 58.84; H, 5.58; N, 2.98. Found: C, 58.96; H, 5.76; N, 2.83.

Dienone **8a**: mp 125 °C, solidifies and remelts at 161–162 °C (ether); UV λ_{max}(EtOH) (log ϵ) 243 (4.33), 286 (3.67); mass spectrum *m/e* 437 (M^+).

Anal. Calcd for $C_{22}H_{22}NO_5F_3$: C, 60.41; H, 5.07; N, 3.20. Found: C, 60.53; H, 5.13; N, 3.40.

Dienone **7a**: mp 171.5–172.0 °C (ethanol); UV λ_{max}(EtOH) (log ϵ) 235 (4.23), 259 (4.07), 284 (3.88), 340 (3.73) nm; mass spectrum *m/e* 437 (M^+).

Anal. Calcd for $C_{22}H_{22}NO_5F_3$: C, 60.41; H, 5.07; N, 3.20. Found: C, 60.52; H, 5.49; N, 2.96.

VOF_3 Oxidation of 6d. Oxidation of 213 mg (0.5 mmol) of **6d** yielded 250 mg of a pale yellow foam. Preparative TLC (ether–5% acetone) and crystallization from ether gave 165 mg (78%) of **8b**: mp 202–203.5 °C (lit.[24] 198–200 °C); NMR ($CDCl_3$) δ 6.74, 6.46 (both s, 2 H, ArH), 6.29 (s, 1 H, C-1 H), 5.94 (s, 1 H, C-4 H), 5.67 (s, 1 H, OH), 3.74, 3.62 (both s, 6 H, OCH_3).

VOF_3 Oxidation of 6e. Oxidation of 133 mg (0.25 mmol) of **6e** yielded 150 mg of a yellow glass. Separation of the mixture by preparative TLC (ether–5% acetone) afforded 55 mg (50%) of **8a** and 54 mg (42%) of **7b**: mp 109.5 °C, solidifies and remelts at 169–170 °C; UV λ_{max}(EtOH) (log ϵ) 235 (4.23), 258 (4.07), 285 (3.85), 342 (3.74) nm; IR ($CHCl_3$) 1690 (C=O), 1665, and 1640 cm^{-1} (C=C); NMR ($CDCl_3$) δ 7.36 (s, 5 H, $PhCH_2O$), 6.64 (s, 2 H, ArH), 6.48 (s, 1 H, C-1 H), 5.76 (s, 1 H, C-4 H), 5.03 (s, 2 H, OCH_2Ph), 3.88 and 3.86 (each s, 6 H, OCH_3); mass spectrum *m/e* 513 (M^+), 485, 422, 394.

Anal. Calcd for $C_{28}H_{26}NO_5F_3$: C, 65.49; H, 5.10; N, 2.73. Found: C, 65.54; H, 5.30; N, 2.90.

VOF_3 Oxidation of 6f. Oxidation of 133 mg (0.25 mmol) of **6f** gave 110 mg of a yellow residue. Separation of the mixture by preparative TLC ($CHCl_3$–2% methanol) afforded 58.4 mg (60%) of **7a** and 5.5 mg (3%) of **8c**: mp 134–134.5 °C (ether); UV λ_{max}(EtOH) (log ϵ) 243 (4.37), 285 (3.72) nm; IR ($CHCl_3$) 1688 (C=O), 1668, and 1645 cm^{-1} (C=C); NMR ($CDCl_3$) δ 7.31 and 6.62 (both s, 2 H, ArH), 6.27 (s, 1 H, C-1 H), 5.99 (s, 1 H, C-4 H), 4.87 (s, 2 H, $ArCH_2O$), 3.89 and 3.77 (both s, 6 H, OCH_3); mass spectrum *m/e* 513 (M^+), 422.

Anal. Calcd for $C_{28}H_{26}NO_5F_3$: C, 65.49; H, 5.10; N, 2.73. Found: C, 65.56; H, 5.09; N, 2.73.

VOF_3 Oxidation of *N*-Carbethoxyhomonorlaudanosine (6i). Oxidation of 215 mg (0.5 mmol) of **6i** gave 230 mg of a yellow glass.

Preparative TLC (ether–5% acetone) afforded 134 mg (60%) of **11b** as colorless crystals: mp 139.5 –140.5 °C (ether); IR ($CHCl_3$) 3465 (NH), 2830 and 2710 (CHO), 1720 cm^{-1} (C=O); NMR ($CDCl_3$) δ 9.25 (s, 1 H, **CHO**), 6.80 (s, 1 H, ArH), 6.76 (s, 1 H, ArH), 6.65 (s, 2 H, **ArH**), 4.05 (q, 2 H, $COOCH_2CH_3$, J = 7.1 Hz), 3.92 (s, 6 H, OCH_3), 3.84 (s, 6 H, OCH_3), 1.26 (t, 3 H, $COOCH_2CH_3$, J = 7.1 Hz), 3.58–2.53 (m, 8 H, CH_2); mass spectrum m/e 445 (M^+), 299.

Anal. Calcd for $C_{24}H_{31}O_7N$: C, 64.70; H, 7.01; N, 3.14. Found: C, 64.79; H, 6.94; N, 3.19.

Methylation of Diphenolic Homoaporphine 9b to 1,2,10,11-Tetramethoxyhomoaporphine (9a). A solution of 20.0 mg of **9b** in 5.0 mL of methanol was treated with an excess of an ether solution of diazomethane, and the solution was kept at room temperature for 4 h. The reaction mixture was evaporated to dryness, and the residue was dissolved in 2 mL of methanol, made acidic with concentrated HCl, and evaporated to leave a yellow residue. Crystallization from methanol–ether gave 15.6 mg (70%) of **9a** as the hydrochloride salt: mp 242–244 ° dec; the melting point, mixture melting point, TLC, UV, NMR, and mass spectrum were identical with those described earlier for **9a**.

Rearrangement of 10a with Boron Trifluoride Etherate. A mixture of 80.0 mg of dienone **10a**, 5.0 mL of CH_2Cl_2, and 1.5 mL of boron trifluoride etherate was stirred at room temperature for 24 h. After the solution had been diluted with CH_2Cl_2 to 25 mL, the solution was washed with water and 10% ammonia and water, dried, and evaporated to give 90.0 mg of a yellow glass. Preparative TLC ($CHCl_3$–15% methanol) gave 69.5 mg (87%) of **9b**: mp 185–187 °C (methanol–ether) (lit.[22] 185–187 °C); NMR ($CDCl_3$) δ 7.03 (s, 1 H, C-12 H), 6.74 (s, 1 H, ArH), 6.61 (s, 1 H, ArH), 5.41 (s, 2 H, OH), 3.89 (s, 6 H, OCH_3), 2.37 (s, 3 H, NCH_3).

2,10,11-Trimethoxy-*N*-trifluoroacetylhomoproerythrinadienone (8a). A solution of 52 mg of **8b** in 5 mL of methanol was treated with an excess of an ether solution of diazomethane and kept at room temperature for 1 h. Evaporation of the solvent and crystallization of the residue from ether gave 50 mg (94%) of **8a**: mp 125.5 °C, solidifies and remelts at 161–162 °C. The melting point, mixture melting point, TLC, UV, IR, NMR, and mass spectrum were identical with those of a sample obtained by oxidation of **6c**.

Conversion of *N*-Trifluoroacetyl-1,2,10,11-tetramethoxyhomoaporphine (9c) to N-Methyl-1,2,10,11-tetramethoxyhomoaporphine (9a). A solution of 100 mg of **9c** in 25 mL of 1 N methanolic sodium hydroxide was stirred at room temperature for 2 h, at which time the solution was evaporated to dryness and the residue was suspended in 10 mL of water and extracted with three 20-mL portions of ether. The ether solution was washed with water, dried, and evaporated to give 78 mg of a colorless glass. The glass was taken up in 3 mL of methanol and treated with 0.3 mL of 37% formaldehyde solution, and the mixture was stirred at room temperature for 3 h. The reaction was diluted with 10 mL of methanol; 50 mg of $NaBH_4$ was added at room temperature, portionwise, with stirring, over 10 min and the reaction was stirred for an additional 0.5 h. The methanol was evaporated and the residue was suspended in 15 mL of water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried, and evaporated to give 85 mg of a yellow oil. Preparative TLC ($CHCl_3$–5% methanol) and crystallization of the residue as the hydrochloride salt from methanol–ether gave 67 mg (75%) of **9a**: mp 242–244 °C dec. The melting point, mixture melting point, TLC, UV, NMR, and mass spectrum were identical with those of a sample obtained by anodic oxidation of **6a**.

Conversion of Aldehyde-Amide 11a to Tetramethoxydibenzazecine 14a. A solution of 20.0 mg of **11a** in 5 mL of 1 N methanolic sodium hydroxide was stirred at room temperature for 6 h, at which time 200 mg of $NaBH_4$ was added and the reaction was stirred for an additional 0.5 h. The methanol was evaporated and the residue was suspended in water and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried, and evaporated to give 15 mg of a yellow glass. Preparative TLC ($CHCl_3$–10% methanol) and crystallization of the residue as the hydrochloride salt from methanol–ether gave 7.3 mg of **14a**: mp 166–168 °C; NMR ($CDCl_3$) δ 6.77, 6.73, 6.60, and 6.55 (all s, 4 H, ArH), 3.94, 3.92, 3.85, and 3.83 (all s, 12 H, OCH_3), 3.30–2.30 (m, 10 H, CH_2); mass spectrum m/e 357 (M^+), 342, 325, 299.

Anal. Calcd for $C_{21}H_{28}NO_4Cl{\cdot}2.5H_2O$: C, 57.46; H, 7.57; N, 3.19. Found: C, 57.17; H, 7.31; N, 3.19.

Conversion of Homoproerythrinadienone 8b to Tetramethoxydibenzazecine 14a. A solution of 60 mg of **8b** in 5 mL of 1 N methanolic sodium hydroxide was stirred at 0 °C for 24 h, at which time 50 mg of $NaBH_4$ was added, in portions, over 10 min, and stirring was continued for 4 h. The reaction mixture was evaporated to dryness and the residue was suspended in water, the pH adjusted to 7.5, and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed with brine, dried, and evaporated to leave 35 mg of a yellow glass. Preparative TLC ($CHCl_3$–15% methanol) gave 15 mg of **14b** as a colorless glass which was dissolved in 5 mL of methanol and treated with an excess of an ether solution of diazomethane. The reaction mixture was allowed to stand at room temperature for 2 h and then evaporated to give 15 mg of a yellow glass. Separation of the mixture by preparative TLC ($CHCl_3$–15% methanol: two elutions) afforded the following products. **14a**, 5 mg: mp 165–167.5 °C; the melting point, mixture melting point, IR, NMR, and mass spectrum were identical with those of the product obtained from aldehyde–amide **11a**. **14c**, 8 mg: NMR ($CDCl_3$) δ 6.80, 6.74, 6.60, and 6.56 (all s, 4 H, ArH), 3.95, 3.92, 3.86, and 3.82 (all s, 12 H, OCH_3), 2.45 (s, 3 H, NCH_3); mass spectrum m/e 371 (M^+).

Rearrangement of 8a with Boron Trifluoride Etherate. A mixture of 30 mg of dienone **8a**, 5 mL of CH_2Cl_2, and three drops of boron trifluoride etherate was stirred at room temperature for 24 h. After the solution had been diluted with CH_2Cl_2 to 25 mL, the solution was washed with water and 10% ammonia and water and dried over $NaSO_4$. Evaporation of the solvent and crystallization of the residue from ether gave 26 mg (87%) of **15**: mp sintering at 198 °C, melts at 221–222 °C; UV λ_{max}(EtOH) (log ϵ) 267 (4.09), 289 (3.99); NMR ($CDCl_3$) δ 7.07 and 7.03 (each s, 1 H, **ArH**), 6.80 (s, 1 H, **ArH**), 6.75 (s, 1 H, **ArH**), 5.87 (s, 1 H, OH), 3.95, 3.87, and 3.31 (each s, 9 H, OCH_3); mass spectrum m/e 437 (M^+).

Anal. Calcd for $C_{22}H_{22}NO_5F_3$: C, 60.41; H, 5.07; N, 3.20. Found: C, 60.47; H, 5.11; N, 3.27.

1,2,10,11-Tetramethoxy-*N*-trifluoroacetylhomoaporphine (9c). A solution of 11.0 mg of **15** in 5 mL of methanol was treated with an excess of an ether solution of diazomethane and kept at room temperature for 1 h. Evaporation of the solvent and crystallization from ether gave 10.0 mg (88%) of the product (**9c**): mp 166–168 °C. The melting point, mixture melting point, IR, NMR, TLC, UV, and mass spectrum were identical with those of the product obtained by VOF_3 oxidation of **6c**.

Rearrangement of 7a with Boron Trifluoride Etherate. A mixture of 100 mg of dienone **7a**, 10 mL of CH_2Cl_2, and three drops of boron trifuloride etherate was stirred at room temperature for 22 h. After the solution had been diluted with CH_2Cl_2 to 50 mL, the solution was washed with water and 10% ammonia and water, and dried. Evaporation of the solvent and crystallization of the residue from ether gave 83 mg (84%) of **17**: mp 200–201 °C; UV λ_{max}(EtOH) (log ϵ) 265 (4.05), 296 (3.93) nm; IR ($CHCl_3$) 3550 (OH), 1690 cm^{-1} (C=O); mass spectrum m/e 437 (M^+); NMR ($CDCl_3$) δ 7.12 and 7.08 (each s, 1 H, **ArH**), 6.79 and 6.63 (each s, 2 H, **ArH**), 5.74 (s, 1 H, **OH**), 3.93 (s, 6 H, OCH_3), 3.86 (s, 3 H, OCH_3).

Anal. Calcd for $C_{22}H_{22}NO_5F_3$: C, 60.41; H, 5.07; N, 3.20. Found: C, 60.50; H, 5.17; N, 3.18.

1,2,10,11-Tetramethoxy-*N*-trifluoroacetylhomoaporphine (9c). A solution of 30 mg of **17** in 3 mL of methanol was methylated according to the procedure given for the methylation of **15**, yielding 25.5 mg (87%) of the product (**9c**): mp 167–169 °C. The melting point, mixture melting point, TLC, IR, UV, NMR, and mass spectrum were identical with those of the product obtained by VOF_3 oxidation of **6c**.

Treatment of 11b with Ethylene Glycol in the Presence of *p*-Toluenesulfonic Acid. A mixture of 75 mg of **11b**, 50 mL of benzene, 1 mL of ethylene glycol, and 50 mg of *p*-toluenesulfonic acid was heated at reflux with azeotropic removal of water. After 7 h the mixture was poured into aqueous sodium carbonate and extracted with CH_2Cl_2. The extract was washed with water, dried, and evaporated to give a residue. Preparative TLC (ether–10% acetone) afforded 70 mg of **22** as a colorless glass: NMR ($CDCl_3$) δ 6.81 and 6.79 (both s, 2 H, ArH), 4.71 [t, 1 H, J = 4.7 Hz, c-(–$CHOCH_2CH_2O$)], 4.64 (mound, 1 H, **NH**), 4.05 (q, 2 H, J = 7.0 Hz, CH_3CH_2O), 3.92 (s, 6 H, OCH_3), 3.84 (s, 10 H, 2-OCH_3 and OCH_2CH_2O), 2.17 (m, 2 H, $CH_2NHCOOEt$), 2.45 (m, 4 H, $ArCH_2$), 1.80 (m, 2 H, CH_2CH), 1.19 (t, 3 H, CH_3CH_2O, J = 7.0 Hz).

Conversion of Acetal-Urethane (22) into Tetramethoxydibenzazecine (14a). A mixture of 60 mg of **22**, 5 mL of 20% aqueous sodium hydroxide, and 5 mL of methanol was heated at reflux on a steam bath for 48 h. The methanol was evaporated and the aqueous solution was extracted with CH_2Cl_2. The extract was washed with water, dried, and evaporated to give 50 mg of **23** as a colorless glass: mass spectrum m/e 417 (M^+); IR 3490 cm^{-1} (NH_2). The glass was treated with 5 mL of 5% aqueous HCl and heated on a steam bath for 10 min. The acidic solution was neutralized with powdered sodium bicarbonate and extracted with CH_2Cl_2. The CH_2Cl_2 solution was washed with brine, dried, and evaporated to leave 50 mg of a yellow glass. The glass was dissolved in 5 mL of methanol containing 10 mg

of PtO_2 and 5 drops of concentrated HCl. Hydrogenation was carried out under 1 atm of pressure of hydrogen for 5 h. The solution was filtered through Celite and the solvent removed in vacuo to leave a colorless oil. Crystallization from methanol–ether gave 30 mg of the hydrochloride salt of **14a**: mp 166–168 ° C; NMR and IR identical with those of **14a** obtained from aldehyde–amide **11a**.

Acknowledgments. This investigation was supported by grants from the National Cancer Institute (CA-12059) and the American Cancer Society (CI-102K). We thank the National Science Foundation for a grant which assisted in the purchase of a FT NMR spectrometer.

Registry No.—**1c**, 36455-21-7; **2a**, 2107-70-2; **2c**, 36418-96-9; **2e**, 1135-15-5; **3c**, 20872-69-9; **3d**, 65899-35-6; **4a**, 20944-14-3; **4b**, 30034-51-6; **4c**, 65899-36-7; **4d** HCl, 65899-37-8; **4e**, 65899-38-9; **5a**, 65899-28-7; **5a** HCl, 32487-02-8; **5c**, 65899-29-8; **5c** HCl, 65899-19-6; **5d**, 65899-30-1; **5d** HCl, 65899-20-9; **5e**, 65899-31-2; **5e** HCl, 65899-21-0; **6a** perchlorate, 65899-22-1; **6h**, 65899-23-2; **9a** HCl, 61660-06-8; **9b**, 61660-05-7; **10** isomer I, 51744-25-3; **10** isomer II, 30040-57-4; **14a** HCl, 65899-24-3; **14b**, 58141-98-3; **14c**, 65899-25-4; **22**, 65899-26-5; **23**, 65899-27-6.

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Utilization of β,γ-Unsaturated Aldehyde Equivalents in the Synthesis of Substituted 2-Halonicotinic Acid Derivatives

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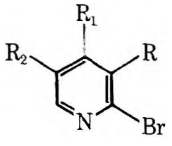
A convenient synthetic method is described for the preparation of 4- and/or 5-substituted 2-halonicotinic acid derivatives. The condensation of alkylidenemalononitriles or alkylidenecyanoacetates with either $HC(OEt)_3$ or DMF acetal yields the equivalent of a β,γ-unsaturated aldehyde which undergoes cyclization with acid to provide polysubstituted pyridines. However, the general utility of the reaction between DMF acetal and alkylidenemalononitriles is severely limited by the formation of dimeric type derivatives, **31–34**. This complication is overcome by the acid-catalyzed reaction of $HC(OEt)_3$ with alkylidenemalononitriles. Conversion of substituted ethyl nicotinates derived from alkylidenecyanoacetates to the corresponding trifluoromethyl derivatives is also described. Reaction of the unsymmetrical olefin 1-methylpropylidenemalononitrile with DMF acetal and with $HC(OEt)_3$ yields, in a regiospecific manner, two different β,γ-unsaturated aldehyde equivalents, which after acid cyclization afford 4-ethyl- and 4,5-dimethyl-2-bromonicotinonitriles, respectively.

An interest in derivatives of 2-halonicotinic acid of the type **1** led to a search for a synthetic method capable of generating such systems. Although several syntheses of the parent, ethyl 2-halonicotinate, and certain substituted derivatives have been described,[1,2] none of these have been extended to provide a versatile method for the introduction of alkyl or aryl groups into the 4 and/or 5 positions.[3]



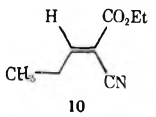
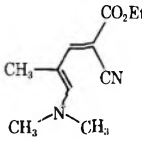
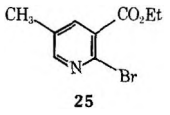
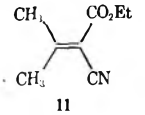
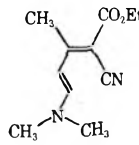
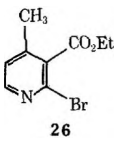
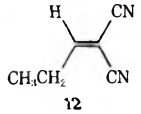
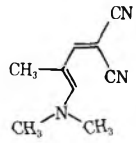
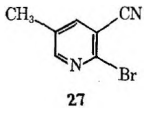
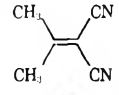
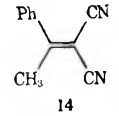
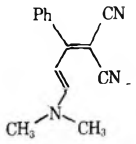
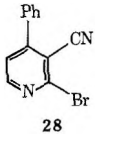
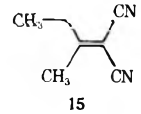
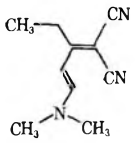
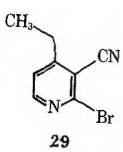
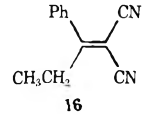
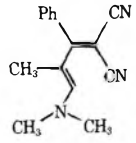
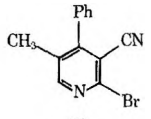
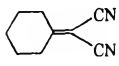
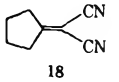
1

R = CO_2Et, CN, or CF_3
R_1,R_2 = alkyl, aryl, or H

One of the most general of these reported methods involves the Knoevenagel condensation of 1,3-dicarbonyl compounds (**2**) (or their chemical equivalents) with α-cyanoacetamide (**3**). This condensation is accompanied by cyclization, yielding 2-pyridones of the type **4** which are convertible by standard methods[4] to 2-halopyridines (Scheme I). Although a number of 6-substituted and 4,6-disubstituted 2-hydroxynicotinic acid derivatives have been prepared by this procedure, the method

0022-3263/78/1943-2529$01.00/0

Table I. Nicotinic Acid Derivatives Via DMF Acetal Route (Method A)[a]

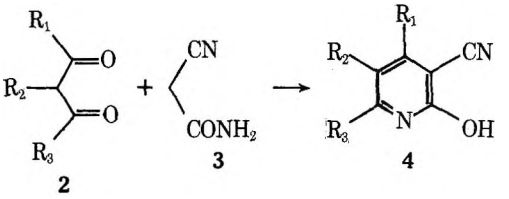
Knoevenagel product	β,γ-Unsaturated aldehyde equivalent	Nicotinic acid derivative	Overall yield, %
 10	 19	 25	35
 11	 20	 26	58
 12	 21	 27	5
 13	Not obtained		
 14	 22	 28	22
 15	 23	 29	16
 16	 24	 30	3
 17	Not obtained		
 18	Not obtained		

[a] Registry no.: **10**, 56569-41-6; **11**, 759-58-0; **12**, 52833-34-8; **14**, 5447-87-0; **15**, 13017-50-0; **16**, 10432-39-0; **19**, 65996-10-3; **20**, 65996-11-4; **21**, 65996-12-5; **22**, 65996-13-6; **23**, 65996-14-7; **24**, 65996-15-8; **25**, 65996-16-9; **26**, 65996-17-0; **27**, 65996-18-1; **28**, 65996-19-2; **29**, 65996-20-5; **30**, 65996-21-6.

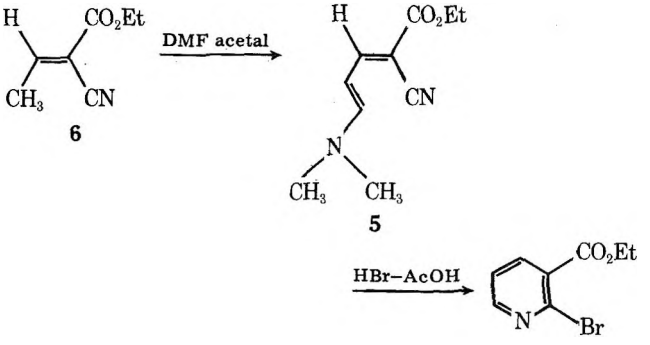
is not amenable to the synthesis of the corresponding 4- and/or 5-substituted compounds. In the case of 5-substituted derivatives,[5,6] this limitation is due to the lack of a convenient synthesis for 2-substituted malonaldehydes. The only example of a 4-substituted 2-hydroxynicotinic acid derivative has been reported by Powers and Ponticello,[7] but the synthesis suffers from low yields and a lack of general applicability.

