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THE JOURNAL OF Organic Chemistry®

VOLUME 36, NUMBER 6

MARCH 26, 1971

Conformational Analysis. LXX. The Perhydrophenanthrenes[1,2]

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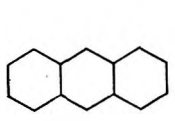
Received October 2, 1970

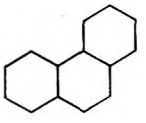
The geometries and energies of the six perhydrophenanthrenes have been calculated by the Westheimer method. Four of the isomers have been synthesized and characterized. Preliminary measurements of the composition of a perhydrophenanthrene sample equilibrated over a palladium catalyst are consistent with the structural assignments and calculated energies.

Fused ring systems have long been of interest to organic chemists, both because of their wide occurrence in the compounds of nature, and because they present challenging problems in relating chemical behavior to three-dimensional structure. Monocyclic compounds have been studied at length, and bicyclic compounds reasonably so.[5,6] Tricyclic compounds are, on the whole, not a well-studied group.[5,6]

Among the more simple (from a conformational point of view) of the tricyclic compounds are the perhydroanthracenes (PHA) and the perhydrophenanthrenes (PHP). There are five diastereoisomers of PHA, all of



PHA

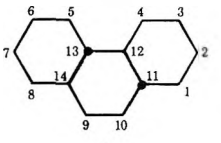


PHP

which are known compounds,[7] and six isomers of PHP, of which none has previously been reported in pure form.

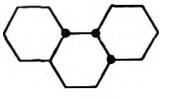
Cyclohexane is conformationally a very simple molecule, which exists essentially completely in one conformation. Decalin, which has two cyclohexane rings fused together, exists in two diastereomeric forms, cis and trans. The latter consists of a single conformation, and the former is a mixture of rapidly equilibrating enantiomers. In the PHA and PHP molecules, the isomer problem is much more complicated and was examined in some detail many years ago by Johnson[8].

The six diastereomers of PHP are shown in projection and perspective formulas, and the relative energies of



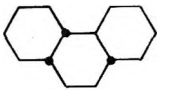
1

trans-anti-trans (tat), 0.8 kcal



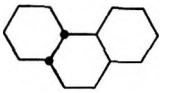
2

trans-syn-cis (tsc), 3.2 kcal



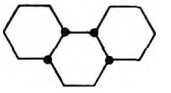
3

cis-anti-trans (cat), 3.2 kcal



4

cis-anti-cis (cac), 4.8 kcal



5

cis-syn-cis (csc), 7.2 kcal

6

trans-syn-trans (tst), 5.6 kcal

each as estimated by Johnson are also shown. These energies were obtained by counting gauche interactions, and allowing 0.8 kcal/mol for each. Two of the molecules contain features for which Johnson could only guess energies: the trans-syn-trans isomer (tst) has ring B in a boat or twist–boat conformation, and the cis-syn-cis isomer (csc) contains a 1,3-syn-diaxial interaction. These features are best seen with the aid of perspective formulas.

The energy of a boat form of a cyclohexane ring, relative to a chair, was approximately known to Johnson from early work by Pitzer[9] on cyclohexane itself. The value in a related (perhydroanthracene) compound was

(1) Paper LXIX: N. L. Allinger, M. T. Tribble, M. A. Miller, and D. H. Wertz, *J. Amer. Chem. Soc.*, in press.

(2) This work was supported in part by Public Health Service Research Grant No. AM-5836 from the National Institute of Arthritis and Metabolic Diseases.

(3) Correspondence concerning this work should be directed to this author at the University of Georgia.

(4) U. S. Public Health Service Post-Doctoral Research Fellow, 1968–1970.

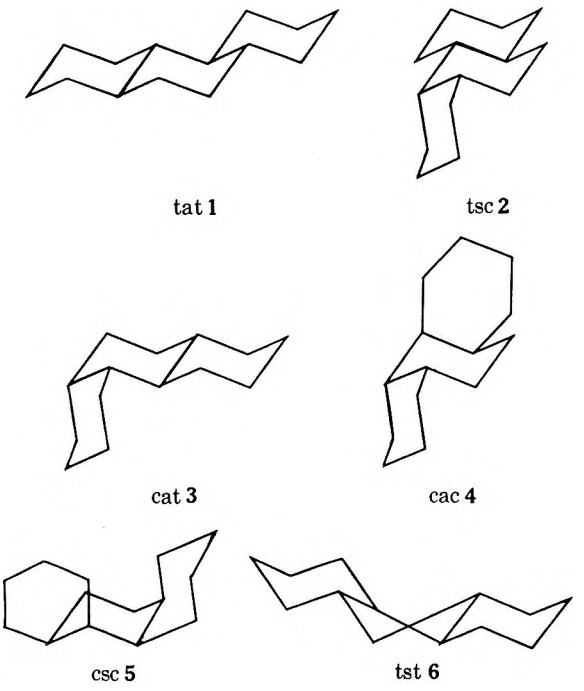
(5) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965.

(6) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962.

(7) R. L. Clarke, *J. Amer. Chem. Soc.*, **83**, 965 (1961).

(8) W. S. Johnson, *ibid.*, **75**, 1498 (1953).

(9) C. W. Beckett, K. S. Pitzer, and R. Spitzer, *ibid.*, **69**, 2488 (1947).



subsequently determined by heat of combustion measurements,[10] and it supports the earlier estimates.

The energy of a 1,3-syn-diaxial interaction had been guessed at by Pitzer,[11] and the value subsequently measured on methylated cyclohexanes[12] supported Pitzer's estimate.

Johnson counted one 1,3-syn-diaxial interaction of the methyl–methyl type in csc (**5**), but there are actually *two* interactions of this type. There are also seven *skew*-butane interactions, so that the estimate should have been $7 \times 0.8 + 2 \times 2.8 = 11.2$ kcal/mol. Since deformation of the ring system to relieve the syn-diaxial interactions acts in the same direction for both interactions, the ΔE value calculated by molecular mechanics is somewhat lower (9.0 kcal).

Results and Discussion

In this paper, some experimental and calculational results concerning the PHP isomers will be presented. The PHA isomers will be discussed separately later.

Calculational Work.—In previous papers we have discussed the Westheimer method for obtaining molecular geometries and energies.[1,13] This calculational method has been applied to the present problem, and the results are summarized in Table I. Data on the decalins are also included for reference purposes.

Since the calculational method is known to be quite good for hydrocarbons which are not excessively strained, the calculated values for the decalins come out in good agreement with experiment as expected. The calculated values for the perhydrophenanthrenes are thought to be similarly good, but no experimental values are available for comparison. The agreement between

(10) J. L. Margrave, M. A. Frisch, R. G. Bautista, R. L. Clarke, and W. S. Johnson, *J. Amer. Chem. Soc.*, **85**, 546 (1963).

(11) C. W. Beckett, K. S. Pitzer, and R. S. Spitzer, *ibid.*, **69**, 2488 (1947).

(12) N. L. Allinger and M. A. Miller, *ibid.*, **83**, 2145 (1961).

(13) (a) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *ibid.*, **91**, 337 (1969); (b) N. L. Allinger, J. A. Hirsch, M. A. Miller, and I. J. Tyminski, *ibid.*, **90**, 5773 (1968); (c) N. L. Allinger, J. A. Hirsch, M. A. Miller, I. J. Tyminski, and F. A. Van-Catledge, *ibid.*, **90**, 1199 (1968); (d) N. L. Allinger, M. A. Miller, F. A. Van-Catledge, and J. A. Hirsch, *ibid.*, **89**, 4345 (1967).

TABLE I

THE ENERGIES OF THE ISOMERIC PERHYDROPHENANTHRENES AND DECALINS (GAS PHASE, 25°)

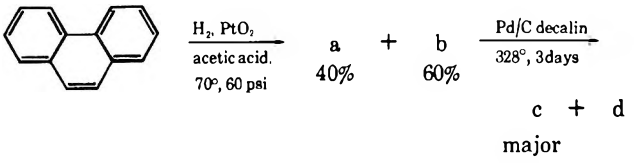
		Relative enthalpies		
Compd	$H_f°$ (calcd)	This work	Johnson	Experimental
trans-decalin	−43.68	0.0	0.0	0
cis-decalin	−40.89	2.79	2.4	3.09 ± 0.77[a]
tat 1	−56.03	0.0	0.0	
tsc 2	−53.60	2.44	2.4	
cat 3	−53.47	2.57	2.4	
cac 4	−52.02	4.01	4.0	
csc 5	−47.03	9.01	7.2	
tst 6	−49.01	7.03	5.6	

[a] D. M. Speros and F. D. Rossini, *J. Phys. Chem.*, 64, 1723 (1960).

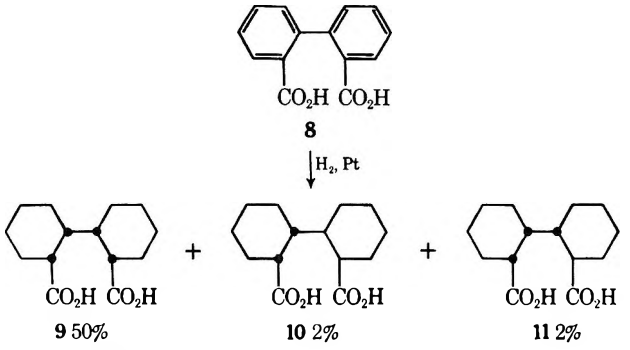
our detailed calculations and the estimates by Johnson is very close, except for the two isomers containing the unusual steric interactions. As we had supposed, these latter two structures give calculated energies somewhat higher than do estimates based on simple compounds, but the early estimates are pretty good. It is of interest that for tst (**6**) the B ring is found to be in a twist–boat form. The classical boat is almost 1 kcal/mol higher in energy.

We wished to test the theoretical predictions experimentally and to that end have undertaken the synthesis of the isomeric perhydrophenanthrenes. In this paper are reported the syntheses and structure proofs of four of the six isomers. We hope to report on the remaining two isomers at a later date.

Experimental Work.—A reasonable starting place appeared to be the hydrogenation of phenanthrene itself.[14] When phenanthrene was hydrogenated with the aid of a platinum catalyst, there were formed two isomers, a (40%) and b (60%), as established by vpc.



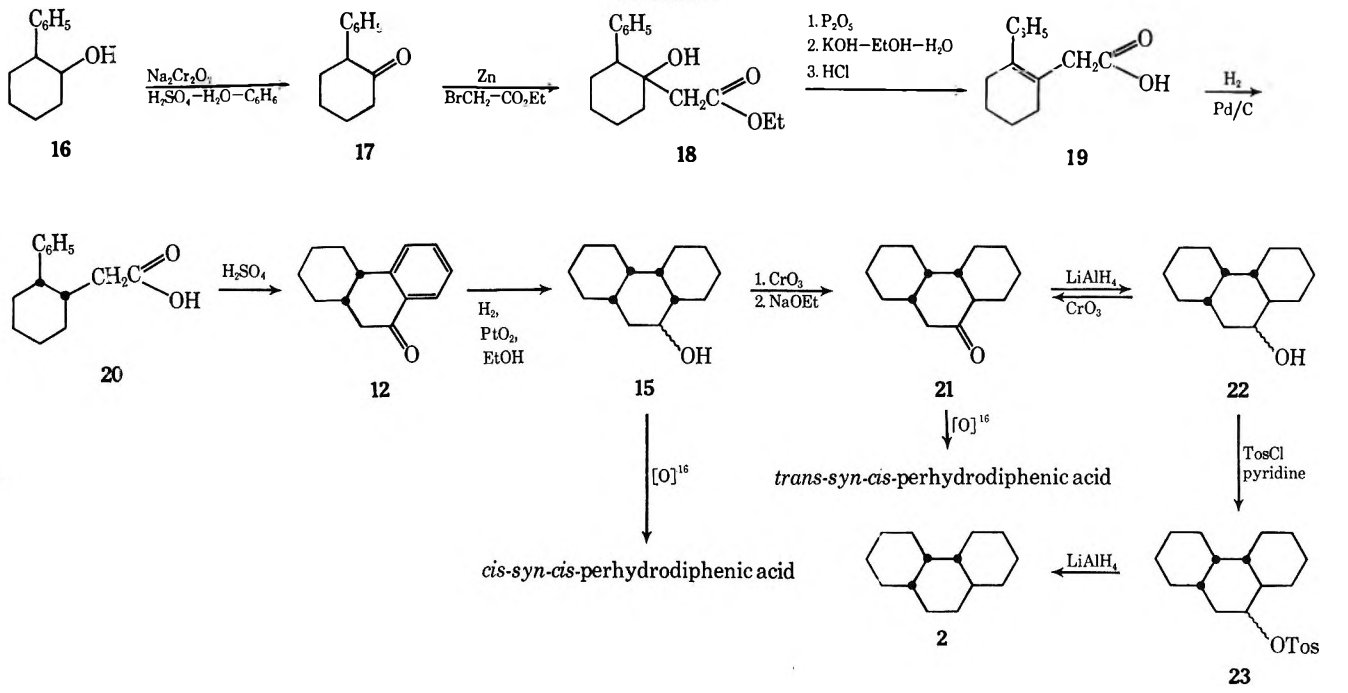
Diphenic acid (**8**) has been observed to give the products shown under similar conditions.[15] In view of these re-



(14) We have been able to carry out this reaction in the Parr low pressure apparatus. The following workers have studied the conditions of high pressure hydrogenation of phenanthrene, but not with the intent of identifying the resulting isomers: (a) I. Kagehira, *Bull. Chem. Soc. Jap.*, **6**, 241 (1931); (b) J. R. Durland and H. Adkins, *J. Amer. Chem. Soc.*, **59**, 135 (1937).

(15) R. P. Linstead, W. v. E. Doering, S. B. Davies, P. Levine, and R. R. Whetstone, *ibid.*, **64**, 1985 (1942).

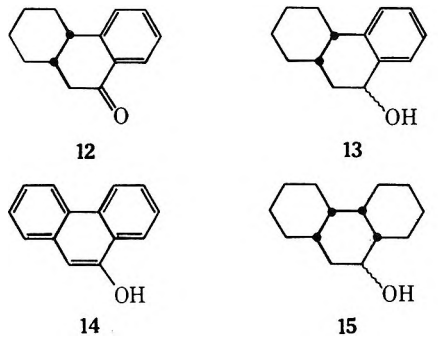
SCHEME I



sults, as well as the expected cis addition by hydrogen, it was thought that the hydrogenated phenanthrenes, a and b, should correspond to materials with these largely cis-stereochemical backbones.

Preliminary investigation also included the equilibration of the mixture, a and b, over a Pd/C catalyst, whereby there were produced two isomers, c and d, with c constituting about 80% of the mixture. Some material with the same retention time as a remained, although b seemed to have completely disappeared. In light of these results and previously mentioned considerations, it was concluded that b, the major isomer from the hydrogenation of phenanthrene, was **5**, the all-cis isomer, and a was either **2** or **4**, analogous to the case of the perhydrodiphenic acids. Compound c, produced by equilibration, was almost certainly **1**, the most stable all-trans isomer; d, also produced in the equilibration, could be either **2** or **3**, the next most stable of the isomers.

It has been said that b must be **5**. Further evidence supports this assignment. When the related compounds **12**, **13**, or **14** were hydrogenated, the same hydrocarbon mixture of a and b was obtained. The products from *cis*-9-ketooctahydrophenanthrene (**12**), *cis*-octahydro-9-phananthrol (**13**), and 9-phenanthrol (**14**) all gave the same two peaks on vpc with b accounting for 80, 80, and 53% of the mixture, respectively.



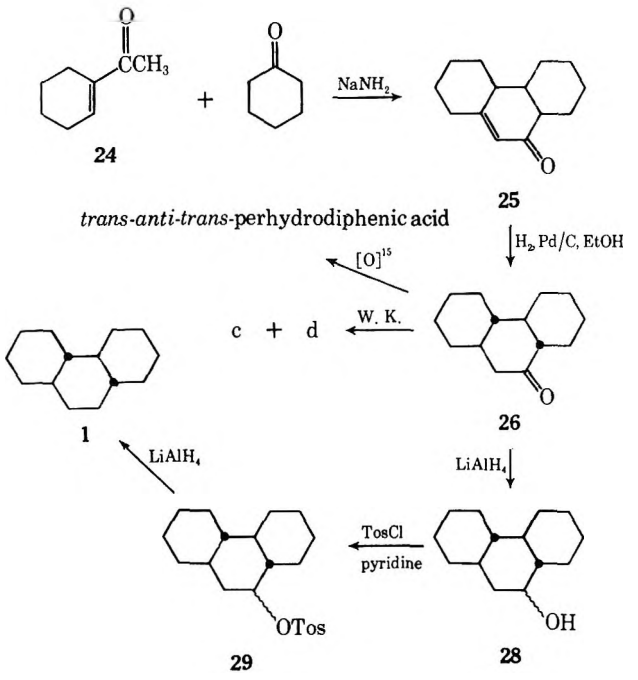
The hydrogenation of **12** was of particular value, as there was also isolated (in addition to a and b) the known solid *cis-syn-cis*-9-perhydrophenanthrol (**15**). With b now assigned as isomer **5**, it was separated by preparative vpc and may be obtained readily in this manner. Next, isomer a was shown to be **2**, *trans-syn-cis*-perhydrophenanthrene, as it was identical with the compound obtained from Scheme I.

Although the scheme to **22** has been reported previously,[16] enough anomaly was encountered to warrant its inclusion here (see Experimental Section). The stereochemical integrities of **15** and **22** have been demonstrated by oxidation to the respective known perhydrodiphenic acids.[16] Conversion of **22** to the trans-syn-cis isomer **2**, proceeded *via* reduction of the tosylate **23**, and the resulting pure liquid material corresponded in all respects to a (vpc, refractive index, nmr).

Attention was then focused on c, thought to be the trans-anti-trans isomer **1**, and indeed this was shown to be the case when the material from Scheme II proved to be identical with c. The *trans-anti-trans*-9-ketoperhydrophenanthrene (**26**) was prepared essentially by the method of Rapson and Robinson.[17] Proof of structure was *via* oxidation to the known perhydrodiphenic acid. Initially an attempt was made to reduce the carbonyl *via* some direct route; however, this proved to be unsatisfactory for complete and unambiguous conversion to a single isomer. Wolf–Kishner reduction, for example, gave two peaks c and d, with c predominating. Since these materials arose from the known trans-anti-trans precursors, it is logical that c should be the trans-anti-trans isomer (product of either thermodynamic or kinetic control), and this was proven later. If this proof is anticipated for the moment, d can only be the trans-anti-cis isomer **3**, arising from epimerization (by either acid or base catalysis) of the center adjacent to the carbonyl, followed by reduction of the resulting ketone. The isomeric hydrocarbon pair c and d could not be

(16) R. P. Linstead and R. R. Whetstone, *J. Chem. Soc.*, 1428 (1950).
(17) W. S. Rapson and R. Robinson, *ibid.*, 1285 (1935).

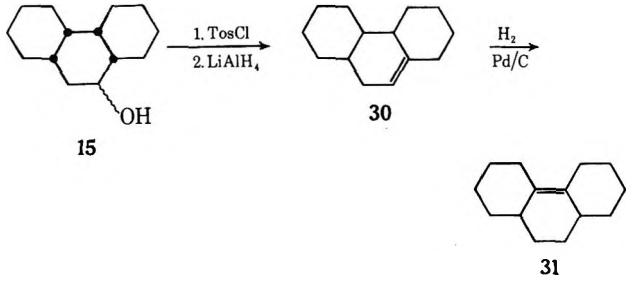
SCHEME II



effectively separated preparatively, and hence d or **3** was not studied further.

Final proof of the identity of c was by way of the tosylate **29** and reduction to a single pure liquid. This material must be *trans-anti-trans*-perhydrophenanthrene (**1**); it was identical with c as judged by vpc, nmr, and refractive index.

Finally, although b has been clearly shown to be **5**, an attempt was also made to prepare it from **15**. The tosylate route now was no longer successful, since **15** could not be completely converted to a tosylate. The infrared spectrum indicated that a mixture of alcohol and tosylate was obtained (despite repeated attempts, the pure tosylate could not be isolated). Reduction of the mixture that was obtained did give material with retention time of b, but this was an olefin as demonstrated by bromine in chloroform and tetranitromethane tests, as well as analysis and nmr. Attempted hydrogenation changed this olefin to material with retention time of a; this was also olefinic. The absence of vinyl hydrogen absorption in the nmr spectrum of the latter olefin suggests that it was the ditertiary olefin **31**. The material still reacted readily with bromine in chloroform.



Similar unsuccessful hydrogenations accompanied by subsequent isomerization to ditertiary olefins have been recorded in the literature.[18]

Equilibration of the isomers **1**–**6** at 328° over a palladium catalyst was carried out, and the mixture was analyzed by vpc. It was not possible to accurately establish the free-energy differences in this way. The separations were not clean, and it was only possible to measure the composition of the mixture approximately as follows: **1** (85%), **2** (10%), **3** (5%), **4**, **6** (not detected), **5** (less than 0.5%). While of very limited accuracy, these values are consistent with the structural assignments and calculated energies.

Experimental Section[19]

Infrared spectra were recorded with a Beckman Model IR-4 spectrophotometer. Nmr spectra were taken on a Varian A-60 spectrometer; chemical shifts are relative to internal TMS = 0 ppm. The two columns used for vpc analyses were 0.25 in. o.d. × 10 ft 5% silicone oil on firebrick (column A) and 0.25 in. o.d. × 6 ft 10% polyglycol on firebrick (column B).

Hydrogenation of Phenanthrene.—A solution of 25 g of phenanthrene in 200 ml of acetic acid was hydrogenated in the presence of 3 g of platinum oxide catalyst at 70° and an initial pressure of 60 psig. Since very little hydrogen was taken up in the first 3 days, the catalyst was removed by filtration and a fresh 3-g portion was added. Hydrogenation under the same conditions then proceeded at a reasonable rate. After the theoretical amount of hydrogen had been taken up, the mixture was allowed to remain under these conditions 1 day more. The solution was cooled and the catalyst was again removed. The solvent was removed with the use of an aspirator while heating on the steam bath. The remaining oil was taken up in pentane, washed with sodium carbonate solution and water, and dried, and the solvent was removed. The residue was distilled *in vacuo* to give 19 g (80%) of a main fraction, bp 119–125° (4 mm). This product gave a positive (yellow) tetranitromethane test and showed two main vpc peaks on column A at 200° and 7 psig. A shoulder peak (a) was immediately followed by the main peak (b). If the temperature and pressure were lowered, the first peak (a) gave indications of a third component. These two isomeric compounds were later identified as the cis-syn-cis isomer **5** (peak b), which comprised 60% of the mixture, and the trans-syn-cis isomer **2** (peak a) present to the extent of 40%. The mixture had n^{25}D 1.5084.

Equilibration of the Perhydrophenanthrenes.—A solution of 10 g of the perhydrophenanthrene mixture from the hydrogenation of phenanthrene (40% tst, 60% csc) in 20 g of decalin, together with 1.5 g of palladium on charcoal, was allowed to stand for 3 days in a sealed tube at 328°. Vpc analysis of the resulting material showed it to contain roughly 85% *trans-anti-trans*-, 5% *cis-anti-trans*-, and 10% *trans-syn-cis*-perhydrophenanthrene. The separations were not clean, and more accurate analyses will have to await the availability of more efficient equipment.

***cis-syn-cis*-Perhydrophenanthrene (5).**—Isolation of the main product from hydrogenation of phenanthrene (b) by preparative vpc gave a liquid which gave a negative tetranitromethane test and showed now only one vpc peak. This material has been assigned the cis-syn-cis structure. The nmr confirmed that no olefinic material was present, and the material had n^{25}D 1.5120.

Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.28; H, 12.58.

***trans*-Δ^{10}-9-Ketododecahydrophenanthrene (25).**—To a stirred, cooled slurry of 30 g of sodium amide in 1 l. of anhydrous ether, a solution of 75 g of cyclohexanone in 500 ml of ether was added over a period of 1 hr. After an additional 0.5 hr, a solution of 88 g of freshly distilled acetylcyclohexene was added over a period of 3 hr. Overnight stirring at room temperature was followed by the cautious addition of 500 ml of water. The ether layer was separated, washed with water, and dried, and the solvent was removed. The oily residue was distilled to give a forerun, bp 65–154° (3 mm), followed by the product, bp 154–160° (3.5 mm). This fraction soon solidified and was recrystallized from ether to give 30 g (29%, based on recovered cyclohexanone) of the product, mp 85–90° (reported[20] mp 87–88°).

***trans-anti-trans*-Perhydro-9-phenanthrol (28).**—Reduction of the α,β-unsaturated ketone **25** to the saturated ketone **26** (mp 48–50°) with hydrogen and a palladium catalyst, followed by

(18) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 112.

(19) The authors are indebted to Drs. L. A. Tushaus and A. R. Perry for some preliminary experiments on this problem.

(20) R. P. Linstead and A. L. Walpole, *J. Chem. Soc.*, 842 (1939).

lithium aluminum hydride reduction, gave the alcohol **28**, mp 118.5–120° (reported[20] mp 119°).

trans-anti-trans-**Perhydrophenanthrene-9-*p*-toluenesulfonate** (**29**).—To a stirred solution of 3.1 g of *trans-anti-trans*-perhydro-9-phenanthrol (**28**) in 20 ml of dry pyridine was added a solution of 3.42 g of *p*-toluenesulfonyl chloride in 8 ml of pyridine over a period of 0.5 hr at room temperature. After stirring for 2 hr, the mixture was allowed to stand overnight. Ice was added and the solution was allowed to stand for 1 hr. Concentrated hydrochloric acid was added followed by additional ice, and the solution was allowed to stand 1 hr more. The ether layer was separated and the aqueous layer was extracted with additional ether. The combined ether layers were washed with sodium carbonate solution and water and dried, and the solvent was removed. At this point, 25 ml of ether and 25 ml of 95% ethanol were added, and the material was crystallized in a Dry Ice–acetone bath. The solid was recrystallized three times in this manner to give 1.8 g (33%) of the product, which softened at 94° and melted at 108.5–110°. The infrared spectrum showed bands at 7.9, 8.4, and 8.5 μ characteristic of a tosylate.