Another approach to ethyl 2-halonicotinate has been reported by Bryson et al.[8] and involves the intramolecular cyclization of ethyl 5-(*N,N*-dimethylamino)-2-cyano-2,4-pentadienoate (**5**), obtainable by the base-catalyzed[8c] reaction of *N,N*-dimethylformamide dimethyl acetal (DMF acetal) with

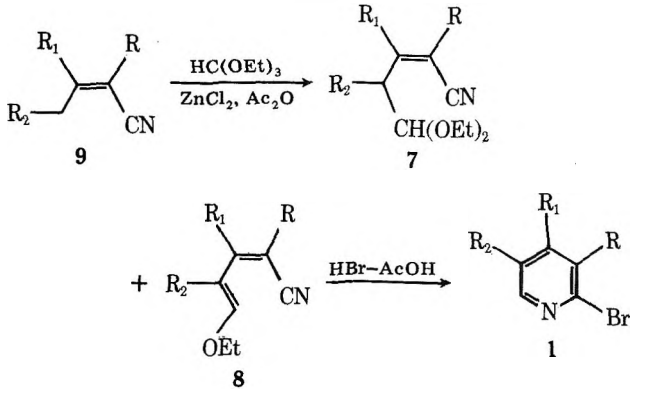
Scheme I



Scheme II



Scheme III



R = CO_2Et or CN

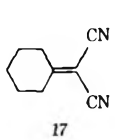
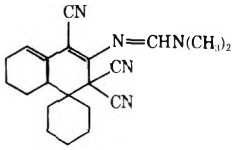
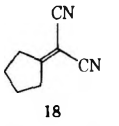
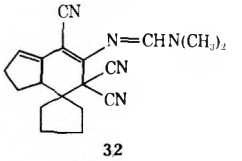
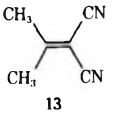
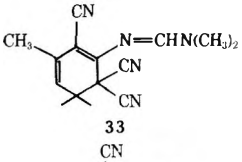
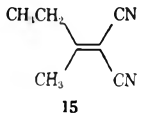
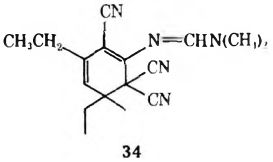
olefin **6**, as illustrated in Scheme II. In this paper, we wish to report on the extension of this method to the synthesis of substituted pyridines of the type **1** and on the utilization of β,γ-unsaturated acetals **7** and enol ethers **8** obtained from the acid-catalyzed reaction of triethyl orthoformate with vinylogous active methylene compounds **9** (Scheme III).

Results and Discussion

Our initial studies involved the reaction of olefins **10**–**18** with DMF acetal (method A, Table I). These olefins, in turn, were prepared by Knoevenagel condensation[9] of the apppropriate aldehyde or ketone with ethyl α-cyanoacetate or malononitrile. For the alkylidenecyanoacetates **10** and **11**, the reaction yielded the β,γ-unsaturated aldehyde equivalents **19** and **20**, which were converted directly by acid cyclization (HBr–AcOH) to **25** and **26** in yields of 35 and 58%, respectively. In the case of the alkylidenemalononitriles **12**–**18**, the reaction gave variable results. The yield of 2-bromo-4-phenylnicotinonitrile (**28**) from **14** was 22%; this represents a significant improvement over the previously reported[7] yield of 5% for 3-cyano-4-phenyl-2-pyridone. Overall, the nicotinonitriles **27**–**30** were obtained in low yield. Three substrates, **13**, **17**, and **18**, failed to yield the intermediate dienes on reaction with DMF acetal.

As summarized in Table II, the reaction of DMF acetal with **13**, **15**, **17**, and **18** gave the complex formamidines **31**–**34** as the

Table II. Dimers[a]

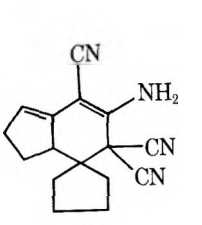
Olefin	Product	NMR, δ	Mass spectra
 17	 31	7.82 (1 H, s), 6.3 (1 H, m), 3.15 (6 H, d), 3.0–1.2 (17 H, m)	Calcd for $C_{21}H_{25}N_5$: 347.2096 Found: 347.2110
 18	 32	7.9 (1 H, s), 5.95 (1 H, q), 3.15 (6 H, d), 2.9–1.3 (13 H, m)	Calcd for $C_{19}H_{21}N_5$: 319.1797 Found: 319.1796
 13	 33	8.1 (1 H, s), 5.25 (1 H, q), 3.15 (6 H, d), 1.95 (3 H, d), 1.35 (6 H, s)	Calcd for $C_{15}H_{17}N_5$: 267.1484 Found: 267.1486
 15	 34	8.0 (1 H, s), 5.25 (1 H, bs), 3.15 (6 H, d), 2.8–0.8 (13 H, m)	Calcd for $C_{17}H_{21}N_5$: 295.1797 Found: 295.1790

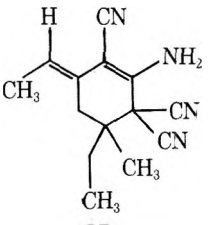
[a] Registry no.: **13**, 13166-10-4; **17**, 354-73-8; **18**, 5660-83-3; **31**, 65996-22-7; **32**, 65996-23-8; **33**, 65996-24-9; **34**, 66017-99-0.

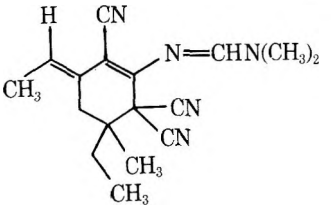
sole or major product. The structural assignment of these compounds was based on their proton NMR and high-resolution mass spectra. Integration of the olefinic signal relative to the formamidine proton revealed a 1:1 ratio, thereby confirming the relative positions of the double bonds in structures **31–33**. The structure of **34** is clearly supported by the appearance of the olefinic proton as a weakly coupled triplet at δ 5.25 (J = 0.5 Hz) rather than as a quartet which would be expected for the alternative exo possibility (**38**).

Since alkylidenemalononitriles are known to dimerize under base catalysis,[10–13] it was postulated that **31–34** resulted from the reaction of the intermediate dimers with DMF acetal. To test this hypothesis, cyclohexylidenemalononitrile (**17**) was treated (neat) with a catalytic amount of piperidine, according to the method of Weir and Hyne,[11,12] to yield the dimer **35**. Subsequent treatment of **35** with DMF acetal afforded the formamidine **31**, which was identical in all respects (IR and NMR spectra and mixed melting point) with the product formed directly from the reaction of **17** with DMF acetal. (Scheme IV).

Similarly, transformation of cyclopentylidenemalononitrile (**18**) with piperidine yielded dimer **36**, which was converted to **32** in an analogous manner. The dimeric product formed on treating **15** with base, according to the method of Weir and Hyne,[12] was assigned structure **37** based on NMR spectroscopy and is in agreement with the previously reported structure. Treatment of **37** with DMF acetal gave formamidine **38**,


36


37


38

which was not identical with formamidine **34** obtained on reaction of **15** with DMF acetal.

Thus, this last example tends to argue against the formation of the formamidine from the intermediate dimer. Therefore, the exact mechanism for the formation of these formamidine dimeric products **31–34** must be left undefined.

The thermodynamic products **31–33** were obtained in all cases, except for **34**, where the product of kinetic control was isolated. Refluxing **34** in xylene resulted in almost complete conversion of kinetic product **34** to the thermodynamic product **38** (~80%), while compounds **31–33** remained unchanged under the same conditions.

It was found that the use of alkylidenecyanoacetates in place of the malononitriles obviates the problems encountered in the DMF acetal reaction. Thus, the cyanoesters are the substrate of choice for entry into the desired 2-halonicotinate system; this is best illustrated in examples **25** and **26**.

In addition, **25** and **26** were hydrolyzed with 10% NaOH solution to the corresponding acids **39** and **40** in high yield (Scheme V). Reaction of these acids with SF_4–HF gave the trifluoromethylpyridines **41** and **42**.[14] In the NMR spectrum

Scheme IV

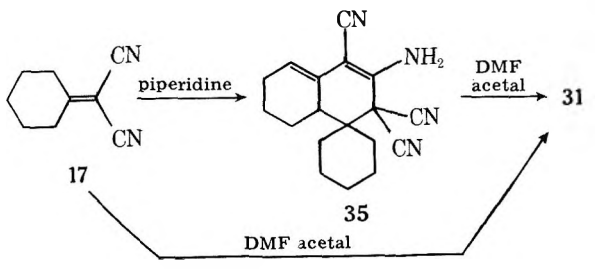
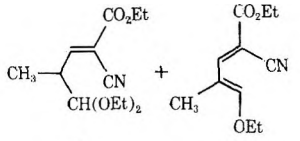
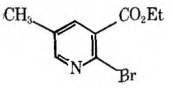
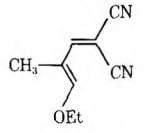
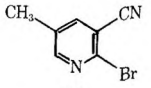
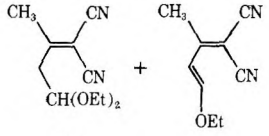
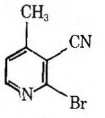
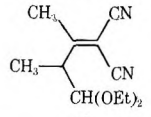
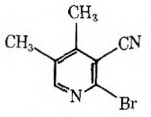
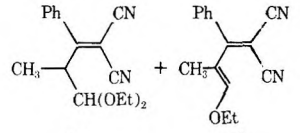
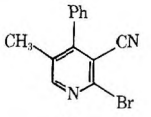
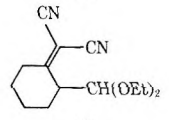
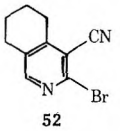
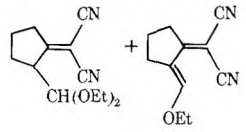
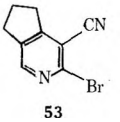


Table III. Nicotinic Acid Derivatives Via $HC(OEt)_3$ Route (Method B)[a]

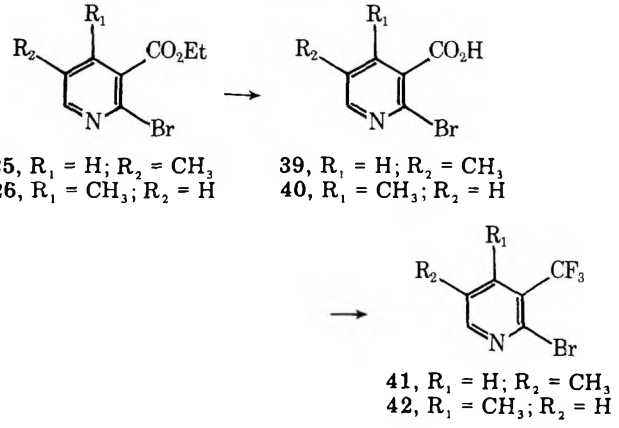
Knoevenagel product	β,γ-Unsaturated aldehyde equivalent	Yield, %	Nicotinic acid derivative	Overall yield, %
10	 43a + 43b	74	 25	40
12	 44	67	 27	15
13	 45a + 45b	*b*	 50	23
15	 46	70	 51	29
16	 47a + 47b	95	 30	42
17	 48	29	 52	15
18	 49a + 49b	36	 53	15

[a] Registry no.: **43a**, 65995-91-7; **43b**, 65995-92-8; **44**, 65995-93-9; **45a**, 65995-94-0; **45b**, 65995-95-1; **46**, 65995-96-2; **47a**, 65995-97-3; **47b**, 65995-98-4; **48**, 65995-91-5; **49a**, 65996-00-1; **49b**, 65996-01-2; **50**, 65996-02-3; **51**, 65996-03-4; **52**, 66017-97-8; **53**, 66996-04-5. [b] See footnote *b* in Table V.

of **42**, the C-4 methyl group was characteristically coupled to the adjacent trifluoromethyl moiety as a quartet with $J = 3$ Hz.

The difficulties encountered in the preparation of halonicotinonitriles from certain alkylidenemalononitriles (**13**, **17**, and **18**) using DMF acetal prompted a search for an alternate way to generate the β,γ-unsaturated aldehyde equivalents. As outlined in Scheme III, the limitations inherent in the Bryson method were overcome by the synthesis and utilization of the β,γ-unsaturated acetals **7** and enol ethers **8**. Although the reaction of triethyl orthoformate with diethyl malonate to afford ethyl ethoxymethylenemalonate has been reported,[15] its reaction with vinylogous active methylene compounds to generate the β,γ-unsaturated aldehyde derivatives **7** and **8** has not been described.

Scheme V



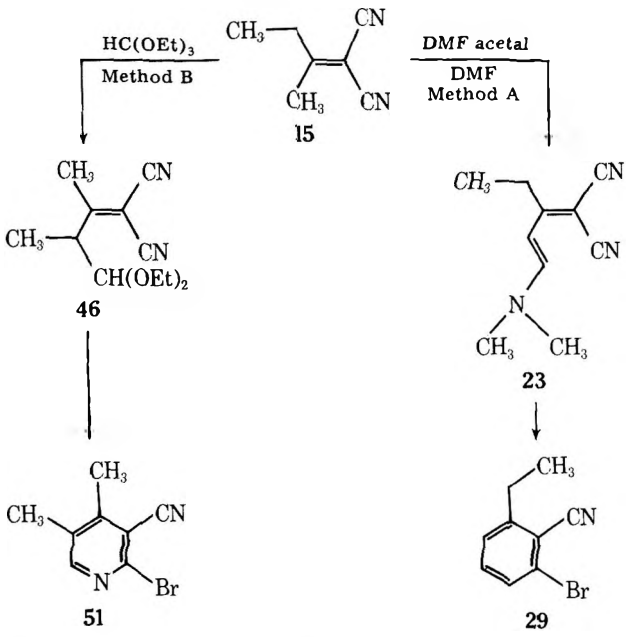
25, $R_1 = H$; $R_2 = CH_3$
26, $R_1 = CH_3$; $R_2 = H$

39, $R_1 = H$; $R_2 = CH_3$
40, $R_1 = CH_3$; $R_2 = H$

41, $R_1 = H$; $R_2 = CH_3$
42, $R_1 = CH_3$; $R_2 = H$

The general versatility and utility of this conversion are illustrated by the examples presented in Table III. Reaction of these olefins, prepared by the Knoevenagel condensation, with $HC(OEt)_3$ (method B) yielded the corresponding β,γ-unsaturated acetals as the major products; in the case of propylidenemalononitrile (**12**), only the β,γ-unsaturated enol ether **44** was isolated. In the reaction of dialkyl olefins **13**, **15**, **17**, and **18**, the ratio of olefin to $HC(OEt)_3$ to Ac_2O was 1:1:2. For condensations where only one alkyl group was available for reaction, as in olefins **10**, **12**, and **16**, the same ratio of reactants was used; however, after refluxing overnight, the volatiles were distilled off, additional reagents ($HC(OEt)_3$–

Scheme VI



Ac_2O) were added, and the reaction mixture was heated at 150 °C for an additional 3 h. In most cases, the unsaturated acetals **43–49** were purified by distillation and their structures determined by proton NMR spectroscopy. All of the acetals exhibited a doublet in the region of δ 4.5 for the $-CH(OEt)_2$ proton, except for **45** where the expected triplet appeared at δ 4.7. In the NMR spectra of compounds **43, 45, 47,** and **49,** the presence of the corresponding enol ethers was also indicated.

Inspection of Tables I and III reveals that the yields of nicotinic acid derivatives are generally higher using the $HC(OEt)_3$ method. As an illustration, compounds **27** and **30** were prepared by both procedures; the overall yields were 5 and 3% using DMF acetal and 15 and 42%, respectively, using the $HC(OEt)_3$ method. For alkylidenemalononitriles **13, 17,** and 18 the DMF acetal method failed to yield β,γ-unsaturated aldehyde equivalents, while the sequence utilizing the acid-catalyzed $HC(OEt)_3$ method proved successful. Thus, the base-catalyzed dimerization reaction is a severe synthetic limitation on the possible extension of the enamine diene system. This difficulty is entirely overcome by the $HC(OEt)_3$ method, thereby making the β,γ-unsaturated acetals much more versatile synthons. Of special note is the utilization of this method and the failure of the DMF acetal procedure for the synthesis of the novel tetrahydroisoquinoline **52** and 4,5-cyclopentenopyridine **53** (see Table III).

As illustrated in Scheme VI, 1-methylpropylidenemalononitrile (**15**) afforded 2-bromo-4-ethylnicotinonitrile (**29**) by the DMF acetal method and 2-bromo-4,5-dimethylnicotinonitrile (**51**) by the $HC(OEt)_3$ procedure. The methylene carbon atom of the ethyl group in **15** reacted with $HC(OEt)_3$ under acid catalysis to yield the β,γ-unsaturated acetal **46,** while the methyl group of **15** reacted with DMF acetal under base catalysis to afford the enamine diene **23.** This result is *in accord with the* observation that methyl ethyl ketone undergoes reaction on the methyl group in base and on the methylene carbon in acid.[16] Thus, the availability of methods A and B permits a regioselective synthesis of **29** and **51** from the same precursor (**15**).

Although the overall yields of these nicotinic acid derivatives are moderate, no effort was made to optimize the reaction conditions. With the ease of reaction and the ready availability of starting materials, the $HC(OEt)_3$ method offers a relatively simple synthesis of substituted pyridines of type **1.** In addition, the Bryson procedure involving the reaction of DMF acetal with Knoevenagel products has been extended and its utilization in the synthesis of mono- and disubstituted 2-halonicotinic acid derivatives established.

Experimental Section

Infrared spectra were obtained on Perkin-Elmer Model 137 and 257 spectrophotometers. NMR spectra were determined in the indicated solvent on a Varian T-60 spectrometer using tetramethylsilane as an internal standard for proton spectra and fluorotrichloromethane for ^{19}F spectra. Splitting patterns are designated as follows: s, singlet; bs, broad singlet; d, doublet; t, triplet; q, quartet; p, pentet; and m, multiplet. Mass spectra were taken on an AEI MS-902 high-resolution mass spectrometer at an ionizing voltage of 70 eV and an ionizing current of 500 mA. The samples were processed by a DS50 data acquisition system. The low-resolution spectra were run at an ionizing voltage of 70 eV and an ionizing current of 100 mA. Melting points were determined on a Thomas-Hoover apparatus in open capillary tubes and are uncorrected. Liquids were distilled by short-path distillation through a Vigreux column, and boiling points are uncorrected. Silica gel 60 (E. Merck, Darmstadt) was used for column chromatography. Concentration of solutions was accomplished using a Büchi rotary evaporator under water aspirator pressure (20 mm).

Preparation of 1-Propylidenemalononitrile (12). Using the general procedure of Prout,[17] a solution of malononitrile (50 g, 0.76 mol), propionaldehyde (47 g, 0.81 mol), AcOH (10 mL), benzene (140 mL), and alanine (0.5 g) was refluxed for 1.5 h with removal of H_2O in a Dean–Stark trap. After cooling, the solution was poured into H_2O and separated. The aqueous layer was washed with benzene (2 × 200 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was distilled to yield 61.7 g (77%) of **12:** bp 45 °C (0.6 mm); ^1H NMR ($CDCl_3$) δ 1.2 (3 H, t), 2.55 (2 H, q), and 7.35 (1 H, t).

The following olefins were prepared by literature procedures: ethyl propylidenecyanoacetate (**10**),[18] ethyl isopropylidenecyanoacetate (**11**),[18] isopropylidenemalononitrile (**13**),[9] 1-phenylethylidenemalononitrile (**14**),[19] 1-methylpropylidenemalononitrile (**15**),[20] 1-phenylpropylidenemalononitrile (**16**),[20,21] cyclohexylidenemalononitrile (**17**),[9] and cyclopentylidenemalononitrile (**18**).[22]

General Procedure for the Preparation of Butadienamines 19–24 Using DMF Acetal (Method A). The preparation of ethyl 2-cyano-5-(*N,N*-dimethylamino)-4-methyl-2,4-pentadienoate (**19**) is presented as an example; details for the synthesis of compounds **20–24** are presented in Table IV.

DMF acetal (8.9 g, 0.75 mol) was added dropwise to a solution of **10** (11.4 g, 0.074 mol) in absolute EtOH (75 mL). After the addition, the solution was heated at reflux for 6 h and then concentrated to dryness to yield 16.9 g of crude **19:** ^1H NMR ($CDCl_3$) δ 1.4 (3 H, t), 2.35 (3 H, s), 3.25 (6 H, s), 4.3 (2 H, q), 6.85 (1 H, s), and 7.6 (3 H, t). This material was used in the next step without further purification.

General Procedure for the Preparation of β,γ-Unsaturated Aldehyde Equivalents 43–49 Using $HC(OEt)_3$ (Method B). The preparation of 1,1-dicyano-4-ethoxy-3-methyl-1,3-butadiene (**44**) is presented as an example; details for the synthesis of compounds **43** and **45–49** are presented in Table V.

A mixture of **12** (11.3 g, 0.104 mol), Ac_2O (21 mL), $HC(OEt)_3$ (16.3 g, 0.11 mol), and $ZnCl_2$ (100 mg) was heated overnight at 145 °C. After 18 h, the volatiles were removed by distillation at atmospheric pressure, Ac_2O (5 mL) and $HC(OEt)_3$ (4 mL) were added, and the mixture was heated at 150 °C. After 10 h, the solution was cooled and added to saturated Na_2CO_3 solution. The aqueous solution was extracted with $CHCl_3$ (3 × 100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was distilled at 138–158 °C (0.3 mm) to give 11.2 g of **44** (67%): ^1H NMR δ 1.4 (3 H, t), 2.05 (3 H, s), 4.15 (2 H, q), 7.0 (1 H, bs), and 7.05 (1 H, s). This material was used in the next step without further purification.

General Procedure for the Preparation of Nicotinic Acid Derivatives Using HBr–AcOH. The preparation of ethyl 2-bromo-5-methylnicotinate (**25**) is presented as an example; details for the synthesis of compounds **26–30** and **50–53** are outlined in Table VI.

Compound **19** (16.9 g) was dissolved in AcOH (50 mL) and the mixture heated at 40 °C. A solution of 30% HBr–AcOH (100 mL) was added dropwise, and then the mixture was heated to 55 °C with stirring. After heating for 0.75 h, the solution was poured onto ice, neutralized with solid Na_2CO_3, and extracted with CH_2Cl_2 (4 × 200 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was distilled at 114–120 °C (0.4 mm) to yield 6.3 g (35%) of **25:** ^1H NMR ($CDCl_3$) δ 1.4 (3 H, t), 2.35 (3 H, s), 4.35 (2 H, q), 7.83 (1 H, d), and 8.23 (1 H, d); MS *m/e* (M^+) 243

Table IV. Experimental Details for DMF Acetal Reaction (Method A)

Olefin (g; mol)	DMF acetal, g (mol)	Solvent (mL)	Temp, °C	Diene (g)	^{1}H NMR, δ
11 (5.7; 0.37)	4.43 (0.037)	Absolute EtOH (50)	25	**20** (7.4)	*a*
12 (8.0; 0.075)	9.0 (0.076)	DMF[b] (30)	25	**21** (8.8)	*a*
14 (10.3; 0.061)	7.61 (0.064)	DMF[b] (14)	0[c]	**22** (13.53)	3.0 (6 H, d), 5.8 (1 H, d), 6.8 (1 H, d), 7.4 (5 H, m)
15 (12.0; 0.1)	12.0 (0.1)	DMF[b] (50)	0[c]	**23** (5.4)[d]	1.05 (3 H, t), 2.6 (2 H, q), 3.15 (6 H, d), 5.5 (1 H, d), 7.3 (1 H, d)
16 (9.0; 0.05)	6.5 (0.055)	DMF[b] (3)	0[c]	**24** (1.3)[d]	2.25 (3 H, s), 3.1 (6 H, s), 6.6 (1 H, s), 7.2 (5 H, m)

[a] NMR spectrum of crude material was too complicated to assign proton resonances. [b] When DMF was used as solvent, the reaction mixture was poured into H_2O, extracted with ether, and backwashed with H_2O. The ether layer was dried, filtered, concentrated to dryness, and used directly in the next step. [c] After the addition of DMF acetal at 0 °C, the reaction mixture was stirred overnight at room temperature. [d] The compound was purified by chromatography on silica gel on elution with $CHCl_3$.