Anal. Calcd for $C_{21}H_{30}O_3S$: C, 69.57; H, 8.39. Found: C, 69.48; H, 8.54.

trans-anti-trans-**Perhydrophenanthrene** (**1**).—To a stirred solution of 2 g of lithium aluminum hydride in 100 ml of ether, a solution of 1.75 g of tosylate **29** in 25 ml of ether was added during a period of 0.5 hr. Stirring was discontinued 2 hr after the addition was complete, and the solution was allowed to stand overnight. Water was added, followed by 10% hydrochloric acid. The solution was then washed with sodium carbonate solution and water and dried, and the solvent was removed. The remaining yellow oil was taken up in the minimum amount of pentane and chromatographed on 8 g of neutral activity I Woelm alumina. The first fraction contained 200 mg (21%) of the product, mp 18–19° (no other material was detected in later fractions). The compound gave a negative TNM test; vpc showed one peak on column A at 200° and 7 psig, $n^{25}D$ 1.4942. The nmr spectrum also showed the absence of olefinic material.

Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.67; H, 12.46.

Wolff–Kischner Reduction of *trans-anti-trans*-9-Ketoperhydrophenanthrene (**26**).—A solution of 2.5 g of *trans-anti-trans*-9-ketoperhydrophenanthrene (**26**), 4.5 g of 85% hydrazine hydrate, and 5 g of sodium hydroxide in 50 ml of redistilled diethylene glycol was heated until the temperature in the reaction flask reached 150°. This temperature was maintained for 1.5 hr to allow the completion of hydrazone formation. The temperature was gradually increased to distil excess hydrazine and water from the reaction vessel, until the temperature of the mixture had reached 225°. This temperature was maintained for 4 hr. After the mixture had cooled, it was extracted with pentane; the extract was washed with water and dried. The ether solution was concentrated to a small volume and chromatographed on A-540 Fisher alumina. From the first fractions was obtained an oil which gave a negative TNM test. The material gave one main peak with a shoulder on vapor phase chromatography on column A at 198° and 8 psig; the resolution was worse on column B at 146° and 5 psig. The major peak had the same retention time as the previously described trans-anti-trans isomer prepared by the reduction of the corresponding tosylate. On column A, the two peaks again were identical with the two major peaks (a and b) from the hydrogenation of phenanthrene. Since the material gave a completely negative TNM test, the shoulder peak must be the cis-anti-trans isomer **3**, an isomer which was not obtained by other means.

cis-**9-Keto-1,2,3,4,9,10,11,12-octahydrophenanthrene** (**12**).—2-Phenylcyclohexanol (Aldrich) was oxidized with dichromate to 2-phenylcyclohexanone, mp 58–60° (reported mp 50–53°,[21] 53–55°[22]), which underwent a Reformatsky reaction with ethyl bromoacetate and zinc to give ethyl 2-phenylcyclohexanol-1-acetate, bp 155–175° (4 mm) [reported[21] bp 146–154° (0.8 mm)]. Dehydration of this material with phosphorus pentoxide gave the unsaturated ester, bp 144–154° (3 mm) [lit. bp 123–125° (0.8 mm),[21] 146–153° (3 mm)[23]]. The latter was saponified with potassium hydroxide and gave 2-phenyl-Δ^1-cyclohexenylacetic acid (**19**) as a gum, bp 165–180° (1.5 mm) [lit. bp 150–155° (0.4 mm),[21] 180–190° (3 mm)[23]]. Hydrogenation of this compound with palladium on carbon in acetic acid gave *cis*-2-phenylcyclohexaneacetic acid (**20**), mp 165–170° (lit.[21,23] mp 168–170°).

To 11 g of *cis*-2-phenylcyclohexaneacetic acid (**20**), 55 g of concentrated sulfuric acid was added in one portion. The mixture was heated on a steam bath with occasional swirling for 15 min and then poured directly onto ice. The resulting milky solution was allowed to come to room temperature and was extracted with ether. The ether layer was washed with sodium carbonate solution and water and dried, and the solvent was removed. The resulting yellow oil was distilled to give 8.7 g (86%) of the product, bp 155–157° (2 mm) [lit. bp 132–135° (0.5 mm),[21] 162–163° (5 mm)[23]].

cis-syn-cis-**Perhydro-9-phenanthrol** (**15**).—The hydrogenation of a solution of 13.4 g of **12** in 60 ml of ethanol was carried out on the presence of 0.5 g of platinum oxide at room temperature and an initial pressure of 39 psig. Six days were required for the the theoretical amount of hydrogen to be taken up. During this time two more 0.25-g portions of catalyst were added so that the total amount of catalyst used was 1 g. At the end of this time the solution was filtered through Celite, and the solvent was removed with the use of an aspirator. The resulting oil was dissolved in hexane and cooled to give 6 g of material having mp 80–100° (lit.[24] mp 70–85°). This material did not crystallize readily and was best separated by first cooling in a Dry Ice–acetone bath thoroughly and then slowly warming in a beaker of water. Recrystallization from cyclohexane gave 5.0 g (36)% of material of mp 108–110° (lit.[24] mp 108–110°). The infrared spectrum was characteristic of an alcohol. The perhydrophenanthrene residue which was obtained from the hexane mother liquor showed 20% a and 80% b by vpc.

Attempt to Synthesize *cis-syn-cis*-Perhydrophenanthrene from *cis-syn-cis*-9-Perhydrophenanthrol (**15**). **A. Tosylation of *cis-syn-cis*-9-Perhydrophenanthrol** (**15**).—To a stirred solution of 1.9 g of *cis-syn-cis*-perhydro-9-phenanthrol (**15**) in 15 ml of dry pyridine, a solution of 2.86 g of *p*-toluenesulfonyl chloride in 5 ml of pyridine was added at room temperature over a period of 0.5 hr. Stirring was continued for 3 hr and the resulting solution was allowed to stand for 3 days. At the end of this time an excess of ice was added, followed by 10 ml of concentrated hydrochloric acid. After the mixture was allowed to stand for 2 hr, it was extracted with ether. The ether layer was washed with sodium carbonate solution and water and dried, and the solvent was removed. Attempted crystallization of the resulting oil from ether–95% ethanol at −78° was unsuccessful. Although a small amount of solid material separated, most of the material remained as an oil. The infrared spectrum of this oil showed absorption at 2.9, 7.9, and 8.5 μ, indicating a mixture of starting alcohol and tosylate. This was used directly in the next step.

B. Reduction of Tosylate Mixture.—To a stirred solution of 0.75 g of lithium aluminum hydride in 30 ml of ether, a solution of the previously described oil from the tosylation of 0.9 g of **15** in 20 ml of ether was added over a period of 0.5 hr. After 3 hr of additional stirring, the solution was allowed to stand at room temperature for 3 days. Water was added, followed by 75 ml of 10% hydrochloric acid solution. The ether layer was separated and the aqueous layer was extracted with additional ether. The combined ether extracts were washed with water and dried, and the solvent was removed. The remaining oil was taken up in pentane and chromatographed on 5 g of neutral activity I Woelm alumina. From the first fraction was obtained 400 mg (52%) of a clear liquid, which had $n^{25}D$ 1.5115. The product gave a positive (yellow) TNM test. The vpc retention time (column A at 200° and 7 psig) was identical with that of isomer b from the hydrogenation of phenanthrene. The uptake of the peak showed some distortion. The nmr spectrum showed vinyl proton absorption at τ 4.8. The nmr spectrum and the infrared spectrum, which had strong bands at 11.7–12.5 μ characteristic of a trisubstituted olefin, suggest structure **30**. It was calculated from the nmr spectrum that about 83% of the material was compound **30**.

Anal. Calcd for $C_{14}H_{22}$: C, 88.36; H, 11.80. Found: C, 88.30; H, 11.80.

C. Atttempted Hydrogenation of Olefin 30 from the Reduction of the Tosylate Mixture from *cis-syn-cis*-9-Perhydrophenanthrol

(21) J. W. Cook, C. L. Hewett, and C. A. Lawrence, *J. Chem. Soc.*, 71 (1936).

(22) C. C. Price and J. V. Karabinos, *J. Amer. Chem. Soc.*, **62**, 1159 (1940).

(23) R. P. Linstead, R. R. Whetstone, and P. Levine, *ibid.*, **64**, 2014 (1942).

(24) R. P. Linstead, R. R. Whetstone, and P. Levine, *ibid.*, **64**, 2014 (1942).

(15).—A mixture of 240 mg of olefin **30**, 56 mg of 10% Pd/C catalyst, and 10 ml of ethanol showed hardly any uptake of hydrogen after 2 hr at atmospheric pressure. Removal of the catalyst and solvent gave a material which had $n^{25}D$ 1.501. Although the nmr spectrum revealed that the vinyl protons were now completely gone, the material readily reacted with an excess of a 2% bromine in chloroform solution (the mixture of a and b from the hydrogenation of phenanthrene did not), and gave a strong (brown) TNM test. These results indicate that an olefin such as **31** was formed which is resistant to hydrogenation.

cis-as-Octahydro-9-phenanthrol (**13**). **A. Lithium Aluminum Hydride Reduction of Ketone.**—Reduction of 5 g of *cis*-octahydro-9-ketophenanthrene (**12**) with lithium aluminum hydride in ether solution was followed by acidic work-up. Recrystallization of the product from cyclohexane gave 4.3 g (84%) of **13**, mp 114–116° (reported mp 115–116°,[24] 114–115°[21]).

B. Hydrogenation of the Ketone.—A mixture of 9.55 g of *cis*-octahydro-9-ketophenanthrene (**12**) and 4.15 g of slightly impure *cis-as*-octahydro-9-phenanthrol (**13**) was dissolved in 75 ml of ethanol and hydrogenated in the presence of 0.75 g of platinum oxide catalyst. The reaction was complete after 4 days at room temperature and 30–50 psig. The catalyst was removed by filtration and the solvent was removed with the use of an aspirator. The resulting material was recrystallized twice from cyclohexane to give 13 g of crystals, mp 108–113° (lit. 115–116°,[24] 114–115°[21]).

Hydrogenation of *cis-as*-Octahydro-9-phenanthrol (13). A. In Ethanol–Platinum Oxide.—One gram of **13** was dissolved in 35 ml of ethanol and 1.5 ml of acetic acid and hydrogenated at room temperature and 30 psig in the presence of 0.25 g of platinum oxide catalyst. After 3 days, hydrogen uptake became slow. Removal of the catalyst and solvent gave an oil which was taken up in ether. The ether solution was washed with water and dried, and the solvent was removed. The resulting oil showed two vpc peaks on column A at 109° and 9 psig which were identical in retention time with those observed for the products of hydrogenation of phenanthrene and of 9-phenanthrol (a and b). In this case, the second peak (b) (the cis-syn-cis isomer, **5**) comprised about 80% of the mixture.

B. In Ethanol–Rhodium/Alumina.—Hydrogenation of a solution of 1.85 g of the alcohol in 20 ml of methanol and 1.5 ml of acetic acid in the presence of 2.5 g of rhodium-on-alumina catalyst, under the conditions described above, gave the same two isomers (a and b), together with the starting alcohol. Since this hydrogenation did not proceed well and did not go to completion, it was not pursued further.

Hydrogenation of 9-Phenanthrol (14). A. With Platinum Oxide in Acetic Acid.—To a solution of 11 g of 9-phenanthrol (**14**) in 100 ml of ether, Norit was added. After the solution was allowed to stand for 2 hr, it was filtered, and 1 teaspoon of W-2 Raney nickel was added. After standing again for 2 hr, the solution was filtered through Celite and the solvent was removed. The solid now had mp 151–153° (lit.[25] 153–155°) and started to take on a color; it was immediately taken up in 200 ml of acetic acid and hydrogenated in the presence of 2 g of platinum oxide catalyst at an initial pressure of 40 psig. The theoretical amount of hydrogen was taken up in 24 hr. After filtration through Celite, 200 ml of water was added and the solution was extracted with ether. The ether solution was washed with water and dried, and the solvent was removed. The resulting oil, which solidified upon standing overnight, was taken up in the minimum amount of pentane–benzene and chromatographed on 322 g of neutral activity I Woelm alumina. Fractions of 200 ml were taken and the following series of solvents was used: 50, then 75% benzene–pentane; benzene; 1, 5, 10, 25, and 50% ether–benzene; ether; 1, 5, and 10% methanol–ether. The second fraction was found by vpc (column A at 210° and 7 psig) to contain the same two isomers (a and b) obtained from the hydrogenation of phenanthrene, in the ratio of about 53% b (cis-syn-cis) to 47% a (trans-syn-cis). The latter fractions contained an oil which solidified upon standing. Two recrystallizations from Norit-treated hexane solutions gave 1 g of sym-octahydro-9-phenanthrol, mp 133–135° (lit.[24] 134–135°).

trans-syn-cis-Perhydrophenanthrene-9-*p*-toluenesulfonate (**23**). **A.** *cis-syn-cis*-9-Ketoperhydrophenanthrene.—To a stirred solution of 1.5 g of *cis-syn-cis*-9-perhydrophenanthrol (**15**) in 25 ml of acetone, Jones reagent was added until the orange color of the reagent remained. After stirring for 5 min, isopropyl alcohol was added to decompose the excess reagent. The resulting solution was filtered through Celite, and ether was added. The ether solution was washed with water and dried, and the solvent was removed. The absence of hydroxyl absorption and the presence of a strong carbonyl band at 5.8 μ in the infrared spectrum of the resulting oil demonstrated that the oxidation was complete. The oil was crystallized from petroleum ether at −78° to give 1 g (71%) of solid material, mp 39–41.5° (reported[24] mp 43–44°).

B. *trans-syn-cis*-9-Ketoperhydrophenanthrene (**21**).—A mixture of 1 g of the cis-syn-cis ketone and 25 ml of 0.75 *M* sodium ethoxide soluion was heated to reflux for 3 hr, cooled, and allowed to stand at room temperature overnight. Ether was then added to the solution, which had turned dark brown. The ether solution was washed with water and dried, and the solvent was removed. The resulting material was recrystallized from petroleum ether (after standing overnight with Norit) at −78° to give 0.5 g (50%) of the product, mp 51.5–55° (lit.[24] mp 56.5–57.5°). The infrared spectrum (CCl_4) of the crystalline material was very similar to the spectrum of the cis-syn-cis ketone. However, the melting point of a mixture of the two ketones was depressed to 24–35°.

C. *trans-syn-cis*-Perhydro-9-phenanthrol (**22**).—A solution of 0.5 g of *trans-syn-cis*-9-keto-perhydrophenanthrene (**21**) in 15 ml of ether was added during 2 min to a stirred slurry of 0.5 g of lithium aluminum hydride in 25 ml of ether. Stirring was continued for 2.5 hr, after which the mixture was allowed to stand overnight. Water was added, followed by 10% hydrochloric acid. The ether layer was separated, the aqueous layer was thoroughly extracted with ether, the combined ether layers were washed with water and dried, and the solvent was removed. The residue was difficult to crystallize but could be obtained as a crude solid by removing all of the solvent. The material in this state softened at 62° and melted at 69–76°. The infrared spectrum showed strong hydroxyl absorption at 2.9 μ and no carbonyl absorption and was similar to that of the cis-syn-cis alcohol (**15**) except for the presence of an additional band at 7.9 μ. Thin layer chromatography showed the crude material to contain essentially one compound, and to be different from the cis-syn-cis alcohol (**15**) which was not eluted so fast by ether. Recrystallization of the crude material from petroleum ether at −78° (requires 20–30 min to separate) gave 0.3 g (60%) of the product, mp 91–94° (lit.[24] mp 88–89°). The melting point of a mixture of this material with the cis-syn-cis alcohol (**15**) was depressed to 74–88°. The material was thus proven to be totally different and not an epimer of the starting cis-syn-cis alcohol (**15**) by this sequence.

D. *trans-syn-cis*-Perhydrophenanthrene-9-*p*-toluenesulfonate (**23**).—A solution of 1 g of *p*-toluenesulfonyl chloride in 3 ml of dry pyridine was added during 15 min to a stirred solution of 0.3 g of *trans-syn-cis*-9-phenanthrol (**22**) in 8 ml of pyridine. The mixture was stirred for 3 hr and then allowed to stand at room temperature overnight. Excess ice was added and the mixture was allowed to stand for 2 hr. It was then taken up in ether; the ether solution was washed with sodium carbonate solution and water and dried. Removal of the solvent gave an oil which was recrystallized twice from hexane to give 0.3 g (60%) of the product, mp 103–104.5°. The infrared spectrum showed strong bands at 7.9 and 8.5 μ characteristic of a tosylate.

The melting point of a mixture with the *trans-anti-trans*-perhydrophenanthrene-9-*p*-toluenesulfonate (**29**) (mp 101–103°) was depressed to 85–96°.

Anal. Calcd for $C_{21}H_{30}O_3S$: C, 69.57; H, 8.39. Found: C, 69.63; H, 8.34.

trans-syn-cis-Perhydrophenanthrene (**2**). **A. Reduction of Tosylate (23).**—A solution of 0.65 g of *trans-syn-cis*-phenanthrene-9-*p*-toluenesulfonate (**23**) in 15 ml of ether was added during 15 min to a stirred solution of 1 g of lithium aluminum hydride in 35 ml of ether. After 2 hr of additional stirring, the solution was allowed to stand at room temperature overnight. Water was added carefully, followed by 10% hydrochloric acid. The ether layer was separated, washed with sodium carbonate solution and water, and dried. Removal of the solvent gave an oil which was chromatographed on 12 g of neutral activity I Woelm alumina in pentane. The first fraction gave an oil, $n^{25}D$ 1.5015, which still gave a positive (yellow) TNM test. This material showed a single vpc peak (column A at 200° and 7 psig) of the same retention time as the first isomer (peak a) in the hydrogenation of phenanthrene. Peak a was therefore assigned to the trans-syn-cis isomer (**2**). The nmr spectrum revealed the absence of olefinic material.

(25) L. F. Fieser, R. P. Jacobsen, and C. C. Price, *J. Amer. Chem. Soc.*, **58**, 2163 (1936).

Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.45; H, 12.39.

B. From the Hydrogenation of Phenanthrene.—Separation of the first (a) of the two isomers obtained from the hydrogenation of phenanthrene by preparative vpc gave a product which was identical by its vpc retention time, index of refraction, and nmr spectrum with that obtained from the reduction of the tosylate **23**. After separation by vpc, this isomer was chromatographed on 5 g of neutral, activity I Woelm alumina in pentane. The material obtained gave a negative TNM test and had $n^{25}D$ 1.5015.

Anal. Calcd $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.37; H, 12.78.

Registry No.—**1**, 2108-89-6; **2**, 27425-35-0; **3**, 27389-73-7; **4**, 27389-74-8; **5**, 26634-41-3; **6**, 27389-76-0; **23**, 27389-77-1; **29**, 27389-78-2; **30**, 27389-79-3.

Studies of Acenaphthene Derivatives. XXI.[1] Reaction of 2-Diazoacenaphthenone with Olefins and Acetylenes

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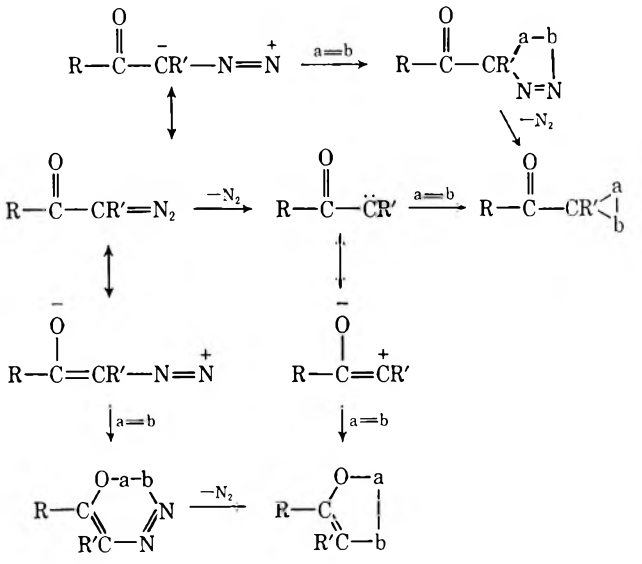
No thermal decomposition of 2-diazoacenaphthenone (**1**) occurred in boiling benzene or toluene for a long while. Copper-catalyzed thermolysis of **1** in boiling toluene led to the formation of biacenedione, although **1** was not decomposed in boiling benzene under the influence of copper powder. On the other hand, thermolysis of **1** in boiling xylene gave biacenedione, together with a trace amount of acenaphthenequinone ketazine. Reactions of **1** with ethyl acrylate (**2a**), acrylonitrile (**2b**), ethyl α-bromoacrylate (**2c**), methyl vinyl ketone (**2d**), and diethyl fumarate and maleate in refluxing benzene gave the corresponding spiro[acenaphthenone-2,1′-cyclopropanes] (**3a–d**, **4a–c**, **7**); with **2a**, **2b**, and **2c**, two stereoisomers obtained respectively. Although **1** did not react with cyclohexene and indene, the reaction with bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride gave the spiro-[acenaphthenone-2,3′-tricyclooctanedicarboxylic anhydride] (**8**). However, **1** reacted with acrolein to give two isomers of 2′-hydroxymethylspiro[acenaphthenone-2,1′-cyclopropanes] (**5**, **6**) corresponding to dihydro derivatives of the expected 2′-formyl compounds. On the other hand, addition of **1** to phenylacetylene and to diethyl acetylenedicarboxylate gave the corresponding spiro[acenaphthenone-2,3′(3′H)-pyrazoles] (**9**, **10**).

The thermal and photochemical reactions of α-diazo ketones, such as diazoacetophenone, azibenzil, and *o*-benzoquinone diazide, have received considerable attention.[3] Although α-diazo ketones exhibit a different behavior depending on their nature and reaction conditions, the reaction can be classified into three categories from a viewpoint of the cycloaddition, as illustrated in Scheme I. Little attention has been paid to the reaction of α-diazo ketone with olefins under such conditions that the ketocarbene is not generated, although the low temperature reactions of diazomethanes have been investigated considerably.

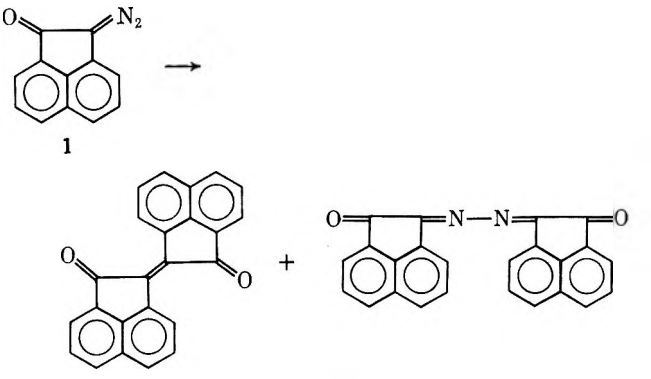
In order to clarify whether 2-diazoacenaphthenone (**1**) reacts with an olefin to lead to the spiropyrazoline or -cyclopropane ring formation, or to give the dihydro-1,4,5-oxadiazepine or dihydrofuran, the reaction of **1** with various olefins in refluxing benzene has been investigated. Also, this paper deals with the reaction of **1** with acetylenes.

SCHEME I



Results and Discussion

The diazo ketone **1** was not decomposed in boiling benzene or toluene for a long while; **1** was recovered quantitatively. Thermolysis of **1** in boiling toluene



was greatly accelerated by copper powder and led to the formation of diacenaphthylidenedione (biacenedione), although the decomposition of **1** did not take place in the presence of copper powder in boiling benzene. As shown by Ried and Lohwasser,[4] thermolysis of **1** in boiling xylene gave biacenedione as the main product, accompanied by a trace amount of acenaphthenequinone

(1) (a) Presented in part at the 22th Annual Meeting of the Chemical Society of Japan, Tokyo, April 1969. (b) Part XX of this series: O. Tsuge and I. Shinkai, *Bull. Chem. Soc. Jap.*, **43**, 3514 (1970).

(2) Author to whom correspondence should be directed.

(3) For reviews, see M. Regitz, *Angew. Chem.*, **79**, 786 (1967); see also G. Pfundt and G. O. Schenck, "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press, New York and London, 1967, p 405.

(4) W. Ried and H. Lohwasser, *Justus Liebigs Ann. Chem.*, **683**, 118 (1965).

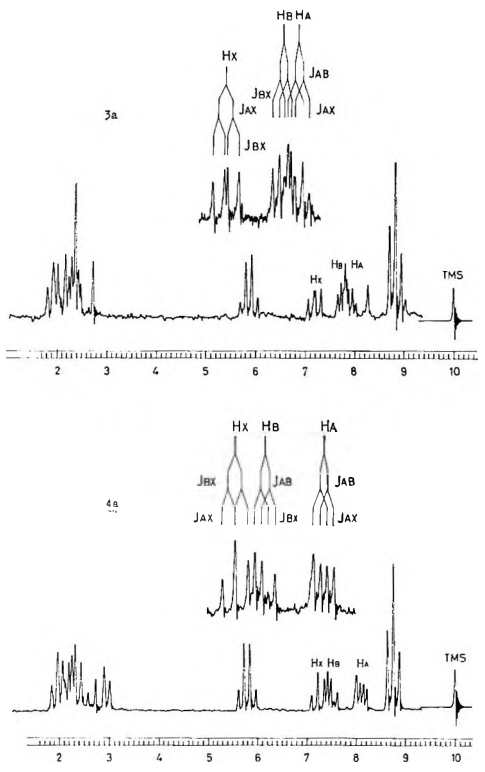


Figure 1.—Nmr spectra of **3a** and **4a**.

ketazine. The ketazine was not converted into biacenedione under the above conditions.[5] Although the mechanism of these decompositions has not been established, biacenedione appears to be derived from the reaction of **1** with the ketocarbene intermediate and/or dimerization of the ketocarbene.

It has been found that, in refluxing benzene or in xylene at the temperature at which benzene boils, **1** reacted with olefins under the elimination of nitrogen and no biacenedione was formed.

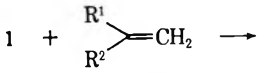
When a solution of **1** and ethyl acrylate (**2a**) in benzene was refluxed for 10 hr, two products, **3a** (mp 74–75°) and **4a** (mp 110–111°), were obtained in 30 and 35% yields, respectively. Elemental analyses and molecular weight (M^+ *m/e* 266) of both **3a** and **4a** agreed with the molecular formula ($C_{17}H_{14}O_3$) derived from a 1:1 adduct of **1** and **2a** under the elimination of nitrogen. The ir spectrum of **3a** showed the bands ascribed to carbonyl groups at 1710 and 1728 cm^{-1}, while the bands appeared at 1713 and 1740 cm^{-1} in that of **4a**. However, the mass spectrum of **4a** was very similar to that of **3a**. The compound **3a** was proved, by a mixture melting point determination and by the ir spectrum, to be identical with an authentic sample of 2′-ethoxycarbonylspiro[acenaphthenone-2,1′-cyclopropane] previously[1b] prepared from ethoxycarbonylmethyleneacenaphthenone and dimethyloxosulfonium methylide.

The nmr spectra of **3a** and **4a** are illustrated in Figure 1. A typical ABX pattern for cyclopropyl protons appears in the nmr spectrum of **4a** as well as in that of **3a**. It is well known that *cis*-cyclopropanes exhibit higher coupling constants (8–10,[6] 7.9–9.3 Hz[7]) than those (4–7,[6] 5.3–6.6 Hz[7]) of the corresponding trans isomers. Also, Graham and Rogers[7] have reported that the values of $J_{cis} + J_{trans}$ and $J_{cis} + J_{trans} + J_{gem}$ in 1,1,2-trisubstituted cyclopropanes are virtually constant (about 16 and 21 Hz, respectively), regardless of the nature of substituents. The respective values in **3a** and **4a** are shown in Table II.

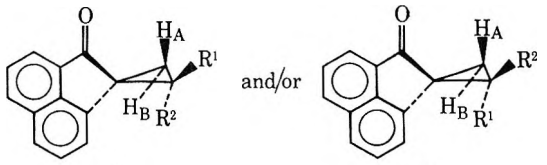
From the above observations, it may be deduced that **4a** is a stereoisomer of **3a**. Two stereoisomers owing to the conformation of the spirocarbon atom are possible for 2′-ethoxycarbonylspiro[acenaphthenone-2,1′-cyclopropane]. It has previously been reported that **3a** is consistent with the configuration in which H_A and H_X are situated cis and the ethoxycarbonyl group sees the acenaphthene ring.

As Figure 1 shows, the methyl protons signal of the ethoxycarbonyl group in **3a** appears at a field higher than that in **4a**. This fact can be understood in terms of the shielding effect of acenaphthene ring and supports the proposed configuration for **3a**.

From a comparison of chemical shifts of methyl protons in two stereoisomeric ethoxycarbonylmethyleneacenaphthenones[8] with those in **3a** and **4a**, and from a study of coupling constants of cyclopropyl protons in **3a** and **4a**, it may be considered that **4a** is the spiro[acenaphthenone-2,1′-cyclopropane] in which H_A and H_X are situated trans and the ethoxycarbonyl group overlooks the carbonyl group in the acenaphthenone ring.



2a, $R^1 = H$; $R^2 = CO_2Et$
b, $R^1 = H$; $R^2 = CN$
c, $R^1 = Br$; $R^2 = CO_2Et$
d, $R^1 = H$; $R^2 = COCH_3$



3 **4**

a, $R^1 = H_X$; $R^2 = CO_2Et$
b, $R^1 = H_X$; $R^2 = CN$
c, $R^1 = Br$; $R^2 = CO_2Et$
d, $R^1 = H_X$; $R^2 = COCH_3$

Similar reactions of **1** with acrylonitrile (**2b**) and ethyl α-bromoacrylate (**2c**) gave the corresponding spiro[acenaphthenone-2,1′-cyclopropanes] (**3b** and **4b**, **3c** and **4c**), respectively. However, **1** reacted with methyl vinyl ketone (**2d**) to give only one 2′-acetylspiro[acenaphthenone-2,1′-cyclopropane] (**3d**). The respective configurations for **3** and **4** were assumed on the basis of spectral studies.

The yields, physical properties, elemental analyses, and spectral data of **3** and **4** are summarized in Tables I and II.

(5) When acenaphthenequinone ketazine was decomposed at 300° for 1 hr, biacenedione was obtained in 65% yield.

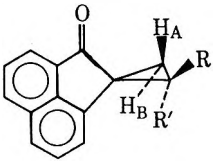
(6) K. B. Wiberg and B. J. Nist, *J. Amer. Chem. Soc.*, **85**, 2788 (1963).

(7) J. D. Graham and M. T. Rogers, *ibid.*, **84**, 2249 (1962).

(8) In the nmr spectrum ($CDCl_3$) of ethoxycarbonylmethyleneacenaphthenone whose ethoxycarbonyl group overlooks the carbonyl group in acenaphthenone ring, methyl and methylene protons appeared at τ 8.60 (t, 3) and 5.60 (q, 2), while the respective protons appeared at τ 8.75 (t, 3) and 5.70 (q, 2): O. Tsuge, M. Tashiro, and I. Shinkai, *Bull. Chem. Soc. Jap.*, **42**, 181 (1969).

TABLE I

SYNTHESES OF 3 AND 4



Olefin	Reaction time, hr	Compd	R	R′	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Mol wt, m/e
2a	10	3a	H	CO_2Et	30	74–75	76.67	5.30		76.78	5.04		266
		4a	CO_2Et	H	35	110–111	76.67	5.30		76.48	5.11		266
2b	13	3b[a]	H	CN	39	118–119	82.17	4.14	6.39	81.99	4.17	6.30	219
		4b[a]	CN	H	44	163–164	82.17	4.14	6.39	81.92	3.97	6.45	219
2c	8	3c	Br	CO_2Et	57	120–121	59.13	3.77		59.25	3.81		344, 346
		4c	CO_2Et	Br	12	160–162	59.13	3.77		59.06	3.82		344, 346
2d	2	3d	H	$COCH_3$	65	106–107	81.34	5.12		81.17	4.91		236

[a] It was temporarily assigned that the compound with lower melting point was **3b** and that with higher melting point was **4b**.

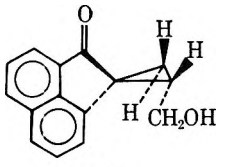
TABLE II

SPECTRAL DATA OF 3 AND 4

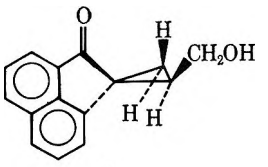
Compd	$\nu_{C=O}^{KBr}$, cm^{-1}	Chemical shift, τ: H_A	H_B	R or R′ (Hx)	R or R′ (CH_3)	R or R′ (CH_2)	Coupling constant, Hz: J_{trans}	J_{cis}	J_{gem}	$J_{trans} + J_{cis}$	$J_{trans} + J_{cis} + J_{gem}$
3a	1728, 1710	7.95	7.75	7.25	8.82	5.86	6.5	9.9	4.5	16.4	20.9
4a	1740, 1713	8.08	7.48	7.21	8.76	5.78	8.1	8.4	4.2	16.5	20.7
3b	1700, 2240[a]	8.02	7.80	7.46			7.2	8.4	4.5	15.6	20.1
4b	1713, 2260[a]	7.94	7.73	7.52			6.9	9.6	3.6	16.5	20.1
3c	1716	7.60	7.14		8.82	5.84			6.9		
4c	1736, 1710	7.86	7.10		8.72	5.72			6.9		
3d	1705, 1690	7.95	7.66	6.90	7.84		7.1	8.4	5.1	15.5	20.6

[a] $\nu_{C\equiv N}^{KBr}$.

Although a similar reaction of **1** with acrolein gave also two products, **5** (mp 134–136°) and **6** (mp 114–116°), in 13 and 24% yields, respectively, the molecular formula of both **5** and **6** did not agree with the expected 2′-formylspiro[acenaphthenone-2,1′-cyclopropanes] but agreed with their dihydro derivatives. The ir spectra of **5** and **6** displayed the bands ascribed to the hydroxyl and carbonyl groups; the absorption of hydroxyl group in **5** appeared as a sharp band at 3620 cm^{-1} and that in **6** was revealed as a broad band at 3450 cm^{-1} in the respective spectrum in a dilute benzene solution. The nmr spectrum of **5** showed signals at τ 8.10 (1 H, OH, exchanged with D_2O) and 6.00 (2 H, CH_2OH), while that of **6** exhibited signals at τ 7.54 (1 H, OH, exchanged with D_2O) and 5.93 (2 H, CH_2OH), besides signals ascribed to cyclopropyl and aromatic protons. The appearance of the hydroxyl proton in **6** at a higher field than that in **5** may be attributable to the shielding effect of acenaphthene ring in **5** and to the hydrogen bonding between the hydroxyl and carbonyl groups in **6**.



5

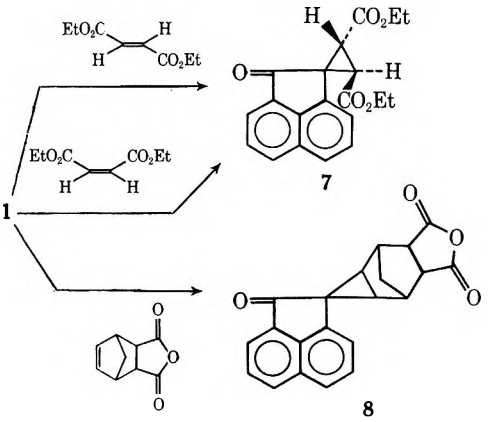


6

From a consideration of the above results, it seems reasonable to assume that **5** is 2′-hydroxymethylspiro[acenaphthenone-2,1′-cyclopropane] in which the hydroxymethyl group sees the acenaphthene ring, while **6** is the isomer in which the hydroxymethyl group overlooks the carbonyl group in the acenaphthenone ring. However, the reduction course of the formyl to hydroxymethyl group is not clear yet.

Jones[9] has reported that the reaction of ethyl diazoacetate with *cis*- or *trans*-stilbene at 180–200° gave the *cis*- or *trans*-cyclopropane, respectively.

When the reaction of **1** with diethyl fumarate or maleate was conducted in refluxing benzene, the same product, *trans*-2′,3′-diethoxycarbonylspiro[acenaphthenone-2,1′-cyclopropane] (**7**), was obtained in 89 or 37% yield. The compound **7** was identical with an authentic sample[1b] prepared from ethoxycarbonylmethyleneacenaphthenone and dimethylethoxycarbonylsulfonium methylide. Also, the reaction of **1** with diethyl fumarate in the presence of copper in refluxing toluene gave **7** in 65% yield, together with a small amount of biacenedione.



7

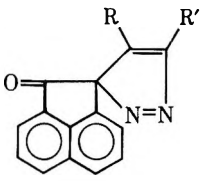
8

(9) W. M. Jones, *J. Amer. Chem. Soc.*, **81**, 3776 (1959).

Similar reactions of **1** with cyclohexene and indene did not take place, but **1** was quantitatively recovered. On the other hand, **1** reacted with bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride to give spiro[acenaphthenone-2,3′-tricyclo[3.2.1.0$^{2',4'}$]octane-6′,7′-dicarboxylic anhydride] (**8**), mp 274–276° dec, in 25% yield. The structure of **8** was confirmed by ir, nmr, and mass spectra as well as by the elemental analysis. Unfortunately its configuration could not be clarified yet.

It has been reported that disubstituted diazomethanes reacted with acetylenes to give pyrazolenines or pyrazoles depending on the nature of reagents and reaction conditions.[10] Also, diazoacetophenone reacted with phenylacetylene at 100°, affording 3-benzoyl-5-phenylpyrazole in a good yield.[11] Recently, Snatzke and Langen[12] have observed that 3,3-diphenylpyrazolenine obtained from diphenyldiazomethane and acetylene, isomerized to 3,4-diphenylpyrazole on treatment with acetic acid, and gave 1,1-diphenylcyclopropene on photolysis.

When the reactions of **1** with phenylacetylene and with diethyl acetylenedicarboxylate were performed in refluxing benzene, 5′-phenyl- (**9**), mp 243–244°, and 4′,5′-diethoxycarbonylspiro[acenaphthenone-2,3′(3′H)-pyrazole] (**10**), mp 147.5–148.5°, were obtained in 25 and 80% yields. The structures of **9** and **10** were confirmed by ir, nmr, and mass spectra as well as by elemental analyses.



9, R = H; R′ = Ph
10, R = R′ = CO_2Et

The compounds **9** and **10** were stable on heating in boiling *o*-dichlorobenzene for 8 hr. Also, when a benzene solution of **9** or **10** was irradiated by a 100-W high-pressure mercury lamp with a Pyrex filter at room temperature for 8 hr, **9** or **10** was recovered quantitatively.

Experimental Section[13]

Materials.—2-Diazoacenaphthenone (**1**) was prepared by the reported method[14] and purified by chromatography (alumina), mp 93–94° (lit.[14] 94°). Olefins purchased from Wako Pure Chemical Co. were purified by distillation.

Thermolysis of 2-Diazoacenaphthenone (1). A. In Xylene.—After a solution of **1** (580 mg, 3 mmol) in xylene (25 ml) was refluxed for 24 hr, the solvent was removed under vacuum. The residue was triturated with benzene (10 ml) and then filtration gave acenaphthenequinone ketazine, mp 295° dec, whose ir spectrum was identical with that of an authentic sample, yield 15 mg (2.8%). The filtrate was chromatographed on alumina using benzene as eluent. The foreband gave unreacted **1** (160 mg, 28%), and further elution with chloroform afforded 210 mg (42%) of biacenedione, mp 294°, which was identical with the authentic sample prepared from acenaphthenequinone and acenaphthenone.

B. Copper-Catalyzed Decomposition in Toluene.—A solution of **1** (500 mg, 2.6 mmol) in toluene (20 ml) was refluxed over copper powder (300 mg) for 1 hr. The reaction mixture was filtered and washed with hot toluene to leave copper (300 mg). After the filtrate and washings were concentrated under vacuum, the residue was purified by chromatography on alumina in a similar manner as above; unreacted **1** (80 mg, 16%) and biacenedione (340 mg, 79.5%) were obtained.

In refluxing benzene for 6 hr in the presence of copper powder, **1** was not decomposed but recovered quantitatively. Also, no decomposition of **1** occurred in refluxing toluene for 24 hr in the absence of copper powder.

Reaction of 1 with Ethyl Acrylate (2a).—A solution of **1** (290 mg, 1.5 mmol) and **2a** (450 mg, 4.5 mmol) in benzene (25 ml) was refluxed for 10 hr; during this time an initial orange solution became pale yellow. Solvent was removed under vacuum, leaving a semicrystalline residue which was triturated with *n*-pentane (20 ml) to give crystals. The crystals were collected by filtration and recrystallized from petroleum benzine (bp 42–60°), giving 140 mg (35%) of **4a**, mp 110–111°, as colorless prisms.

The *n*-pentane filtrate was concentrated to dryness under vacuum, leaving a semicrystalline compound. Purification by chromatography (alumina) using benzene as eluent followed by recrystallization from petroleum ether (bp 38–50°) gave 120 mg (30%) of **3a**, mp 74–75°, as colorless prisms. This compound was identical with an authentic sample[1b] prepared from ethoxycarbonylmethyleneacenaphthenone and dimethyloxosulfonium methylide.

Similar reactions of **1** with acrylonitrile (**2b**), ethyl α-bromoacrylate (**2c**), and methyl vinyl ketone (**2d**) gave the corresponding spiro[acenaphthenone-2,1′-cyclopropanes] **3** and **4**. The yields, physical properties, elemental analyses, and spectral data are summarized in Tables I and II.

Reaction of 1 with Acrolein.—After a solution of **1** (870 mg, 4.5 mmol) and acrolein (1.12 g, 20 mmol) in benzene (25 ml) was refluxed for 10 hr, the reaction mixture was concentrated under vacuum. The residue was chromatographed (alumina), eluting with chloroform. The obtained crystals were recrystallized twice from benzene, giving 90 mg (13%) of **5**, mp 134–136°, as colorless needles: ir (KBr) 3390 (OH), 1680 cm^{-1} (C=O); ir (dilute benzene solution) 3620 (OH), 1722 cm^{-1} (C=O); nmr τ 8.55–7.5 (m, 3, cyclopropyl ring protons), 8.10 (s, 1, OH, exchanged with D_2O), 6.00 (m, 2, CH_2OH), 2.85–1.8 (m, 6, aromatic protons); mass spectrum *m/e* (rel intensity) 224 (50), 206 (10), 205 (21), 194 (16), 181 (29), 180 (100), 178 (14), 168 (37), 166 (13), 165 (72), 164 (19), 163 (23), 153 (17), 152 (82), 151 (26), 150 (14), 139 (13).

Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.33; H, 5.39. Found: C, 80.30; H, 5.21.

The benzene filtrate was concentrated under vacuum, and three recrystallizations of the residue from ligroin (bp 80–110°) gave 170 mg (24%) of **6**, mp 114–116°, as colorless prisms: ir (KBr) 3430 (OH), 1680 cm^{-1} (C=O); ir (dilute benzene solution) 3450 (OH), 1717 cm^{-1} (C=O); nmr τ 8.55–7.5 (m, 3, cyclopropyl ring protons), 7.54 (s, 1, OH, exchanged with D_2O), 5.93 (m, 2, CH_2OH), 3.05–1.8 (m, 6, aromatic protons); mass spectrum *m/e* (rel intensity) 224 (72), 206 (11), 205 (26), 194 (13), 181 (43), 180 (100), 178 (24), 168 (48), 166 (14), 165 (73), 164 (26), 153 (24), 151 (28), 150 (16), 139 (16).

Anal. Calcd for $C_{15}H_{12}O_2$: C, 80.33; H, 5.39. Found: C, 80.38; H, 5.48.

***trans*-2′,3′-Diethoxycarbonylspiro[acenaphthenone-2,1′-cyclopropane] (7). A. In Benzene.**—A solution of **1** (870 mg, 4.5 mmol) and diethyl fumarate (1.55 g, 9 mmol) in benzene (25 ml) was refluxed for 6 hr. Solvent was removed under vacuum, giving a semicrystalline residue which was triturated with petroleum benzine (bp 42–60°). The crystals were collected by filtration and then recrystallized from methanol, giving 1.35 g (89%) of **7**, mp 109–110° (lit.[1b] 110–111°), as colorless prisms. This compound was proved, by the mixture melting point and by the ir spectrum, to be identical with an authentic sample[1b] prepared from ethoxycarbonylmethyleneacenaphthenone and dimethylethoxycarbonylsulfonium methylide. A similar reaction of **1** with diethyl maleate for 12 hr gave **7** in 37% yield.

B. In Toluene in the Presence of Copper Powder.—After a solution of **1** (500 mg, 2.6 mmol) and diethyl fumarate (660 mg, 3.8 mmol) in toluene (20 ml) was refluxed over copper powder (300 mg) for 3 hr, the hot reaction mixture was filtered to leave

(10) R. Hüttel, J. Riedl, H. Martin, and K. Franke, *Chem. Ber.*, **93**, 1425 (1960).

(11) W. Ried and J. Omran, *Justus Liebigs Ann. Chem.*, **666**, 144 (1963).

(12) G. Snatzke and H. Langen, *Chem. Ber.*, **102**, 1865 (1969).

(13) All melting points are uncorrected. The ir spectra were measured in KBr disks, and the nmr spectra were determined in $CDCl_3$ at 60 MHz with a Hitachi R-20 nmr spectrometer using TMS as an internal reference. The mass spectra were obtained on a Hitachi RMS-4 mass spectrometer using a direct inlet and an ionization energy of 70 eV.

(14) M. P. Cava, R. L. Litle, and D. R. Napier, *J. Amer. Chem. Soc.*, **80**, 2257 (1958).

copper (300 mg). The filtrate was cooled and then filtration gave 40 mg (9.3%) of biacenedione. The filtrate was concentrated under vacuum, and the residue was triturated with petroleum ether (bp 38–50°) (20 ml) to give pale yellow crystals. Recrystallization from methanol gave 565 mg (65%) of **7** as colorless prisms.

Spiro[acenaphthenone-2,3′-tricyclo[3.2.1.0$^{2',4'}$]octane-6′,7′-dicarboxylic anhydride] (8).—A solution of **1** (580 mg, 3 mmol) and bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride (660 mg, 4 mmol) in benzene (30 ml) was refluxed for 40 hr. Concentration of the solution was followed by addition of methanol (20 ml). After standing overnight, the product was collected by filtration. Recrystallization from chlorobenzene gave 250 mg (25%) of **8**, mp 274–276° dec, as colorless prisms: ir (KBr) 1845, 1770, 1708 cm^{-1} (C=O); mass spectrum *m/e* 330 (M$^+$).

Anal. Calcd for $C_{21}H_{14}O_4$: C, 76.35; H, 4.27. Found: C, 76.32; H, 4.32.

Reaction of 1 with Phenylacetylene.—After a solution of **1** (580 mg, 3 mmol) and phenylacetylene (2.0 g, 19.6 mmol) in benzene (25 ml) was refluxed for 48 hr, the solvent was removed under vacuum to leave a semicrystalline residue. A solution of the residue in 20 ml of petroleum benzine (bp 42–60°) was heated under reflux for 30 min and then allowed to stand overnight. Filtration gave yellow crystals, which on two recrystallizations from ethanol afforded 200 mg of **9**, mp 243–244°, as pale yellow needles. The petroleum benzine filtrate was concentrated under vacuum, and the residue was chromatographed over alumina (elution with benzene and chloroform), giving 400 mg of **1** and 20 mg of **9**: yield of **9**, 220 mg (25%); ir (KBr) 1710 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 296 (100), 268 (34), 267 (12), 240 (21), 239 (70), 238 (11), 237 (18), 120 (10).

Anal. Calcd for $C_{20}H_{12}N_2O$: C, 81.06; H, 4.08; N, 9.45. Found: C, 81.12; H, 4.10; N, 9.35.

Reaction of 1 with Diethyl Acetylenedicarboxylate.—After a solution of **1** (970 mg, 5 mmol) and diethyl acetylenedicarboxylate (1.2 g, 7 mmol) in benzene (20 ml) was refluxed for 16 hr, the same procedure as above gave crude **10**. Two recrystallizations from ethyl acetate gave 1.45 g (80%) of pure **10**, mp 147.5–148.5°, as pale yellow prisms: ir (KBr) 1742, 1712 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 364 (39), 320 (15), 291 (25), 258 (26), 257 (26), 221 (26), 220 (100), 180 (31), 152 (20).

Anal. Calcd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43; N, 7.69. Found: C, 65.65; H, 4.49; N, 7.70.

Registry No.—**1**, 2008-77-7; **3a**, 27544-92-9; **3b**, 27544-93-0; **3c**, 27610-03-3; **3d**, 27610-04-4; **4a**, 27544-94-1; **4b**, 27544-95-2; **4c**, 27544-96-3; **5**, 27544-97-4; **6**, 27544-98-5; **8**, 27544-99-6; **9**, 27545-00-2; **10**, 27545-01-3.

Synthesis of 3-Substituted 1,4-Pentadiyn-3-ols

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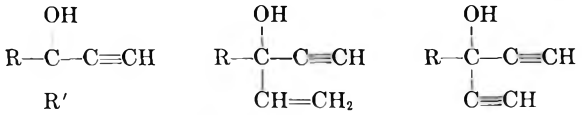
Received July 25, 1969

A convenient synthesis of 3-substituted 1,4-pentadiyn-3-ols is described. This synthesis employs the treatment of a phenyl ester with a metal acetylide in liquid ammonia, using dichloromethane as cosolvent. Triethynylmethanol was synthesized by a similar method.

Reports in the literature on the preparation of tertiary ethynyl carbinols have been numerous, and a wide variety of reagents and reaction conditions have been described. For compounds having an unsubstituted terminal acetylenic group, the most familiar method has involved the use of a metal acetylide in liquid ammonia.[1,2] These include monoethynyl carbinols with various alkyl or aryl substituents on the α carbon.



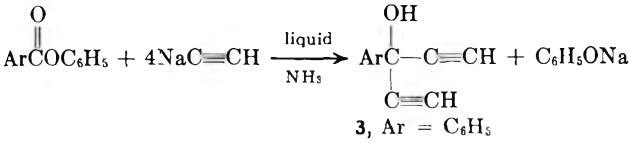
R, R′ = alkyl or aryl

1, R = H
2, R = CH_3
3, R = C_6H_5

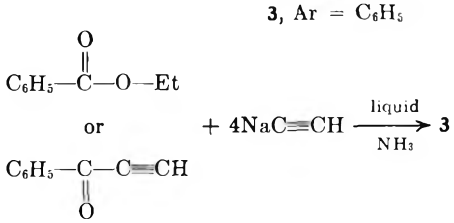
Although several diethynyl carbinols that are terminally substituted on the triple bond have been described,[3] only a few examples of diethynyl carbinols that are not substituted at this position have been reported. Jones, *et al.*,[4] developed the ethynyl Grignard reagent which was reacted with EtO_2CH to give **1**. The methyl derivative **2** was obtained by treating diethynyl ketone with MeMgBr or by reacting 3-butyn-2-one with ethynylmagnesium bromide.[5] The phenyl compound **3** was obtained similarly from phenyl ethynyl ketone.[6] All of these methods employ the ethynyl Grignard which is not always successful.