Table V. Experimental Details for $HC(OEt)_3$ Reaction (Method B)

Olefin (g; mol)	$HC(OEt)_3$, g (mol)	Ac_2O, mL	Recovered olefin (g)	β,γ-Unsaturated aldehyde derivative (g; % yield)	Bp, °C (mm)	^{1}H NMR, δ
10 (11.0; 0.072)	11.1 (0.075) 2.2 (0.015)[a]	15 3	**10** (3.9)	**43a,b** (8.7; 74)	104–127 (0.2)	**43a:** 1.3 (12 H, m), 3.6 (3 H, m), 4.4 (5 H, m), 7.6 (1 H, d)
13 (40.0; 0.38)	61.0 (0.41)	76	**13** (21.0)	**45a,b** (19.2)[b]	125–150 (1.0)	**45a:**[e] 1.4 (6 H, t, J = 7 Hz), 2.35 (3 H, s), 2.85 (2 H, d, J = 5 Hz), 3.6 (4 H, m), 4.7 (1 H, t, J = 5 Hz) **45b:**[e] 1.4 (3 H, t, J = 8 Hz), 2.3 (3 H, s), 4.1 (2 H, q, J = 7 Hz), 6.2 (1 H, d, J = 12 Hz), 7.4 (1 H, d, J = 12 Hz)
15 (25.0; 0.21)	35.0 (0.24)	45	**15** (14.4)	**46** (16; 70)	55–80 (0.2)	**46:** 1.2 (9 H, m), 2.2 (3 H, s), 2.65 (1 H, m), 3.55 (4 H, m), 4.5 (1 H, d)
16 (9.0; 0.05)	7.6 (0.05) 3.8 (0.026)[a]	9.5		**47a,b** (11.5; 95)[c]		**47a:** 1.2 (9 H, m), 2.8–4.2 (5 H, m), 4.4 (1 H, d), 7.4 (5 H, m)
17 (7.3; 0.05)	8.1 (0.055)	9.6		**48** (4; 29)[d]		**48:** 1.1–3.9 (19 H, m), 4.75 (1 H, d)
18 (19.8; 0.15)	24.3 (0.165)	28.8	**18** (7)	**49a,b** (7.5; 36)	120–140 (0.5)	**49a:** 1.0 (6 H, m), 2.0 (3 H, m), 2.8 (3 H, m), 3.5 (4 H, m), 4.1 (1 H, m), 4.7 (1 H, d)

[a] An additional amount of $HC(OEt)_3$ was added after heating overnight at 130 °C. [b] A mixture of **45a** and **45b** was obtained by short-path distillation; therefore, no yield was calculated. [c] Crude residue. [d] Obtained as an oil by chromatography on silica gel on elution with $CHCl_3$. [e] NMR spectrum was determined on fractionation of a mixture of **45a** and **45b**; **45a**, bp 112–117 °C (0.5 mm); **45b**, bp 125–130 °C (0.5 mm).

(^{79}Br) and 245 (^{81}Br). MS Calcd for $C_9H_{10}BrNO_2$: 242.9895. MS Found: 242.9897.

Spectral and Analytical Properties of 26–30 and 50–53. Ethyl 2-Bromo-4-methylnicotinate (26): ^{1}H NMR ($CDCl_3$) δ 1.4 (3 H, t), 2.4 (3 H, s), 4.5 (2 H, q), 7.5 (1 H, d), and 8.25 (1 H, d); MS *m/e* (M^+) 243 (^{79}Br) and 245 (^{81}Br). MS Calcd for $C_9H_{10}BrNO_2$: 242.9895. MS Found: 242.9890.

2-Bromo-5-methylnicotinonitrile (27): ^{1}H NMR δ 2.4 (3 H, s), 7.75 (1 H, d), and 8.4 (1 H, d); MS *m/e* (M^+) 196 (^{79}Br) and 198 (^{81}Br). Anal. Calcd for $C_7H_5BrN_2$: C, 42.67; H, 2.56; N, 14.22. Found: C, 42.49; H, 2.61; N, 14.30.

2-Bromo-4-phenylnicotinonitrile (28): ^{1}H NMR ($CDCl_3$) δ 7.4 (1 H, d), 7.55 (5 H, s), and 8.5 (1 H, d). Anal. Calcd for $C_{12}H_7BrN_2$: C, 55.62; H, 2.72; N, 10.81. Found: C, 55.72; H, 2.78; N, 10.79.

2-Bromo-4-ethylnicotinonitrile (29): ^{1}H NMR ($CDCl_3$) δ 1.35 (3 H, t), 2.9 (2 H, q), 7.35 (1 H, d), and 8.5 (1 H, d); MS *m/e* (M^+) 210 (^{79}Br) and 212 (^{81}Br). Anal. Calcd for $C_8H_7BrN_2$: C, 45.52; H, 3.34; N, 13.27. Found: C, 45.65; H, 3.66; N, 13.27.

2-Bromo-5-methyl-4-phenylnicotinonitrile (30): ^{1}H NMR ($CDCl_3$) δ 2.15 (3 H, s), 7.4 (5 H, m), and 8.45 (1 H, s). Anal. Calcd for $C_{13}H_9BrN_2$: C, 57.16; H, 3.32; N, 10.26. Found: C, 56.88; H, 3.70; N, 10.16.

2-Bromo-4-methylnicotinonitrile (50): ^{1}H NMR ($CDCl_3$) δ 2.6 (3 H, s), 7.25 (1 H, d), and 8.35 (1 H, d); MS *m/e* (M^+) 196 (^{79}Br) and 198 (^{81}Br). Anal. Calcd for $C_7H_5BrN_2$: C, 42.67; H, 2.56; N, 14.22. Found: C, 42.58; H, 2.55; N, 14.38.

2-Bromo-4,5-dimethylnicotinonitrile (51): ^{1}H NMR ($CDCl_3$) δ 2.3 (3 H, s), 2.55 (3 H, s), and 8.2 (1 H, s); MS *m/e* (M^+) 210 (^{79}Br) and 212 (^{81}Br). Anal. Calcd for $C_8H_7BrN_2$: C, 45.52; H, 3.34; N, 13.27. Found: C, 45.34; H, 3.19; N, 13.32.

2-Bromo-3-cyano-5,6,7,8-tetrahydroisoquinoline (52): ^{1}H NMR ($CDCl_3$) δ 1.85 (4 H, p), 2.85 (4 H, m), and 8.2 (1 H, s). Anal. Calcd for $C_{10}H_9BrN_2$: C, 50.65; H, 3.82; N, 11.82. Found: C, 51.09; H, 3.82; N, 11.90.

2-Bromo-3-cyano-4,5-cyclopentenopyridine (53): ^{1}H NMR ($CDCl_3$) δ 2.2 (2 H, m), 3.1 (4 H, m), and 8.25 (1 H, s). Anal. Calcd for $C_9H_7BrN_2$: C, 48.45; H, 3.16; N, 12.56. Found: C, 48.37; H, 3.12; N, 12.52.

General Procedure for the Preparation of Compounds 31–34. The preparation of **31**, the *N*-(*N'*,*N'*-dimethylaminomethylene) derivative of the cyclohexylidenemalononitrile dimer, is presented as an example. To DMF acetal (13 g, 0.11 mol) and DMF (1.5 mL) was added cyclohexylidenemalononitrile (14.6 g, 0.1 mol) dropwise with stirring and ice cooling. After warming to room temperature overnight, the reaction mixture was poured into Et_2O (100 mL) and washed with H_2O (2 × 50 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was chromatographed on silica gel and the product eluted with 3% MeOH–$CHCl_3$ to yield 3.0 g of **31** (17%), mp 149–153 °C (from *n*-butyl chloride). Anal. Calcd for $C_{21}H_{25}N_5$: C, 72.59; H, 7.25; N, 20.16. Found: C, 72.23; H, 7.44; N, 20.31.

Compounds **32**, **33**, and **34** were prepared in a manner similar to **31** in yields of 25 (mp 145–146.5 °C, from *n*-butyl chloride), 62 (mp 83–85 °C from ligroin), and 60% (mp 128–130 °C, from ligroin), respectively.

Table VI. Experimental Details for HBr–AcOH Cyclization Reaction

β,γ-Unsaturated aldehyde equivalent (g)	AcOH, mL	30% HBr–AcOH, mL	Product (g; % yield)[a]	Bp (mm) or mp, °C
20 (7.4)	50	50	**26** (5.2; 58)	110–112 (0.7)
21 (8.8)	30	50	**27**[b] (0.4; 5)[c]	109–111
22 (13.5)	100	100	**28**[b] (3.8; 22)[d]	122–125
23 (4.0)	20	40	**29**[b] (2.4; 16)[c]	64–65
24 (1.3)	3.7	5.6	**30**[b] (0.15; 3)[c]	123–124
43a,b (8.7)	60	60	**25** (4.3; 40)	115–130 (0.25)
44 (11.2)	50	100	**27**[b] (3.0; 15)[c]	109–111
45a,b (19.2)	80	160	**50**[b] (1.0; 23)[c]	109–111
46 (16.0)	50	100	**51**[b] (6.3; 29)[c]	93–95
47a,b (11.5)	100	100	**30**[b] (5.7; 42)[c]	123–124
48 (4.0)	10	15	**52**[b] (2.0; 15)[c]	128.5–130.5
49 (7.5)	20	35	**53**[b] (3.4; 15)[c]	103–105

[a] Yields reported are for the overall two-step process. [b] The nicotinonitrile derivatives were obtained by chromatography on silica gel and the products eluted with $CHCl_3$. [c] Purified by recrystallization from ligroin. [d] Purified by recrystallization from cyclohexane.

High-resolution mass spectral and NMR data for compounds **31–34** are presented in Table II. Anal. Calcd for $C_{19}H_{21}N_5$ (**32**): C, 71.44; H, 6.63; N, 21.93. Found: C, 71.47; H, 6.97; N, 21.76. Anal. Calcd for $C_{15}H_{17}N_5$ (**33**): C, 67.39; H, 6.37; N, 26.20. Found: C, 67.74; H, 6.61; N, 26.23. Anal. Calcd for $C_{17}H_{21}N_5$ (**34**): C, 69.12; H, 7.17; N, 23.71. Found: C, 69.46; H, 7.48; N, 23.82.

Preparation of Compound 38. To **37** (1.6 g, 0.0067 mol) and DMF (5 mL) was added DMF acetal (0.8 g, 0.007 mol). After stirring overnight at room temperature, the mixture was poured in Et_2O (50 mL) and washed with H_2O (2 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness to yield 1.8 g (91%) of **38**: mp 120–121 °C (from ligroin); ^1H NMR ($CDCl_3$) δ 0.95 (3 H, t), 1.25 (3 H, s), 1.75 (5 H, m), 2.4 (2 H, bs), 3.1 (6 H, d), 6.0 (1 H, q), and 7.8 (1 H, s). Anal. Calcd for $C_{17}H_{21}N_5$: C, 69.12; H, 7.17; N, 23.71. Found: C, 69.32; H, 7.35; N, 23.99. The exact mass was 295.1803 (calcd, 295.1797).

Preparation of the Cyclopentylidenemalononitrile Dimer (36). Following the procedure of Weir and Hyne[11] for the synthesis of **35** and **37**, compound **36** was prepared by essentially the same manner in 38% yield, mp 178–182 °C (from H_3CCN). Anal. Calcd for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 73.03; H, 6.31; N, 21.50. The exact mass was 264.1365 (calcd, 264.1375).

Stability of Compounds 31–34 and 38. Refluxing a solution of dimer **34** (150 mg) in xylene overnight gave by ^1H NMR spectroscopy a mixture of 16% of **34** and 84% of **38**. After heating **38** (50 mg) for 3 days in refluxing xylene, no change was observed in the ^1H NMR spectrum. On refluxing **31**, **32**, and **33** overnight in xylene, no change was observed by ^1H NMR spectroscopy.

Preparation of 2-Bromo-5-methylnicotinic Acid (39). A mixture of **25** (7.1 g, 0.03 mol) and 10% NaOH solution (500 mL) was heated on a steam bath with stirring. After 3 h, the solution was cooled and neutralized with 12 N HCl. After cooling in an ice bath, the mixture was filtered to yield 5.6 g (89%) of **39**: mp 170–171 °C (from H_2O–MeOH); ^1H NMR (Me_2SO-d_6) δ 2.35 (3 H, s), 7.9 (1 H, d), and 8.3 (1 H, d); MS *m/e* (M^+) 215 (^{79}Br) and 217 (^{81}Br). Anal. Calcd for $C_7H_6BrNO_2$: C, 38.91; H, 2.80; N, 6.48. Found: C, 39.22; H, 2.97; N, 6.59.

Preparation of 2-Bromo-4-methylnicotinic Acid (40). Compound **26** (12.1 g, 0.05 mol) in 10% NaOH (500 mL) yielded 9.3 g (87%) of **40**: mp 173–174 °C (from H_2O); ^1H NMR (Me_2SO-d_6) δ 2.35 (3 H, s), 7.4 (1 H, d), and 8.3 (1 H, d); MS *m/e* (M^+) 215 (^{79}Br) and 217 (^{81}Br). Anal. Calcd for $C_7H_6BrNO_2$: C, 38.91; H, 2.80; N, 6.48. Found: C, 39.09; H, 2.88; N, 6.39.

Preparation of 2-Bromo-5-methyl-3-trifluoromethylpyridine (41). Into a steel bomb was placed **39** (5.0 g, 0.023 mol), SF_4 (31 g, 0.29 mol), and HF (5.3 mL). The contents were heated at 120 °C for 8 h. After cooling to room temperature, the bomb was opened and the contents were poured onto saturated Na_2CO_3 solution and extracted with $CHCl_3$ (3 × 100 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to dryness. The residue distilled at 45–49 °C (0.1 mm) to yield 4 g (59%) of **41**: ^1H NMR ($CDCl_3$) δ 2.35 (3 H, s), 7.7 (1 H, d), and 8.25 (1 H, d); ^{19}F NMR ($CDCl_3$) +63.1 (s); MS *m/e* (M^+) 239 (^{79}Br) and 241 (^{81}Br). MS Calcd for $C_7H_5BrF_3N$: 238.9558. MS Found: 238.9555.

Preparation of 2-Bromo-4-methyl-3-trifluoromethylpyridine (42). Similarly, compound **40** (9.3 g, 0.05 mol), SF_4 (58 g, 0.53 mol), and HF (9.8 mL) yielded 6.2 g (60%) of **42**: bp 45–50 °C (0.1 mm); ^1H NMR ($CDCl_3$) δ 2.80 (3 H, q), 7.2 (1 H, d), and 8.3 (1 H, d); MS *m/e* (M^+) 239 (^{79}Br) and 241 (^{81}Br). Anal. Calcd for $C_7H_5BrF_3N$: C, 35.02; H, 2.10; N, 5.84. Found: C, 34.56; H, 2.22; N, 5.65.

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New Synthesis of 5*H*-Pyrrolo[3,2-*d*]pyrimidines via Pyrimido[5,4-*c*]pyridazines[1]

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A new, practical synthesis of 5*H*-pyrrolo[3,2-*d*]pyrimidines (**5, 8,** and **15**) from 6-methyl-5-phenylazopyrimidines (**1, 6,** and **12,** respectively) is described. The method involves conversion of the pyrimidines to the intermediate pyrimido[5,4-c]pyridazines (**4, 7,** and **14**) by treatment with formylating agents such as *tert*-butoxybis(dimethylamino)methane (BBDM). Hydrogenolytic ring contractions to the 5*H*-pyrrolo[3,2-*d*]pyrimidines complete the sequence. Two other methods related to this conversion are also discussed.

The recently demonstrated antitumor activity of some pyrazolo[1,5-*a*]-1,3,5-triazine C-nucleosides[2] which are synthetic isosteres of common naturally occuring purine nucleosides has induced us to undertake the synthesis of the corresponding 5*H*-pyrrolo[3,2-*d*]pyrimidine C-nucleosides which are also isosteres of these natural metabolites. We describe herein some synthetic model studies which were developed specifically for their applicability to the preparation of potentially active C-nucleoside analogues.

A survey of methods for the preparation of 5*H*-pyrrolo[3,2-*d*]pyrimidines has appeared recently.[3] From these and other reported syntheses[4] we can classify the strategic approaches to this heterobicyclic system into three broad categories: (a) from pyrimidines substituted at C-5 by a nitro group which facilitates the nucleophilic substitution of a C-4 chloro group by a suitable carbon nucleophile,[5,6] or (b) from a 5-acylamino-4-methylpyrimidine by application of the Madelung indole synthesis utilizing strong base at high temperatures,[7] or (c) from a 4-methyl-5-nitropyrimidine by condensation of the methyl group with diethyl oxalate,[8] substituted benzaldehydes,[9] or activated DMF derivatives[4b] followed by reduction of the nitro group and concomitant ring closure.

Of all three general strategies, the last seemed most applicable to the synthesis of C-7 ribosylated 5*H*-pyrrolo[3,2-*d*]-pyrimidines. Of particular relevance to this study was the reported use of DMF–dimethyl acetal or DMF–dimethyl sulfate complex for the conversion of 5-nitro-1,3,6-trimethyluracil to a 6-(2-dimethylaminovinyl) derivative which afforded the 5*H*-pyrrolo[3,2-*d*]pyrimidine by hydrogenation of the nitro group.[4b] Applicability of this procedure to the C-nucleosides however seemed doubtful in view of the unstable nature of the ribofuranosyl entity (which probably would contain an acid labile group) to the generally harsh conditions necessary for the nitration of pyrimidines[10] and also because of the reported ability of DMF–dimethyl acetal to methylate the relatively acidic NH groups of pyrimidines (thus leading to unwanted N-1 and N-3 dimethylated 5*H*-pyrrolo[3,2-*d*]pyrimidines).[11]

The possible utilization of a 5-arylazo group in lieu of a 5-nitro radical was therefore considered since arylazo groups can generally be introduced in pyrimidines under relatively mild conditions either at the diacyl stage of their primary synthesis or at the pyrimidine stage itself.[10,12] Furthermore, the electron-withdrawing effect of this group could be readily modulated by suitable choice of its phenyl substituents. Utilization of *tert*-butoxybis(dimethylamino)methane (BBDM)[13] which has been reported to formylate activated methylene groups[14] was also considered as a possible substitute for DMF–dimethyl acetal.

Treatment of 6-methyl-4-oxo-5-phenylazo-2-thioxo-1*H*,3*H*-pyrimidine (**1**) with BBDM in hot, dry DMF overnight afforded unexpectedly 6-dimethylamino-8-oxo-2-phenylpyrimido[5,4-c]pyridazine (**4**) as a major product (52% yield) together with a small amount of 2-dimethylamino-6-methyl-4-oxo-3*H*-pyrimidine[12] (**2**, <10%). By careful TLC monitoring of the reaction it was found that **2** was readily formed as a primary product which was slowly converted to the final product **4** (as shown in Scheme I) presumably via the short-lived intermediate **3**. Further evidence for this proposed sequence was obtained from the conversion of **2** to **4** in 76% yield by treatment with BBDM under the conditions described above. This cyclization of **2** to **4** is reminiscent of the recently reported conversion of 3-amino-4-phenylazophenol to a 6-oxo-2-phenyl-1,2,4-benzotriazine by treatment with ethyl orthoformate[15] which, like BBDM, is also a formylating agent. The identities of **2** and **4** were established by ^{1}H NMR data and by elemental analyses. The unexpected formation of **2** could be best explained by initial alkylation of the thioxo group with BBDM followed by displacement of the S-alkyl radical by dimethylamine (possibly produced during the alkylation step or from partial degradation of BBDM in hot DMF[13]).

Hydrogenation of the pyrimidopyridazine **4** over Pd/C in glacial acetic acid afforded 2-dimethylamino-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (**5**) in 78% yield. Reduction of **4** with Raney nickel in ethanol gave the same product in lower yields. Identity of **5** was confirmed on the basis of ^{1}H NMR data, elemental analysis, and the close resemblance of its ultraviolet data with that of the known 2-amino derivative **15**.[16] This reductive ring contraction necessarily involves three steps: (a) hydrogenolytic cleavage of the N_1–N_2 bond, (b) an additional hydrogenating step, and (c) ring closure to **5** with simultaneous liberation of aniline. The exact order of these events (each of which could involve a large number of postulable intermediates) is uncertain.

Similarly, treatment of 6-methyl-5-phenylazouracil **6** with BBDM in DMF afforded the now-expected pyrimido[5,4-c]pyridazine **7** which was converted by hydrogenolysis to the known 2,4-dioxo-1*H*,3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (**8**).[16,17] Application of this procedure to 6-methyl-5-phenylazoisocytosine (**12**) afforded pyrimido[5,4-*c*]pyridazine **13** as an N^6-dimethylaminomethylene derivative, which was readily unblocked by treatment with ammonium hydroxide[11] to afford **14**. Hydrogenolysis of **14** over Pd/C in acetic acid afforded the desired 2-amino-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (**15**).[16]

Various modifications of this general procedure have been investigated to further extend the flexibility of this approach to the synthesis of 5*H*-pyrrolo-[3,2-*d*]pyrimidines. Because the use of BBDM for cyclization to the pyridazines involves strongly basic conditions it was of interest to explore the use of other formylating reagents under different conditions. Thus, treatment of **12** with triethyl orthoformate at room

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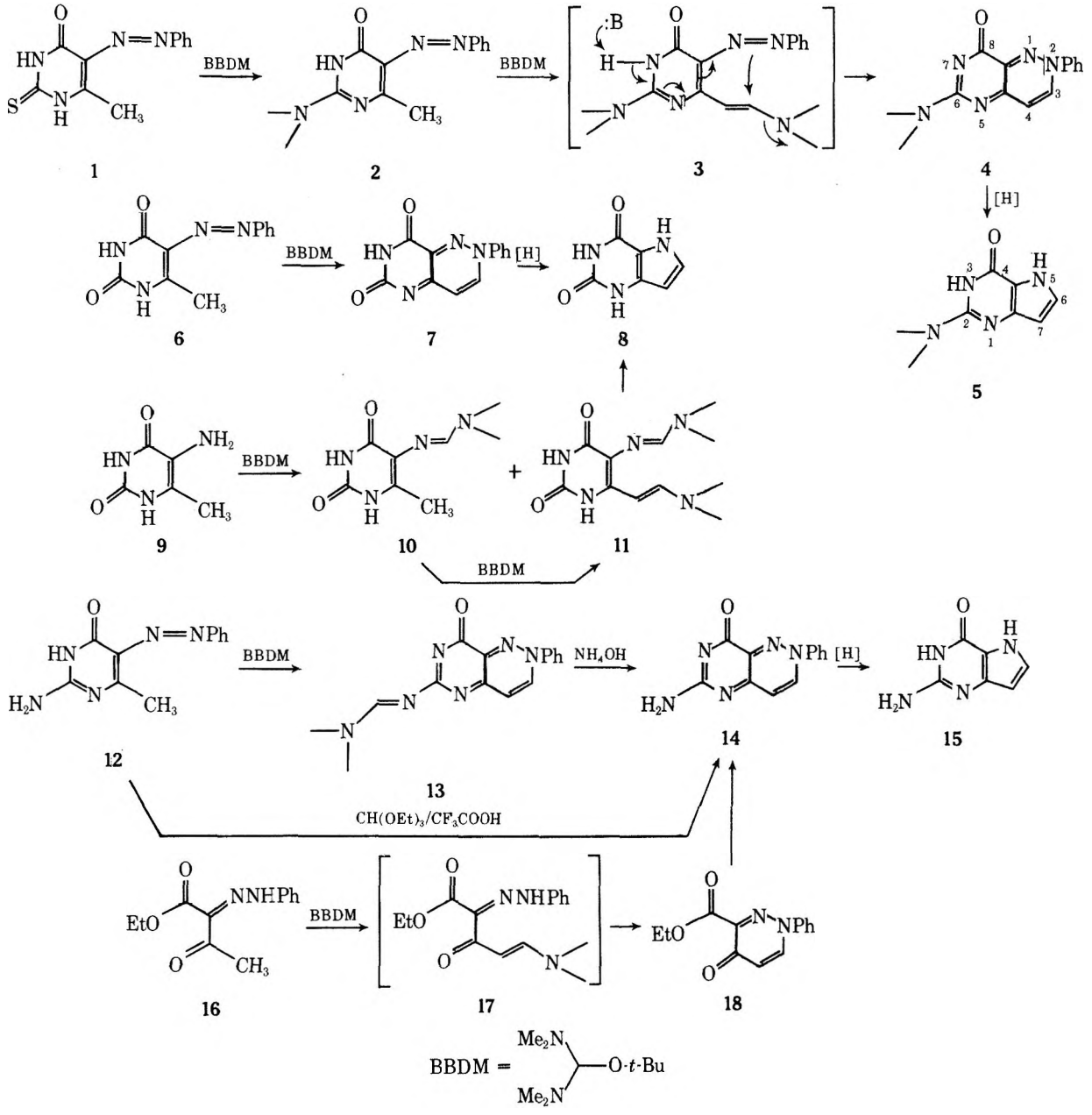
Scheme I



temperature in the presence of trifluoroacetic acid afforded directly pyrimido[5,4-c]pyridazine **14**, which was isolated as its trifluoroacetate salt in 87% yield.