We wish to report a convenient synthesis of tertiary diethynyl carbinols using a metal acetylide in liquid ammonia. Earlier work in these laboratories has shown that CH_2Cl_2 is a very effective cosolvent in ethynylation reactions involving liquid ammonia.[7] Use of this cosolvent in the ethynylation of appropriately substituted phenyl esters proved to be beneficial in obtaining a large variety of 3-substituted 1,4-pentadiyn-3-ols.

3-Aryl-1,4-pentadiyn-3-ols.—Phenyl benzoate dissolved in CH_2Cl_2 was added to 4 equiv of sodium acetylide in liquid ammonia to give 3-phenyl-1,4-pentadiyn-3-ol (**3**) in 20–30% yield. Lithium acetylide



3, Ar = C_6H_5



(1) K. N. Campbell, B. K. Campbell, and L. T. Eby, *J. Amer. Chem. Soc.*, **60**, 2882 (1938).

(2) W. M. McLamore, M. Harfenist, A. Bavley, and S. Y. P'An, *J. Org. Chem.*, **19**, 570 (1954).

(3) H. G. Viehe, *Chem. Ber.*, **92**, 1950 (1959); K. Hess and W. Weltzien, *Ber.*, **54B**, 2511 (1921).

(4) E. R. H. Jones, L. Skattebol, and M. C. Whiting, *J. Chem. Soc.*, 4765 (1956); E. R. H. Jones, H. H. Lee, and M. C. Whiting, *ibid.*, 3483 (1960).

(5) T. Bohm-Gossl, W. Hunsmann, L. Rohrschneider, W. M. Schneider, and W. Ziegenbein *Chem. Ber.*, **96**, 2504 (1963).

(6) J. G. Noltes and G. J. M. Van der Kerk, *Recl. Trav. Chim. Pays-Bas*, **81**, 41 (1962).

(7) It was noted in these laboratories that ethynylation of diaryl ketone in liquid NH_3–CH_2Cl_2 solvent consistently gave complete conversions to the 1,1-diaryl-2-propynyl-1-ols which was not the case when NH_3–ether solvent was employed.

TABLE I

3-ARYL-1,4-PENTADIYN-3-OL, ArC(OH)(C≡CH)$_2$

Compd no.	Ar	Mp or bp (mm), °C	% yield	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
3	C_6H_5	58–60	20	$C_{11}H_8O$	84.59	5.16	84.21	5.26
4	4-FC_6H_4	68–70 (0.2)	32	$C_{11}H_7FO$	75.85	4.05	75.92	4.37
5	4-ClC_6H_4	85–88 (0.08)	27	$C_{11}H_7ClO$	69.30	3.70	69.14	3.81
6	3,4-$Cl_2C_6H_3$	94–96 (0.05)	14	$C_{11}H_6Cl_2O$	58.69	2.68	58.84	2.75
7	4-$CH_3C_6H_4$	86–90 (0.15)	12	$C_{12}H_{10}O$	84.68	5.92	84.41	6.19
8	3-$CF_3C_7H_4$	80–85 (0.2)	45	$C_{12}H_7F_3O$	64.28	3.14	64.27	3.38
9	4-$CH_3OC_6H_4$	111–114 (0.08)	11	$C_{12}H_{10}O_2$	77.40	5.41	77.32	5.71
10	2-$C_{10}H_7$	145–155 (0.2)	23	$C_{15}H_{10}O$	87.35	4.89	86.97	4.96
11	3-C_5H_4N	120–122	3	$C_{10}H_7NO$	76.42	4.49	76.69	4.70
12	2-C_4H_3S	107–111 (4)	1.7	C_9H_6OS	66.67	3.73	66.44	4.25
13	2-(5-BrC_4H_2O)	76–80 (0.01)	7.4	$C_9H_5BrO_2$	48.03	2.23	48.28	2.49

TABLE II

3-ALKYL-1,4-PENTADIYN-3-OLS, RC(OH)(C≡CH)$_2$

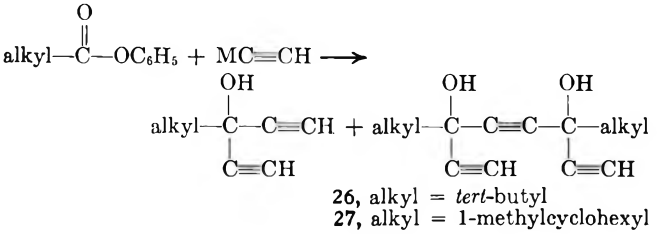
Compd no.	R	Mp or bp (mm), °C	% yield	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
14	CH_3CH_2	54–56	6.0	C_7H_8O	77.75	7.46	77.65	7.64
15	$(CH_3)_2CH$	63–65	21.0	$C_8H_{10}O$	78.65	8.25	78.60	8.26
16	$(CH_3)_3C$	48–52 (4)	50.0	$C_9H_{12}O$	79.37	8.88	79.33	9.04
17	$CH_3(CH_2)_4$	102–106 (4)	8.1	$C_{10}H_{14}O$	79.95	9.39	79.94	9.35
18	$CH_3(CH_2)_2CH(CH_3)$	28–30	16.4	$C_{10}H_{14}O$	79.95	9.39	79.77	9.38
19	Cyclopropyl	50–52	23.0	C_8H_8O	79.97	6.71	79.75	6.58
20	Cyclobutyl	86–88	35.6	$C_9H_{10}O$	80.56	7.51	80.46	7.46
21	Cyclopentyl	50–52	1.6	$C_{10}H_{12}O$	81.04	8.16	80.81	8.19
22	Cyclohexyl	73–75	52.0	$C_{11}H_{14}O$	81.44	8.70	81.23	8.92
23	1-Methylcyclohexyl	39–40	32.0	$C_{12}H_{16}O$	81.77	9.15	81.53	9.31
24	1-Cyclohexenyl	86–88	17.0	$C_{11}H_{12}O$	82.46	7.55	82.40	7.47
25	1-Adamantyl	113–115	17.0	$C_{15}H_{18}O$	81.77	9.15	81.53	9.31

was as effective as sodium acetylide. Phenyl esters of substituted aromatic acids (see Table I), including the heteroaromatics **11**, **12**, and **13**, on this treatment gave the appropriately substituted carbinols. Yields ranged from 2 to 45%.

Ethyl benzoate was treated with NaC≡CH as described above, and **3** was isolated in 40% yield (yields were erratic when the ethyl esters were used). Use of phenyl ethynyl ketone[8] with NaC≡CH resulted in only a 9% yield of **3**. When *p*-chlorophenyl ethynyl ketone was treated with sodium acetylide, no corresponding diethynyl carbinol could be isolated.

3-Alkyl-1,4-pentadiyn-3-ols.—The ethynylation was extended to the phenyl alkanoates to give the 3-alkyl-1,4-pentadiyn-3-ols (see Table II). It was noted that the amount of substitution on the α carbon atom of the ester greatly influenced the yields. The methyl compound could not be isolated using this method, whereas the ethyl (**14**) was isolated in 6% yield, isopropyl (**15**) in 20.5%, and *tert*-butyl (**16**) in 50% yield. The cycloaliphatics (**19**–**25**) worked quite well in this ethynylation.

In two cases, alkyl being *tert*-butyl (**26**) or 1-methylcyclohexyl (**27**), the diacetylenic glycols were isolated in addition to the expected carbinols.

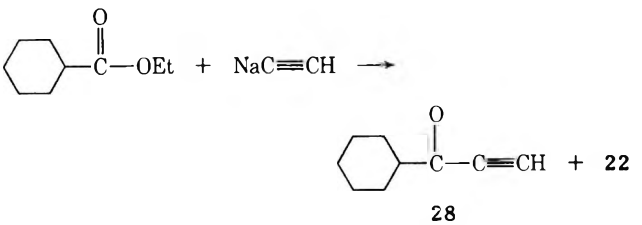


26, alkyl = *tert*-butyl
27, alkyl = 1-methylcyclohexyl

(8) When phenyl ethynyl ketone was treated with ethynylmagnesium,[6] **3** was obtained in 15% yield.

In order to determine which of the metal acetylides was superior in this reaction, phenyl cyclohexanecarboxylate was treated with lithium, sodium, potassium, and calcium acetylide in liquid ammonia with isolated yields of 40, 52, 60, and 0%, respectively. In general, for cycloalkyl derivatives the use of potassium acetylide gives the highest yields.

The ethyl ester of cyclohexanecarboxylic acid was treated with sodium acetylide to give, in addition to 5% of the expected diethynyl carbinol, cyclohexyl ethynyl ketone (**28**) in 10% yield. Use of other ethyl esters gave erratic results, and the reaction mixtures were usually contaminated with starting esters.

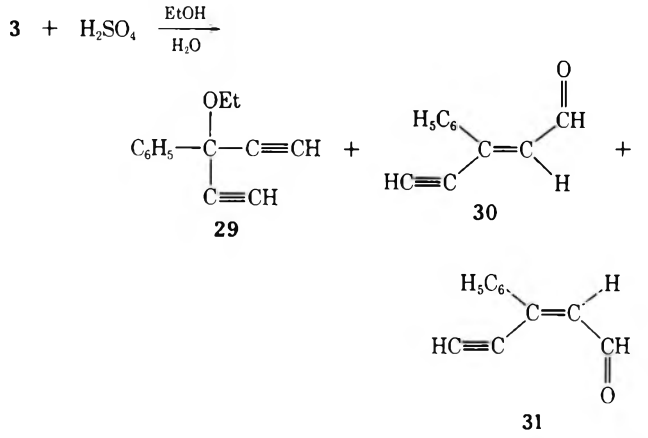


28

Although the aryl and alkyl diethynyl carbinols are quite stable, once purified, precaution should be taken in working with crude reaction mixtures. In most cases, the crude product was distilled at reduced pressure until evidence of decomposition was noted, and the source of heat was then removed. The crude reaction mixture of the *p*-nitrophenyl derivative exploded during attempted distillation. Redistillation of these compounds afforded no problems. In some instances column chromatography was used. Usually, the products were solids and could be recrystallized from benzene and low-boiling petroleum ether mixtures. In none of

the above reactions using the phenyl esters were any starting phenyl esters isolated.

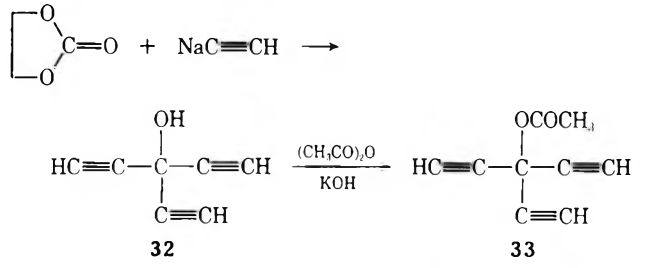
Treatment of **3** with H_2SO_4 in aqueous EtOH at room temperature gave on distillation, as a major product, the ethyl ether **29**. The minor components, based on the nmr and ir spectra (see Experimental Section), were



29 **30** **31**

cis- (**30**) and *trans*- (**31**) β-ethynylcinnamaldehydes. By treating **3** with H_2SO_4 in aqueous EtOH at reflux temperature for a brief time, **31** could be isolated in 33% yield. (Neither **29** nor **30** was present.) Heating for longer times gave only intractable tars. The formation of the cinnamaldehydes from **3** is related to the Meyer–Schuster rearrangement,[9] involving allenization of the triple bond.

Triethynylmethanol.—Although terminally substituted triethynylmethanols have been reported,[10] **32** has not been described in the literature. Utilizing our synthetic method, several attempts were made to prepare this compound. The only intermediate that



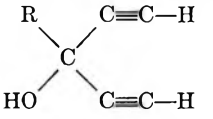
32 **33**

proved successful was ethylene carbonate. When the latter compound was added to 5 equiv of sodium acetylide in liquid NH_3, **32** was isolated upon neutralization with NH_4Cl by first column chromatography and then distillation in 1–8% yields. The material was a low-melting solid that showed the expected nmr and ir spectra. The compound exploded on combustion for elemental analyses. Attempted recrystallization of this material was unsuccessful. However, its acetate (**33**) crystallized readily from a benzene–petroleum ether mixture.

Nmr Spectra. It was noted that the chemical shifts of the acetylenic protons varied depending upon the substitution at the 3 position of the pentadiynols. The fact that the acetylenic protons are shifted downfield in **32** relative to **16**, contrary to expectations based on acetylenic anisotropy, indicates that other screening mechanisms are probably operative. Presumably, the acetylenic π electrons increase the conjugation of the system, allowing the 3 substituent to affect the electronic density at the terminal acetylenic carbons.

In comparing the chemical shifts in Table III, it seems that the greater the polarizability of R, the greater the shift to lower field, *i.e.*, the greater the deshielding.

Table III
Chemical Shifts of Acetylenic Protons



Compd no.	R	Chemical shifts of acetylenic protons, τ
16	*tert*-Butyl	7.43
19	Cyclopropyl	7.38
24	1-Cyclohexenyl	7.35
3	C_6H_5	7.27
8	$3\text{-}CF_3C_6H_4$	7.20
32	HC≡C—	7.25

Experimental Section

All melting points are uncorrected and were obtained in an open capillary tube. The ir spectra were determined in $CHCl_3$ with a Perkin-Elmer spectrophotometer, Model 21. The nmr spectra were determined in $CDCl_3$ on a Varian A-60 nmr spectrometer, using tetramethylsilane as an internal standard. Chemical shifts are reported using the τ scale.

Preparation of 3-Substituted 1,4-Pentadiyn-3-ols. General Procedure.—To 2 mol of sodium acetylide prepared by usual methods in 2.5 l. of liquid NH_3 was added dropwise over a 1-hr period 0.5 mol of the phenyl ester in 500–1000 ml of CH_2Cl_2. The NH_3 was allowed to evaporate as the reaction proceeded. After 4 hr, 1.5 l. of ether was added, the remaining ammonia was evaporated, and the mixture was decomposed with ice and water (total volume, 1.5 l.). The organic layer was separated, and the aqueous phase was extracted three times with ether. The combined organic solvents were washed three times with 200-ml portions of water and dried ($MgSO_4$), and the solvent was removed. The residue was distilled (Vigreux) at reduced pressure until decomposition was evident. The distillates that solidified were recrystallized from mixtures of benzene and petroleum ether (bp 35–60°). The distillates that remained oils were redistilled. In some cases column chromatography was used (Florisil). Yields are reported in Tables I and II.

The nmr spectra of the aliphatic and cycloaliphatic derivatives gave singlets (2 H) for the acetylenic protons in the range τ 7.46–7.42. The signals for each particular substituent were those expected. For the aromatic derivatives the singlets for the acetylenic protons were in the range τ 7.32–7.20.

The ir spectra of these compounds showed a sharp absorption peak at 3.02–3.05 μ and a weak absorption peak at 4.7–4.8 μ for the acetylenic group, and a sharp OH peak at 2.8–2.85 μ.

Treatment of Phenyl Pivalate with Sodium Acetylide.—Using the previously described reaction conditions, 0.5 mol of phenyl pivalate was allowed to react with 2 mol of sodium acetylide. Distillation of the crude reaction mixture gave a 50% yield of **16** (see Table II), bp 48–52° (4 mm). The portion that did not distil was crystallized from benzene–petroleum ether (bp 35–60°) to give 7.1 g of the acetylenic glycol **26**, mp 103–105°. *Anal.* Calcd for $C_{16}H_{22}O_2$: C, 78.00; H, 9.00. Found: C, 78.16; H, 9.10.

Phenyl 1-methylcyclohexanecarboxylate (0.27 mol) was treated similarly with sodium acetylide to give 12.5 g (26%) of **23** (see Table II) and 5 g of 3,6-bis(1-methylcyclohexyl)-1,4,7-octatriyne-3,6-diol (**27**), mp 114–116° (crystallized from petroleum ether, bp 60–71°). *Anal.* Calcd for $C_{22}H_{30}O_2$: C, 80.92; H, 9.26. Found: C, 81.16; H, 9.21.

Reaction of Ethyl Cyclohexanecarboxylate with Sodium Acetylide.—Ethyl cyclohexanecarboxylate (0.5 mol) was treated

(9) K. H. Meyer and K. Schuster, *Ber.*, **55**, 819 (1922); G. F. Hennion and B. R Fleck, *J. Amer. Chem. Soc.*, **77**, 3253 (1955).

(10) Yu. Yu. Tsmur and B. N. Dashkevich, *Zh. Obshch. Khim.*, **33**, 1357 (1963); D. D. Coffman, J. C.-Y. Tsao, L. E. Schniepp, and C. S. Marvel, *J. Amer. Chem. Soc.*, **55**, 3792 (1933); M. Siemiatycki, *Ann. Chim. (Paris)*, **2**, 189 (1957).

with 2 mol of NaC≡CH as previously described; after the NH_3 had evaporated, the mixture was decomposed with 800 ml of water; and solid CO_2 was added until the pH of the solution was approximately 8. The ether layer was separated and dried ($MgSO_4$), and the solvent was removed. Distillation of the residue gave two fractions. The first fraction, bp 64–66° (4 mm), weight 7.5 g (10%), was cyclohexyl ethynyl ketone (**28**): nmr ($CDCl_3$) τ 6.65 (1 H, s, ≡C–H), 8.42 (11 H, broad m, cyclohexyl); ir ($CHCl_3$) 3.02 (≡C–H), 4.76 (C≡C), 6.0 μ (CO). *Anal.* Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.21; H, 8.86.

The higher boiling fraction crystallized from petroleum ether (bp 35–60°) to give 3.5 g of solid with ir and nmr spectra identical with those of **22**.

Treatment of 3 with H_2SO_4. A.—A solution of 10 g (0.064 mol) of **3** in 250 ml of EtOH was cooled with an ice–water bath, and 25 ml of concentrated H_2SO_4 in 100 ml of water was added slowly. The mixture was allowed to stir for 5 days at room temperature. After being diluted with water, the mixture was extracted with ether. The ether solution was washed several times with water and dried ($MgSO_4$); distillation gave 8 g of oil, bp 60–65° (0.05 mm).

An analysis of the nmr spectrum of this oil indicated 72% 3-ethoxy-3-phenyl-1,4-pentadiyne (**29**), 16% *cis*-β-ethynylcinnamaldehyde (**30**), and 12% trans isomer (**31**).[11]

The ether **29** was purified by column chromatography (Florisil, benzene) and distillation: bp 54° (0.01 mm); nmr ($CDCl_3$) τ 8.75 (3 H, t, methyl), 6.20 (2 H, q, methylene), 8.96 (2 H, s, C≡CH), and 2.56 and 2.26 (5 H, 2 m, phenyl); ir ($CHCl_3$) 3.06 μ (C≡CH). *Anal.* Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.47; H, 6.47.

B.—To 10 g (0.064 mol) of **3** in 150 ml of EtOH was added 25 ml of H_2SO_4 in 100 ml of H_2O; the resulting mixture was heated to reflux temperature. A vigorous reaction ensued, and after 5 min, the mixture was worked up as above. The crude oil was distilled, bp 74–84° (0.03 mm). The distillate (**31**) which solidified was crystallized twice from petroleum ether (bp 60–71°): weight 3.5 g; mp 64–66°; nmr ($CDCl_3$) τ 6.21 (1 H, s, C≡CH), 3.85 (1 H, d, J = 8 Hz, vinyl), −0.33 (1 H, d, J = 8 Hz, adlehyde), and 2.53 and 2.30 (5 H, 2 m, phenyl); ir ($CHCl_3$) 3.05 (C≡CH), 4.75 (C≡C), 6.0 μ (CO). *Anal.* Calcd for $C_{11}H_8O$: C, 84.59; H, 5.16. Found: C, 84.86; H, 5.45.

Triethynylmethanol (32).—Ethylene carbonate (0.4 mol) dissolved in 300 ml of CH_2Cl_2 was treated with 2 mol of sodium acetylide in 2.5 l. of liquid NH_3 as before, and, after evaporating the NH_3, dry NH_4Cl (150 g), followed by ice and water (2 l.), was added. The mixture was allowed to stand for 30 min, and the aqueous layer was separated. The ether layer was washed with water (difficult emulsion) and dried ($MgSO_4$), and the ether was removed at reduced pressure. The residue was passed over a Florisil column with 9:1 C_6H_6–EtOAc, and the eluate was distilled, bp 50–55° (4 mm). This distillate solidified on cooling, mp 28–30°. Yields of 1–8% were obtained. Elemental analysis was not possible on this compound because of its explosive nature when combustion is attempted.

The nmr spectrum showed two peaks, 7.25 (3 H, s, acetylenic protons) and 6.70 (1 H, s, OH, D_2O exchangeable).

The ir spectrum had peaks at 3.05 μ for the acetylenic CH, 4.7 μ for the triple bond, and 2.84 μ for the OH (no peaks in the carbonyl region).

Triethynylmethyl Acetate (33).—An ethereal solution of **32** (0.05 mol) was added to a suspension of 30 g of powdered KOH in 500 ml of ether, cooling with an ice–ethanol bath and vigorously stirring. At −5° 20.2 g (0.2 mol) of acetic anhydride in an equal volume of ether was added dropwise over 20 min. Stirring and cooling were maintained for 45 min, and 500 ml of water was added. The ether solution was separated, washed twice with water, and dried ($MgSO_4$), and the ether was removed at reduced pressure. The residue was recrystallized from benzene–petroleum ether (bp 35–60°) to give 1.6 g (23%) of product, mp 88–89°. *Anal.* Calcd for $C_9H_6O_2$: C, 73.96; H, 4.14. Found: C, 73.93; H, 4.33.

(11) The nmr spectra of pure samples of **29** and **31** are described below. The assignment of the cis compound **30** was based on the presence of two additional doublets centered at τ 4.52 and 0.03 (J = 8 Hz). Isolation of this compound was not attempted.

Registry No.—**3**, 27410-03-3; **4**, 27410-04-4; **5**, 27410-05-5; **6**, 27410-06-6; **7**, 27410-07-7; **8**, 27410-08-8; **9**, 27410-09-9; **10**, 27410-10-2; **11**, 27410-11-3; **12**, 27410-12-4; **13**, 27410-13-5; **14**, 27410-14-6; **15**, 27410-15-7; **16**, 27410-16-8; **17**, 27410-17-9; **18**, 27410-18-0; **19**, 27410-19-1; **20**, 27410-20-4; **21**, 27410-21-5; **22**, 27410-22-6; **23**, 27410-23-7; **24**, 27410-24-8; **25**, 27410-25-9; **26**, 27410-26-0; **27**, 27410-27-1; **28**, 7560-69-2; **29**, 27410-29-3; **31**, 27390-88-1; **32**, 27410-30-6; **33**, 27410-31-7.

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A New Method for the Preparation of α,β-Unsaturated Carbonyl Compounds

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A unique preparation of α,β-unsaturated aldehydes and ketones from the corresponding saturated analogs is reported. The procedure involves a homogeneous liquid-phase oxidative dehydrogenation by air or oxygen in the presence of a group VIII metal [preferably Pd(II)] catalyst and a cocatalyst. Particular attention is given to the synthesis of 2-cyclohexen-1-one (**2**). The scope and limitations of this reaction are discussed. In addition, probable and alternative mechanisms of this selective dehydrogenation technique are examined.

The preparation of α,β-unsaturated ketones and aldehydes customarily involves allylic oxidation of olefins,[1] elimination reactions on α substituted carbonyl compounds,[2] or dehydration of aldols.[3] Most methods either involve several steps or are often complicated by low yields and unwanted by-products. Typical of an excellent, but several-step synthesis of an α,β-unsaturated ketone is that pictured in Scheme I for 2-cyclohexen-1-one (**2**) from dihydroresorcinol.[4] Since no short and easy synthetic scheme was available for the preparation of a highly versatile compound such as **2**, it was advantageous to develop a one-step dehydrogenation of the corresponding saturated ketone or aldehyde. In contrast to the present liquid-phase reaction, only

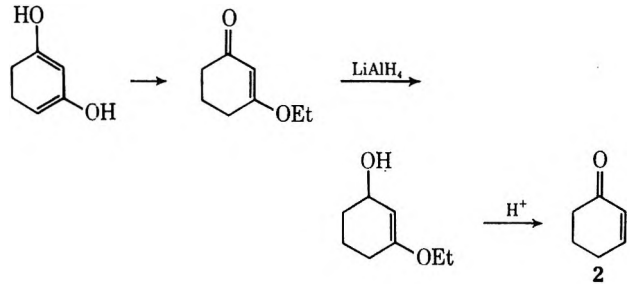
(1) N. Rabjohn, *Org. React.*, **5**, 339 (1949); A. Robertson and W. A. Waters, *Trans. Faraday Soc.*, **42**, 201 (1946); F. E. Mertz and L. D. Dermer, *Proc. Okla. Acad. Sci.*, **30**, 134 (1949); E. H. Farmer and C. G. Moore, *J. Chem. Soc.*, 149 (1953).

(2) E. A. Braude and E. A. Evans, *ibid.*, 607 (1954); W. S. Johnson, *et al.*, *J. Org. Chem.*, **27**, 1612 (1962).

(3) A. T. Neilsen and W. J. Houlihan, *Org. React.*, **16**, 1 1968.

(4) W. F. Gannon and H. O. House, *Org. Syn.*, **40**, 14 (1960).

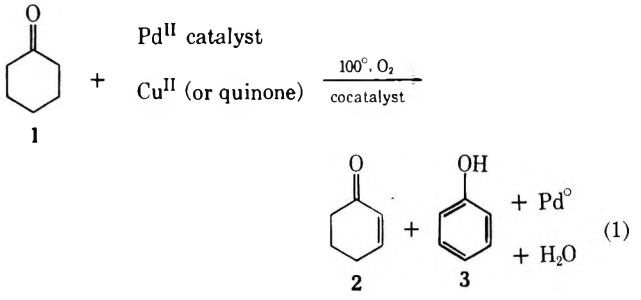
Scheme I



vapor phase procedures for the preparation of olefinically unsaturated ketones from the corresponding saturated carbonyl compounds or alcohols have been reported.[5]

Results

A study of group VIII [particularly Pd(II)] metal complex catalysis has revealed a unique liquid-phase oxidative dehydrogenation of ketones and aldehydes. As illustrated (eq 1) for cyclohexanone (**1**), the oxidation is effected by air or oxygen in the presence of a catalyst and a cocatalyst.



Usual conversions of **1** in the range of 15–30% and at selectivities to **2** of 95–80% were obtained in the presence of a Pd(II) catalyst and either a Cu(II) or a quinone cocatalyst.[6] By comparison, a combination of Cu(II) and quinone cocatalysts gave 43–48% conversions of **1** with selectivities to **2** of 88–83%. However, synthesis of unsaturated ketone **1**, as with all other substrates, is limited by (1) catalyst deactivation, (2) aldol condensation reactions, and (3) secondary oxidations, *e.g.*, **1** to adipic acid. The latter two reactions, although minimal at lower conversions, become significant at higher ones. Thus, total estimated conversions and selectivities were 50–53% and 73–66%, respectively. Table I lists typical results in reactions with **1**.

This unique oxidative dehydrogenation technique has modest general applicability for the preparation of α,β-unsaturated materials. Except for **1**, the reaction conditions generally were not optimized. Thus, in several cases only preliminary screening runs are listed which employ no cocatalyst or solvent. Usually, however, the Pd(II) catalyst was about 0.2–0.4 molar % of substrate. The cocatalyst, except where noted, was *p*-benzoquinone (*p*-BQ), and the solvent was neat substrate, HOAc, or HOBz. The reactions were run for 1–24 hr at 90–110° bubbling oxygen or air into the solution at 10–15 cc/min.

(5) H. F. Hardman and R. K. Grasselli, U. S. Patent 3,364,264 (1968); R. W. Etherington and K. L. Liauw, U. S. Patent 3,476,808 (1969).

(6) Conversion and selectivity are defined as

$$\% \text{ convn} = \frac{\text{moles (2 + 3)}}{\text{moles (1) charged}} \times 100$$

$$\% \text{ select} = \frac{\text{moles (2)}}{\text{moles (2 + 3)}} \times 100$$

References to total conversion and total selectivity are based upon all products observed by vpc analysis.

Table I

Conversion and Selectivity in Reactions of Cyclohexanone (1)

	% convn of 1	% select to 2	Pd(II)[a] activity
Usual range[b]	15–30	95–80	50–1000
Highest range[c] (based on vpc)	43–48	88–83	1300–2700
Highest actual range (based on isolation)	50–53	73–66	1300–2700

[a] The catalyst activity is defined as cat. act. = moles of desired product/moles of Pd(II) catalyst. [b] Conversions depend on the choice of solvent as well as the concentration and type of catalyst and cocatalyst used. [c] The best results were obtained from a combination of Cu(II) and quinone cocatalysts.

Analyses of reaction products were carried out by vpc. In general, all significant products were separated by preparative vpc and their structures confirmed by infrared and nmr spectra. Tables II–V list the results and products obtained from cyclic ketones, substituted cyclic ketones, acyclic ketones, and aldehydes.

Table II

Reactions of Cyclic Ketones[a]

Substrate	% convn	Theor % convn[b]	% select	Product
Cyclopentanone	17	18	97	Cyclopentenone
Cyclopentanone[c]	22	1	91	Cyclopentenone
Cyclohexanone	15–30	15–30	98–90	Cyclohexenone
Cyclohexanone[c]	15–30	2	95–90	Cyclohexenone
Cycloheptanone[d]	2	0.3	38	Cycloheptenone
Cyclooctanone[d]	0.7	0.4	30	Cyclooctenone

[a] Except where noted, *p*-benzoquinone (*p*-BQ) was employed in all reactions as "cocatalyst." [b] Theoretical per cent conversion is equivalent to the stoichiometric amount of cocatalyst or to the Pd(II) catalyst in systems containing no cocatalyst. Thus, since *p*-BQ is a stoichiometric reagent, the theoretical per cent conversion is equivalent to the amount present, whereas reoxidation of copper or palladium complexes may yield actual conversions greater than the theoretical (stoichiometric) conversion. [c] $Cu(acac)_2$ was used as cocatalyst, time 15-25 hr. [d] Preliminary screening runs; no cocatalyst or solvent was used.

In attempting to optimize reaction conditions, especially for those employing **1** as substrate, several variables were studied. These included (1) catalyst, (2) cocatalyst, (3) temperature, (4) oxygen and pressure dependence, and (5) solvent.

Over 45 catalysts, primarily the group VIII metal salts and complexes, were investigated. Palladium compounds are the most active and selective with rhodium, osmium, iridium, and platinum showing decreasing catalytic activity. The best complexes are soluble ones such as dichlorobis(triphenylphosphine)palladium(II) and palladium(II) acetylacetonate. Palladium(II) chloride itself has modest catalytic activity and an initial selectivity of >90% to **2**. However, the Lewis acid character of this simple salt readily promotes aldol condensations which are minimized in the case of the complexes.

In all cases, conversion of **1** to **2** and **3** stops (see Figures 1 and 2) when a mirror and/or Pd° (black) are observed. Continued contact with metallic Pd slowly

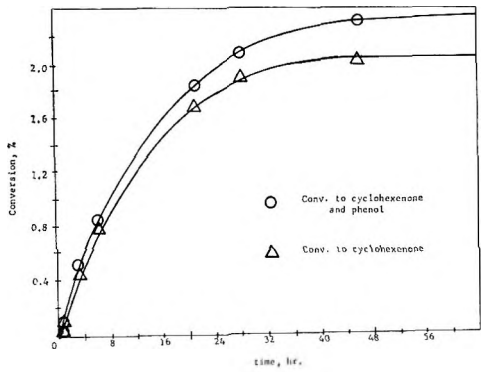
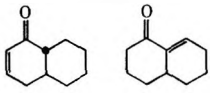
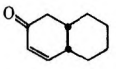
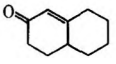
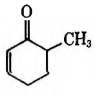
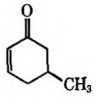
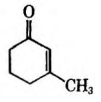


Figure 1.—Conversion of cyclohexanone (0.5 mol) to cyclohexenone and phenol at 110° and 10 cc of O_2/min catalyzed by $[Pd(PPh_3)_2Cl_2]$ (7×10^{-4} mol).

TABLE III

REACTIONS OF SUBSTITUTED CYCLIC KETONES[a]

Substrate	% convn	Theor % convn[b]	% select	Product
α-Decalone[c] (t/c = 19/1)	32	100	36	
β-Decalone[c] (t/c = 2/1)	20	100	1.5	
			43	
2-Methylcyclohexanone	47	37	80	
3-Methylcyclohexanone	36	100	58	
			23	
3-Cholestanone	82	64	>95	Δ′-Cholesten-3-one

[a] See footnote *a*, Table II. [b] See footnote *b*, Table II. [c] See footnote *d*, Table II.

TABLE IV

REACTIONS OF ACYCLIC KETONES[a]

Substrate	% convn	Theor % convn[b]	% select	Product
2-Butanone[c]	4	18	100	1-Buten-3-one
3-Pentanone[c]	6	18	94	1-Penten-3-one
			6	1,4-Pentadien-3-one
3-Methyl-2-butanone[c]	4	18	100	2-Methyl-1-buten-3-one
Propiophenone	3	36	100	3-Phenyl-1-propen-3-one
4-Heptanone	7	18	83	*trans*-2-Hepten-4-one
			17	*trans,trans*-2,5-Heptadien-4-one
2-Octanone	5–7	18	100	*trans*-3-Octen-2-one

[a] See footnote *a*, Table II. [b] See footnote *b*, Table II. [c] Reaction carried out in pressure bottle.

converts 2 to **3**. In the presence of only a Pd catalyst and at low levels of conversion (<2%), *i.e.*, before Pd^0 deposition, it is possible to recover the catalyst which can be recycled.

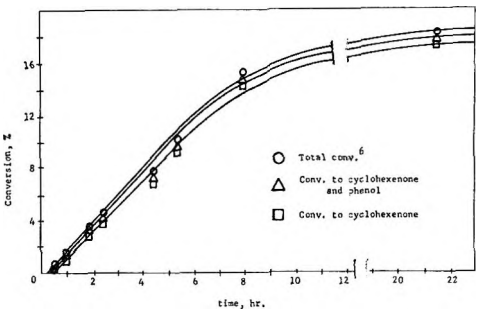


Figure 2.—Conversion of cyclohexanone (1.0 mol) to cyclohexenone and phenol at 100° and 10 cc of O_2/min catalyzed by $[Pd(PPh_3)_2Cl_2]$ (3×10^{-3} mol) and $[Cu(PPh_3)_2Cl_2]$ (1.5×10^{-2} mol).

TABLE V

REACTIONS OF ALDEHYDES[a]

Substrate	% convn	Theor % convn[b]	% select	Product
Propanal[c]	6	18	100	Propenal
Butanal	15–18	18	80	*trans*-2-Butenal
2-Methylpropanal[c]	4	18	100	2-Methylpropenal
n-Heptanal	20	18	>90	*trans*-2-Heptenal
n-Nonanal	26	27	91	*trans*-2-Nonenal

[a] See footnote *a*, Table II. [b] See footnote *b*, Table II. [c] See footnote *c*, Table IV.

Catalyst activity is extended by the use of both inorganic and organic cocatalysts. These materials do not produce the desired compound by themselves but substantially increase both the rate and conversion when combined with the primary catalyst.

Of most of the 1st row transition metal salts and complexes (V through Cu) studied, copper compounds are superior for reoxidation of the palladium catalysts.[7] In practice, a 5–500 molar excess of Cu(II) is used. Reoxidation of Cu(I) is achieved by air or oxygen. Cupric acetylacetonate or dichlorobis(triphenylphosphine)copper(II) are preferred. Cupric acetate may also be used, but hydrolysis of cuprous acetate to insoluble cuprous oxide is competitive with reoxidation.

The organic cocatalysts, quinones, theoretically function as redox systems, but their main role is to act as hydrogen acceptors.[8] *p*-Benzoquinone is the most effective cocatalyst for regeneration of Pd(II); however, it is consumed and must be used as a stoichiometric reagent.

The temperature dependence of this reaction with **1** as substrate is illustrated in Figure 3. The rate of reaction progressively increases from 50–140°, but the activity of the catalyst[9] is a maximum at *ca.* 110°. The higher temperature favors the formation of phenol and aldol condensation products, in addition to numerous other unknown by-products.

Some oxygen is required for the reaction, although, except for reoxidation of Cu(I) and of a possible palladium hydride intermediate (see discussion of mechanism), its role is uncertain. However, in analogous systems the reaction appears to be more complex than a

(7) G. Szonyi, *Advan. Chem. Ser.*, **70**, 53 (1968); R. G. Schultz and D. E. Gross, *ibid.*, **97** (1968).

(8) I. I. Moiseev, M. N. Vargaftik, and Ya. K. Syrkin, *Dokl. Acad. Nauk SSSR*, **133**, 377 (1969); Rhone-Poulenc, British Patent 990,447 (1965); D. Clark, P. Hayden, W. D. Walsh, and W. D. Jones, British Patent 964,001 (1964); D. Clark, W. D. Walsh, W. D. Jones, and C. B. Cotterill, British Patent 975,709 (1964).

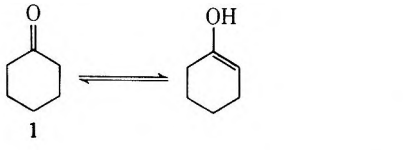
(9) See footnote *a*, Table I.

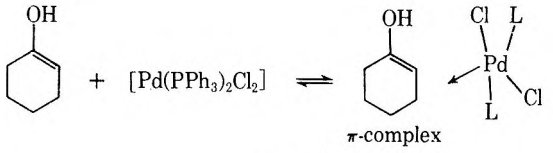
simple series of redox steps.[10] Systems which contain only catalyst and catalyst–Cu(II) cocatalyst show little or no formation of **2** in the absence of air or oxygen. However, they function normally when open to an air atmosphere or when air or oxygen is bubbled into the solution. There is no readily apparent advantage of oxygen over air. High pressures or flow rates of oxygen rapidly convert **1** to adipic acid. As might be expected, reactions employing *p*-BQ as a cocatalyst proceed even in a nitrogen atmosphere. However, for uniform reaction conditions, an air or oxygen atmosphere was used in *p*-BQ experiments the same as in Cu(II) systems.

The oxidative dehydrogenation of **1** to **2** can be carried out in a variety of solvents, whose utility depends upon the choice of Pd(II) catalyst and inorganic or organic cocatalyst. A completely homogeneous solution is favored both from the standpoint of reaction rate and catalyst activity. Neat substrate, *e.g.*, **1**, is the best reaction medium with a Cu(II) cocatalyst. On the other hand, a protonic acid solvent, such as acetic or benzoic acid, is best when using *p*-BQ.

Discussion

The exact reaction mechanism is uncertain and the following explanation, illustrated by the reaction of **1** with $[Pd(PPh_3)_2Cl_2]$, is highly speculative. However, reports in the literature[10,11] seem to indicate an initial enolization (eq 2), followed by a π complex (eq 3) which


(2)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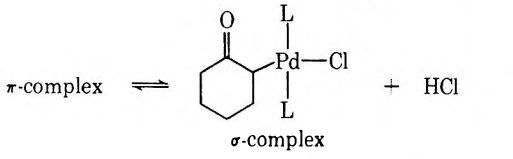
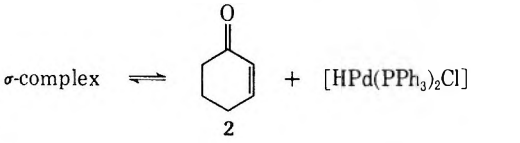

(4)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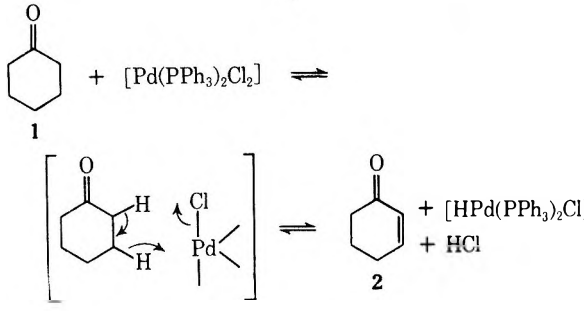
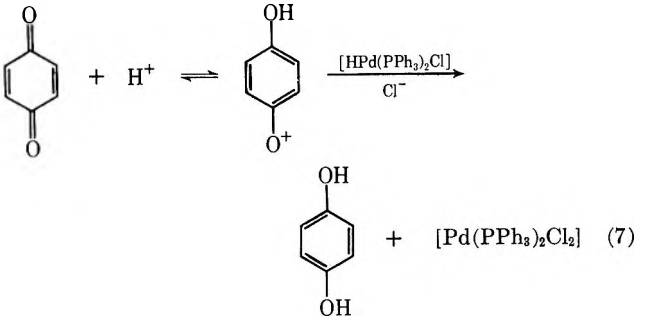

(6)

rearranges to a σ complex (eq 4). Ultimate decomposition of the σ complex yields the desired product (eq 5), but, without any real proof for a stepwise sequence, a fully concerted one-step reaction (eq 6) is entirely possible.

The catalyst and/or metallic palladium, from catalyst decomposition, may subsequently convert **1** to **3**. Whether this reaction occurs by dehydrogenation or oxidative dehydrogenation of **1** is unknown. Separate experiments under identical conditions ($[Pd(PPh_3)_2Cl_2]$ catalyst) were compared for the conversion of **1** to **2** and for the conversion of **2** to **3**. The relative rate of the latter reaction was 3–5 times faster than the former. This result would indicate that the maximum conversion to **2** is about 16–25% based only on a mass law effect. However, other pertinent factors must be involved since conversions to **2** twice as large have been obtained, without an appreciable amount of **3** being formed. The above proposed palladium hydride is very unstable,[11a] but a number of hydride complexes do exist[11b] and such intermediates have been proposed for a number of formally similar oxidation–reduction systems.[10,11c]

Subsequent catalyst regeneration in Cu–Pd redox reactions is well documented.[7,10] In addition, alternate modes of catalyst regeneration and destruction are known for analogous group VIII metal complexes.[12a]

Based upon a proposed palladium hydride intermediate, the function of *p*-benzoquinone as cocatalyst in the absence of oxygen is readily explained. A protonated species (eq 7) would be a more likely cocatalyst.


(7)

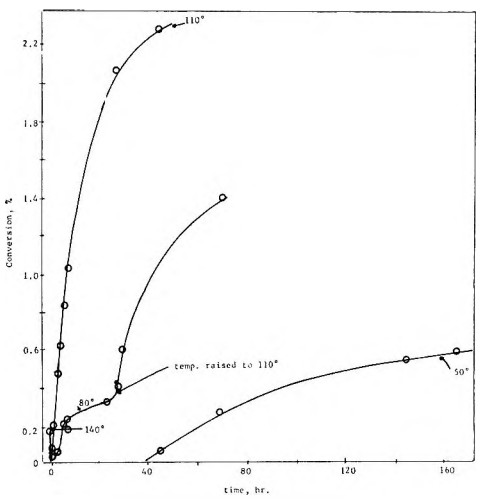
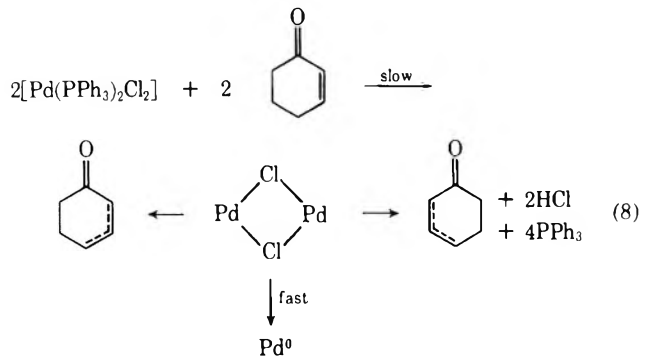


Figure 3.—Temperature dependence on conversion of cyclohexanone (0.5 mol) to cyclohexenone and phenol with 10 cc of O_2/min catalyzed by $[Pd(PPh_3)_2Cl_2]$ (7×10^{-4} mol).

(10) E. Stern, *Catal. Rev.*, **1**, 73 (1967).

(11) (a) J. Chatt, L. A. Duncanson, and B. L. Shaw, *Chem. Ind. (London)*; 859 (1959); (b) E. H. Brooks and F. Glockling, *J. Chem. Soc.*, 1030 (1967); (c) W. G. Lloyd, *J. Org. Chem.*, **32**, 2816 (1967), and references cited therein.

(12) (a) H. B. Charman, *Nature*, **212**, 278 (1966); (b) J. Tsuji and S. Imamura, *Bull. Chem. Soc. Jap.*, **40**, 197 (1967).



π-Allylic palladium complexes with α,β-unsaturated compounds are well known.[12b] The present system may also be complicated by the possible formation of a cyclohexenone–palladium complex (eq 8). This complex is known to decompose in solution to give a palladium mirror.[13] This cyclohexenonyl–palladium complex probably formed slowly (if at all) under normal reaction conditions, since the catalyst promoted the equivalent of up to 1000–2000 dehydrogenation reactions. This proposal is also supported by the observation that the concentration of **2** could be raised to 26% by oxidation of **1** initially containing 17.5% **2**. However, deposition of a palladium mirror did occur more readily.

Further catalyst decomposition can result from oxidation of triphenylphosphine, which, although it is not oxidized by air, can be oxidized to triphenylphosphine oxide in the presence of Pd^0, Pt^0, and Ni^0.[14]

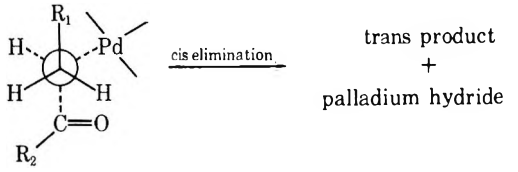
Several observations are readily apparent from a consideration of the list of substrates and products listed in Tables II–V. The first is that most cyclic ketones and aldehydes are more reactive and give higher conversions to α,β-unsaturated products than do acyclic ketones. As indicated, the proposed first step in the reaction mechanism is an enolization which is known to be favored in cyclic ketones.[15]

A second finding is that the aldehydes giving the lowest conversions, namely propanal and 2-methylpropanal, have a common feature with the first four acyclic ketones in Table IV. The products all possess a terminal vinyl grouping, $CH_2{=}C$. Possible explanations for this result may include the thermodynamic stability of the terminal vinylic compounds as well as a mechanistic hypothesis on the stability of possible π- and σ-palladium complex intermediates. Most of these substrates are low boiling and could be dehydrogenated only by use of a pressure bottle apparatus in order to attain the optimum temperature of 100–110°.

A third and unexpected observation is seen in reactions of substrates yielding internally unsaturated olefins. The α,β-unsaturated products all have a trans orientation around the carbon–carbon double bond. No cis products have been observed. In addition, when there is a possibility of forming an α,β,α′,β′-unsaturated product, as is the case with 4-heptanone, the diolefin produced has complete trans geometry.

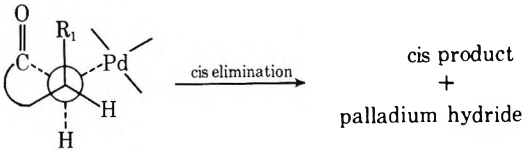
According to the proposed mechanism, the staggered conformation of the intermediate palladium σ complex,

Scheme II
Elimination from a Staggered Acyclic Intermediate



pictured in Scheme II, is expected to be the most stable.[16] The formation of trans product and the subsequent palladium hydride intermediate can arise by a cis-elimination pathway.[18] On the other hand, the most favorable conformation for an intermediate of a cyclic substrate is illustrated in Scheme III. Here cis

Scheme III
Elimination from a Staggered Cyclic Intermediate



elimination yields only a cis product. Cyclooctanone is the lowest cyclic ketone homolog in which twisting is sufficiently unrestricted to give either the cis or trans isomer.[19a] However, only *cis*-cyclooctenone was formed and its spectral properties are in complete agreement with published data.[19] The trans isomer, even if formed initially, would undoubtedly isomerize at the required reaction temperature and is known to readily convert to the cis isomer in the presence of mineral acid.[19a]

Finally, attempted extension of this oxidative technique to the preparation of other α,β-unsaturated compounds was unsuccessful. Acids, esters, and nitriles are almost totally unreactive. The homogeneous liquid-phase dehydrogenation of alcohols in the presence of group VIII metal catalysts, *e.g.*, Rh[20] and Pd[11c] complexes, is well known, but, in the present endeavor, alcohols gave only modest amounts (1–5% conversion) of α,β-unsaturated products. In contrast to the present study, the oxidation of cyclohexanol in the presence of a $PdCl_2$–$Cu(NO_3)_2$ system is reported[11c] to give low conversions, *ca.* 2%, to **1** only. Conversions for a number of other primary and secondary alcohols vary from 1–30%. No α,β-unsaturated ketones or aldehydes were observed.

The method of synthesis described by this study lends itself to the preparation of small to medium-sized quantities of material. Since it is applicable to a number of aldehydes and ketones, the primary disadvantages can often be minimized. It thus may offer a new and at-

(13) A. Kashara, K. Tanaka, and K. Asamiya, *Bull. Chem. Soc. Jap.*, **40**, 351 (1967).

(14) G. Wilke, H. Schott, and P. Heimbach, *Angew. Chem., Int. Ed. Engl.*, **6**, 92 (1967); S. Takahashi, K. Sonogashira, and N. Hagihara, *Nippon Kagaku Zasshi*, **87**, 610 (1966).

(15) L. F. Fieser and M. Fieser, "Advanced Organic Chemistry," Reinhold, New York, N. Y., 1963, p 409.

(16) As seen by Dreiding models of compounds depicted in Scheme II, steric repulsions are significantly minimized by a trans orientation of R_1 and COR_2. Interaction of R_1 with the Pd complex is significantly less severe due to a C–Pd bond distance of *ca.* 2.05–2.2 Å.[17]

(17) M. R. Churchill and R. M. Mason, *Advan. Organometal. Chem.*, **5**, 93 (1967).

(18) A counterclockwise rotation of the group CH_2R_1 by 120° would have PdL_2X flanked by two H atoms. A nonselective elimination of a palladium–hydrido complex would be expected to yield a mixture of cis and trans products.

(19) (a) P. E. Eaton and K. Lin, *J. Amer. Chem. Soc.*, **86**, 2087 (1964); (b) O. L. Chapman, *ibid.*, **85**, 2014 (1963).

(20) H. B. Charman, *J. Chem. Soc.*, 629 (1967); *Nature*, **212**, 278 (1966).

tractive route to certain olefinically unsaturated carbonyl compounds.

Experimental Section

Analyses of reaction products were done by vpc on an Aerograph Model A-90-P gas chromatograph, using one of the three following columns: (1) 10% neopentylglycol succinate on 60–80 mesh Chromosorb W, 10 ft × 3/8 in.; (2) 10% free fatty acid phthalate on 60–80 mesh Chromosorb W, 10 ft × 3/8 in.; and (3) 20% free fatty acid phthalate on 60–80 mesh Chromosorb W, 10 ft × 1/4 in. In general, all significant products were preparatively separated. Infrared spectra were obtained on a Beckman IR-5 spectrometer and nmr spectra were obtained with a Varian A-60 spectrometer in $CDCl_3$ solution with TMS as an internal standard.