While all methods described so far involve the initial elaboration of a pyrimidine ring followed by cyclization of the pyridazine ring to give the pyrimido[5,4-c]pyridazine system, it is possible to invert this sequence. Thus, pyrimido[5,4-c]-pyridazine **14** was also obtained from 2-phenylazoacetoacetate **16** (a possible synthetic precursor of all phenylazopyrimidines **1**, **6**, and **12**[10]) by reaction with BBDM to afford oxopyridazine **18** (presumably via intermediate **17**) in 87% yield. Subsequent treatment of **18** with guanidine carbonate in refluxing ethanol afforded **14** in 85% yield. Several attempts to obtain satisfactory yields of a 6-thioxo- or 6-methylthiopyrimidopyridazine by cyclization of **18** with thiourea or *S*-methylisothiourea have been so far unsuccessful.

Another possible alternate route to the 5*H*-pyrrolo[3,2-*d*]pyrimidine system was explored by reaction of 5-amino-6-methyluracil (**9**) (which is readily available from reduction of **6**) with an excess of BBDM in DMF. Initial conversion of **9** to the 5-*N*-dimethylaminomethylene derivative **10** occurred at room temperature.[11] Higher temperatures and longer reaction times however were necessary to convert **10** to the desired dimethylaminovinyl derivative **11**. Even under such forcing conditions the reaction yielded only equal amounts of **10** and **11**. After separation, product **11** could be readily converted to **8** in 88% yield by treatment with ammonium hydroxide at room temperature. The intermediate formed in conversion **11** → **8** presumably would be the corresponding 5-amino-6-(2-dimethylaminovinyl) derivative which would spontaneously ring close to **11** by attack of the free 5-NH_2 group on the vinylic function with liberation of dimethylamine.

One interesting physical property common to all pyrimido[5,4-c]pyridazines (**4**, **7**, **13**, and **14**) described in this investigation is the characteristic fluorescence they emit when spotted on silica gel plates illuminated by near ultraviolet light. This property facilitated considerably the visual detection and identification of these intermediates. Another common feature to these pyrimidopyridazines is the appearance of a pair of doublets ($\delta_{H\text{-}3}$ ~9.2, $\delta_{H\text{-}4}$ ~7.4, and $J_{3,4}$ = 7.1–7.6 Hz) in their ^1H NMR spectra. The ^1H NMR of the corresponding pyrrolopyrimidines **5**, **8**, and **15** on the other hand exhibit two apparent triplets caused by additional

coupling with the pyrrolo-NH group ($\delta_{H\text{-}6} \sim 7.2$, $\delta_{H\text{-}7} \sim 6.0$ and $J_{6,7} \sim J_{6,NH} \sim J_{7,NH} \sim 2.7$ Hz).

It is apparent from these model studies that the utilization of 6-alkyl-5-arylazopyrimidines (or of their synthetic precursors) in conjunction with various formylating agents can serve as a simple and versatile synthetic route to 5*H*-pyrrolo[3,2-*d*]pyrimidine systems.

Further investigations of the scope of the transformations described above and of their direct application to the synthesis of 7-ribosylpyrrolo[3,2-*d*]pyrimidine C-nucleosides are now underway in our laboratory and will be the subject of a separate report.

Experimental Section

General Procedures. Melting points were determined with a Thomas-Hoover apparatus and are uncorrected. The ^{1}H NMR spectra were obtained with a Jeol PS-100 spectrometer with Me_4Si as internal standard; ultraviolet and visible absorption data were determined with a Varian Super-Scan 3 ultraviolet–visible spectrophotometer. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Thin layer chromatography (TLC) was performed on microscope slides coated with Merck silica gel GF-254 and the components were visualized either by UV and visible absorption or in an iodine vapor tank. Column chromatography was performed on Woelm silica gel (70–230 mesh).

6-*N*-Dimethylamino-8-oxo-2-phenylpyrimido[5,4-*c*]pyridazine (4) and 2-*N*-dimethylamino-6-methyl-4-oxo-3*H*-5-phenylazopyrimidine (2). To a solution of 1[12] (1.23 g, 10 mmol) in DMF (10 mL, dried over molecular sieve 4 Å) was added BBDM (5 mL). The reaction mixture was stirred for 16 h at 60–65 °C and then cooled in an ice bath. The resulting precipitate was collected by filtration and washed with DMF to afford crude product 4 (0 8 g, 52%) as a chromatographically homogeneous yellow solid. One recrystallization from DMF afforded the analytical sample: mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.18 (s, 3 H, NCH_3), 3.28 (s, 3 H, NCH_3), 7.44 (d, 1 H, H-4, $J_{3,4}$ = 7.6 Hz), 7.48–7.92 (m, 5 H, C_6H_5), 9.16 (d, 1 H, H-3); UV (pH 1) λ_{max} 202 (ϵ 20 810), 272 (9 460), 344 (sh) (17 840), 379 nm (21 890), λ_{min} 244 (ϵ 5 140), 298 nm (6 490); (pH 7) λ_{max} 204 (ϵ 24 600), 309 (12 970), 390 nm (19 730), λ_{min} 246 (ϵ 4 860), 337 nm (9 460); (pH 13) λ_{max} 219 (ϵ 17 300), 309 (12 430), 390 nm (19 180), λ_{min} 246 (ϵ 4 860), 337 nm (ϵ 9 730). Anal. Calcd for $C_{14}H_{13}N_5O$: C, 62.91; H, 4.90; N, 26.20. Found: C, 62.81; H, 4.81; N, 26.03.

To the filtrate and DMF washing was added some crushed ice. Product 2 (25 mg) precipitated as orange needles which were recrystallized from DMF–H_2O to afford the analytical sample: mp 168 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.56 (s, 3 H, CH_3), 3.18 (s, 3 H, NCH_3), 3.29 (s, 3 H, NCH_3), 7.26–7.74 (m, 5 H, C_6H_5), 11.48 (broad s, 1 H, NH exchange with D_2O). Anal. Calcd for $C_{13}H_{15}N_5O$: C, 60.69; H, 5.88; N, 27.22. Found: C, 60.75; H, 5.71; N, 27.26.

Compound 2 was converted to 4 in 76% yield according to the procedure described above for the preparation of 4 from 1.

2-*N*-Dimethylamino-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (5). A solution of 4 (534 mg, 2 mmol) in 10 mL of glacial acetic acid was hydrogenated in the presence of 10% Pd/C at room temperature and atmospheric pressure for 5 h and then filtered through Celite. The filtrate was evaporated in vacuo, methanol (2 mL) was added to the residue, and the insoluble material was collected and washed with a small amount of ethyl ether to afford 5 (274 mg, 78%) as a white, chromatographically homogenous solid. Recrystallization from hot methanol afforded an analytical sample of 5 as colorless prisms: mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.98 (s, 6 H, $N(CH_3)_2$), 6.03 (t, 1 H, H-7, $J_{7,6}$ = 2.8, $J_{7,NH} \sim 2.7$ Hz), 7.16 (t, 1 H, H-6, $J_{6,NH} \sim 2.7$ Hz), 10.58 (broad s, 1 H, NH exchange with D_2O), 11.45 (broad s, 1 H, NH exchange with D_2O); UV (pH 1) λ_{max} 238 (ϵ 23 390), 272 nm (13 930), λ_{min} 256 nm (ϵ 11 430); (pH 7) λ_{max} 230 (ϵ 28 040), 263 (8 750) 282 nm (9 290), λ_{min} 254 nm (ϵ 8 570); (pH 13) λ_{max} 232 (ϵ 27 320) 295 nm (5 180), λ_{min} 275 nm (4 110). Anal. Calcd for $C_8H_{10}N_4O$: C, 53.92; H, 5.66; N, 31.44. Found: C, 53.84; H, 5.60; N, 31.43.

6,8-Dioxo-7*H*-2-phenylpyrimido[5,4-*c*]pyridazine (7). A mixture of 6[12] (1.7 g 7.4 mmol) and BBDM (7 mL) in dry DMF (20 mL) was heated at 60–65 °C for 16 h and evaporated in vacuo. The residue was triturated with ethanol and the suspension was chilled in an ice bath. The yellow precipitate was collected and washed with ethyl ether to give 7 (1.38 g, 78%). An analytical sample was obtained after recrystallization from DMF: mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 7.38 (d, 1 H, H-4, $J_{3,4}$ = 7.3 Hz), 7.59–7.90 (m, 5 H, C_6H_5), 9.12 (d, 1 H, H-3), 11.32 (s, 1 H, NH exchange with D_2O); UV (pH 1) λ_{max} 203 (ϵ 19 510), 306 (shoulder) (9 150), 330 nm (10 490), λ_{min} 286 nm (ϵ 5 370); (pH 7) λ_{max} 205 (ϵ 20 240), 263 (8 290), 324 (12 680), 363 nm (14 880), λ_{min} 240 (ϵ 6 340), 286 (6 590), 336 nm (12 200); (pH 13) λ_{max} 218 (ϵ 10 000), 291 (17 810), 366 nm (12 440), λ_{min} 249 (ϵ 4 150), 320 nm (8 780). Anal. Calcd for $C_{12}H_8N_4O_2$: C, 60.00; H, 3.36; N, 23.32. Found: C, 59.82; H, 3.46; N, 23.39.

2,4-Dioxo-1*H*,3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (8). A solution of 7 (394 mg, 1.6 mmol) in glacial acetic acid (10 mL) was hydrogenated over 10% Pd/C at room temperature at atmospheric pressure for 5 h. After filtration through Celite, the clear solution was evaporated in vacuo and the residue was triturated with a small amount of ethanol. Product 8 (163 mg, 62%) collected by filtration was obtained as a white solid. Recrystallization from methanol afforded an analytically pure sample as colorless needles: mp >300 °C; ^{1}H NMR (Me_2SO-d_6) δ 5.83 (t, 1 H, H-7, $J_{7,6}$ = 2.8 $J_{7,NH} \sim 2.4$ Hz), 7.13 (t, 1 H, H-6, $J_{6,NH} \sim 2.8$ Hz), 10.55, 10.73, and 11.81 (3 s, 1 H each, NH all exchange with D_2O). Anal. Calcd for $C_6H_5N_3O_2$: C, 47.69; H, 3.33; N, 27.80. Found: C, 47.54; H, 3.37; N, 27.77.

5-(*N*-dimethylaminomethylene)amino-6-methyluracil (10) and 5-(*N*-dimethylaminomethylene)amino-6-(2-dimethylaminovinyl)uracil (11). To a suspension of 9 (1.51 g, 10 mmol) in dry DMF (20 mL) was added BBDM (5 mL). The reaction mixture was heated, with stirring, at 60 °C for 16 h, cooled, and evaporated to dryness in vacuo. The residue was triturated with ethanol to give after filtration crude product 11 as a yellow solid. Recrystallization from ethanol afforded an analytical sample of 11 (550 mg, 21.8%) as yellow needles: mp 242 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.84 (m, 12 H, 2-$N(CH_3)_2$), 5.19 (d, 1 H, $(CH_3)_2NCH_\alpha$=CH_β, J_{CH_α,CH_β} = 13.7 Hz), 7.59 (d, 1 H, CH_α), 8.30 (s, 1 H, $(CH_3)_2NCH$=N), 9.86 and 10.42 (2 broad s, 1 H each, NH exchange with D_2O). Anal. Calcd for $C_{11}H_{17}N_5O_2$: C, 52.58; H, 6.82; N, 27.87. Found: C, 52 62; H, 6.71; N, 27.82.

The filtrate was evaporated to dryness and methanol was added to the residue. Collection of the white precipitated solid and recrystallization from methanol afforded 10 (653 mg, 33%) as prisms: mp 285 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 2.03 (s, 3 H, CCH_3), 2.85 (s, 6 H, $N(CH_3)_2$), 8.19 (s, 1 H, $(CH_3)_2NCH$=N), 10.48 and 10.85 (2 broad s, 1 H each, NH exchange with D_2O). Anal. Calcd for $C_8H_{12}N_4O_2$: C, 48.97; H, 6.16; N, 28.55. Found: C, 49.11; H, 5.84; N, 28.66.

Preparation of 8 from 11. To a solution of 11 (100 mg, 0.4 mmol) in methanol (1 mL) was added 57% NH_4OH (5 mL). The reaction mixture was warmed until it cleared and left at room temperature for 2 h. Evaporation to dryness afforded a residue which was suspended in 10 mL of methanol and briefly heated to reflux. Cooling and filtration of the solid gave 8 (28 mg) identical in all respects with authentic material. A second crop of 25 mg (88% total yield) could be obtained from the mother liquor.

6-(*N*-Dimethylaminomethylene)amino-8-oxo-2-phenylpyrimido[5,4-*c*]pyridazine (13) and 6-Amino-8-oxo-2-phenylpyrimido[5,4-*c*]pyridazine (14). To a solution of 12[12] (4.58 g, 20 mmol) in dry DMF (50 mL) was added BBDM (15 mL) and the mixture was heated for 16 h at 60–65 °C. It was then chilled in an ice bath. The formed precipitate was collected and washed with DMF to afford 13 (4.6 g, 78.4%) as a yellowish-brown solid chromatographically homogeneous: ^{1}H NMR (Me_2SO-d_6) δ 3.10 (s, 3 H, NCH_3), 3.21 (s, 3 H, NCH_3), 7.61–7.95 (m, 6 H, C_6H_5 and H-4), 8.88 (s, 1 H, $(CH_3)_2$-NCH=N), 9.25 (d, 1 H, H-3, $J_{3,4}$ = 7.1 Hz).

Without further purification, 13 (1 g) was dissolved in 50 mL of 57% NH_4OH and the solution was left at room temperature for 3 h. The yellow precipitate which had formed was filtered and washed with cold water to give 14 (0.70 g, 86%): ^{1}H NMR (Me_2SO-d_6) δ 7.34–8.00 (m, 8 H, C_6H_5, H-4 and NH_2), 9.12 (d, 1 H, H-3, $J_{3,4}$ = 7.4 Hz). Further characterization was possible by converting crude 14 to its analytically pure hydrochloride salt: mp 245 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 7.67–8.00 (m, 6 H, C_6H_5 and H-4), 8.34, 9.28, and 12.65 (3 broad s, 1 H each, NH exchange with D_2O), 9.60 (d, 1 H, H-3, $J_{3,4}$ = 7.3 Hz). Anal Calcd for $C_{12}H_9N_5O$·HCl·H_2O: C, 49.02; H, 4.08; N, 23.83; Cl, 12.08. Found: C, 49.10; H, 4.05; N, 23.83; Cl, 12.05.

2-Amino-4-oxo-3*H*,5*H*-pyrrolo[3,2-*d*]pyrimidine (15). A solution of 14 (1 g, 6.6 mmol) in glacial acetic acid (20 mL) was hydrogenated over 10% Pd/C at room temperature and atmospheric pressure for 5 h. After filtration through Celite, the solution was evaporated to dryness in vacuo. The residue was triturated with ethyl ether to afford the crude product 15 as a white solid. This was further purified by dissolving in 2 N HCl, filtering the insoluble impurities, and carefully neutralizing the clear solution with 1 N NaOH to precipitate 15 (412 mg, 68%) which was collected by filtration: ^{1}H NMR (Me_2SO-d_6) δ 6.05 (t, 1 H, H-7, $J_{7,6}$ = 2.7 Hz, $J_{7,NH} \sim 2.3$ Hz), 6.92 and 11.91 (2 broad s, 3 H, NH_2 and NH, exchange with D_2O), 7.24 (t, 1 H, H-6, $J_{6,7}$ = 2.7 Hz, $J_{6,NH} \sim 2.9$ Hz). An analytical sample was obtained by conversion to its hydrochloride salt. Anal. Calcd for $C_6H_6N_4O$·HCl: C, 38.58; H, 3.75; N, 30.01; Cl, 19.02. Found: C, 38.51; H, 3.83; N, 29.96;

Cl, 19.00.

2-Ethoxycarbonyl-4-oxo-1-phenylpyridazine (18). To a solution of ethyl 2-phenylazoacetoacetate (4.69 g, 20 mmol) in DMF (15 mL) was added BBDM (10 mL) and the mixture was heated at 70 °C overnight. The mixture was then evaporated in vacuo and the residue was chromatographed on 85 g of silica gel with petroleum ether (30–60 °C)–ethyl acetate (1:2) to give, from evaporation of the proper fractions, pyridazinone 18 as a colorless oil (4.24 g, 87%) which spontaneously crystallized on standing. Recrystallization from ethanol afforded an analytically pure sample: mp 99–100 °C; ^{1}H NMR ($CDCl_3$) δ 1.39 (t, 3 H, CH_3), 4.43 (q, 2 H, CH_2), 6.74 (d, 1 H, H-5, $J_{5,6}$ = 7.9 Hz), 7.45–7.56 (m, 5 H, C_6H_5), 8.33 (d, 1 H, H-6). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.88; H, 5.01; N, 11.39.

Preparation of 14 from 18. A mixture of 18 (3 g, 12.3 mmol), guanidine carbonate (3.3 g, 18.3 mmol), and ethanol (40 mL) was heated to reflux with stirring for 4 h and then cooled in a ice bath. The precipitate was collected and washed thoroughly with cold water to afford 14 (2.5 g, 85%) identical in all respects with an authentic sample prepared from 12 (vide supra).

Preparation of 14 from 12 with Triethyl Orthoformate. A mixture of 12 (229 mg, 1 mmol), triethyl orthoformate (5 mL), and trifluoroacetic acid (2 mL) was stirred overnight at room temperature. To the yellow suspension was added 15 mL of ethyl ether. After stirring for 20 min, the solid was collected by filtration to afford 14 (309 mg, 87.4%) as its analytically pure trifluoroacetate salt: mp >300 °C; UV (pH 1) λ_{max} 203 (ϵ 23 210), 260 (10 000), 328 (shoulder) (16 430), 362 nm (22 500), λ_{min} 241 (ϵ 8 210), 288 nm (7 500); (pH 7) λ_{max} 203 (ϵ 21 100), 292 (18 210), 376 nm (15 000), λ_{min} 247 (ϵ 3 930) 325 nm (6 790); (pH 13) 218 (ϵ 15 000), 292 (22 500), 376 nm (18 210), λ_{min} 247 (ϵ 5 000), 325 nm (8 930). Anal. Calcd for $C_{12}H_9N_5O{:}CF_3COOH$: C, 47.57; H, 2.83; N, 19.82; F, 16.14. Found: C, 47.60; H, 2.92; N, 19.90; F, 16.17.

Registry No.—1, 14985-77-4; 2, 23947-86-6; 4, 65996-47-6; 5, 65996-48-7; 6, 15020-66-3; 7, 65996-49-8; 8, 65996-50-1; 9, 6270-46-8; 10, 65996-51-2; 11, 65996-52-3; 12, 65996-53-4; 13, 65996-54-5; 14, 65996-55-6; 14 HCl, 65996-56-7; 14 CF_3COOH salt, 65996-57-8; 15, 65996-58-9; 15 HCl, 65996-59-0; 16, 5462-33-9; 18, 65996-60-3; BBDM, 5815-08-7.

References and Notes

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Notes

Synthesis of γ-Amino Alcohols

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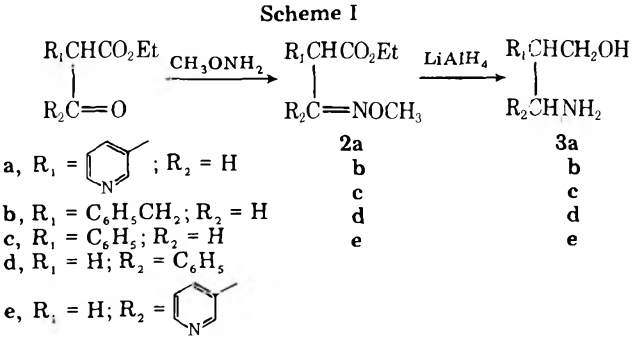
Substituted γ-amino alcohols have been of considerable interest for some time in that they frequently possess interesting pharmacological properties.[1] Their synthesis has been accomplished by a variety of procedures: addition of ammonia or amines to acrylic esters or α,β-unsaturated ketones, followed by reduction;[1b,2] reduction of α-cyano esters;[3] the reduction of isoxazoles or isoxazolines;[4] reduction of Mannich products;[5] and reaction of bromo alcohols with sodium azide followed by reduction.[6] All of these methods suffer from certain restrictions. Addition of amines to acrylates frequently leads to the formation of amides as side products. The reduction of cyano esters precludes preparation of compounds bearing a substituent α to the nitrogen. The synthesis of isoxazoles or isoxazolines is often a difficult undertaking. The Mannich reaction is restricted to the preparation of tertiary amines. Lastly the use of the azide procedure assumes the availability of the precursor bromo alcohol.

In this note we describe a new method for the synthesis of γ-amino alcohols, utilizing 1,3-dicarbonyl compounds as starting materials, which circumvents many of the problems that detract from established procedures.

The ease of preparation of α-formyl and β-keto esters makes them attractive intermediates for the synthesis of γ-amino alcohols. Unfortunately, nitrogen functionality cannot be introduced via oxime formation since the intermediate oximino ester cyclizes spontaneously to an isoxazolone which cannot be reductively cleaved.[7] Use of an alkoxime, however, avoids cyclization since a blocked oximino ester is formed which can then be reduced to give the desired amino alcohol (Scheme I).

The methoxylimine **2a** of ethyl 2-formyl-2-(3-pyridyl)-acetate (**1a**) was reduced with $LiAlH_4$ to the γ-amino alcohol

Scheme I



	2a	**3a**
1a, R_1 = 3-pyridyl; R_2 = H	**b**	**b**
	c	**c**
b, $R_1 = C_6H_5CH_2$; R_2 = H	**d**	**d**
c, $R_1 = C_6H_5$; R_2 = H	**e**	**e**
d, R_1 = H; $R_2 = C_6H_5$		
e, R_1 = H; R_2 = 3-pyridyl		

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3a in 64% overall yield from **1a**. Although $LiAlH_4$ reduction of oximes β to an aromatic ring is frequently accompanied by side products,[8] particularly aziridines, no such complication was observed in the preparation of **3a–d**. An inability to purify amino alcohol **3a** by either distillation or crystallization prompted its derivatization as the ditosylate which gave spectral data consistent with the assigned structure. The syntheses of 2-benzyl-3-amino-1-propanol (**3b**) and 2-phenyl-3-amino-1-propanol (**3c**) were also achieved by an analogous sequence in yields of 90 and 42%, respectively.

The preparation of a 3-substituted 3-amino-1-propanol was then carried out via a similar synthetic pathway using a β-keto ester as the starting material (Scheme I). Treatment of ethyl benzoylacetate (**1d**) with *O*-methylhydroxylamine hydrochloride and base gave a 75% yield of **2d**. Reduction of **2d** with $LiAlH_4$ gave a crystalline product in 79% yield with spectral data consistent with **3d**.

Application of this scheme to the 3-pyridyl β-keto ester **1e** was unsuccessful. Preparation of methoxylimine **2e** followed by its reduction under a variety of conditions led to a complex mixture of products. Treatment of the crude reaction mixture in each case with tosyl chloride and comparison of the products, using TLC, with the authentic ditosylate of **3e**[9] showed only trace amounts of material corresponding to the ditosylate of the desired amino alcohol.

In summary, we have described a two-step procedure for the preparation of substituted γ-amino alcohols from readily available starting materials.

Experimental Section

All of the melting points are uncorrected. ^1H-NMR spectra were recorded on a Varian A-60A spectrophotometer. Infrared spectra were obtained on a Perkin-Elmer No. 621 spectrophotometer. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Ethyl 2-Formyl-2-(3-pyridyl)acetate (1a). A mixture of 25 g (0.151 mol) of ethyl 3-pyridylacetate and 6.6 g (0.151 mol) of 55% NaH dispersion in 250 mL of benzene was heated under reflux for 30 min and then treated with 25 mL of ethyl formate after cooling to 15 °C. After being stirred for 1 h at 15 °C and being heated under reflux for 45 min, the solution was cooled to 5 °C and 87 mL of an ice-cold solution of dilute HCl (6.35%, 0.151 mol) was added. The separated benzene phase was concentrated to give a solid which was collected, washed with ether, and dried in vacuo to afford 23 g (80%) of **1a**, mp 121–125 °C. Recrystallization from benzene gave the analytical sample, mp 122–123 °C. This compound is relatively unstable and should be used without delay: IR (tf) 2470 (enol), 1702 cm^{-1} (ester); ^1H NMR (Me_2SO-d_6) δ 1.20 (t, 3, J = 7 Hz, CH_3), 4.13 (q, 2, J = 7 Hz, CH_2), 7.33 (m, 1, 5-PyH), 7.68 (dt, 1, J = 8, 2, 2, Hz, 4-PyH), 8.02 (s, 1, C=C*H*OH), 8.40 (dd, 1, J = 5.5, 2 Hz, 6-PyH), 8.55 (d, 1, J = 2 Hz, 2-PyH). Anal. ($C_{10}H_{11}NO_3$): C, H, N.

Ethyl 2-(3-Pyridyl)-3-methoxyliminopropionate (2a). A mixture of 36.8 g (0.44 mol) of $NaHCO_3$ and 36.2 g (0.43 mol) of *O*-methylhydroxylamine hydrochloride in 1.5 L of methanol was agitated until gas evolution ceased. The mixture was cooled to 5 °C and 81.8 g (0.42 mol) of **1a** was added. The reaction mixture was stirred for 12 h at room temperature and concentrated to a small volume under reduced pressure and the residue was distributed between water and CH_2Cl_2. The organic phase was washed with saturated $NaHCO_3$, dried ($MgSO_4$), concentrated, and distilled (114–116 °C (0.15 mm)) to give 74.0 g (78.5%) of **2a**: IR (neat) 1750 (ester), 1590, 710 cm^{-1} (pyridine). Anal. ($C_{11}H_{14}N_2O_3$): C, H, N.

2-(3-Pyridyl)-3-amino-1-propanol (3a). To a slurry of 17.45 g (0.46 mol) of $LiAlH_4$ in 1 L of 1,2-dimethoxyethane was added 22.65 g (0.10 mol) of **2a** over 2.5 h. The temperature was maintained from −5 to 0 °C during the addition. The reaction mixture was then stirred for 5 days at room temperature, cooled to 0 °C, and slowly combined with 85 mL of saturated brine. After being stirred for 4 h, the mixture was filtered and concentrated at reduced pressure and the resulting oily residue was dried by azeotroping with benzene and ethanol. After concentration, 11.50 g (74%) of crude **3a** was obtained as a viscous yellow oil.

A solution of 11.5 g (0.0755 mol) of **3a** in 115 mL of dry pyridine was cooled to 0 °C and treated with 31.7 g (0.1655 mol) of tosyl chloride. The reaction mixture was stirred at 0 °C for 22 h and then diluted with ice water. The aqueous portion was extracted with CH_2Cl_2 and the combined extracts were dried (Na_2SO_4) and concentrated to give 28.85 g (83%) of crude ditosylate, mp 150–153 °C. An analytical sample was obtained by chromatography on silica gel followed by recrystallization from acetonitrile: mp 170–170.5 °C; IR (nm) 3180 (NH), 815, 710 cm^{-1} (pyridine); ^1H NMR (Me_2SO-d_6) δ 2.36 (s, 3, CH_3), 2.40 (s, 3, CH_3), 3.02 (m, 3, CH + CH_2N), 4.26 (br d, 2, J = 4 Hz, CH_2O), 7.48 (m, 10, phenyl + 4,5-PyH), 8.30 (m, 2, 2,6-PyH). Anal. ($C_{22}H_{24}N_2O_5S_2$): C, H, N, S.

Ethyl 2-Benzyl-3-methoxyliminopropionate (2b). Ethyl 2-formylhydrocinnamate[10] (6.0 g, 29.1 mmol) was added to a stirred solution of 60 mL of dry pyridine containing 2.49 g (29.8 mmol) of *O*-methylhydroxylamine hydrochloride. The reaction mixture was heated at 70 °C for 18 h and worked up as before to give 6.73 g of crude product. Distillation (105–107 °C (0.1 mm)) gave 5.80 g (86%) of **2b**: IR (neat) 1740 (ester), 1610, 1590, 745 cm^{-1} (phenyl). Anal. ($C_{13}H_{17}NO_3$): C, H, N.

2-Benzyl-3-amino-1-propanol (3b). To a slurry of 482 mg (12.75 mmol) of $LiAlH_4$ in 50 mL of 1,2-dimethoxyethane was added 1.0 g (4.25 mmol) of **2b**. The reaction mixture was heated under reflux for 1.5 h, cooled to 0 °C, treated with 2.5 mL of saturated brine, heated at 60 °C for 1 h, and worked up as described for **3a** to give 680 mg (98%) of crude **3b**. A 316-mg sample of **3b** was treated with 173 mg of oxalic acid in 3 mL of absolute EtOH to give 372 mg (92%) of the oxalate, mp 149–150 °C (lit.[3d] mp 150–152 °C).

Ethyl 2-Phenyl-3-methoxyliminopropionate (2c). The preparation of **2c** was carried out using the procedure described for **2b** from 3.52 g (42.0 mmol) of *O*-methylhydroxylamine hydrochloride and 8.0 g (41.7 mmol) of ethyl 2-formyl-2-phenylacetate in 60 mL of pyridine. The yield of distilled (83–84 °C (0.05 mm)) product was 8.21 g (89%): IR (neat) 1740 (ester) 1605, 1590, 750 cm^{-1} (phenyl). Anal. ($C_{12}H_{15}NO_3$): C, H, N.

2-Phenyl-3-amino-1-propanol (3c). The preparation of **3c** was carried out using the procedure described for **3a** from 1.0 g (4.52 mmol) of **2c** and 513 mg (13.5 mmol) of $LiAlH_4$ in 5 mL of glyme. The crude product was isolated as its hydrochloride salt (358 mg. 42%): mp 152–153 °C; IR (nm) 3210 (OH), 1610, 1595, 755 cm^{-1} (phenyl); ^1H NMR (D_2O) δ 3.23 (m, 3, CH_2N + CH), 3.74 (br d, 2, J = 5.5 Hz, CH_2O), 7.20 (s, 5, C_6H_5). Anal. ($C_9H_{14}ClNO$): C, H, Cl, N.

Ethyl 3-Phenyl-3-methoxyliminopropionate (2d). The preparation of **2d** was carried out using the procedure described for **2b** from 880 mg (10.55 mmol) of *O*-methylhydroxylamine hydrochloride and 2.0 g (10.4 mmol) of ethyl benzoylacetate (**1d**) in 20 mL of pyridine. The yield of distilled (117–120 °C (0.1 mm)) product was 1.75 g (76%); IR (neat) 1740 (ester), 1625, 1595, 760 cm^{-1} (phenyl). Anal. ($C_{12}H_{15}NO_3$): C, H, N.

3-Amino-3-phenyl-1-propanol (3d). The preparation of **3d** was carried out using the procedure described for **3b** from 1.0 g (4.5 mmol) of **2d** and 512 mg (13.5 mmol) of $LiAlH_4$ in 25 mL of glyme. The reaction was heated under reflux for 2 h. A solid product was isolated which was recrystallized from benzene to give 540 mg (79%) of **3d**, mp 72–73 °C (lit.[2d] mp 74.5–75 °C).

Ethyl 3-(3-Pyridyl)-3-methoxyliminopropionate (2e). To a solution of 2.16 g (25.9 mmol) of *O*-methylhydroxylamine hydrochloride in 25 mL of MeOH was added 2.18 g (25.9 mmol) of $NaHCO_3$. The solution was stirred for 1 h at room temperature and then filtered. The filtrate was added to a solution of 5 g (25.9 mmol) of ethyl nicotinoylacetate[11] (**1e**) in 25 mL of MeOH at 0 °C. The reaction mixture was worked up as described for **2a** after stirring at 0 °C for 20 h and distilled (116–118 °C (0.15 mm)) to give 4.09 g (71%) of **2e**: IR (neat) 1735 (ester), 1605, 1585, 1555, 805, 705 cm^{-1} (pyridine). Anal. ($C_{11}H_{14}N_2O_3$): C, H, N.

Registry No.—**1a**, 62247-40-9; **1b**, 2016-00-4; **1c**, 17838-69-6; **1d**, 94-02-0; **1e**, 6283-81-4; *E*-**2a**, 66102-59-8; *Z*-**2a**, 66102-60-1; *E*-**2b**, 66102-61-2; *Z*-**2b**, 66102-62-3; *E*-**2c**, 66102-63-4; *Z*-**2c**, 66102-64-5; *E*-**2d**, 66102-65-6; *Z*-**2d**, 66102-66-7; *E*-**2e**, 66102-67-8; *Z*-**2e**, 66102-68-9; **3a**, 62247-29-4; **3a** ditosylate, 62247-30-7; **3b**, 66102-69-0; **3b** oxalate, 66102-70-3; **3c** HCl, 21464-48-2; **3d**, 14593-04-5; ethyl 3-pyridylacetate, 39931-77-6; ethyl formate, 109-94-4; *o*-methylhydroxyamine hydrochloride, 593-56-6.

Supplementary Material Available: Full NMR data for compounds **2a–e** (2 pages). Ordering information is given on the masthead page.

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Transformations of *N*-Hydroxyimides.[1] Mechanistic Aspects of the Reaction between *N*-Hydroxyimides, Phenols, Diethyl Azodicarboxylate, and Triphenylphosphine

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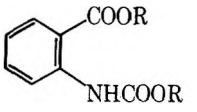
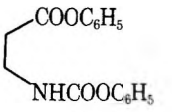
Recently it has been shown that the reaction of alcohols with *N*-hydroxyphthalimide in the presence of equimolar amounts of diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP) leads to *N*-alkoxyphthalimides.[1a] Under the same conditions alcohols react with phenols to give alkyl aryl ethers.[2] These observations suggested the possibility of a direct route to *N*-aryloxyphthalimides through arylation of *N*-hydroxyphthalimide with phenols. In this paper we present our studies on the reactions of *N*-hydroxyphthalimide and *N*-hydroxysuccinimide with phenols in the presence of DEAD and TPP.

As a result of the reaction of equimolar amounts of *N*-hydroxyphthalimide, phenol, DEAD, and TPP in tetrahydrofuran as solvent, instead of the expected *N*-phenoxyphthalimide, we obtained phenyl *N*-phenoxycarbonylanthranilate **1**, whose properties (cf. Table I and Experimental Section) were identical with those of a substance obtained earlier in the reaction of *N*-hydroxyphthalimide-*O*-triflate with sodium phenoxide.[3] Likewise, phenyl *N*-phenoxycarbonyl-β-alanate **5** obtained in this laboratory displayed identical properties with those of the compound described by Chapman.[3] Compounds **2**, **3**, and **4** were also obtained by the above procedure.

Under conditions of equimolar amounts of substrates the reaction yield did not exceed 30%; this became understandable after the structure of products had been established. When the proportion of substrates was changed so that per 1 mol of *N*-hydroxyimide, 1 mol of DEAD, 1 mol of TPP, and 2 mol of phenol were used, the reaction yields increased about twofold (Table I). We suggest the reaction mechanism in Scheme I.

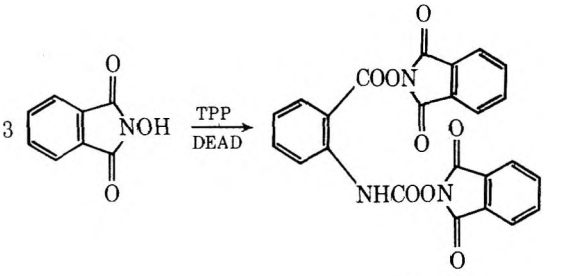


1, R = C_6H_5
2, R = p-$C_6H_4CH_3$
3, R = p-$C_6H_4OCH_3$
4, R = p-C_6H_4Br



5

At the first stage betaine I, postulated by Morrison,[4] is formed and gives with *N*-hydroxyphthalimide present in the reaction mixture ion pair II. We postulate an equilibrium between ion pairs II and III;[5] this postulate is based on our earlier observations of the properties of *N*-hydroxyphthalimide which in the presence of other reagents in the discussed type of reaction plays the part of a nucleophilic agent (e.g., in the reaction with alcohols[1a]) or of a electrophilic agent (e.g., in the reaction with carboxylic acids[1c]). Such a nature of *N*-hydroxyphthalimide was confirmed experimentally; namely, the reaction of *N*-hydroxyphthalimide (3 mol) with DEAD (1 mol) and TPP (1 mol) afforded **6** in high yield.



6

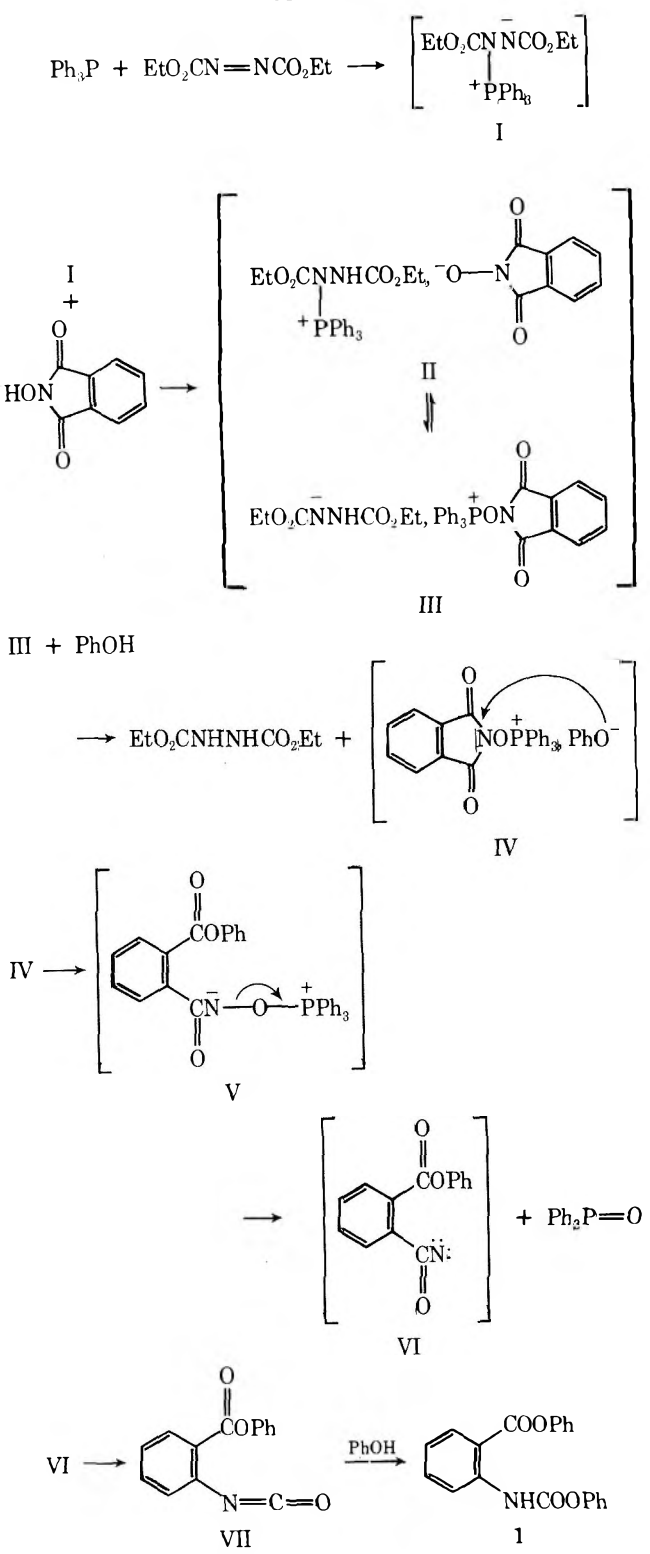
At the next stage of the suggested mechanism, as a result of reaction with a phenol molecule, ion pair III is transformed into a new ion pair IV accompanied by formation of a molecule of diethyl hydrazodicarboxylate. Subsequently the phenolate anion attacks the carbonyl group, thus causing the opening of the imide ring, Lossen rearrangement to isocyanate, and reaction with the second molecule of phenol. The results of the reaction confirm that $OPPh_3$ is a very good leaving group (cf. structure V), being transformed into the neutral molecule of phosphine oxide. All our observations supporting the proposed reaction mechanism are in agreement[7] with the results of Chapman obtained for the nucleophilic reactions of *N*-hydroxyimide-*O*-triflates[3] and with the results of Bittner concerning the Lossen rearrangement of hydroxamic acids in the presence of betaine I.[6] In addition, it has to be stressed that the occurrence of steric hindrance in phenols either greatly

Table I. Products of the Title Reactions

Compd	Registry no.	Yield, %	Mp, °C	Anal., % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
1	33067-24-2	69	95–96	72.1	4.5	4.2	72.2	4.6	4.4
2	65956-55-0	75	147–148	73.1	5.3	3.9	73.1	5.3	3.9
3	65956-56-1	72	123–124	67.1	4.9	3.6	66.7	4.9	3.6
4	65956-57-2	68	155–156	48.9	2.7	2.9	48.8	2.8	3.0
5	41580-56-7	75	82–83	67.4	5.3	4.9	67.5	5.4	4.8
6	65956-58-3	61	192–193	61.2	2.8	8.9	61.2	2.7	8.9

0022-3263/78/1943-2541$01.00/0

Scheme I



limits their reactivity (in case of 2,4-xylenol the reaction yield is much decreased) or it renders them completely unreactive (e.g., 2,6-di-*tert*-butyl-4-methylphenol); this behavior is quite clear in the light of the proposed mechanism.

Experimental Section

General. Melting points are uncorrected. Infrared spectra were obtained as KBr disks with a Unicam SP-200 spectrophotometer. ^{1}H-NMR spectra were recorded with a Jeol JNM-4H-100 spectrometer for $CDCl_3$ solutions (δ scale, Me_4Si = 0 ppm), silica gel G Merck was used for TLC, and silica gel 100–200 mesh Macherey-Nagel was used for column chromatography.

Phenyl *N*-Phenoxycarbonylanthranilate (1). A solution of *N*-hydroxyphthalimide (326 mg, 2 mmol), phenol (376 mg, 4 mmol), and TPP (524 mg, 2 mmol) in 10 mL of THF was treated with 380 mg (2.2 mmol) of DEAD and left overnight at room temperature. The solvent was evaporated in vacuo, and the residue was chromatographed on silica gel column with a mixture of benzene and ether (9:1 v/v) as eluent affording 460 mg (69%) of **1**: IR 3300, 3050, 1740, 1700, 1250–1130 cm^{-1}; ^{1}H NMR (δ 7.05–7.75 (complex, 12 H, aromatic), 8.25 (dd, 1 H, J_1 = 1.5 Hz, J_2 = 8.0 Hz, aromatic), 8.6 (d, 1 H, J_3 = 7.5 Hz, aromatic), 10.8 (s, 1 H, NH).

The compounds **2, 3, 4, 5,** and **6** were obtained in the same manner.

***p*-Methylphenyl *N*-*p*-Methylphenoxycarbonylanthranilate (2):** IR 3300, 3050, 1745, 1700, 1260–1130 cm^{-1}; ^{1}H NMR δ 2.35, 2.4 (2s, 6 H, $2CH_3$), 6.95–7.35 (complex, 9 H, aromatic), 7.6 (t, 1 H, J_1 = 7.5 Hz, aromatic), 8.3 (dd, 1 H, J_2 = 1.5 Hz, J_3 = 8.0 Hz, aromatic), 8.55 (d, 1 H, J_4 = 7.5 Hz, aromatic), 10.6 (s, 1 H, NH).

***p*-Methoxyphenyl *N*-*p*-Methoxyphenoxycarbonylanthranilate (3):** IR 3350, 3020, 1760, 1695, 1260–1140 cm^{-1}; ^{1}H NMR δ 3.8, 3.85 (2s, 6 H, $2OCH_3$), 6.85–7.4 (complex, 9 H, aromatic), 7.6 (t, 1 H, J_1 = 7.5 Hz, aromatic), 8.3 (dd, 1 H, J_2 = 1.5 Hz, J_3 = 8.0 Hz, aromatic), 10.7 (s, 1 H, NH).

***p*-Bromophenyl *N*-*p*-Bromophenoxycarbonylanthranilate (4):** IR 3350, 3100, 1755, 1700, 1255–1130 cm^{-1}; ^{1}H NMR δ 7.0–7.8 (complex, 10 H, aromatic), 8.3 (dd, 1 H, $J_1 \sim 1.0$ Hz, J_2 = 8.0 Hz, aromatic), 8.55 (d, 1 H, J_3 = 7.5 Hz, aromatic), 10.5 (s, 1 H, NH).

Phenyl *N*-Phenoxycarbonyl-β-alaninate (5): IR 3300, 3050, 1745, 1720, 1695, 1280–1150 cm^{-1}; ^{1}H NMR δ 2.8 (t, 2 H, $J_1 = J_2$ = 7.5 Hz, CCH_2O), 3.6 (q, 2 H, J_3 = 7.5 Hz, CCH_2N), 5.7 (broad t, 1 H, NH), 6.9–7.55 (complex, 10 H, aromatic).

Phthalimidyl *N*-Phthalimidoxycarbonylanthranilate (6): IR 3300, 3050, 1810, 1795, 1745, 1250–1130 cm^{-1}; ^{1}H NMR δ 7.5–8.1 (complex, 10 H, aromatic), 8.33 (dd, 1 H, $J_1 \sim 1.0$ Hz, J_2 = 8.0 Hz, aromatic), 8.4 (d, 1 H, J_3 = 7.5 Hz, aromatic), 10.3 (s, 1 H, NH).

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Registry No.—DEAD, 1972-28-7; TPP, 603-35-0; *N*-hydroxyphthalimide, 524-38-9; *N*-hydroxysuccinimide, 6066-82-6; phenol, 108-95-2; *p*-methoxyphenol, 150-76-5; *p*-methylphenol, 106-44-5; *p*-bromophenol, 106-41-2.