The usual technique for work-up and isolation was as follows. First all organic volatiles were distilled from the catalyst–cocatalyst system under reduced pressure. Then, depending upon the boiling point and solubility of the product and the starting material, either fractional distillation, preparative vpc, or liquid column chromatography was used for separation.

Alternatively, in some instances, the reaction could be diluted with hexane to precipitate most of the catalyst. Then, after distillation of solvent one of the above three methods was used for separation.

Cyclohexenone (2). Procedure A.—A stirred mixture of cupric acetate monohydrate (8.5 g, 0.0425 mol) and dichlorobis(tripheny.phosphine)palladium(II) (1.5 g, 0.00214 mol) in cyclohexanone (100 g, 1.02 mol) and acetic acid (50 g, 0.84 mol) was warmed to 77° while an oxygen bubble (15 cc/min) was maintained below the surface. The blue-green solution slowly changed to brown and a red-brown precipitate (cuprous oxide) formed. The progress of the reaction was monitored by vpc; after 10.5 hr the conversion was 8.0% with selectivities to cyclohexenone and phenol of 95 and 5%, respectively. Total conversion as indicated by vpc was 8.3% with a total selectivity to cyclohexenone of 92%. After distillation of all volatiles, the residue was extracted with base, which upon acidification gave a crude acid, whose infrared spectrum was very similar to that of adipic acid.

Procedure B.—A stirred mixture of dichlorobis(triphenylphosphine)copper(II) (10.0 g, 0.0151 mol) and dichlorobis(triphenylphosphine)palladium(II) (2.0 g, 0.00286 mol) in cyclohexanone (100 g, 1.02 mol) was warmed to 100° with 15 cc of O_2/min bubbling into the solution. A mirror and a gray-black haze formed slowly on the flask. After a 6-hr reaction time, the conversion was 17% (98% cyclohexenone and 2% phenol) while the total conversion was 17.6% with a 94% selectivity to cyclohexenone. A vacuum distillation gave 97.5 g of volatile organic materials, the vpc analysis of which closely corresponded to that of the reaction mixture.

Procedure C.—A stirred mixture of cupric acetylacetonate (5.5 g, 0.021 mol) and palladium acetylacetonate (0.05 g, 0.000164 mol) in cyclohexanone (98.0 g, 1.00 mol) and acetic acid (52.0 g, 0.87 mol) was heated to 105° with 150 cc of O_2/min bubbling into the green-blue solution. A gray-black film slowly formed on the flask and a brown precipitate formed. Analysis of the reaction mixture after 24 hr showed a 19.7% conversion (95% cyclohexenone and 5% phenol). The total conversion based on vpc was 21.5% with an 85% selectivity to cyclohexenone. It was evident, however, that upward of 20% of the cyclohexanone had been oxidized to higher boiling materials (likely adipic acid). As a result the estimated total conversion is 36% with cyclohexenone selectivity about 39%.

Procedure D.—A stirred solution of *p*-benzoquinone (20.0 g, 0.185 mol) and palladium acetylacetonate (0.5 g, 0.00164 mol) in cyclohexanone (100 g, 1.02 mol) and acetic acid (52 g, 0.87 mol) was heated to 110° with 10 cc of O_2/min bubbling into the solution. After 15 min the solution had turned a dark brown and a heavy palladium mirror was on the flask. Analysis after 1 hr showed 15.3% conversion (98% cyclohexenone and 2% phenol). The total conversion was 15.5% with a cyclohexenone selectivity of 96%. No further increase in conversion was observed with continued heating.

Procedure E.—A stirred mixture of *p*-benzoquinone (20.0 g, 0.185 mol), palladium acetylacetonate (0.1 g, 0.00033 mol), cupric acetylacetonate (2.6 g, 0.01 mol), and benzoic acid (50.0 g, 0.41 mol) in cyclohexanone (98.0 g, 1.0 mol) was heated to 110° while 15 cc of O_2/min was bubbled into the solution. The initial green slurry turned brown-green with heating and some gray-black haze as well as a green precipitate was formed on the flask. After 3.5 hr the total conversion was 18.6% (94% cyclohexenone). This after 23 hr had increased to 43.0% (88% selectivity to cyclohexenone). At this point, it was estimated that about 13% of the cyclohexanone had been oxidized to higher boiling materials not observed by vpc so that the estimated actual total conversion and selectivity were 50 and 73%, respectively.

Propenal.—Into a pressure bottle equipped with a release valve was placed *p*-benzoquinone (20.0 g, 0.185 mol), palladium acetylacetonate (0.5 g, 0.00164 mol), and benzoic acid (25.0 g, 0.205 mol) in propanal (58.0 g, 1.0 mol). The bottle was sealed and the stirred solution heated to 110° at which temperature a palladium mirror formed rapidly. After 4 hr of heating, the conversion was 6.3% with an approximate 100% selectivity to propenal.

Butenal.—Butanal (72.0 g, 1.0 mol) in a similar reaction to that for propanal, but under atmospheric pressure at 90° with an O_2 bubble of about 10 cc/min gave a 14.6% conversion after 5 hr to *trans*-2-butenal (79%) and the aldol condensation product from 2 mol of butanal (21%).

1-Penten-3-one.—In a pressure-bottle reaction identical with that for propanal but with 3-pentanone (86.0 g, 1.0 mol), the conversion was 6.0% after 2.5 hr with selectivities to 1-penten-3-one and 1,4-pentadien-3-one of 94 and 6%, respectively.

Cyclopentenone.—A stirred mixture of cupric acetylacetonate (5.5 g, 0.021 mol) and palladium acetylacetonate (0.5 g, 0.00164 mol) in acetic acid (52 g, 0.87 mol) and cyclopentanone (84.0 g, 1.0 mol) was heated to 105° while 15 cc of O_2/min flowed into the blue-green solution. The solution slowly turned a dark brown color and a palladium mirror formed. The conversion after a 25-hr reaction time was 21.8% with a 91% selectivity to cyclopentenone.

Δ′-Cholesten-3-one.—A stirred solution of cholestan-3-one (0.2 g, 0.00052 mol) and palladium acetylacetonate (0.16 g, 0.00052 mol) in acetic acid (8.0 g, 0.13 mol) was heated at 110° for 18 hr while 1–2 cc of O_2/min was bubbled into the solution. A palladium mirror had formed and the reaction was a green-yellow at the end of the reaction. The solution was filtered free of precipitated Pd^0 (black) and the acetic acid solution diluted with water (50 ml) to give a tan-brown precipitate (270 mg). Unused catalyst (120 mg) was recovered from this brown solid by dissolving the organic material in the minimum amount of hexane and filtering. The crude reaction product (150 mg) was freed of residual catalyst by chromatography on alumina with diethyl ether as eluent. Infrared and nmr spectra confirmed an 82% conversion with the primary product being Δ′-cholesten-3-one.

Registry No.—**1**, 108-94-1; **2**, 930-68-7; **3**, 108-95-2; dichlorobis(triphenylphosphine)palladium(II), 13965-03-2; dichlorobis(triphenylphosphine)copper(II), 27396-56-1; cupric acetylacetonate, 13395-16-9; palladuim(II) acetylacetonate, 14024-61-4; *p*-benzoquinone, 106-51-4.

Carbonium Ion–Silane Hydride Transfer Reactions. V. *tert*-Alkyl Cations

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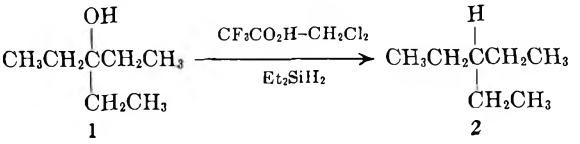
A number of *tert*-alkyl cations have been generated from alcohol or alkene precursors in methylene chloride–trifluoroacetic acid and their reactivity toward intermolecular hydride-transfer reactions with organosilicon hydride donors has been studied. In some cases this reaction could be synthetically useful: 3-methyl-5α-cholest-2-ene was converted to 3β-methyl-5α-cholestane, 3-ethyl-3-pentanol to 3-ethylpentane, and 2-methyl-2-admantanol to 2-methyladamantane. Rearrangements occurred faster than hydride transfer in the conversion of *cis,cis,trans*-perhydro-9b-phenalenol to *trans,trans,trans*-perhydrophenalene and the formation of an unidentified hydrocarbon from cholest-5-ene. The 9-decalyl cation yielded a decalin mixture in which the cis/trans ratio was 3:2.

Organosilicon hydrides have been shown to be quite reactive in intermolecular hydride transfer to carbonium ions. Stable carbonium ions of the arylmethyl type,[1,2] tropylium cation,[3] and ferrocenylmethyl cations[4] are all converted rapidly and in high yield to the corresponding hydrocarbons. Cyclopropylmethyl cations which form readily but rapidly undergo ring-opening reactions are converted to cyclopropylmethanes at rates competitive with and, in many cases, exceeding the rate of ring opening.[5] In a reaction which is potentially useful synthetically, Kursanov has reported that *tert*-alkyl cations generated by protonation of olefins also abstract hydride from organosilicon hydrides.[6] In order to explore these synthetic possibilities, we have examined a number of *tert*-alkyl cations as hydride acceptors. Our approach was not one of a thorough investigation of many representative *tert*-alkyl cations but rather that of choosing selected compounds of more general interest in which the information gained would be more useful than simply a report of yield data on structurally similar compounds.

Results

3-Ethyl-3-pentyl Cation.—Suitable experimental conditions for carrying out the hydride transfer reactions were determined using 3-ethyl-3-pentanol (**1**) and measuring its conversion to 3-ethylpentane (**2**) by gas chromatography. Using diethylsilane as the hydride donor in methylene chloride at 25° and trifluoroacetic acid as the proton source (0.5 *M*), conversion to **2** was complete to the extent of only about 19% in 0.5 hr. Increasing the trifluoroacetic acid concentration to 6 *M* in methylene chloride and the reaction time to 24 hr brought about the complete conversion of **1** to **2**. It was determined by gas chromatography that **1** is not stable under these reaction conditions and is rapidly converted to 3-ethyl-2-pentene which is the actual species undergoing reaction. The experimental conditions can be varied within rather wide limits since in a reaction carried out on a preparative scale using triphenylsilane as the donor and a trifluoroacetic acid concentration of 1.5 *M* pure **2** was isolated in 78% yield.[7]



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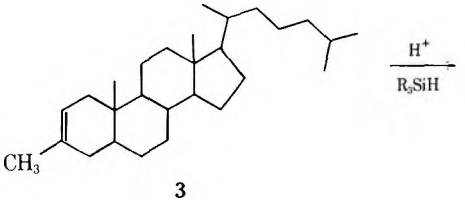
3-Methyl-3-cholestanyl Cation.—Reduction of 3-methyl-5α-cholest-2-ene (**3**) by the two-step protonation–hydride transfer sequence was examined as a synthetic alternative to catalytic hydrogenation, as well as to observe the stereoselectivity of hydride transfer. Using triphenylsilane as the donor, the product was 3β-methyl-5α-cholestane (**4**) in 66% yield of purified product. This is the equatorial methyl epimer and is also the product of catalytic hydrogenation.[8]



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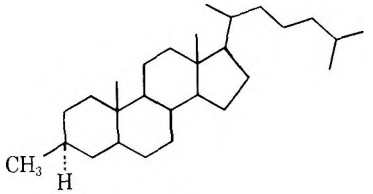

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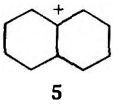
9-Decalyl Cation (5).—Examination of the stereoselectivity associated with hydride transfer to the 9-decalyl cation (**5**) was undertaken in view of the recent interest in tertiary carbonium ions at bridgeheads in condensed ring systems.[9] The stereoselectivity of capture of **5** by a number of reagents has been reported and



5

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(2) T. A. Serebryakova, Z. N. Parnes, A. V. Zakharychev, S. N. Anachenko, and I. V. Tergov, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 662 (1969).

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(8) D. H. R. Barton, A. da S. Campos-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956).

(9) A review of the literature through 1965 may be found in the chapter by R. C. Fort, Jr., and P. v. R. Schleyer, *Adv. Alicyclic Chem.*, **1**, 283 (1966); R. C. Fort, Jr., and R. E. Hornish, *Chem. Commun.*, 11 (1969); A. F. Boschung, M. Geisel, and C. A. Grob, *Tetrahedron Lett.*, 5169 (1968).

found to be variable. Kinetically controlled carbonylation of **5** gives a mixture of *cis*-decalin-9-carboxylic acid (**6**) and *trans*-decalin-9-carboxylic acid (**7**) in ratio of 1:9. When carried out under conditions of thermodynamic control, the ratio of **6**:**7** is reversed.[10]

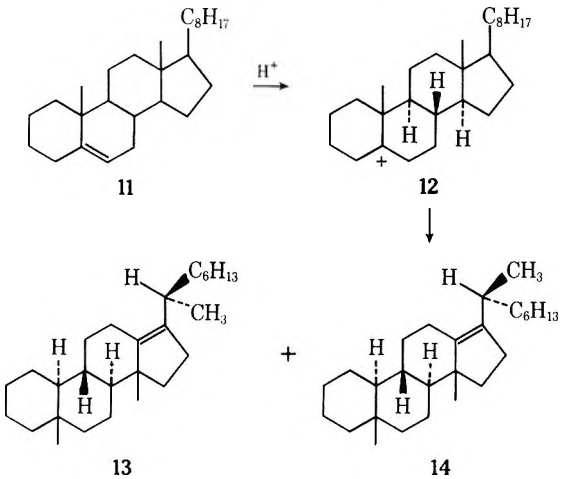
Addition of hydrogen chloride to $\Delta^{9,10}$-octalin (**8**) under conditions of kinetic control affords approximately equal amounts of *cis*- and *trans*-9-chlorodecalin (54% cis:46% trans).[11]

Hill and Carlson[12] have reported that hydride transfer to **5** from carbon donors gives mixtures of *cis*-decalin (**9**) and *trans*-decalin (**10**) in which the cis/trans ratio ranges from 4.5 to 6.5. This reaction is clearly kinetically controlled and the results were rationalized by proposing delivery of hydride to the less hindered face of the carbonium ion.

We have generated **5** by protonation of an octalin mixture containing 92% **8** and 8% the $\Delta^{1,9}$ isomer in methylene chloride–trifluoroacetic acid at 25° in the presence of triphenylsilane and determined the composition of decalins by gas chromatography. The ratio of **9** to **10** was substantially different from that observed for hydride transfer from carbon donors in that decalin composition was 61–64% cis:36–39% trans for three runs.

5-Cholestanyl Cation (12).—The steroidal olefin cholest-5-ene (**11**) was chosen as a model compound to investigate the effect of an angular methyl group in influencing the stereochemistry of attack in decalyl cations. Hydride transfer to carbonium ion **12** from the α face would yield 5α-cholestane while hydride transfer from the β face would yield 5β-cholestane.

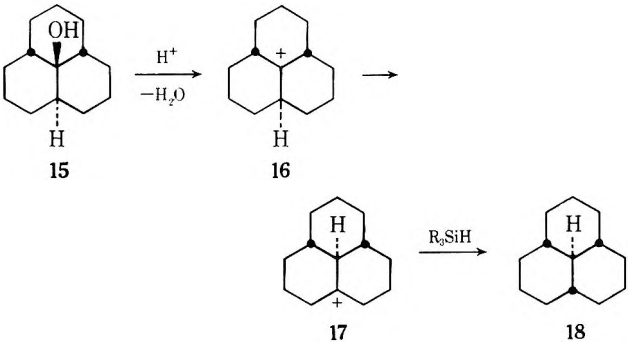
When the reaction of **11** with either triethylsilane or triphenylsilane was carried out under the usual conditions it was found that the product was an uncrystallizable syrup, the nmr of which clearly indicated that it was neither 5α-cholestane nor 5β-cholestane. The parent peak in the mass spectrum of the product appeared at *m/e* 372 and thus corresponds to the addition of a proton and a hydride to the double bond. Intense peaks were also observed at *m/e* 259, 257, and 217 and were comparable in peak height to that of the molecular ion and were the most intense peaks in the mass spectrum. By way of comparison the most intense peak in the mass spectrum of cholestane is *m/e* 217. The failure to obtain either 5α- or 5β-cholestane can be attributed to the slowness of hydride transfer relative to the rate at which **12** undergoes the backbone rearrangement to **13** and **14**.[13]



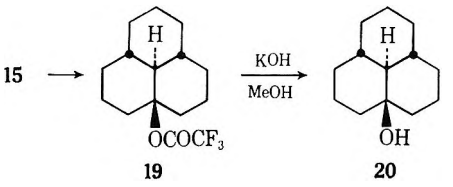
11 **12** **13** **14**

The product obtained is therefore formulated as a mixture of diastereomers derived from protonation of **13** and **14** followed by hydride transfer.[14] This experiment points out a serious limitation to the use of this reaction for synthetic purposes in that skeletal rearrangements may be faster than intermolecular hydride transfer.

Carbonium Ions Derived from *cis,cis,trans*-Perhydro-9b-phenalenol[15] (15).—The *cis,cis,trans*-tercyclanol (**15**)[16] was converted in high yield and stereoselectively to *trans,trans,trans*-perhydrophenalene (**18**)[17] when allowed to react with either triethylsilane or triphenylsilane in methylene chloride–trifluoroacetic acid. The sequence of intermediates is believed to be as shown on the basis of this experiment and reactions carried out in the absence of hydride donors.



By monitoring the reaction of **15** with triethylsilane by gas chromatography, it was found that formation of **18** was relatively slow and that **15** was rapidly converted to another substance which decreased as **18** increased. This intermediate was identified as **19** by allowing **15** to react with a solution of trifluoracetic acid in methylene chloride for 30 min, quenching the reaction mixture, and cleaving the crude product which exhibited trifluoroacetate ester absorbance in the infrared with potassium hydroxide in methanol. The product obtained in 72% yield was identified as **20** by comparing its ir and melting point with those of authentic material.



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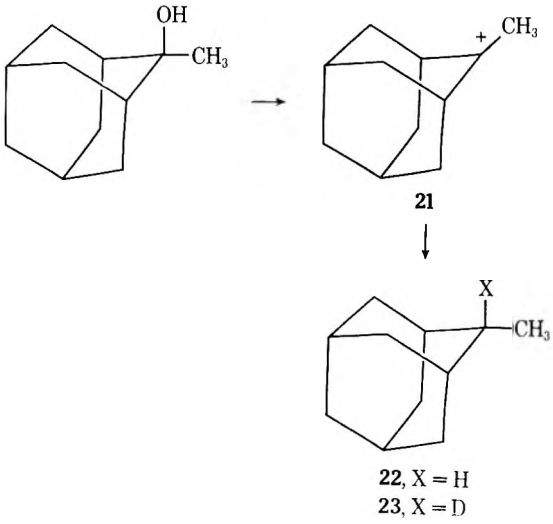
(14) Experiments carried out by Mr. D. S. Watt using a more reactive hydride donor (Et_2SiH_2) at −10° did not alter the product composition.

(15) We wish to acknowledge the invaluable assistance of Dr. W. C. Dickason and Professor H. C. Brown in this study. Dr. Dickason generously provided samples of **15** and **18** and copies of ir spectra as well as many timely and helpful suggestions.

(16) H. C. Brown and E. Negishi, *J. Amer. Chem. Soc.*, **89**, 5478 (1967); H. C. Brown and W. C. Dickason, *ibid.*, **91**, 1226 (1969).

(17) A. Schneider, R. W. Warren, and E. J. Janoski, *J. Org. Chem.*, **31**, 1617 (1966); *J. Amer. Chem. Soc.*, **86**, 5365 (1964).

2-Methyl-2-adamantyl Cation (21).—Recent interest has developed in 2-adamantyl cations as examples of carbonium ions which are formed with little, if any, solvent participation during the ionization process.[18] Ion **21** also has been reported to be converted to the 2-methyl-1-adamantyl cation in 95% sulfuric acid and so would provide further information as to the relative rates of hydride transfer and isomerization.[19] It was found by an nmr experiment that **21** was not converted to the 2-methyl-1-adamantyl cation under conditions (2.5 *M* trifluoroacetic acid in $CDCl_3$) where efficient hydride transfer takes place. In addition, the use of triphenyldeuteriosilane afforded **23** as evidenced by the fact that the methyl signal which appears as a doublet (J = 7 Hz) in **22** was a broadened singlet (triplet, J = 1 Hz on scale expansion) due to the smaller magnitude of the coupling constant to deuterium. These small-scale experiments performed in nmr tubes clearly showed the conversion to **22** and **23** to be quantitative. When the hydride transfer was carried out on a preparative scale using triethylsilane as the donor, **22** could be isolated in a yield of only 41%. The problems here appeared to be manipulative rather than inefficiency of reaction, since **22** is rather volatile and difficult to recrystallize without significant loss.



22, X = H
23, X = D

Discussion

The carbonium ion to alkane conversions described here serve as examples of the synthetic possibilities of intermolecular hydride transfer reactions by extending the observations of Kursanov[6] to conditions of decreased acidity and also illustrate the present deficiencies of the reaction in that rearrangements often occur faster than hydride transfer. In favorable cases the reaction of a tertiary alcohol with an organosilicon hydride in 2.5–6 *M* trifluoroacetic acid in methylene chloride constitutes an excellent means of effecting the reduction of an alcohol to a hydrocarbon. Reduction of olefins capable of generating tertiary carbonium ions under these conditions offers the novel feature of allowing the introduction of protium at one end of the double bond and deuterium at the other through use of the appropriate combinations of CF_3CO_2H, CF_3CO_2D, R_3SiH, and R_3SiD.

The relatively direct approach allowing alcohols and organosilicon hydrides to react in trifluoroacetic acid media appears to be limited to reduction of those alcohols which can form carbonium ions at least as stable as tertiary.

Experimental Section

Nmr spectra were recorded on a Hitachi Perkin-Elmer R-20 spectrometer in $CDCl_3$, and chemical shifts are reported in ppm (δ) from internal tetramethylsilane. Infrared spectra were measured on a Perkin-Elmer 337 grating instrument as KBr disks for solids and pressed films for neat liquids. Melting points are corrected and were determined on a Thomas-Hoover apparatus. The gas chromatograph used was a Varian Aerograph 90-P unit equipped with a Disc integrator. The mass spectra were obtained using a Hitachi Perkin-Elmer RMU-6E mass spectrometer at an ionizing potential of 70 eV.

Reduction of 3-Ethyl-3-pentanol.—To a solution of 2.0 g (17.4 mmol) of 3-ethyl-3-pentanol and 5.36 g (20.6 mmol) of triphenylsilane in 68 ml of methylene chloride was added 11.76 g (113 mmol) of trifluoroacetic acid. After 24 hr at room temperature solid sodium carbonate was added, the solution filtered, and the solvent removed by distillation. The residue was then chromatographed on 25 g of alumina and eluted with pentane (100 ml) to yield 1.34 g (78%) of 3-ethylpentane. The infrared and nmr spectra of the product matched those of an authentic sample, and analysis by glpc on a 10-ft 20% SE-30 on Chromosorb W column at 100° and 60 cc of helium per minute revealed a single peak having the same retention time as 3-ethylpentane.

Reduction of 3-Methyl-5α-cholest-2-ene (3) by Hydride Transfer.—To a solution containing 150 mg (0.39 mmol) of **3**[8] and 0.5 ml of triethylsilane in 5 ml of methylene chloride was added 1.0 ml of trifluoroacetic acid, and the solution allowed to stand at room temperature for 16 hr. The reaction mixture was then shaken with 20 ml of methylene chloride and 30 ml of saturated sodium bicarbonate solution, and the organic layer was separated and dried over magnesium sulfate. Evaporation of the solvent and recrystallization of the residue from ethanol afforded 99.1 mg (66%) of 3β-methyl-5α-cholestane, mp 90.5–92°, $[\alpha]^{25}D$ +27.9° ($CHCl_3$). The nmr and ir spectra were identical with those of an authentic sample,[20] mp 99–100°, $[\alpha]^{25}D$ +23.3°.

Hydride Transfer to 9-Decalyl Cation.—An octalin mixture composed of 92% $\Delta^{9,10}$-octalin and 8% $\Delta^{1,9}$-octalin was prepared from decahydro-2-naphthol by the procedure of Campbell and Harris.[21] Trifluoroacetic acid (0.648 g, 6.0 mmol) was added to 1 ml of methylene chloride containing 0.136 g (1.0 mmol) of the octalin mixture and 1.2 mmol of triphenylsilane. After 24 hr solid sodium carbonate was added, and the solution was analyzed by glpc[22] using a 10-ft 20% Carbowax 20M on Chromosorb W column at 145° and a flow rate of 60 cc of He/min. Conversion of the octalin mixture to decalins was on the order of 90% under these conditions. *cis*- and *trans*-decalin were identified by comparing their retention times (2.9 and 2.2 min, respectively) with those of standard samples. In a typical experiment triphenylsilane yielded a mixture of 32% *trans*-decalin, 57% *cis*-decalin, and 11% octalins.

Attempted Reduction of Cholest-5-ene (11) by Hydride Transfer.—A solution containing 740 mg (2 mmol) of **11**[23] and 598 mg (2.3 mmol) of triphenylsilane in 8 ml of methylene chloride and 2 ml of trifluoroacetic acid was allowed to stand 50 hr at room temperature. Methylene chloride (30 ml) was added and the solution was extracted with three 30-ml portions of sodium bicarbonate. The organic phase was dried over magnesium sulfate, concentrated, and chromatographed on 40 g of Woelm silica gel. Elution with pentane (90 ml) and evaporation yielded 667 mg of a clear syrup which resisted all attempts at crystallization. The nmr spectrum of the product was similar to that of a saturated

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(22) For gas chromatographic data on octalins and decalins, see J. W. Powell and M. C. Whiting, *Tetrahedron*, **12**, 163 (1961).