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Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy. Furazans and Related Systems[1]

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Introduction

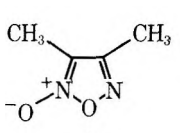
In the past few years, nitrogen-15 nuclear magnetic resonance spectroscopy, ^{15}N NMR, has shown considerable utility in solving organic structural problems.[2-4] A particular advantage of ^{15}N NMR is the large range of chemical shifts and

Table I. Nitrogen-15 NMR Resonances[a] for Furazans and Related Compounds

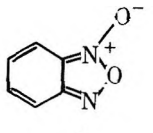
Registry no.	Compd	Solvent (concn)	^{15}N shift			^{14}N shift[b]
2518-42-5	1	Acetone (20% v/v)	+7.0		+19.1	+23[c]
		Trifluoroethanol (20% v/v)	+7.9		+21.7	
		Trifluoroacetic acid (20% v/v)	+6.3		+25.3	
480-96-6	2	Acetone (2 M); at +55 °C		+5.0		+26[d]
		Acetone (2 M); at −10 °C	−1.7		+11.8	
4975-21-7	3	Acetone (20% v/v)		−31.0		−26[c]
		Trifluoroethanol (20% v/v)		−24.5		
		Trifluoroacetic acid (20% v/v)		−13.0		
273-09-6	4	Acetone (2 M)		−42.5		−28[d]
		Trifluoroethanol (2 M)		−35.9		
		Trifluoroacetic acid (2 M)		−28.5		
273-13-2	5	Acetone (2 M)		+43.4		
		Dimethyl sulfoxide (2 M)		+44.3		
		Trifluoroethanol (2 M)		+54.4		
		Trifluoroacetic acid (2 M)		+66.1		
273-15-4	6	Acetone (2 M)		+0.8		
		Trifluoroethanol (2 M)		+19.3		
		Trifluoroacetic acid (2 M)		+62.5		
6766-90-1	7	Dimethyl sulfoxide (2 M)		+83.1		
	8	Dimethyl sulfoxide (2 M)		+113.7		

[a] In parts per million from external nitric acid (1 M 98% ^{15}N-enriched nitric acid in D_2O); positive shifts are upfield. [b] From G. Englert, *Z. Electrochem.*, **65**, 854 (1961). [c] Neat. [d] In CH_2Cl_2.

the general sensitivity of these shifts to structural changes. In this paper, we report on the insight that high-resolution ^{15}N NMR offers as to the electronic effects operating in compounds **1–8.**



1



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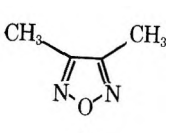
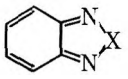
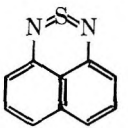


3



4, X = O
5, X = S
6, X = Se



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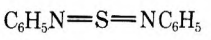


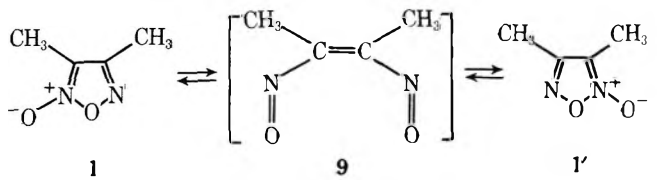
8

Although there presently appears to be no published ^{15}N NMR data on **1–8**, the ^{14}N NMR spectra of some of them have already been reported.[5] The problem with ^{14}N NMR is that nitrogen-14 has a larger nuclear quadrupole moment, which often results in large line widths and consequent uncertainties in chemical-shift measurements. In some cases, as will be shown later in this paper, these uncertainties may be greater than the chemical-shift differences which are of interest.

Results and Discussion

Nitrogen-15 chemical shifts of compounds **1–8** in various solvents, together with the extant ^{14}N NMR data, are given in Table I. These shifts will be seen to cover a relatively large range and to display rather substantial solvent dependencies.

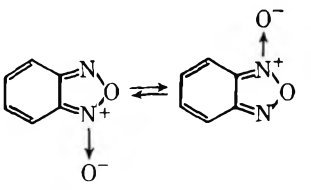
Dimethylfurazan 2-oxide (**1**) in acetone shows two resonances about 12 ppm apart at room temperature. The free energy of activation ($\Delta G^{\ddagger}$) for valence tautomerism of **1**, presumably by way of the dinitrosoalkene **9**, is known from many studies to be 34 kcal/mol,[6] and two different ^{15}N resonances are expected. The lower field ^{15}N resonance of **1** is almost insensitive to the nature of the solvent used, while the higher field line moves to still higher fields by 2.6 and 6.2 ppm in 2,2,2-trifluoroethanol and trifluoroacetic acid, respectively. Because the ^{15}N resonance of dimethylfurazan (**3**) is also solvent dependent (see Table I), the resonance at +19.1 ppm has been assigned to the nitrogen atom with the lone pair of electrons, and the resonance at +7.0 ppm to the *N*-oxide nitrogen of **1.**



1 **9** **1′**

The ^{15}N NMR of a 2 M solution of benzofurazan 1-oxide (**2**) in acetone at room temperature did not give a usable signal, even after a 20 h accumulation of free-induction decays. The other compounds reported here usually gave useful spectra after 2–3 h under the same conditions. When the temperature was raised to about 55 °C, a relatively broad line appeared at 5 ppm upfield from the nitric acid resonance. Lowering the temperature to about −10 °C results in two fairly sharp resonances equally spaced from the line observed at high temperature. The separation between the two resonances of **2** at −10 °C in acetone (13.5 ppm) was a little larger than that found for **1.**

Observation of two different resonances for benzofurazan 1-oxide below 0 °C is in agreement with the unsymmetrical structure, as indicated by much other physical data.[7] The free-energy barrier for valence tautomerism of benzofurazan 1-oxide (**2a** ⇌ **2b**) has been reported from many NMR measurements to be 14 kcal/mol.[7] This $\Delta G^{\ddagger}$, in combination with the chemical-shift difference of the two ^{15}N resonances of **2** at −10 °C, gives a predicted coalescence temperature of about 20 °C, which is in full accord with our observations.



2a **2b**

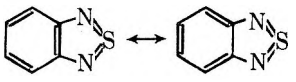
The lower field ^{15}N resonance of **2** was assigned to the *N*-oxide nitrogen by analogy with **1.**

The ^{15}N chemical shifts of **1** and **2** are at about 45 ppm higher field than those of dimethylfurazan and benzofurazan in the same solvent (see Table I). Comparable upfield shifts for ^{15}N resonance of pyridines upon N-oxidation have also been observed.[8]

Furazans and furazan oxides are weak bases (the pK_a values of **2** and **4** are −8.3 and −8.4, respectively[9]) and are not protonated in trifluoroacetic acid ($pK_a = -2.5$[10]), but are expected to be extensively hydrogen bonded to this solvent. The relatively small solvent shifts (6–18 ppm) observed for **1–4** are in agreement with this conclusion. The influence of trifluoroacetic acid on the ^{15}N chemical shift of 2,1,3-benzothiadiazole (**5**) is only slightly larger than that observed for compounds **1–4**. On the other hand, substantial upfield shifts are observed for the ^{15}N resonance of 2,1,3-benzoselenadiazole (**6**) in trifluoroethanol and trifluoroacetic acid (18.5 and 61.7 ppm, respectively). The solvent shift of 61.7 ppm observed in trifluoroacetic acid seems to be too large to be accounted for by hydrogen bonding and therefore is attributed to protonation.

Replacement of the oxygen in benzofurazan by sulfur to give 2,1,3-benzothiadiazole (**5**) leads to a large upfield shift of about 85 ppm. Interestingly, the ^{15}N chemical shift of 2,1,3-benzoselenadiazole (**6**) appears only 43 ppm upfield from that of benzofurazan. The unexpectedly high-field position of the ^{15}N resonance of **5** indicates that the type of bonding between sulfur and nitrogen may well be different from that between oxygen and nitrogen (and selenium and nitrogen as well). Participation of 3d orbitals of sulfur to form sulfur diimide type resonance structures **5a** and **5b** is one possible explanation. Similar resonance is highly unlikely for benzofurazan, and the 4d orbitals of selenium may not be easily involved (because of the large difference in sizes of nitrogen and selenium orbitals) for this type of π bonding.

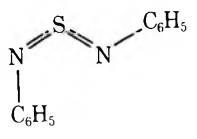
To help determine the importance of resonance structures **5a** and **5b** for 2,1,3-benzothiadiazole (**5**), we have obtained ^{15}N



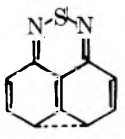
5a **5b**

NMR spectra of two sulfur diimides, namely naphtho[1,8-*cd*][1,2,6]thiadiazine-2-S^{IV} (**7**) and *N,N'*-diphenylsulfur diimide (**8**) (see Table I). The ^{15}N chemical shifts of **7** and **8** are at even higher fields than those of **4**, which lends support to the postulation of the sulfur diimide type resonance forms **5a** and **5b**.

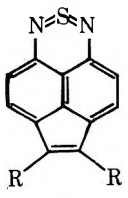
N,N'-Diphenylsulfur diimide (**8**) is known from dynamic NMR spectroscopy to have an unsymmetrical structure (**8a**), and the free-energy barrier ($\Delta G^{\ddagger}$) for its symmetrization is only about 11 kcal/mol.[11] Thus, at room temperature, the time-averaged ^{15}N spectrum of **8** should be observed and the single ^{15}N resonance is consistent with this conclusion. The ^{15}N chemical shift of diphenylsulfur diimide (**8**) is 30 ppm toward higher field than that of **7**. This relatively large difference may be due solely to the possibility of *Z,Z*, *Z,E*, and *E,E* configurations for **8**, but only *Z,Z* for **7**. However, it may be that resonance as exemplified by structure **7a** with a formal bond between the 4,5 carbons contributes to the hybrid and, if this is so, one might well expect a lower field ^{15}N shift for **7** than for **8**. Structure **7a** is consistent with the fact that **7** readily undergoes 1,11-cycloadditions with substances such as dimethyl acetylenedicarboxylate to give compounds of type **10**.[12]



8a



7a



10

Experimental Section

Compounds **1**,[13] **2**,[14] **3**,[15] **4**,[16] **5**,[17] **7**,[18] and **8**[19] were prepared as previously described. Compound **6** was obtained from Aldrich and used without further purification. Reagent grade acetone, dimethyl sulfoxide, trifluoroethanol, and trifluoroacetic acid were employed as solvents.

The natural-abundance ^{15}N spectra were obtained at a frequency of 18.25 MHz with a Bruker WH-180 pulse spectrometer that has been described in detail elsewhere.[20] With 25 mL of 2 M solutions in 25-mm o.d. spinning sample tubes, useful spectra could usually be obtained with accumulation times of 2–3 h, a 45° pulse angle, 4K data points, 3000-Hz spectrum width, and a pulse interval of 30 s. A 5-mm concentric tube containing a 1 M solution of 98% ^{15}N-enriched nitric acid in D_2O provided both the external reference standard and the field-frequency lock. The protons were decoupled at a power of 4 W by the gating technique.[21] The sample temperatures for normal spectra were about 30 °C. Chemical shifts are reported in parts per million from $H^{15}NO_3$ with a precision of about ±0.1 ppm.

Registry No.—(*Z,Z*)-**8**, 66085-13-0; (*Z,E*)-**8**, 66085-14-1; (*E,E*)-**8**, 66085-15-2.

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(21) Gated proton decoupling was employed to quench the NOE. In this technique, the proton decoupler is on only during data acquisition (1.3 s) following the observing pulse, and is off for a relatively long time (30 s) between the end of one data acquisition period and the start of the next.

Improvements in the Osmium-Catalyzed Oxyamination of Olefins by Chloramine-T

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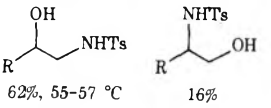
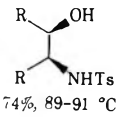
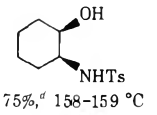
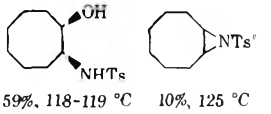
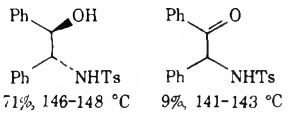
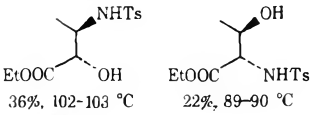
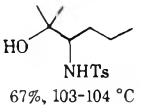
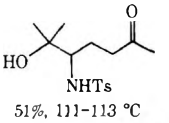
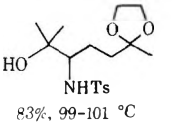
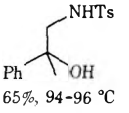
We have reported that Chloramine-T (**1**) reacts with olefins in the presence of an osmium catalyst to afford vicinal hydroxy *p*-toluenesulfonamides (**2**).[1] This catalytic procedure was a

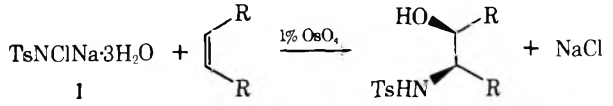
0022-3263/78/1943-2544$01.00/0

Table I[a]

Example	Olefin	Registry no.	Procedure (hours)	Products,[b] yield, mp	Registry no.
1	1-Decene[c]	872-05-9	A (12)	 62%, 55-57 °C; 16%	58107-38-3, 58107-39-4
2	(*Z*)-5-Decene	7433-78-5	A (36)	 74%, 89-91 °C	58162-20-2
3	Cyclohexene	110-83-8	A (12)	 75%,[d] 158-159 °C	58107-40-7
4	Cyclooctene	931-88-4	A (72)	 59%, 118-119 °C; 10%, 125 °C	65996-40-9, 65996-41-0
5	(*E*)-Stilbene	103-30-0	A (12)	 71%, 146-148 °C; 9%, 141-143 °C	65996-42-1, 65996-43-2
6	(*E*)-Ethyl crotonate	623-70-1	A (12)	 36%, 102-103 °C; 22%, 89-90 °C	65996-44-3, 66036-34-8
7	2-Methyl-2-hexene[f]	2738-19-4	B (24)	 67%, 103-104 °C	66027-68-7
8	2-Methyl-2-hepten-6-one[g]	110-93-0	B (2)	 51%, 111-113 °C	65996-45-4
9	2-Methyl-2-hepten-6-ethylene ketal[h]	3695-38-3	B (24)	 83%, 99-101 °C	65996-46-5
10	α-Methylstyrene[i]	98-83-9	B (16)	 65%, 94-96 °C	58107-54-3

[a] Unless noted otherwise, all of the reactions were performed on a 1-mmol scale as described in detail under procedures A and B. All new compounds exhibited appropriate spectral and analytical data. [b] All yields are for isolated pure substances and are based on initial moles of olefin. When mixtures were formed, chromatography on silica gel was employed to separate the regioisomers. When only one hydroxysulfonamide was formed, recrystallization of the crude product was the preferred method of isolation. [c] When Chloramine-T was generated in situ by the reaction of *p*-toluenesulfonamide with Chlorox, similar yields of the oxyamination products were obtained. [d] Comparable yields were also obtained on 0.1-, 0.5-, and 1-mol scale oxyaminations of cyclohexene. [e] A control experiment revealed that the formation of the aziridine was not dependent on the presence of the osmium catalyst. [f] Addition of dicyclohexyl-18-crown-6 or tetraethylammonium acetate (0.05 mmol) accelerated the reaction (presumably by increasing the concentration of the TsNCl anion in solution), but the final yields were not affected by these additives. [g] Due to the presence of the ketone in this substrate, the usual borohydride reduction step in the workup (procedure B) was omitted. [h] Prepared from the ketone under standard conditions (ethylene glycol, TsOH, benzene; reflux). [i] This reaction was run on a 1.0-mol scale with relatively less solvent (1000 mL of *tert*-butyl alcohol; therefore, five times more concentrated).

significant improvement over the stoichiometric oxyamination reaction,[2] but it exhibited an unusual dependence on silver(I) ion. For monosubstituted and sym-disubstituted olefins the addition of silver nitrate generally resulted in faster reactions



2

and better yields of oxyaminated products,[3a] while for unsym-disubstituted and trisubstituted olefins the presence of silver ion generally had a deleterious effect on the desired oxyamination reaction.[3b] This situation led us to recommend two different (one with added $AgNO_3$ and one without) procedures for these two different classes of olefins. We report here a new procedure, employing phase-transfer catalysis (PTC), which is ideal for the oxyamination of monosubstituted and sym-disubstituted olefins. This PTC method is intended to replace the silver nitrate method ("procedure B"

in our original publication[1]). It is not only more economical (no silver salts) but also seems to afford better yields[4] and may have a somewhat greater scope[5] than the earlier method.

The PTC method (procedure A of Table I) employs benzyltriethylammonium chloride as the phase-transfer catalyst. The recipe calls for 5% of the PTC catalyst, and this is the optimum amount; the use of more or less catalyst gives less satisfactory results. Both benzene–water and chloroform–water systems were tried and found to be equally effective.

As with the earlier silver method,[1] the PTC method gives poor results with trisubstituted and unsym-disubstituted olefins.[6] The oxyamination product may still form, but it will usually be accompanied by a number of byproducts. Fortunately, this class of olefins is successfully oxyaminated by a simple alternative procedure. One performs the reaction by dissolving the olefin in *tert*-butyl alcohol, adding Chloramine-T and the osmium catalyst, and then stirring the resulting suspension while heating in an oil bath maintained at 55–60 °C. This is designated as procedure B in this work and is almost identical with "procedure A" in our earlier[1] publication. The only important difference is in the workup procedure employed.

Shortly after the original publication[1] appeared, a rather serious drawback to the recommended isolation procedure was encountered. In order to remove the *p*-toluenesulfonamide byproduct (by conversion to TsNClNa), the methylene chloride extract was washed with a dilute aqueous sodium hypochlorite solution. We and others[7] have since found that some vicinal hydroxy-*p*-toluenesulfonamide products are unstable to this washing procedure. *We therefore recommend that this hypochlorite wash be avoided.* An alternative method for removing the sulfonamide byproduct is employed here. It involves washing with a saturated sodium chloride[8] solution containing 1% sodium hydroxide.

Another difference in the workup applies only to procedure B. In this case sodium borohydride is used to reduce the osmate esters. This has proved superior to the bisulfite reductant used previously.[1] In situations where borohydride would react with another functionality present in the molecule (e.g., example 8 in Table I), one can either try bisulfite or omit the reduction step altogether. In the latter case the small (ca. 1%) amount of reddish-yellow osmate ester is removed by chromatography or crystallization.

The results in Table I are largely self-explanatory, but a few things deserve comment. Cyclooctene (example 4) yields not only the expected vicinal hydroxysulfonamide but also the corresponding aziridine. Interest in this side product was diminished by the observation that its formation is not dependent on the presence of the osmium catalyst.

This osmium-catalyzed oxyamination process seems to be less troubled by the type of over-oxidation problems (i.e., ketol formation and oxidative cleavage of the C–C bond) which accompany the analogous osmium-catalyzed vicinal dihydroxylation of olefins.[9] The *p*-toluenesulfonamide moiety, itself very resistant to oxidation,[10] seems to confer enhanced stability toward oxidants upon the adjacent hydroxyl group. However, in those cases where the product contains a secondary hydroxyl function, traces[11] of the α-ketosulfonamides resulting from further oxidation can usually be observed by GLC analysis.

We[12] have also observed that these α-ketosulfonamides are further oxidized under the reaction conditions in a process which consumes several moles of Chloramine-T.[13] The nature of all of the products formed in this process has not yet been determined,[13] but *p*-toluenesulfonamide is produced. This pathway probably accounts for most of the *p*-toluenesulfonamide byproduct produced in these catalytic oxyaminations. Consistent with this statement is the observation that only traces of *p*-toluenesulfonamide arise in those oxyaminations where the β-hydroxysulfonamide produced has a tertiary hydroxyl group.

An earlier report[14] on the osmium-catalyzed oxidative cleavage of carbonyl compounds with Chloramine-T, and our own observations with α-ketosulfonamides, suggested that ketonic functionality might be incompatible with these oxyaminations. The keto olefin in example 8 reveals that this is not the case. However, this ketone function does seem to interfere to some extent since the yield of oxyaminated product increases by 30% when it is protected as the ethylene ketal (example 9). This latter experiment also demonstrates that ketals are stable to the reaction conditions.

The chloramine derivatives ($ArSO_2NClNa$) of a variety of other arylsulfonamides (Ar = phenyl, *o*-tolyl, *p*-chlorophenyl, *p*-nitrophenyl, and *o*-carboalkoxyphenyl) have been used successfully in these catalytic oxyaminations.[15] Since only Chloramine-T (Ar = *p*-tolyl) and Chloramine-B (Ar = phenyl) are commercially available, we have developed a convenient procedure for generating the chloramines in situ for use in the modification involving phase-transfer catalysis. One simply stirs a suspension of the arylsulfonamide with an appropriate amount of Chlorox until a homogeneous solution is obtained. When this solution is used in the PTC method, the yields of oxyaminated products are comparable with those obtained with isolated chloramine salts.

Although the examples in Table I were performed on a 1-mmol scale, both procedures A and B have been easily carried out on a 1-mol scale. For convenience, these larger scale reactions were performed with relatively less solvent (up to five times more concentrated); high yields were still realized, and excessive heat evolution, which is a common problem for large scale oxidations, was not encountered.

In conclusion, although the improvements described here should significantly increase the utility of these catalytic oxyaminations, the reaction still has important limitations. For example, neither procedure (A or B) succeeds with tetramethylethylene,[16] cholesterol,[16] diethyl fumarate,[17] or 2-cyclohexen-1-one,[17] and it seems reasonable to anticipate negative results with most hindered tri- and tetrasubstituted olefins.[18] Finally, no matter how effective this version of the oxyamination process becomes, it is circumscribed by the obvious fact that the nitrogen is introduced bearing a sulfonamide protecting group. In some cases the sulfonamide moiety may be acceptable or even desirable, but in others the difficulties[19] associated with removing sulfonamide protecting groups will restrict the usefulness of these oxyaminations. Fortunately, for the latter cases, we have recently developed another modification of the osmium-catalyzed oxyaminations.[20] This new method employs *N*-chloro-*N*-argento-*tert*-butyl or benzyl carbamates and therefore produces oxyamination products which bear *t*-Boc or Boc protecting groups on the nitrogen.

Experimental Section

Materials. The olefins were obtained from either Chemical Samples Co. or Aldrich and used without purification. Reagent grade chloroform and *tert*-butyl alcohol were employed as solvents. Chloramine-T trihydrate[34] and benzyltriethylammonium chloride were used as obtained from Aldrich. Osmium tetroxide was purchased from Matthey Bishop, Inc.

Preparation of Osmium Tetroxide Catalyst Solution. Over the past few years we have tried a number of ways of preparing osmium tetroxide stock catalyst solutions. Solvents such as hexane, chloroform, carbon tetrachloride, and *tert*-butyl alcohol have all been used. In all of these solvents an insoluble precipitate (thought to be OsO_2) forms with time. If, however, one adds a small amount of *tert*-butyl hydroperoxide,[21] great stability is imparted to these organic solutions of OsO_4. We now use such stabilized *tert*-butyl alcohol solutions of OsO_4 for all[1,9] of our osmium-catalyzed processes.

Osmium tetroxide is commonly supplied in 1-g (3.94 mmol) amounts in sealed glass ampules. Working in a well-ventilated hood,

one of these ampules is scored in the middle and broken open, and the two halves are dropped into a clean brown bottle containing 199 mL of reagent grade *tert*-butyl alcohol and 1 mL of 90+% *tert*-butyl hydroperoxide (Aldrich). The bottle is capped (use caps with either polyethylene or Teflon liners) and then swirled for a while to ensure dissolution of the OsO_4. Each milliliter of this stock solution contains 5 mg (2.0 mmol) of OsO_4. These solutions are stored in the hood at room temperature and seem to be very stable.[22]

Procedure A (Phase-Transfer Method). A 25-mL one-neck round-bottom flask, equipped with a magnetic stirrer and a reflux condenser, is charged with 1 mmol of olefin, 5 mL of chloroform, 0.50 mL (0.01 mmol) of osmium tetroxide catalyst solution, 352 mg (1.25 mmol) of Chloramine-T trihydrate, 11.4 mg (0.05 mmol) of benzyltriethylammonium chloride, and 5 mL of distilled water. The flask is then placed in an oil bath maintained at 55–60 °C.[23] The mixture is stirred, and the progress of the reaction is monitored by following the disappearance of olefin by TLC or GLC.[24] When the reaction is completed, 104 mg (1 mmol) of sodium bisulfite is added and the mixture is refluxed for 3–6 h.[25] This step reduces[26] the trace (ca. 1%) of osmate ester present. After reduction, the two phases are separated, the flask and separatory funnel are washed with ca. 10 mL of chloroform, and the combined organic phase is washed with saturated brine containing 1% sodium hydroxide until the $TsNH_2$ has been extracted (usually once or twice) and then with saturated brine and dried ($MgSO_4$) to give a clear yellow[27] solution. Concentration affords the crude β-hydroxy-*p*-toluenesulfonamide which is purified by crystallization or chromatography.