(23) W. G. Dauben and K. H. Takemura, *J. Amer. Chem. Soc.*, **75**, 6302 (1953).

steroid but was clearly neither 5α- nor 5β-cholestane.[24] The infrared spectrum indicated the absence of any functional groups such as OH or carbonyl. The molecular weight of the material was 372 by mass spectrometry.

Reduction of *cis,cis,trans*-Perhydro-9b-phenalenol (15) by Hydride Transfer.—Alcohol **15** (1.94 g, 10 mmol) was dissolved in 40 ml of methylene chloride along with 2.99 g (11.5 mmol) of triphenylsilane and 7.3 ml (11.2 mg, 100 mmol) of trifluoroacetic acid. After 48 hr the solution was poured in 250 ml of saturated sodium bicarbonate, the layers separated, and the aqueous layer was extracted with 50 ml of methylene chloride. The combined organic extracts were washed with 50 ml of saturated sodium bicarbonate, dried over magnesium sulfate, concentrated, and chromatographed on 40 g of silica gel (Woelm). Elution with 120 ml of pentane yielded 1.63 g (92%) of **18**. The reaction product was identical with respect to ir, nmr, and retention time (10-ft 15% Carbowax on firebrick at 188°) with an authentic sample. Analysis by glpc under these conditions indicated that the product was 90% pure.

Reaction of 15 with Trifluoroacetic Acid.—To 300 mg (1.55 mmol) of **15** in 10 ml of methylene chloride was added 2.5 ml of trifluoroacetic acid, and the solution was allowed to stand 30 min and then poured into 50 ml of saturated sodium bicarbonate solution. The organic layer was dried over magnesium sulfate and evaporated. Previous experiments had indicated that the product at this point was a trifluoroacetate ester which was difficult to purify directly. For identification purposes the product was taken up in 10 ml of methanol containing 1 g of KOH, allowed to stand 48 hr, then quenched with 50 ml of water, and extracted with four 25-ml portions of pentane. The pentane layers were washed twice with 5-ml portions of water, dried ($MgSO_4$), and evaporated to leave 216 mg (72%) of white solid, mp 81–84°. The infrared spectrum was identical with that of *trans,trans,trans*-perhydrophenalen-3a-ol (**20**). A small amount was recrystallized from pentane to yield material melting at 87.5–88.5°.

Conversion of 2-Methyl-2-adamantanol to 2-Methyladamantane (22).—Trifluoroacetic acid (7.3 ml) was added to a solution of 1.66 g (10 mmol) of 2-methyl-2-adamantanol and 2.0 ml of triethylsilane in 40 ml of methylene chloride. The combined extracts were dried over magnesium sulfate and evaporated, and the residue was recrystallized from ethanol–water to afford 613 mg (41%) of **22** as white crystals, mp 144–146° (reported[25] 143.8–146°). The nmr spectrum of the product provided confirmation of the supposed structure in that it exhibited a three-proton doublet (J = 7 Hz) at 1.05 ppm (reported[26] 1.04 ppm).

To check for completeness of the reaction, because of the low yield realized in the preparative experiment and to ensure that no rearrangment of the carbonium ion was occurring under these reaction conditions, 50 mg of 2-methyl-2-adamantanol and 85 mg of Ph_3SiD were dissolved in 0.4 ml of $CDCl_3$ in an nmr tube and 0.075 ml of trifluoroacetic acid was added. After 48 hr at 25° the nmr spectrum of this solution showed that **23** was formed quantitatively. The methyl signal appeared at 1.05 ppm as a broadened singlet which was found to be a triplet on scale expansion due to vicinal coupling of the methyl protons with one deuterium nucleus (J = 1 Hz).

Registry No.—**1**, 597-49-9; **4** (cation), 27390-89-2; **5**, 23373-80-0; **12**, 27390-90-5; **16**, 27390-91-6; **20**, 27390-92-7; **21**, 27411-03-6; diethylsilane, 542-91-6; triphenylsilane, 789-25-3; triethylsilane, 617-86-7.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work.

(24) 5α-Cholestane was purchased from Applied Science Laboratories, State College, Pa. 5β-Cholestane was obtained from Chemical Procurement Laboratories, College Point, N. Y.

(25) P. v. R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, **83**, 182 (1961).

(26) R. C. Fort, Jr., and P. v. R. Schleyer, *J. Org. Chem.*, **30**, 785 (1965).

Ferrocene Studies. XVIII. Identification and Stereochemistry of Nine Bimolecular Clemmensen Reduction Products of Benzoylferrocene[1a–d]

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In addition to the normal reduction product, benzylferrocene, Clemmensen reduction of benzoylferrocene is shown to give nine bimolecular reduction products: achiral and chiral 1,2-diferrocenyl-1,2-diphenylethanes (**3** and **4**), *trans*-1,2-diferrocenyl-1,2-diphenylethene (**5**), 2,2-diferrocenyl-1,2-diphenylethanone (**6**), 1,2-diferrocenyl-2,2-diphenylethanone (**7**), achiral and chiral 1,2-diferrocenyl-1,2-diphenyl-1,2-ethanediols (**8** and **9**), and achiral and chiral 1,2-diferrocenyl-1,2-diphenylethanols (**10** and **11**). Rigorous stereochemical assignments to the achiral and chiral diastereomers of the ethanes, **3** and **4**, and the diols, **8** and **9**, are based on independent preparations of each pair in the presence of (+)-(*S*)-1-methoxy-2-methylbutane (**12**). These successful procedures of asymmetric selection give an optically active form (chiral) along with an optically inactive partner (achiral) in each case. The olefinic Clemmensen product is shown to consist of only the trans or *E* isomer **5** by its conversion, *via* overall syn addition of hydrogen, to the chiral ethane **4**. Stereochemical assignments to the alcohols, **10** and **11**, are mainly but tentatively based on the relative rates with which these highly unstable compounds undergo fragmentation to benzyl- and benzoylferrocene.

Although the Clemmensen reduction[2] is generally used in the conversion of ketones to $-CH_2-$ groups, bimolecular reduction products are sometimes formed.[3] The present work is concerned with the reduction of benzoylferrocene for which bimolecular products are known to predominate.[4] We have carried out a large

(1) (a) First part of a subseries concerned with Clemmensen reductions of ferrocenyl ketones. Portions of this work have been presented in preliminary form.[1b–d] (b) 19th Southeastern Regional Meeting of the American Chemical Society, Atlanta, Ga., Nov 1967, Abstracts, p 308. (c) S. I. Goldberg and W. D. Bailey, *J. Amer. Chem. Soc.*, **91**, 5113 (1969). (d) S. I. Goldberg and W. D. Bailey, *J. Chem. Soc. D*, 1059 (1969). (e) A part of the experimental work is from the Ph.D. dissertation of M. L. McGregor, University of South Carolina Graduate School, 1969, and the work contributed by W. D. Bailey is to be included in his Ph.D. dissertation.

(2) E. Clemmensen, *Ber.*, **46**, 1838 (1913).

(3) For accounts of much of this work, see E. L. Martin, *Org. React.*, **1**, 155 (1942); J. H. Brewster, *J. Amer. Chem. Soc.*, **76**, 6361, 6364 (1954); D. Staschewski, *Angew. Chem.*, **71**, 726 (1959); T. Nakabayashi, *J. Amer. Chem. Soc.*, **82**, 3900, 3906, 3909 (1959).

(4) The claim[5] that the unidentified material obtained from Clemmensen reductions of benzoylferrocene (Rausch, Vogel, and Rosenberg[6] and Nesmeyanov and Kritskaya[5]) was 2,2-diferrocenyl-1,2-diphenylethane has been refuted.[7] It is likely that those isolations, as well as the unidentified material reported by Weliky and Gould,[8] consisted of various combinations of the bimolecular products incompletely accounted for earlier[1b,9] but more fully recognized in the present work.

(5) A. N. Nesmeyanov and I. I. Kritskaya, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 352 (1962).

(6) M. Rausch, M. Vogel, and H. Rosenberg, *J. Org. Chem.*, **22**, 903 (1957).

(7) S. I. Goldberg and M. L. McGregor, *ibid.*, **33**, 2568 (1968).

(8) N. Weliky and E. S. Gould, *J. Amer. Chem. Soc.*, **79**, 2742 (1957).

(9) M. D. Rausch and D. L. Adams, *J. Org. Chem.*, **32**, 4144 (1967).

SCHEME I

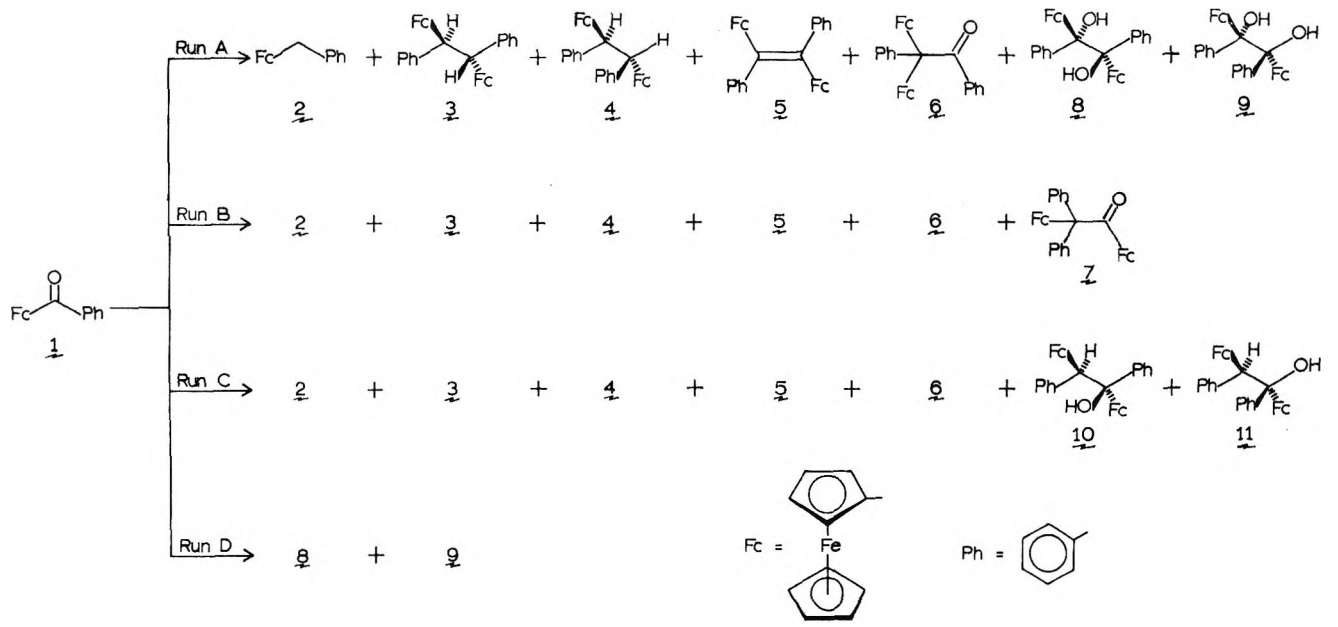


TABLE I

SUMMARY OF PRODUCTS

Run[a]	Products, % yield 2	3	4	5	6	7	8	9	10[b]	11[b]	Material balance, %[c]
A	12.6	5.7	3.2	38.4	*d*	*e*	*d*	*d*	*e*	*e*	61.9
B	5.8	4.5	3.0	21.3	14.7	1.0	*e*	*e*	*e*	*e*	50.3
C	*d*	*d*	*d*	*d*	*d*	*e*	*e*	*e*	*f*	*d*	
D	*e*	*e*	*e*	*e*	*e*	*e*	40.1	23.1	*e*	*e*	80.4[g]

[a] See Experimental Section for reaction details. [b] Stereochemical assignments tentative; see Discussion. [c] Mole per cent of consumed benzoylferrocene as accounted for in terms of purified products. [d] Compound present, but amount not determined. [e] Presence not known. [f] Only a 10-mg purified sample of this difficult to handle compound was obtained. [g] Combined weight of chromatographically pure but unseparated pinacols.

number of reductions of this ketone under a variety of conditions and isolated nine bimolecular products, the majority of which are characterized for the first time.

Results

Four typical reactions are here considered; these (Scheme I and Table I) produced, in the aggregate, all nine of these products.

Run A (97°, 15 min) yielded pinacols **8** and **9**, showing that the stereomeric pinacols were formed rapidly and may thus be considered the principal source of the other bimolecular products. Run D (room temperature, 20 min) gave only pinacols **8** and **9**. These pinacols have been reported[8] to be unstable in solution, but solutions in oxygen-free benzene or carbon disulfide are reasonably stable. It was of interest to learn the relative stereochemistry of the two diastereomers which melted at 202–204 and 207–209°. The uncertainties surrounding choices of conformational preferences in the two isomers and the possibility of several different intramolecular hydrogen bonds (Scheme II) appeared to preclude use of the usual spectral methods for these assignments. In the meantime, relative configurations of the stereomeric ethanes **3** and **4** were established by the means discussed below, and suitable chemical connections were sought in order to correlate configurations of the pinacols with the ethanes.

Raney nickel catalyzed reduction[10] was tried, but each pinacol was cleaved to benzylferrocene (**2**). Each pinacol was also treated with lithium aluminum hydride in the presence of aluminum chloride,[11,12] but the chiral ethane **3** was found to be the major product in each case.

$$\mathbf{8} \xrightarrow[AlCl_3]{LiAlH_4} \mathbf{3}\ (55\%) + \mathbf{2}\ (19\%) + \mathbf{6}\ (8\%)$$

$$\mathbf{9} \xrightarrow[AlCl_3]{LiAlH_4} \mathbf{3}\ (51\%) + \mathbf{2}\ (17\%)$$

Relative configurational assignments of the pinacols were finally secured by carrying out their preparation from benzoylferrocene in the presence of the chiral solvent, (+)-(*S*)-1-methoxy-2-methylbutane (**12**).[13] The use of a chiral solvent or a chiral additive to effect asymmetric selection during a reaction has been carried out in a number of other cases.[1c] Its successful application in the present work provided unequivocal stereo-

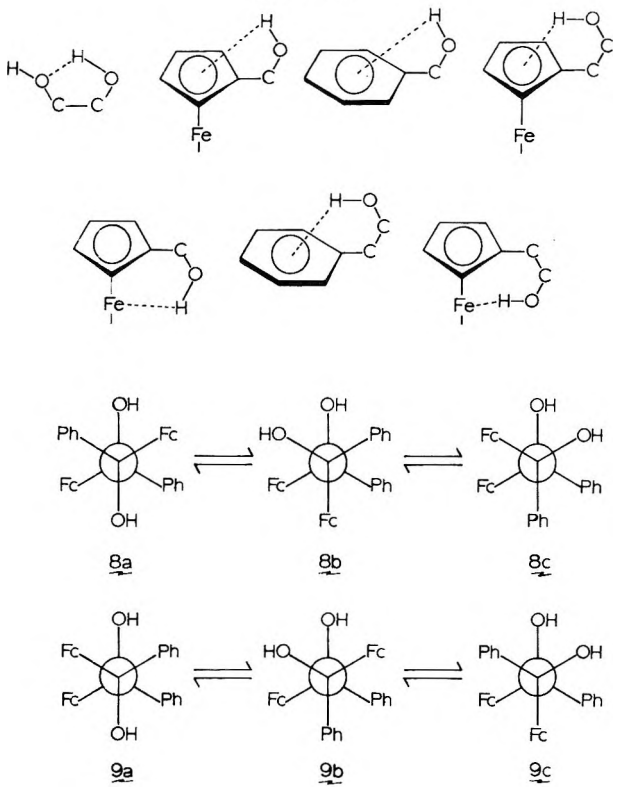
(10) D. J. Cram, *J. Amer. Chem. Soc.*, **76**, 4516 (1954); W. A. Bonner, *ibid.*, **81**, 3336 (1959); S. Mitsui, Y. Senda, and K. Donno, *Chem. Ind. (London)*, **32**, 1354 (1963); T. J. Leitereg and D. J. Cram, *J. Amer. Chem. Soc.*, **90**, 4011 (1968).

(11) This combination appears to be of general utility for effecting reduction of arylcarbinols; *cf* B. T. Brown and A. M. S. White, *J. Chem. Soc.*, 3755 (1957); R. F. Nystrom and R. A. Berger, *J. Amer. Chem. Soc.*, **80**, 2896 (1958); E. A. Hill and J. H. Richards, *ibid.*, **83**, 4216 (1961).

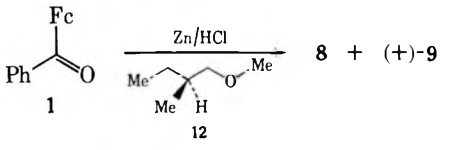
(12) Very recently M. J. A. Habib and W. E. Watts [*J. Chem. Soc. C*, 1469 (1969)] have provided examples in which the reduction occurs with retention of configuration.

(13) H. G. Rule, E. B. Smith, and J. Harrower, *J. Chem. Soc.*, 376 (1933).

SCHEME II

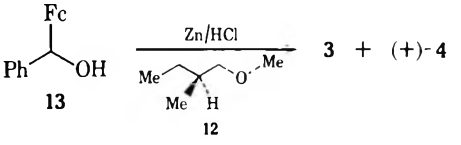


chemical designations for the isomeric pinacols as well as the isomeric ethanes. By taking advantage of the rapid formation of the pinacols, it was possible to avoid the complicating presence of other products by quenching a reaction mixture of benzoylferrocene, zinc dust, concentrated hydrochloric acid, and the chiral solvent **12** in aqueous base after 10 min to provide pure crystalline samples of each pinacol. Since the higher melting diastereomer (207–209°) was found to be optically active and the lower melting form (202–204°) was not, it followed that the former was the chiral isomer **9** or its mirror image, and that the latter was the achiral isomer **8**. In every case where the pinacols were found and separated, the amount of the achiral form always exceeded the chiral form.



The diastereomeric ethanes **3** and **4** were first isolated and characterized by Berger, McEwen, and Kleinberg in their work on the acid-catalyzed decomposition of ferrocenylphenylcarbinyl azide.[14] Both of these isomers were usually found in significant amounts in the Clemmensen reductions of benzoylferrocene. Here, as in the case of the pinacols, clear-cut assignments of relative stereochemistry followed directly from independent preparation of the isomeric ethanes under conditions that allowed for asymmetric selectivity. The successful procedure was modeled after the reductive coupling of ferrocenylphenylmethanol (**13**) carried out by Cais and Eisenstadt.[15] Treatment of (±)-ferrocenylphenylmethanol (**13**) in (+)-(*S*)-1-methoxy-2-methylbutane (**12**) with zinc dust and hydrochloric acid gave the lower melting diastereomeric ethane (mp 218–222°) in 45% yield and the higher melting isomer (mp 276–278°) in 31% yield. Of the two purified compounds, only the higher melting stereomer displayed optical activity, showing it to be the chiral configurational isomer **4** or its mirror image. Optical inactivity of the lower melting isomer corroborated its designation as the achiral form **3**. When this experiment was carried out using zinc amalgam instead of zinc dust, and using a higher proportion of the optically active solvent, the higher melting isomer was obtained in much lower material yield but with more than twice the dextrorotatory magnitude displayed by the chiral sample of the first experiment.[16]

As in the case of the diastereomeric pinacols, the amount of the achiral ethane **3** was found to exceed that of its diastereomer, not only in the reductive coupling reactions[18] but in the numerous Clemmensen reductions as well. It is also significant that in each of the various decompositions of ferrocenylphenylcarbinyl azide[14] amounts of what is now recognized as the achiral ethane **3** exceeded the amounts of chiral isomer **4**.[19]



1,2-Diferrocenyl-1,2-diphenylethene (**5**) was usually found to be the major bimolecular product of Clemmensen reduction of benzoylferrocene. It was previously prepared by Pauson and Watts[20] by treatment of benzoylferrocene with sodium diphenylphosphinite. Careful examination, in the present work, of a number of purified samples always revealed the olefin as chromatographically homogenous, strongly indicating the presence of only one of the two configurational possibilities. This conclusion was substantiated by conversion of the ethene to the corresponding ethane *via* hydroboration of the former, followed by treatment with propionic acid. This procedure did not give any detectable (tlc) achiral ethane **3** but produced only the chiral ethane **4** in good yield, accompanied by a small amount of benzylferrocene. Thus, not only did these results strongly suggest that only one configurational ethene was formed in Clemmensen reduction and in the method used by Pauson and Watts[20] but that the compound must be the *E*-[21] or *trans*-ethene **5**. The configurational assignment

(14) A. Berger, W. E. McEwen, and J. Kleinberg, *J. Amer. Chem. Soc.*, **83**, 2274 (1961).

(15) M. Cais and A. Eisenstadt, *J. Org. Chem.*, **30**, 1148 (1965).

(16) In experiments where an optically active component is utilized and the results are interpreted on the basis of optical activity determined from a product, it is essential to assure that the latter is not contaminated with the former.[17] That the optical activity observed in the two substances of the present work was not due to contamination with the optically active solvent **12** is assured by the following facts: (a) careful purification before polarimeter measurements; (b) the diastereomeric partner, similarly purified in each case, was found to be optically inactive; and, although it happened to have the same rotatory direction, (c) the rotatory magnitude of each purified product significantly exceeded that of even the neat solvent.

(17) See J. E. Baldwin, R. E. Hackler, and R. M. Scott [*J. Chem. Soc. D*, 1415 (1969)] for additional comments on this point.

(18) This was also true in the orginal reductive coupling of **13**.[15]

(19) Isolation of the lower melting ethane (achiral), but failure to isolate the higher melting (chiral) isomer, by Rausch and Adams[9] may also be taken as part of this general pattern.

(20) P. L. Pauson and W. E. Watts, *J. Chem. Soc.*, 2990 (1963).

(21) Chemical Abstracts Staff, *J. Amer. Chem. Soc.*, **90**, 509 (1968).

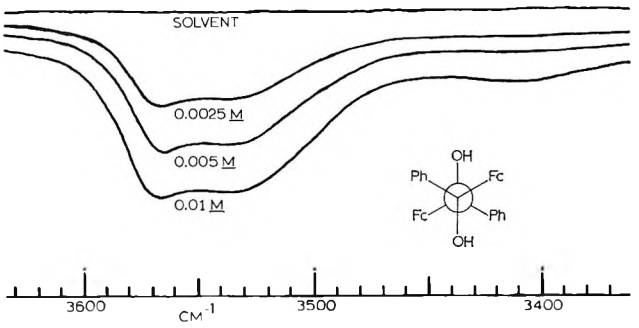


Figure 1.—Infrared spectra of the achiral pinacol 8: Perkin-Elmer 621 grating spectrometer; 0.01, 0.005, and 0.0025 *M* in carbon disulfide; 1-cm cell.

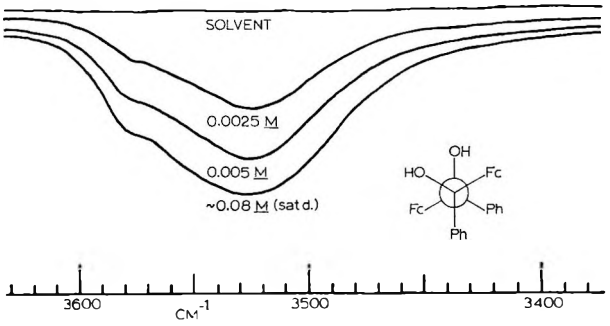
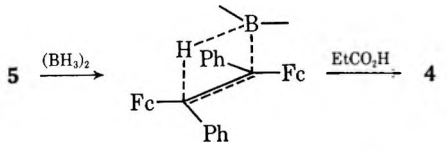


Figure 2.—Infrared spectra of the chiral pinacol 9: 0.008, 0.005, and 0.0025 *M*.

follows from the well-documented[22] overall syn hydrogenation of the hydroboration–acid cleavage sequence.



The pinacolone, 2,2-diferrocenyl-1,2-diphenylethanone (6), was historically the first recognized bimolecular Clemmensen reduction product. Weliky and Gould[8] also showed that it was produced by acid-catalyzed rearrangement of the now recognized mixture of isomeric pinacols 8 and 9. Despite the relative ease with which phenyl migrates in pinacol–pinacolone rearrangements, only the pinacolone 6 (ferrocenyl migration) has heretofore been reported.[5,6,8,9] In the present work (run B, 97°, 90 hr), the isomeric pinacolone 7 (phenyl migration) was isolated and characterized. The two ketones are readily distinguished by their melting points (6, 204–206°, and 7, 245–250° dec) and their spectral properties; the important features of which are recorded in the Experimental Section. While additional aspects are to be treated in a subsequent paper, it should be noted here that 6, the product of ferrocenyl migration, exceeded 7, the product of phenyl migration, by a factor of about 15 in run B, although the ratio was lower when the individual pinacols 8 and 9 were allowed to undergo rearrangement.

Run C (room temperature, 5 hr) is notable because of the occurrence of the stereomeric alcohols, 10 and 11. These previously undetected, extremely unstable alcohols supply an important link in the rationalization of bimolecular Clemmensen reduction of ferrocenyl ketones.

Discussion

It is of interest to appraise the relative degree of nonbonded interactions involving the phenyl and the ferrocenyl groups. The decision is not obvious from consideration of scale conformational models,[23] for along one of the dimensions phenyl is larger than ferrocenyl, while along another dimension the reverse is true. The results of the present study, however, may be consistently interpreted in terms of the ferrocenyl group possessing a significantly larger effective bulk than the phenyl group.