Procedure A has also been performed without difficulty on a 1-mol scale. For convenience, these large scale reactions are run five times more concentrated (with respect to both the $CHCl_3$ and H_2O phases and the OsO_4 catalyst solution) than the 1-mmol scale reactions described in detail above. Thus, 82.2 g (1 mol) of cyclohexene afforded 205 g (76%) of the pure oxyaminated product. For these larger scale more concentrated reactions, it is sometimes necessary to modify the workup to deal with precipitation of the more highly crystalline oxyamination products.[28]

Procedure B (*tert*-Butyl Alcohol Method). A 10-mL one-neck round-bottom flask, equipped with a magnetic stirrer and a reflux condenser, is charged with 1 mmol of olefin, 5 mL of *tert*-butyl alcohol, 0.50 mL (0.01 mmol) of osmium tetroxide catalyst solution, and 352 mg (1.25 mmol) of Chloramine-T trihydrate. The flask is placed in an oil bath maintained at 55–60 °C, and the resulting suspension (Chloramine-T is only slightly soluble under these conditions) is stirred until, as judged by TLC or GLC, all of the olefin has been consumed.[29] Then 11.1 mg (0.03 mmol) of sodium borohydride is added, and the mixture is stirred for 1 h at room temperature.[30] The reaction mixture is concentrated (rotary evaporator) to remove most of the *tert*-butyl alcohol solvent, and the residue is taken up in 20 mL of methylene chloride. The resulting solution is washed with saturated brine containing 1% sodium hydroxide until the $TsNH_2$ has been extracted (usually once or twice) and once with saturated brine and dried ($MgSO_4$) to give a clear yellow[27] solution. Concentration affords the crude β-hydroxy-*p*-toluenesulfonamide which is purified by crystallization or chromatography.

Procedure B has also been performed on a 1-mol scale at five times the concentration described above for the 1-mmol experiments. No problems associated with the scale-up were encountered. Thus, 118.2 g (1 mol) of α-methylstyrene gave 198 g (65%) of the pure oxyamination product.[31]

A Simple Method for In Situ Generation of the Chloramine Salts (from the Arylsulfonamides) for Direct Use in Procedure A. In a 25-mL one-neck round-bottom flask, equipped with a magnetic stirrer, are combined 1.25 mmol of the arylsulfonamide, 3.4 mL of distilled water, and 1.65 mL (ca. 1.25 mmol) of Chlorox.[32] The resulting suspension is stirred for 10 min (or until a homogeneous solution is produced) at room temperature. The flask is then fitted with a reflux condenser, and after adding 5 mL of chloroform, 1 mmol of the olefin, 0.01 mmol of OsO_4 catalyst, and 0.05 mmol of benzyltriethylammonium chloride, one proceeds as described in procedure A above.

Acknowledgment. We are grateful to the National Science Foundation (CHE74-21260), Hoffmann-LaRoche, and Eli Lilly for financial support. The oxyamination of olefins under phase-transfer conditions was first observed in our laboratory by Anthony O. Chong (Ph.D. Thesis, M.I.T., 1976), and we are indebted to him for this discovery.

Registry No.—1, 127-65-1; OsO_4, 20816-12-0.

References and Notes

(1) K. B. Sharpless, A. O. Chong, and K. Oshima, *J. Org. Chem.*, **41**, 177 (1976).
(2) (a) K. B. Sharpless, D. W. Patrick, L. K. Truesdale, and S. A. Biller, *J. Am. Chem. Soc.*, **97**, 2305 (1975); (b) D. W. Patrick, L. K. Truesdale, S. A. Biller, and K. B. Sharpless, *J. Org. Chem.*, in press.
(3) (a) The favorable effect of silver ion on these reactions appears to be due to two effects. Its most obvious role is to scavenge chloride ion. We have previously demonstrated that the presence of chloride ion retards the rate of these catalytic oxyaminations.[1] More recently we have found that the presence of excess silver ion has a general accelerating effect on the catalytic process (see also ref 20). (b) The unfavorable effect of silver ion in the case of these more highly substituted olefins may be rationalized as follows. The silver salt of Chloramine-T (TsNClAg), as demonstrated by control experiments, reacts with olefins in the absence of osmium catalyst to give various aminated products (e.g., allylic sulfonamides). The rate of this uncatalyzed reaction increases as the degree of olefin substitution increases, whereas the rate of the osmium-catalyzed oxyamination process decreases as the degree of olefin substitution increases (see ref 16).
(4) For example, compare the yields for cyclohexene and (*Z*)-5-decene in Table I with those reported previously.[1]
(5) This statement must be regarded as tentative since it is based on only one example (5, Table I). Stilbene did not react in the earlier systems.[1]
(6) Olefins are more prone toward direct (i.e., not involving osmium catalysis) reaction with those chloramine salts having silver or quaternary ammonium species as counterions.
(7) I. Dyong, Q. Lam-Chi, G. Schulte, B. Fraser-Reid, and J. L. Primeau, *Angew. Chem., Int. Ed. Engl.*, **16**, 553 (1977).
(8) Some β-hydroxysulfonamide products show a tendency to be extracted into aqueous base. This problem is prevented by the presence of the brine.
(9) (a) K. B. Sharpless and K. Akashi, *J. Am. Chem. Soc.*, **98**, 1986 (1976); (b) K. Akashi, R. E. Palermo, and K. B. Sharpless, *J. Org. Chem.*, **43**, 2063 (1978).
(10) Numerous attempts to oxidize (dehydrogenate to the imino structure) the allylic *p*-toluenesulfonamide derivative of cyclohexene all met with failure: S. A. Biller and K. B. Sharpless, unpublished results.
(11) Usually only 1–2%, but in the case of stilbene (example 5, Table I) 9%, of the α-ketosulfonamide was actually isolated.
(12) E. Herranz and K. B. Sharpless, unpublished results.
(13) Preliminary results indicate that the rate of further oxidation of the α-ketosulfonamides may vary considerably depending on the specific case. Thus, the fact that only traces of these products are present in most of the cases studied (Table I) may be due to their rapid further transformation. This possibility and the nature of the further transformation products derived from the α-ketosulfonamides are presently under investigation.
(14) S. P. Mushran, R. Saneki, and M. C. Agrawal, *Z. Naturforsch. B*, **27**, 1161 (1972).
(15) Oxyamination was not achieved with two arylsulfonamides bearing electron-donating substituents on the aromatic ring (Ar = 4-methoxyphenyl and 2,5-dimethoxyphenyl). However, failure may have been due to the instability of the chloramine derivatives in these cases.
(16) No reaction occurs, and the Chloramine-T is not consumed (see ref 18).
(17) Both the Chloramine-T and part of the olefin are consumed, but the oxyamination product has not been detected in the reaction mixtures. It seems likely that it forms but is unstable to the reaction conditions. Both of these olefins do form isolable oxyamination products under the milder (room temperature) conditions of a more recent oxyamination procedure.[20]
(18) See ref 9b for a discussion of the problems which are thought to prevent osmium-catalyzed oxidations of hindered olefins.
(19) Arylsulfonamide protecting groups are notoriously difficult to hydrolyze under both acidic and basic conditions.
(20) E. Herranz, S. A. Biller, and K. B. Sharpless, *J. Am. Chem. Soc.*, in press.
(21) In the past, hydrogen peroxide has been used to stabilize osmium tetroxide solutions; see, for example, R. Daniels and J. L. Fischer, *J. Org. Chem.*, **28**, 320 (1963). In our opinion *tert*-butyl hydroperoxide is superior to H_2O_2 for this purpose. It is more stable than H_2O_2 and has the added advantage of being very soluble in organic solvents.
(22) We have been using these solutions too fast to know much about their longevity. They are stable at room temperature for at least 4 months, and long-range stability tests are now under way.
(23) The reactions do not reflux, but the condensation of solvent droplets is observed.
(24) If olefin remains after a long reaction time, the aqueous layer should be tested (starch–iodide paper) for the presence of Chloramine-T. If this test is negative, more Chloramine-T may be added. This will result in consumption of the remaining olefin, but not necessarily a greater yield of the desired oxyamination product. The problem in these cases is thought to be due to over-oxidation or instability of the hydroxysulfonamide product. In extreme cases (see, for example, ref 17), none of the desired oxyamination product is observed.
(25) The rate of reduction of the osmate esters varies considerably. It is rapid for monosubstituted olefins but is much slower in the case of disubstituted olefins such as (*Z*)-5-decene. The reduction process can be monitored by TLC since the osmate esters give rise to a faint reddish-yellow spot which always moves faster than the free β-hydroxysulfonamides.
(26) The nature of the reduced osmium species is unknown. When the reduction is complete, most of the osmium is present as black particles suspended in both the aqueous and organic phases. The last of these particles is removed during the filtration to remove the $MgSO_4$ used to dry the organic phase.
(27) The nature of the substance which imparts this yellow color is unknown. Atomic absorption analysis reveals an osmium content of only 2.4%.

Although soluble in organic solvents, it remains at the origin on TLC plates and is therefore easily separated from the desired products. The yellow color also remains in solution if the products are purified by crystallization instead of chromatography.

(28) The product derived from cyclohexene is especially crystalline and begins to crystallize if the chloroform phase is allowed to cool (this problem does not arise in the more dilute general procedure described above). A detailed procedure for oxyamination of cyclohexene on large scales is being readied for submission to "Organic Syntheses".

(29) As in procedure A (see ref 24), olefin may remain even after all of the Chloramine-T has been consumed (i.e., negative starch–iodide test). This is the case in example 8 of Table I. We suspect that part of the Chloramine-T is spent in side reactions with the ketone function. This hypothesis is supported by the observation that the olefin is completely consumed when the ketone is protected as the ethylene ketal (example 9, Table I).

(30) This replaces the aqueous bisulfite reduction procedure used earlier. We found that although the bisulfite method would slowly reduce osmate esters from unsym-disubstituted olefins, the osmate esters derived from trisubstituted olefins were inert to this treatment. As mentioned earlier (ref 25), the reddish-yellow osmate esters can be detected by TLC. Treatment with $NaBH_4$ reduces even these more hindered osmate esters rapidly at room temperature. As with the bisulfite reduction used in procedure A (ref 26), the nature of the reduced osmium species is unknown. The last of the black, osmium-containing particles is removed when the $MgSO_4$ is separated from the organic phase by filtration.

(31) The procedure for oxyamination of α-methylstyrene on large scales is being readied for submission to "Organic Syntheses".

(32) Chlorox brand commercial household bleach was employed. The bottle states that it contains 5.25% of sodium hypochlorite. The approximate density of the solution is 1.076; thus, 1 mL contains ca. 0.759 mmol of NaOCl. Slight variations in the strength of these bleach solutions have been observed: M. J. Mintz and C. Walling, "Organic Syntheses", Collect. Vol. V, Wiley, New York, N.Y., 1973, p 184.

(33) Address correspondence to this author at the Department of Chemistry, Stanford University, Stanford, Calif. 94305.

(34) Since an explosion has recently been reported [*Chem. Eng. News*, **55** (49), 56 (1977)] while handling anhydrous Chloramine-T, it is important to emphasize the difference in stability between anhydrous Chloramine-T and the corresponding trihydrate, which is required in the present work. Commercially available Chloramine-T trihydrate is a very stable substance, and no special precautions are necessary in handling it.

Attempted Synthesis of 2,4,8,10-Tricyclo[5.4.0.0^{1,6}]undecatetraene: Bisnorcaradiene

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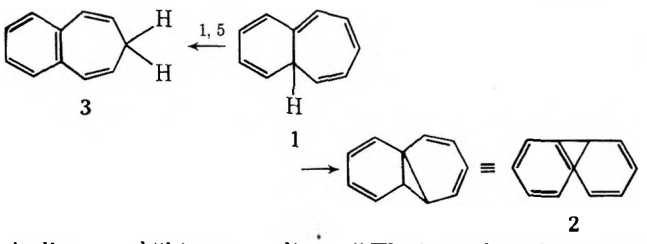
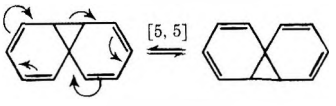
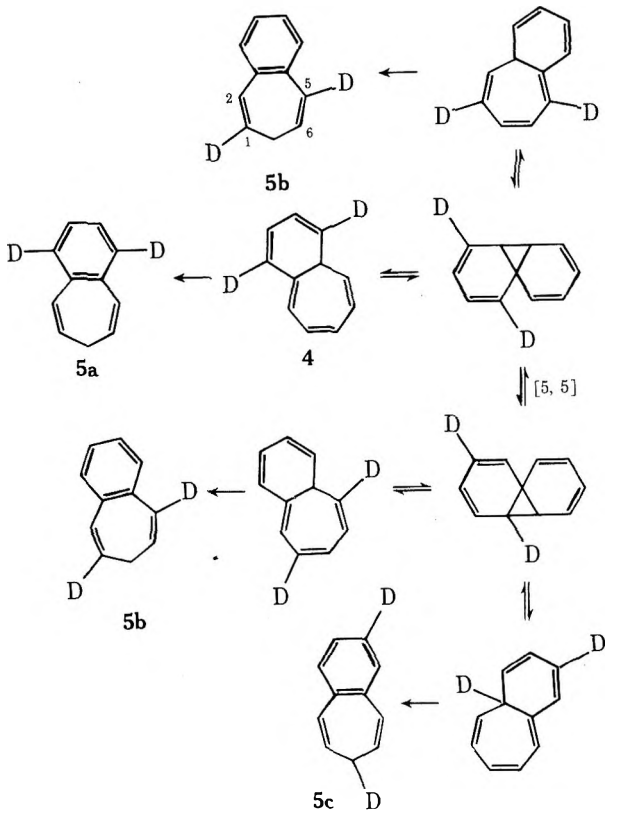
In addition to 1,5-sigmatropic rearrangement of hydrogen, 1,3,5,8,10-bicyclo[5.4.0]undecapentaenes are believed to undergo electrocyclic ring closure to 2,4,8,10-tricyclo[5.4.0.0^{1,6}]undecatetraenes **2** which have been euphemistically named "bisnorcaradienes." The latter have been suggested to explain substituent scrambling in a number of thermal and photochemical reactions[1] and have aroused further interest because they have the potential to undergo symmetry allowed, degenerate, concerted antara,antara[5,5]-sigmatropic rearrangements,[1b] reactions that are intriguingly reminiscent of semibullvalene rearrangements.[2]



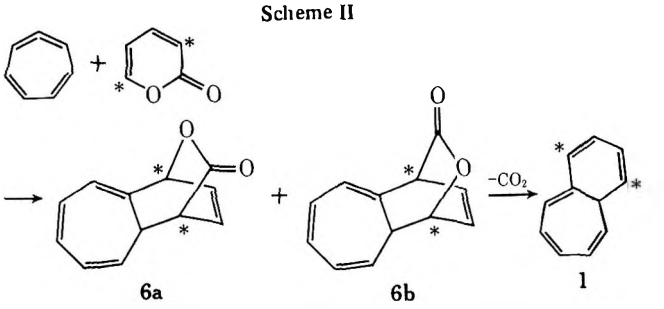


With an eye to exploring this interesting latter possibility, we undertook to generate a deuterium labeled 1,3,5,8,10-bicyclo[5.4.0]undecapentaene **4** which could reveal this degenerate rearrangement. Our plan of attack is outlined in Scheme I where it can be seen that a semibullvalene type of rearrangement would lead to a unique scrambling (**5c**) in the final product.

Scheme I



Scheme II



Our synthetic approach to the labeled bicyclopentaenes is outlined in Scheme II. The essence of the synthesis is a Diels–Alder addition of cycloheptatetraene to 2-pyrone (or, indistinguishably, addition of cycloheptatrienylidene followed by rearrangement) to give one or both of the polycyclic lactones **6a** and/or **6b** which could decarboxylate to the desired polyene.

Cycloheptatrienylidene–cycloheptatetraene has been generated by both base induced dehydrochlorination of a mixture of chlorocycloheptatrienes[3] and photolysis or pyrolysis of the sodium salt of tropone tosylhydrazone.[4] The sensitivity of 2-pyrone to strong base excluded the dehydrochlorination reaction as a viable alternative. The salt of tropone tosylhydrazone was therefore pyrolyzed (110 °C) and photolyzed (to −78 °C) in the presence of 2-pyrone. In no case was there any evidence of the bicyclopentaene **1** but in the pyrolysis reaction there was cleanly (NMR) obtained (30%) isolated 3,4-benzocycloheptatriene. The photolysis was not as clean (in some cases showing the isomeric 1,2-benzocycloheptatriene) but again, even at temperatures as low as −78 °C, there was no evidence for **1**. Again, the predominant product was the benzocycloheptatriene **3**.

Taking formation of **3** as presumptive evidence for **1**, we then undertook to explore the various degenerate rearrange-

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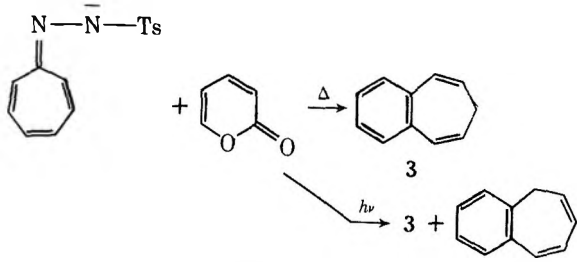
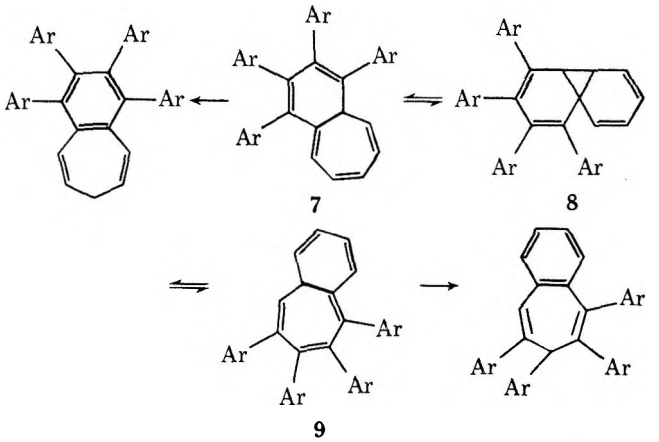


ments. Before attacking the more difficult synthesis of specifically labeled dideuterio-2-pyrone that could identify the semibullvalene rearrangement, we considered it judicious to first assure that the expected bisnorcaradiene rearrangement was faster than aromatization. To test this, 2-pyrone-*6-d* was synthesized by the method of Pirkle[5] and allowed to react at 110 °C with cycloheptatrienylidene–cycloheptatetraene. From Scheme I it can be seen regardless of the regiochemistry of the initial cycloaddition, bisnorcaradiene automerization would bring deuterium into the cycloheptatriene ring. This, in turn, could be unequivocally identified by either (or both) a new singlet in the proton NMR corresponding to an uncoupled hydrogen at C-2 (in **5b**) accompanied by a change in resonances at C-7 and/or a change in the resonances of the hydrogens at C-6. To our surprise, there was no detectable change in either the vinyl or the CH_2 regions of the NMR despite the fact that the mass spectrum showed no loss of deuterium (from peak areas in the NMR, the deuterium is in the aromatic portion of **3**). The same result was obtained at temperatures up to 200 °C.

Thus, on the reasonable assumption that **1** is the source of **3**, it would appear that, unlike the more highly substituted 1,3,5,8,10-bicyclo[5.4.0]undecapentaene[1d] **7**, 1,5-hydrogen migration in **1** occurs more rapidly than ring closure. Thus, even though the addition of cycloheptatetraene–cycloheptatrienylidene to 2-pyrone apparently does provide a way to generate the parent polyene **1**, the latter is not a viable precursor to the parent bisnorcaradiene, at least at modest temperatures.



It might be added in conclusion that from the different behavior of **1** and **7** it would appear that the relative rates of norcaradiene formation and aromatization from 1,5-hydrogen migration in systems of this type must be governed by a rather delicate balance of factors. In principle, these could be either acceleration of norcaradiene formation or retardation of aromatization by the aryl groups in **7**.

Experimental Section

^{1}H-NMR spectra were recorded on a Varian A-60 NMR spectrometer in $CDCl_3$ or CCl_4 relative to internal Me_4Si. Infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer as a film between NaCl plates. Mass spectra were recorded on an AEI MS 30 double beam mass spectrometer. Reagents were not purified except as noted. Solvents were dried by stirring overnight with CaH_2 and filtered through basic alumina, activity grade I (Fisher Scientific Co), into dry septum bottles. The progress of column chromatography was followed by addition of 1% type 609 phosphor (DuPont Photoproducts Dept.) to the absorbent, employing a quartz column, and observing with a hand-held UV unit (Fisher Scientific). Sodium iodine and zinc were dried overnight in a vacuum oven at 130 °C.

2-Pyrone. Coumalic acid (30 g, 0.214 mol), prepared from malic acid by the method of Wiley and Smith,[6] was decarboxylated at 650 °C through copper turnings[7] to yield 12.3 g (0.128 mol, 60%) of 2-pyrone, bp 106–9 °C (26 mm) [lit.[7] bp 110 °C (26 mm)]. This was stored under nitrogen below 0 °C until used.

Sodium Salt of Tropone Tosylhydrazone. The sodium salt of tropone tosylhydrazone was prepared by the method of Jones and Ennis[4] by the reaction of tropone tosylhydrazone with sodium hydride in tetrahydrofuran. The resulting precipitate was recrystallized from 1% Me_2SO in THF to yield purple needles.

2-Pyrone-*6-d*. Glutaconic acid (10 g, 0.077 mol) (Aldrich Chemicals) was allowed to react with phosphorus pentachloride (30 g, 0.144 mol) by the method of Pirkle and Dines[5] to yield 7.1 g (0.054 mol, 71%) of 6-chloro-2-pyrone, bp 64–5 °C (0.5 mm) [lit.[5] 67 °C (9 mm)]. In 30 mL of dry THF 5.8 g of this material was stirred with 11.6 g of sodium iodide for 4 h. The resulting suspension was added[5] to a mixture of 30 g of zinc dust in 20 mL of deuterioacetic acid (Aldrich Chemicals 98 atom %) and allowed to stand overnight. Work-up with CH_2Cl_2, followed by distillation from a 115 °C bath at 25 mm, yielded 607 mg of 2-pyrone-*6-d*. The NMR and mass spectrum of this material were identical to the published spectra.[5,8] ^{1}H NMR ($CDCl_3$) δ 6.28 (s, H_3), 6.38 (s, H_5), 7.42 (m, H_4); mass spectrum *m/e* (rel intensity) 97 (99.9), 69 (100).

Pyrolysis of the Sodium Salt of Tropone Tosylhydrazone in the Presence of 2-Pyrone-*6-d*. In a typical run, 100 mg (1.04 mmol) of 2-pyrone-*6-d* was dissolved in 15 mL of dry diglyme and heated under nitrogen to the appropriate temperature. To this was added, in small portions through an addition tube, 500 mg (1.41 mmol) of the sodium salt over 30 min. The reaction was allowed to continue for another 30 min, then the reaction mixture was poured into 150 mL of water. This was extracted four times with 50 mL of pentane. The combined pentane extracts were washed six times with 50 mL of water and dried over magnesium sulfate. After removal of the pentane via rotary evaporation, the residue was chromatographed on alumina (Fisher basic, activity grade III) with pentane. Typical 3,4-benzocycloheptatriene yields were about 25%. This was identified by comparing its NMR and mass spectra with the same material synthesized from undeuterated α-pyrone (which, in turn, was identified by comparison of its properties with those reported for the known[9] compound). The mass spectrum of the product from monodeuterated 2-pyrone clearly indicated retention of the deuterium. The NMR spectra from monodeuterated and nondeuterated 2-pyrone were identical except for the relative areas of the resonance at δ 7.25 (3.3:4.0, phenyl). The only other product noted was heptafulvalene which was identified by comparison with a known sample:[4] ^{1}H NMR (CCl_4) 2.50 (t, 1.8 H, J = 6 Hz), 5.82 (d of t, 2.1 H, J = 6, 10 Hz), 6.59 (d, 2.0 H, J = 10 Hz), 7.25 (s, 3.3 H); mass spectrum *m/e* (rel intensity) 144 (9.6), 143 (90.0), 142 (100), 116 (26.9); for **3** 143 (8.6), 142 (79.4), 141 (100), 115 (29.8); IR (major peaks) 3010, 2950, 2820, 2220, 1480, 1450, 1430, 895, 820, 800.

Photolysis of the Sodium Salt of Tropone Tosylhydrazone in the Presence of 2-Pyrone. In a Pyrex photochemical immersion apparatus was stirred under nitrogen 1.4 g (0.014 mol) 2-pyrone in 100 mL of dry THF. While irradiating with a 550 W Hanovia medium pressure lamp, 0.5 g (1.4 mmol) of sodium salt was added in portions over 30 min. The mixture was irradiated for 3 h and then poured into 300 mL of water. This mixture was worked up in the same manner as the above reaction. The average yield of benzocycloheptatrienes was 25 mg. The ratio of **3** to 1,2-benzocycloheptatriene is 2:1. In an attempt to study this reaction at low temperature equivalent amounts of the tosylhydrazone salt and 2-pyrone-*6-d* were photolyzed at −78 °C. Unfortunately, the yield of benzocycloheptatriene was too low to be detected in the NMR. No pyrone was recovered suggesting that the cause of the low yield may be its known[10] photolability.

Acknowledgment. The authors gratefully acknowledge support of this work received from the National Science Foundation.

Registry No.—**2**, 65701-68-0; **3**, 264-09-5; 2-pyrone, 504-31-4; 2-pyrone-*6-d*, 20357-66-8; troponetosylhydrazone sodium salt, 18870-24-1; 6-chloro-2-pyrone, 20357-65-7; heptafulvalene, 531-45-3; 1,2-benzocycloheptatriene, 264-08-4.

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One-Step Dialkylation of Phenylacetonitrile in the Presence of Tertiary Amines

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The alkylation of the activated methyne carbon atom is known to occur in aqueous organic medium under standard "phase-transfer" conditions, catalyzed by quaternary ammonium salts.[1-3]

In the course of our studies dealing with the use of macromolecular amines and derived ammonium salts as phase transfer catalysts[4] we have pointed out the activity of tertiary heteroaromatic bases in the monoalkylation of phenylacetonitrile (PAN).[5]

In the previously reported conditions[5] (molar ratio: alkylating agent/PAN = 1.2), the formation of a small amount (<15%) of dialkylated product became appreciable only at PAN conversions larger than 60%.

When an excess of alkylating agent with respect to the starting PAN [5/1 (mol/mol)] was used, conversions to dialkylation product of preparative value were obtained in the same time scale as for standard monoalkylation in the presence of both aliphatic and heteroaromatic amines (Table I).

$$C_6H_5CH_2CN \xrightarrow{RBr(R'Br)/NaOH_{aq}} C_6H_5\overset{\overset{R}{|}}{C}CN \quad (R = \text{or} \neq R')$$

In the case of asymmetric dialkylation of PAN ($R \neq R'$) an excess of the less reactive alkyl bromide (n-C_4H_9Br) was used and the reaction was temporarely stopped at PAN conversion >98% (monoalkylation 90–95% and dialkylation 5–10%). After the removal of the unreacted alkyl bromide under vacuum (no further workup of the reaction mixture) an excess of the more reactive alkyl bromide was added and the reaction was carried on until completion.

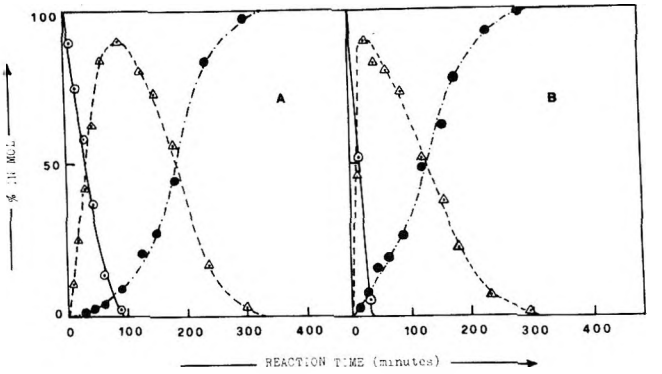

Figure 1. Mono- and dialkylation of phenylacetonitrile (PAN) in the presence of tri-n-butylamine (A) and tetra-n-butylammonium bromide (B): (- ⊙ -) PAN disappearance curve; (- ▲ -) 2-phenylbutanonitrile formation and disappearance curve; (- • ● • -) 2-ethyl-2-phenylbutanonitrile formation curve.

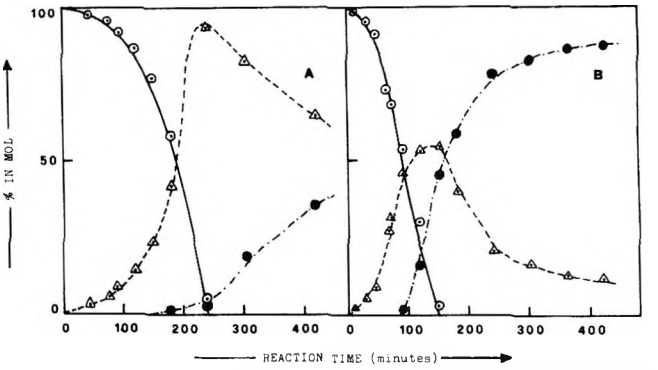

Figure 2. Mono- and dialkylation of phenylacetonitrile (PAN) in the presence of poly(4-vinylpyridine) (A) and 4-methylpyridine (B): (- ⊙ -) PAN disappearance curve; (- ▲ -) 2-phenylbutanonitrile formation and disappearance curve; (- • ● • -) 2-ethyl-2-phenylbutanonitrile formation curve.

The activity of amines, in the examined cases, appears to be comparable to that of the corresponding ammonium salts (Figure 1). When poly(4-vinylpyridine) was used, the reaction rate was markedly lower than that observed for the corresponding low molecular weight analogue (4-methylpyridine) (Figure 2) as previously observed in PAN monoalkylation.[5] This is perhaps obvious because of steric reasons and/or heterogeneity of the reaction medium. The effect of the former factor on rate control is confirmed by the fact that a longer reaction time is required to obtain 50% theoretical yields of 2-ethyl- and 2-butyl-2-phenylhexanonitriles than for 2-ethyl-2-phenylbutanonitrile.

This differentiated reactivity and the reproducibility of the investigated systems, in spite of the complexity of the reaction

Table I. Dialkylation of Phenylacetonitrile[d] (PAN) in Alkaline Aqueous Organic Medium[a]

Amine or quaternary ammonium salt	Registry no.	Alkyl bromide, alkyl =	Registry no.	Time for total disappearance of PAN, min	Time for 50% dialkylation, min	Dialkylated product after 325 min, mol %
Poly(4-vinylpyridine)	25232-41-1	C_2H_5	74-96-4	245	450	19
4-Methylpyridine	108-89-4	C_2H_5		155	160	85
Tri-n-butylamine	102-82-9	C_2H_5		95	190	100
		C_4H_9	109-65-9	125	355	40
		C_4H_9, C_2H_5[b]		90	255	94[c]
Tetra-n-butylammonium bromide	1643-19-2	C_2H_5		45	125	100

[a] Runs carried out at 70 °C under stirring. Molar ratios: alkyl bromide/PAN = 5, NaOH/PAN = 37.5, and catalyst/PAN = 0.167. [b] Run carried out in two steps. Alkylation with n-C_4H_9Br until 98% PAN conversion (90% monoalkylation and 10% dialkylation) then after removal of excess 1-bromobutane C_2H_5Br was added and the reaction carried out again as in footnote *a*. [c] Constituted by 10% of 2-butyl-2-phenylhexane nitrile and 90% of 2-ethyl-2-phenylhexanenitrile. [d] Registry no. 140-29-4.

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mixture, are particularly convenient from a preparative viewpoint as an asymmetrically dialkylsubstituted PAN derivative can be obtained in good yields and practically free from the symmetrically substituted ones, especially if care is taken in the first step of alkylation to maximize the PAN conversion with a minimum extent of symmetric dialkylation. This can be selectively performed by using a relatively small excess of alkylating agent and therefore longer reaction times.

The in situ formation of the quaternary ammonium salt is not the only factor controlling the catalytic activity of amines in the dialkylation and monoalkylation of PAN, at least in the reported conditions. In fact, the extent of quaternization (determined kinetically) of tri-*n*-butylamine reaches only a 30% value after 400 min and therefore does not suffice to explain the kinetic feature of PAN mono- and dialkylation.

Experimental Section

Starting and final product were characterized by a Varian T60 NMR spectrophotometer with Me_4Si as internal standard.

Gas-chromatographic analyses were done on a Perkin-Elmer F 30 gas chromatograph equipped with a 6 ft × ⅛ in. 2% silicon gum rubber SE 30 on high performance Chromosorb W (AW-DMCS) 80–100 mesh columns.

Viscometric measurements were carried out in methanol at 25 °C by using a Desreux-Bishoff dilution viscometer.

Reagents. Commercial grade phenylacetonitrile (PAN), bromoethane, 1-bromobutane, and tri-*n*-butylamine were purified by distillation.

Poly(4-vinylpyridine) was prepared by polymerization of 4-vinylpyridine in bulk at 40 °C in the presence of AIBN. The polymeric product was purified by dissolution in methanol and reprecipitation in diethyl ether (conversion >90%). The average molecular weight ($\bar{M}_v$) as determined by viscometric measurements was 3.15×10^5.[6]

Tetra-*n*-butylammonium Bromide.[7] A mixture of 4.62 g (25 mmol) of tri-*n*-butylamine and 17.1 g (125 mmol) of 1-bromobutane was heated at 70 °C in a sealed vial. After 70 h the reaction product was precipitated into diethyl ether and recrystallized from absolute ethanol–pentane (2:3) as white crystals.

Dialkylation Reactions. The reactions were carried out under nitrogen in a 100-mL two-necked flask equipped with a condenser and a serum cap. To a mixture of PAN (15 mmol) and alkyl bromide (75 mmol) heated at 70 °C (temperature of the heating oil bath) were added under magnetic stirring 2.5 mmol of catalyst (amine or quaternary ammonium salt) immediately followed by 45 mL of aqueous 50% NaOH preheated at 70 °C. At intervals small samples of the organic layer were withdrawn directly from the mixture through the serum cap by a hypodermic syringe and analyzed by gas chromatography.

In the case of asymmetric dialkylation the same procedure was used as far as the amount of reagents and other operative conditions are concerned. When PAN conversion was higher than 98% the reaction mixture was cooled to room temperature and after removal of the unreacted excess alkyl bromide under vacuum 75 mmol of the more reactive alkyl bromide was added and the mixture was heated again at 70 °C until there was complete dialkylation.

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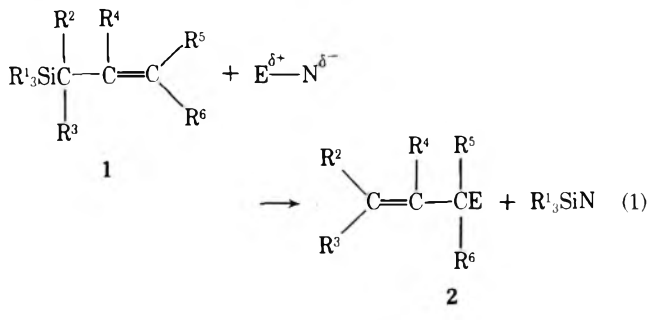
Communications

α-Siloxyallylsilanes as Homoenolate Anion Equivalents. A Novel Synthesis of γ-Keto Aldehydes[1,2]

Summary: This paper reports a versatile method of formation of γ-keto aldehydes by the reaction of α-siloxyallylsilanes with acid chlorides, which takes place under mild conditions to give products in high yields.

Sir: In earlier papers,[3] we have described new synthetic reactions using allylsilanes (**1**), in which allyl transfer accompanied by transposition of the allyl group took place very smoothly from **1** to electrophilic carbons of carbonyl compounds or acetals activated by a Lewis acid such as $TiCl_4$ in the direction shown in eq 1.



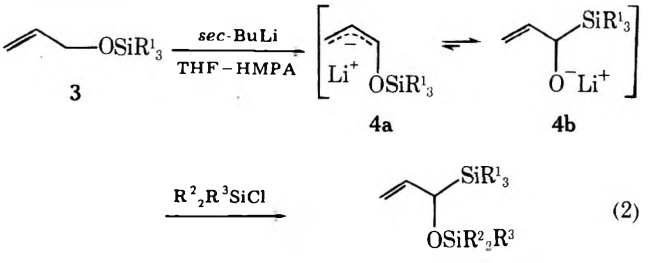
(1)

Introduction of a functionality in the allyl group of **1** will expand the scope of the reaction. For example, introduction of a silyloxy group at the α carbon of **1** (R^2 = silyloxy) could result in the formation of a silyl enol ether which should give a carbonyl compound on hydrolysis. In this paper, we report the synthesis of γ-keto aldehydes,[4] which can serve as valuable precursors for the synthesis of natural cylopentanoids, furans, and pyrroles.

For this strategy of synthesis, we have prepared a variety of α-siloxyallylsilanes, the requisite precursors, by silylation of allyloxy carbanions.[5,6]

Still and Macdonald[6] have suggested that while allyloxy carbanions (**4a**) were in rapid equilibrium with the corresponding silyl alkoxide (**4b**), alkylation of **4** resulted in the formation of only C-alkylated products. We have found, however, that silylation of **4** with chlorosilane occurred exclusively at oxygen to give **5**.[7] Several examples of **5** are shown in Table I.[8]

The reaction of **5** with a variety of acid chlorides in the presence of titanium tetrachloride gave the corresponding γ-keto aldehydes (**6**) after hydrolysis, as shown in Table II.



(2)

5a, $R^1 = R^2 = R^3 = Me$
b, $R^1 = Me$; $R^2 = R^3 = Et$
c, $R^1 = R^2 = Me$; $R^3 = t$-Bu
d, $R^1 = Et$; $R^2 = R^3 = Me$
e, $R^1 = R^2 = R^3 = Et$

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Table I. Reactions of Metalated Allyl Silyl Ethers with Chlorosilanes

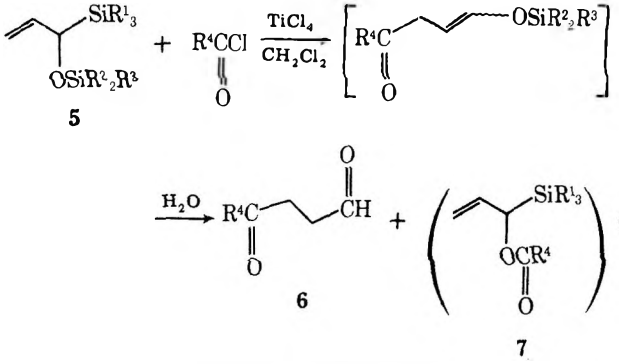
Run	Allyl silyl ether	Chlorosilane	Product[a] (% yield)	Bp, °C (mmHg)	$n^{20}D$
1	CH_2=$CHCH_2OSiMe_3$	Me_3SiCl	**5a** (80)	62 (35)	1.4228
2	CH_2=$CHCH_2OSiMe_3$	Et_3SiCl	**5b** (72)	97 (15)	1.4440
3	CH_2=$CHCH_2OSiMe_3$	t-$BuMe_2SiCl$	**5c** (76)	91 (17)	1.4389
4	CH_2=$CHCH_2OSiEt_3$	Me_3SiCl	**5d** (60)	85 (9)	1.4431
5	CH_2=$CHCH_2OSiEt_3$	Et_3SiCl	**5e** (71)	111 (4)	1.4580

[a] Products have been isolated and fully characterized.

Table II. Reactions of α-Siloxyallylsilanes with Acid Chlorides in the Presence of Titanium Tetrachloride[a]

Run	α-Siloxyallylsilane	Acid chloride	Product	% yield[b]
1	**5a**	$(CH_3)_2CHCOCl$	$(CH_3)_2CHCOCH_2CH_2CHO$	20[c,d]
2	**5b**	$(CH_3)_2CHCOCl$	$(CH_3)_2CHCOCH_2CH_2CHO$	43[c,e]
3	**5c**	$(CH_3)_2CHCOCl$	$(CH_3)_2CHCOCH_2CH_2CHO$	70[c,f] (80)[i]
4	**5c**	$CH_3(CH_2)_3COCl$	$CH_3(CH_2)_3COCH_2CH_2CHO$	45
5	**5c**	$(CH_3)_2CHCH_2COCl$	$(CH_3)_2CHCH_2COCH_2CH_2CHO$	53 (63)[i]
6	**5c**	$CH_3CH_2CH(CH_3)COCl$	$CH_3CH_2CH(CH_3)COCH_2CH_2CHO$	67
7	**5b**	$(CH_3)_3CCOCl$	$(CH_3)_3CCOCH_2CH_2CHO$	79
8	**5c**	$(CH_3)_3CCOCl$	$(CH_3)_3CCOCH_2CH_2CHO$	75[c]
9[g]	**5c**	$(CH_3)_3CCOCl$	$(CH_3)_3CCOCH_2CH_2CHO$	43
10[h]	**5c**	$CH_3(CH_2)_5COCl$	$CH_3(CH_2)_5COCH_2CH_2CHO$[j]	68
11[h]	**5c**	c-$C_6H_{11}COCl$	c-$C_6H_{11}COCH_2CH_2CHO$	65
12[h]	**5c**	$(CH_3)_2C$=$CHCOCl$	$(CH_3)_2C$=$CHCOCH_2CH_2CHO$	58

[a] All reactions were carried out at −78 °C for 3 h unless otherwise noted. [b] Yields after isolation by TLC unless otherwise noted. [c] Determined by NMR relative to an internal standard. [d] The ester (7) was obtained in 30% yield. [e] The ester was obtained in 17% yield. [f] No ester was observed at all. [g] Aluminium chloride was used as a Lewis acid. [h] The reaction was carried out at −78 °C for 4 h. [i] Yields after isolation as a 2,4-dinitrophenylhydrazone. [j] This compound is known as an intermediate for the synthesis of dihydrojasmone; K. Oshima, H. Yamamoto, and H. Nozaki, *J. Am. Chem. Soc.*, **95**, 4446 (1973).



5

6 7 (3)

In some cases, O-acylation of the alkoxy group of **5** affording esters (**7**) can compete with the regiospecific carbon–carbon bond formation at γ carbon of the allylsilane under these reaction conditions. Cleavage of alkoxysilanes with acid chlorides is one of the well-documented reactions in the organosilicon chemistry.[9] However the formation of esters can be efficiently excluded by means of increasing the steric bulkiness of the siloxy groups in **5**. Thus γ-keto aldehydes were obtained effectively by the introduction of *tert*-butyldimethylsiloxy group in place of trimethylsiloxy group into the α position of the allylsilane.

This work demonstrates that α-siloxyallylsilanes (**5**) can be viewed as one of the "homoenolate anion equivalents".[10] The synthetic utility of the present reaction was mostly displayed by complete regiospecificity of the acylation, ready accessibility of starting materials, and simple manipulation of the conversion.

As a general procedure, to a solution of 1 mmol of an acid chloride in 2 mL of dry dichloromethane at −78 °C, titanium tetrachloride (1.1 mmol) was added dropwise with stirring under a nitrogen atmosphere. When addition was completed, 1 mmol of an α-siloxyallylsilane (**5**) in 2 mL of dichloromethane was added slowly and the mixture was stirred continuously for an additional 3 h. The solution was allowed to warm up to 0 °C slowly and a mixture of water and ether was then added. The organic layer was washed with aqueous sodium bicarbonate and water and dried over anhydrous sodium sulfate. Evaporation of the solvent yields crude product which is purified by preparative thin-layer chromatography.

Related works are in progress.

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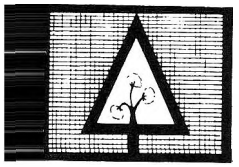

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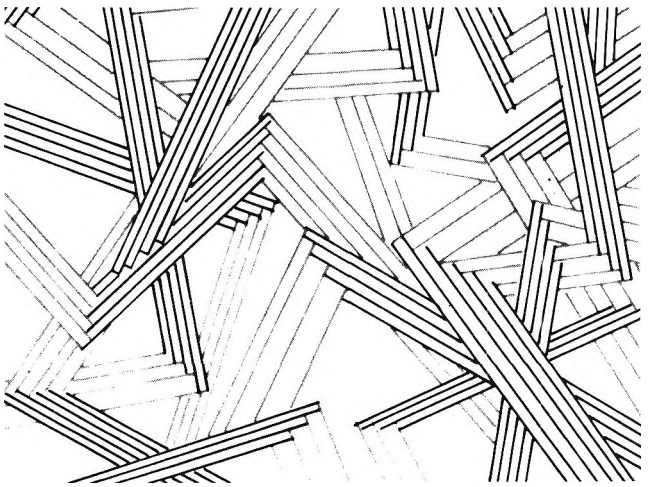

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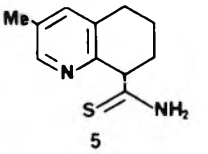
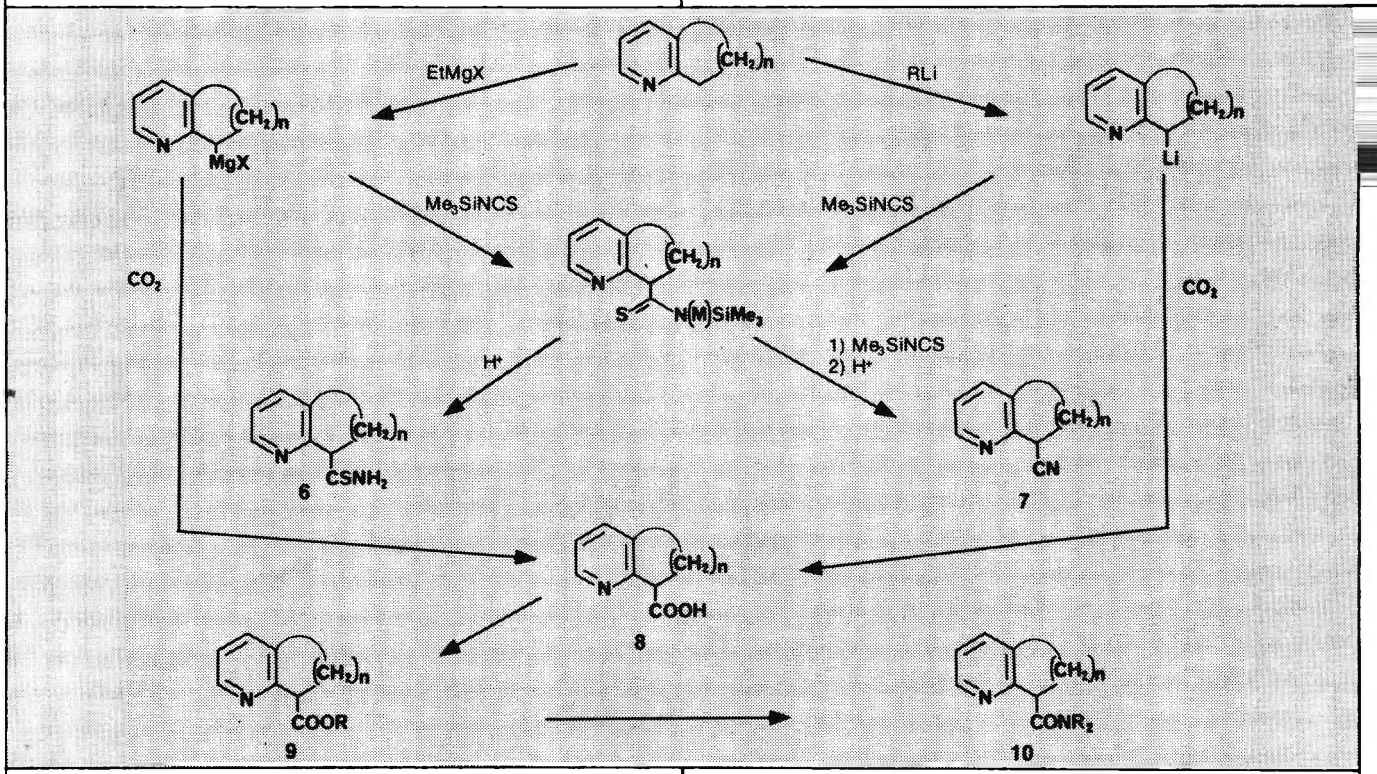
1 2 3 4

These cycloalkenopyridines can be metallated specifically on the side chain,[1] thus providing a general, nonreductive route (see scheme) to the corresponding carboxylic acids (**8**),[2] esters (**9**),[2] carboxamides (**10**),[2] thiocarboxamides (**6**),[2,3] and carbonitriles (**7**).[3]



5

Cycloalkenopyridines may exhibit physiological activity; for example, tetrahydroquinoline derivatives such as **5** are antiulcer-antisecretory agents.[4]



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For a review of the reactions of 2,3-cycloalkenopyridines, see H. Beschke, *Aldrichimica Acta*, **11**, 13 (1978).

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