An interesting manifestation of this may be seen in the OH stretching regions of the infrared spectra determined from each of the stereoisomeric pinacols, 8 and 9. In the reproduced spectra of Figures 1 and 2, neither the achiral pinacol 8 nor the chiral isomer 9 give any detectable amounts of free or nonbonded OH. In each case, however, complex absorptions, owing to concentration independent, intramolecular hydrogen bonds, between 3600 and 3500 cm^{-1}, predominate. These must be due to various combinations of the well-established types[24] illustrated in Scheme II and are consequently too complex to deal with.

The spectrum determined from the achiral pinacol (Figure 1), however, possesses a fairly broad, concentration dependent, band centered near 3420 cm^{-1} which must be due to intermolecular hydrogen bonding. Absorption of this type is absent in the spectra of the chiral isomer. Since 8a (Scheme II) would be expected to be the most highly populated conformer of the achiral pinacol, it is reasonable to conclude that intermolecular hydrogen bonding appears to occur to a detectable extent only when the hydroxyl groups are in the anti relationship. Since absorption owing to intermolecular hydrogen bonding is absent in the chiral spectra, conformer 9a, possessing a ferrocenyl–ferrocenyl gauche interaction, must not be significantly populated. Avoidance of the gauche ferrocenyl–ferrocenyl nonbonded interaction may also be seen in other results of the present study.

Reductive coupling of benzoylferrocene invariably gave the achiral pinacol 8 in greater amount than the chiral isomer 9. This stereoselective manifestation may be accounted for in terms of a minimization of nonbonded interactions during coupling of the protonated benzoylferrocene species 14 or the radical 15 produced from it.[25] If in the two approaches, represented by 16 and 17 (Scheme III), the ferrocenyl groups are kept in a developing anti relationship, then, while each (16 and 17) possess two developing ferrocenyl–phenyl gauche interactions, 17 has in addition a phenyl–phenyl gauche interaction. The more favorable approach (16) leads to the more abundant stereomeric, achiral pinacol 8.

(22) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962, p 128 ff.

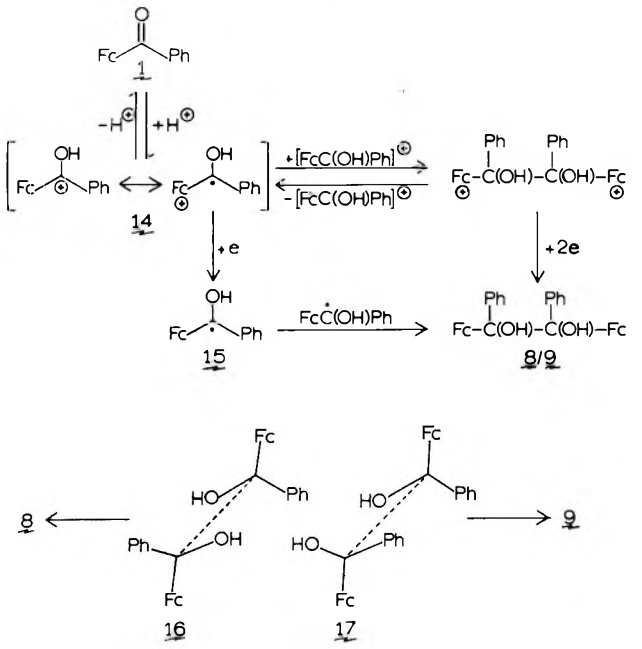
(23) S. I. Goldberg, *J. Chem. Educ.*, **43**, 554 (1966).

(24) D. S. Trifan and R. Bacskai, *J. Amer. Chem. Soc.*, **82**, 5010 (1960); E. A. Hill and J. H. Richards, *ibid.*, **83**, 4216 (1961); I. D. Campbell, G. Eglinton, and R. A. Raphael, *J. Chem. Soc. B*, 338 (1968); M. J. Nugent and J. H. Richards, *J. Amer. Chem. Soc.*, **91**, 6138 (1969).

(25) Cais and Eisenstadt[15] have argued that species like 14 and 18 contribute insignificantly to the formation of dimers. The evidence, however, does not appear to be a conclusive basis for rejection of the dimerization mechanism initially suggested by Rinehart and coworkers.[26]

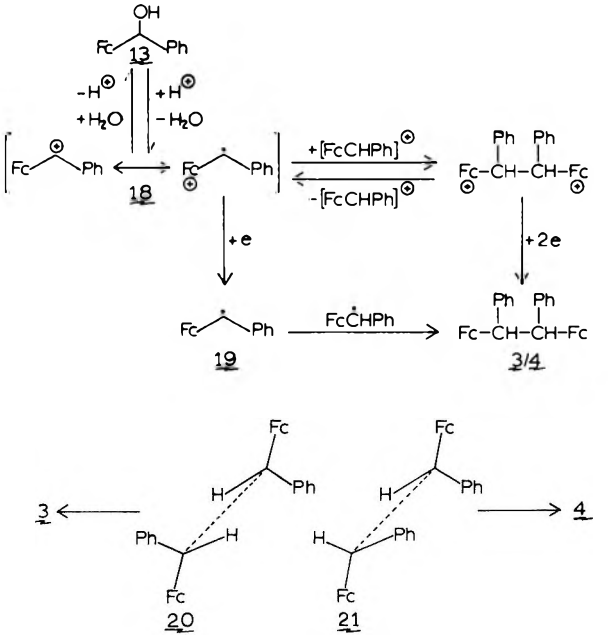
(26) K. L. Rinehart, Jr., C. J. Michejda, and P. A. Kittle, *J. Amer. Chem. Soc.*, **81**, 3162 (1959).

SCHEME III



In a similar way the predominance of the achiral ethane **3** over the chiral form **4** in all of the examples of reductive coupling from ferrocenylphenylmethanol (**13**) may be accounted for (Scheme IV). Whether the

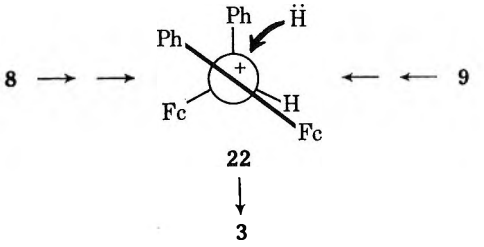
SCHEME IV



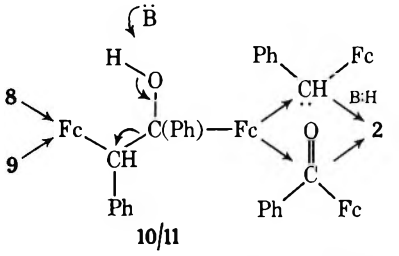
species involved in the two idealized coupling approaches, **20** and **21**, are considered in terms of **18**, the cation radical,[25] or **19**, the radical, need not effect the argument. Minimization of nonbonded interactions favors **20**, which leads to the more abundant achiral ethane **3**.

Avoidance of ferrocenyl–ferrocenyl nonbonded interaction during formation of 1,2-diferrocenyl-1,2-diphenylethene also appears to be the probable basis for production of only the trans isomer **5**.

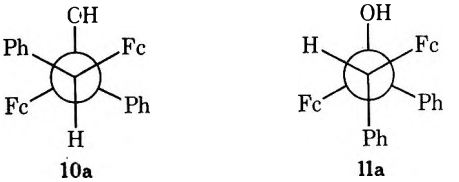
Both stereomeric pinacols, on treatment with lithium aluminum hydride and aluminum chloride, give the achiral ethane, suggesting that the steric outcome is independent of the first stage of reduction (which would give **10** or **11**) but is governed by conformational effects during the second stage. Both **10** and **11** would be expected to give cation **22** in which ferrocenyl is opposed to hydrogen, and hydride delivery to this ion should occur preferentially over phenyl, leading to the achiral ethane **3**.



These reductions, however, were accompanied by a small amount of fragmentation and, to a lesser extent, rearrangement. If the alcohols (**10** and/or **11**) were indeed intermediates in the lithium aluminum hydride–aluminum chloride reduction of the pinacols, their tendency to fragment was not so great as it was found to be under basic or neutral conditions. For example, the only observable product when each pinacol was treated with freshly prepared Raney nickel was benzylferrocene. In light of the ease with which the alcohols, **10** and **11**, underwent fragmentation to benzylferrocene and benzoylferrocene, it is likely that the pinacols **8** and **9** were first reduced to the alcohols **10** and **11**, and these then fragmented[27] to benzylferrocene and benzoylferrocene followed by reduction of the latter to the former.



The great ease with which the alcohols **10** and **11** underwent fragmentation made them extremely difficult to handle and precluded rigorous assignments of stereochemistry. It was observed, however, that the alcohol with the lower R_f value (0.17 *vs.* 0.27) fragmented faster. Assuming that this difference is attributable to the difference in gauche interactions present in the most favorable conformation of the achiral and achiral alcohols (**10a** and **11a**, respectively), then **11a** with its additional phenyl–phenyl gauche interaction may be assigned to the less stable, lower R_f isomer.



While these assignments are considered to be tentative, they are strengthened slightly by the fact that the lower R_f alcohol, assigned as the chiral form **11a**, was

(27) For similar examples of tertiary alcohol fragmentation, see D. J. Cram, W. D. Nielsen, B. Rickborn, L. K. Gaston, and H. Jäger, *J. Amer. Chem. Soc.*, **83**, 2174, 2178, 2183 (1961), and references cited therein.

also found to be the less soluble (hexane) partner, as was the case with the other chiral isomers **4** and **9**. In any case, the presence of **10** and **11** among the bimolecular reduction products provides an important contribution toward a reasonable explanation of the formation of the bimolecular reduction products.

Experimental Section

General.—Temperatures are uncorrected. Melting points were determined in open capillary tubes except where noted. Column (elution) chromatography was with Merck acid-washed alumina. Mixtures to be chromatographed were dissolved in the minimum volumes of benzene and added uniformly to the tops of the alumina columns which were previously prepared by the wet technique in hexane. Due to low solubilities of many of the compounds, it was necessary to use rather high weight ratios of alumina to mixture. These were usually of the order of 100:1. Thin layer chromatography (tlc) was a crucial analytical tool in this work. Glass plates, coated with silicic acid (Brinkmann Instruments Co., Cat. No. 7731), were used. Development solvents are cited along with the relevant R_f values. Visualization of spots on the developed plates required no additional treatment, since all of the ferrocene compounds are colored.

For the Clemmensen reductions, preparations of zinc amalgam (cited simply as amalgam) were carried out in the usual way[28] with the quantities of materials cited in parentheses: grams of zinc, grams of mercuric chloride, milliliters of water, and milliliters of concentrated hydrochloric acid, respectively. Two stirring assemblies, referred to as fast and slow, were used. The former signifies a four-bladed stirrer operated by a 2500-rpm motor, and the latter refers to a 250-rpm motor which operated a two-bladed stirrer.

Infrared (ir) spectra were determined with a Perkin-Elmer Model 337 spectrophotometer. In each case the sampling method is indicated along with the corresponding data. A Varian Model A-60 nuclear magnetic resonance (nmr) spectrometer was used to record ^{1}H nmr spectra at 60 Hz in solutions containing tetramethylsilane (TMS) as internal standard. Chemical shifts are reported in ppm under the δ convention relative to the TMS signal (0 ppm). For ultraviolet (uv) spectra, a Perkin-Elmer Model 202 spectrophotometer was used. Mass spectra were initially determined with an Associated Electrical Industries Model MS-9 instrument,[29] followed by use of a Hitachi Perkin-Elmer Model RMU-6 spectrometer.[30] Chiroptical (optical activity) measurements at 546 and 589 nm were carried out with Rudolph and Sons, Inc., polarimeters. Combustion analyses were made by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

Clemmensen Reduction Products.—Given below are physical and spectral properties determined from each of the individual products isolated from the various Clemmensen reductions of benzoylferrocene (**1**) carried out in this study.

Benzylferrocene (**2**): mp 75–76° (lit.[5,6,8] mp 74.5–75.5°); mass spectrum m/e 276 (M^+); ir (CCl_4) 3080, 3060, 1097, 992 (ferrocenyl), 3030, 1602, 1498, 1063 (phenyl), 2920, 2848, and 1452 cm^{-1} (methylene); nmr ($CDCl_3$) δ 7.18 (5 H, s, protons of unsubstituted ferrocene ring), 4.06 (4 H, apparent s, protons of substituted ferrocene ring), and 3.68 (2 H, s, methylene protons).

Achiral 1,2-Diferrocenyl-1,2-diphenylethane (**3**):[31] mp 220–222° [lit.[15,32] mp 218–220° (α isomer) and 218°, respectively]; mass spectrum m/e 275 (highest observable ion[33]); ir (KBr) 3070, 3050, 1103, 998 (ferrocenyl), 3020, 1600, 1500, 1450 (phenyl), 2920 and 2890 cm^{-1} (methine); nmr ($CDCl_3$) δ 7.05 (10 H, apparent s, phenyl protons), 3.82 (4 H, m, α-ferrocene protons), 3.82 (4 H, m, β-ferrocene protons), 3.72 (2 H, apparent s, methine protons), and 3.68 (10 H, s, protons of unsubstituted ferrocene rings).

Chiral 1,2-Diferrocenyl-1,2-diphenylethane (**4**):[31] mp 276–280° [lit.[15] mp 276–280° (β isomer)]; mass spectrum m/e 275 (highest observable ion[33]); ir (KBr) 3070, 1103, 1000 (ferrocenyl), 3010, 1600, 1495, 1452 (phenyl), and 2900 cm^{-1} (methine); nmr ($CDCl_3$) δ 7.12 (10 H, apparent s, phenyl protons), 3.82 (4 H, m, α- and β-ferrocene protons), and 3.62 (12 H, apparent s, methine protons and protons of unsubstituted ferrocene rings).

(*E*)-1,2-Diferrocenyl-1,2-diphenylethene (**5**):[31] mp 278–280° (lit.[20] 278–280°); mass spectrum m/e 548 (M^+); ir (KBr) 3080, 3045, 1101, 1000 (ferrocenyl), 2020, 1600, 1497, 1450 (phenyl), and 1645 cm^{-1} (double bond?); nmr ($CDCl_3$) δ 4.02 (18 H, m, all ferrocene protons) and 7.43 (10 H, m, phenyl protons); uv max (95% C_2H_5OH) 218 (ϵ 39,000), 241 sh (11,000), 282 sh (4300), and 460 nm (350).

2,2-Diferrocenyl-1,2-diphenylethanone (**6**): mp 203–205° (lit.[5,8] 195–198° dec and 204–206°, respectively); mass spectrum m/e (rel intensity) 564 (15) (M^+) and 459 (20); ir (KBr) 3080, 1108 (ferrocenyl), 1600, 1490 (phenyl), and 1680 cm^{-1} (benzoyl carbonyl); nmr ($CDCl_3$) δ 7.45 (2 H, t, $J \sim 3$ Hz, *o*-benzoyl protons), 7.30 (8 H, m, remaining phenyl protons), 4.20 (4 H, t, $J \sim 2$ Hz, α-ferrocenyl protons), and 4.02 (14 H, apparent s, remaining ferrocenyl protons).

1,2-Diferrocenyl-2,2-diphenylethanone (**7**): mp 245–250° dec; mass spectrum m/e (rel intensity) 564 (20) (M^+) and 351 (100); ir ($CHCl_3$) 3090, 3060, 1110, 1003 (ferrocenyl), 3015, 3000, 1600, 1490, 1445 (phenyl), and 1670 cm^{-1} (ferrocenyl carbonyl); nmr ($CDCl_3$) δ 7.20 (10 H, m, phenyl protons), 4.25 (2 H, t, $J = 2$ Hz, α protons of ferrocenyl), 4.12 (2 H, t, $J \sim 2$ Hz, β protons of ferrocenoyl), 4.05 (12 H, apparent d, protons of unsubstituted rings of ferrocenoyl and ferrocenyl superimposed on α (?) protons of ferrocenyl), and 3.41 (2 H, t, $J \sim 2$ Hz, β (?) protons of ferrocenyl).

Anal. Calcd for $C_{34}H_{28}Fe_2O$: C, 72.37; H, 5.00. Found: C, 72.17; H, 5.19.

Chiral 1,2-Diferrocenyl-1,2-diphenyl-1,2-ethanediol (**9**):[31] mp 207–209° (oxygen-free, sealed capillary tube) [lit.[8] mp 125–140° (mixture of isomers)]; mass spectrum m/e 564;[34] ir (KBr) 3530 m, 3490 s, 3075 m, 3025 m, 3010 w, 1650 m, 1605 w, 1500 m, 1450 s, 1420 m, 1400 m, 1340 m, 1310 s, 1295 s, 1215 m, 1165 s, 1100 s, 1060 s, 1050 s, 1030 s, 1020 s, 995 s, 930 m, 915 w, 890 w, 865 w, 855 w, 845 m, 825 s, 815 s, 795 m, 780 w, 730 s, and 705 s cm^{-1}; nmr (CS_2) δ 7.07 (apparent d, $W = 3$ Hz, 10 H, phenyl protons), 4.03, 3.87, 3.78 (complex array, $W = 2$, 3 and 7 Hz, 8 H, α- and β-ferrocenyl protons), 3.62 (s, $W = 1$ Hz, 10 H, protons of unsubstituted ferocenyl rings), and 2.78 (s, $W = 1.5$ Hz, 2 H, hydroxyl protons).

Anal. Calcd for $C_{34}H_{30}Fe_2O_2$: C, 70.12; H, 5.19. Found: C, 69.50; H, 5.06.

Achiral 1,2-Diferrocenyl-1,2-diphenyl-1,2-ethanediol (**8**):[31] mp 202–204° (oxygen-free, sealed capillary tube) [lit.[8] mp 125–140° (mixture of isomers)]; mass spectrum m/e 564;[34] ir (KBr) 3540 s, 3500 m, 3380 w, 3075 s, 3040 m, 3010 w, 1630 m, 1600 w, 1500 m, 1450 s, 1410 m, 1390 m, 1340 m, 1285 m, 1200 m, 1170 m, 1155 m, 1105 s, 1060 s, 1025 s, 1000 s, 960 w, 910 w, 885 w, 820 s, 755 s, 725 s, and 700 s cm^{-1}; nmr (CS_2) δ 7.45, 7.00 (complex array, $W = 15$ and 25 Hz, 10 H, phenyl protons), 4.05 (m, $W = 8$ Hz, 4 H, α-ferrocenyl protons), 3.87 (m, $W = 7$ Hz, 4 H, β-ferrocenyl protons), 3.62 (s, $W = 1$ Hz, 10 H, protons of unsubstituted ferrocenyl rings), and 2.60 (s, $W = 1.5$ Hz, 2 H, hydroxyl protons).

Anal. Calcd for $C_{34}H_{30}Fe_2O_2$: C, 70.12; H, 5.19. Found: C, 69.88; H, 5.57.

1,2-Diferrocenyl-1,2-diphenylethanol (**10**):[35] mp 178–180°; mass spectrum m/e 566 (M^+); ir (benzene) 3100, 1105, 1000 (ferrocenyl), 1600, 1450 (phenyl), 2910 (methine), and 3520 cm^{-1} (hydroxyl); nmr ($CDCl_3$) δ 7.05 (10 H, m, phenyl protons), 3.95, 3.85 (8–9 H, both m, α- and β-ferrocenyl protons and methine proton), 3.75 (5 H, s, protons of unsubstituted rings of one ferrocenyl), 3.60 (5 H, s, protons of unsubstituted ring of a second ferrocenyl), and 2.68 (1 H, s, hydroxyl proton).

Anal. Calcd for $C_{34}H_{30}Fe_2O$: C, 72.12; H 5.34. Found: C, 71.50; H, 5.63.

(28) E. L. Martin, *Org. React.*, **1**, 163 (1942).

(29) We are grateful to Dr. H. M. Fales, National Heart Institute, for these spectra.

(30) Acknowledgement of the grant awarded by National Science Foundation toward the purchase of this instrument is gratefully made.

(31) Experimental evidence upon which this stereochemical assignment rests is described under the appropriate heading of this section.

(32) A. N. Nesmeyanov, V. N. Drozd, and N. A. Rodionova, *Dokl. Akad. Nauk SSSR*, **160**, 355 (1965).

(33) This behavior of facile symmetric cleavage of the central carbon–carbon appears to be characteristic of tetraarylethanes, 1,1,2,2-tetraferrocenylethane (m/e 383) and 1,1,2,2-tetraphenylethane (m/e 167).

(34) Highest peak observed. It could not be determined whether this peak, which corresponds to M − 18, was due to thermal and/or mass spectral fragmentation.

(35) While good evidence was obtained for the presence of both diastereomeric forms (see experimental account and discussion), only this one (mp 178–180°), which appears to be the achiral isomer, was characterized.

Clemmensen Reductions of Benzoylferrocene.—Four typical Clemmensen reductions, leading together to the total array of compounds, are described. Spectra data and other criteria of identification, presented in the previous section, were applied in each instance. Assignments of the various tlc R_f values, established independently with authentic materials, are included.

A. Aqueous Toluene, Fast Stirrer, and Reflux Heating.—Benzoylferrocene (5.00 g, 17.1 mmol), dissolved in 35 ml of toluene, was added a mixture of amalgam (20 g, 2 g, 20 ml, 1 ml) and 10 ml of water, and the whole mixture agitated with the fast stirrer while concentrated hydrochloric acid (15 ml) was added (15 min) dropwise. Within 5 min after the addition was complete, the mixture had turned from red to yellow, signaling formation of the pinacols **8** and **9**. An aliquot (1 ml) was taken, and the yellow solid was collected on a filter and washed with ether. It had mp 125–140°, previously reported for what is now recognized (experiments described herein) as a mixture of the stereoisomeric pinacols. The sample spontaneously decomposed to benzoylferrocene when dissolved in benzene.

The reaction mixture was then heated under reflux (fast stirring maintained) and monitored by tlc [hexane–benzene, 3:2 (v/v)]. After 4 hr benzoylferrocene was absent, while the presence of each of the following substances was recognized: R_f 0.35 [2,2-diferrocenyl-1,2-diphenylethanone (**6**)], 0.60 [a mixture of achiral and chiral 1,2-diferrocenyl-1,2-diphenylethane (**3** and **4**, respectively)], 0.66 [*trans*-1,2-diferrocenyl-1,2-diphenylethene (**5**)], and 0.80 [benzylferrocene (**2**)].

The reaction mixture was allowed to cool to room temperature, poured into water, and extracted with benzene. The residue left after evaporation of the combined and dried ($MgSO_4$) benzene extracts was chromatographed on alumina. Elution with hexane–benzene [3:1 (v/v)] gave benzylferrocene (**2**), mp 74–76°, 595 mg (12.6% yield). Elution with hexane–benzene [1:1 (v/v)] gave an orange solid (2.31 g) which was shown to be a mixture of **3**, **4**, and **5**. The solid was washed with hexane to separate achiral 1,2-diferrocenyl-1,2-diphenylethane (**3**), mp 218–220°, 270 mg (5.7% yield). The residue left after removal of **3** was dissolved in hot benzene from which chiral 1,2-diferrocenyl-1,2-diphenylethane (**4**) crystallized, mp 278–280° dec, 150 mg (3.2% yield), and *trans*-1,2-diferrocenyl-1,2-diphenylethene (**5**), mp 278–280°, 1.80 g (38.4% yield), was obtained from the benzene supernatant.

B. Aqueous Toluene, Slow Stirrer, and Reflux Heating.—Benzoylferrocene (3.50 g, 12.1 mmol) was dissolved in toluene (12 ml) and added to a mixture of amalgam (12 g, 0.6 g, 12 ml, 0.6 ml) and water (6 ml). While the mixture was stirred (slow), concentrated hydrochloric acid (12 ml) was added dropwise (15 min) before the whole mixture was boiled under reflux for 90 hr. After the mixture was allowed to cool to room temperature, it was poured into water and extracted with benzene. As the combined and dried ($MgSO_4$) benzene extracts were being evaporated, a yellow solid formed. It was collected and shown to be chiral 1,2-diferrocenyl-1,2-diphenylethane (**4**), mp 278–280°, 100 mg (3.0% yield). The residue obtained from the benzene filtrate was chromatographed on alumina. A yellow fraction eluted with hexane–benzene [3:1 (v/v)] gave benzylferrocene (**2**), mp 73–75°, 213 mg (5.8% yield). Elution with hexane–benzene [1:1 (v/v)] led to a mixture (855 mg) of achiral 1,2-diferrocenyl-1,2-diphenylethane (**3**) and *trans*-1,2-diferrocenyl-1,2-diphenylethane (**5**), from which the former was separated by trituration with hexane, mp 200–220°, 147 mg (4.5% yield). The olefin **5** was obtained from the residue, mp 278–280°, 702 mg (21.3% yield). Elution of the column was continued with benzene. First a yellow band gave 2,2-diferrocenyl-1,2-diphenylethanone (**6**), mp 203–205°, 495 mg (14.7% yield). The second band was red, and it provided the isomeric pinacolone, 1,2-diferrocenyl-2,2-diphenylethanone (**7**), 245–250° dec, 37 mg (1.0% yield). Finally, ether eluted recovered benzoylferrocene, mp 106–108°, 32 mg (1% recovery).

C. Aqueous Toluene and Fast Stirrer at Room Temperature.—Benzoylferrocene (5.00 g, 17.1 mmol), dissolved in 35 ml of toluene, amalgam (20 g, 2.0 g, 20 ml, 1.0 ml), and 1 ml of water were stirred (fast) at room temperature while concentrated hydrochloric acid (20 ml) was added dropwise over a 15-min period. Almost immediately after the acid addition was complete, the reaction changed from red to yellow and remained yellow during the next 5 hr. A tlc monitor [hexane–benzene, 3:2 (v/v)] indicated the presence of eight components: R_f 0.06 [benzoylferrocene (**1**)], 0.17 [chiral (?) 1,2-diferrocenyl-1,2-diphenylethanol (**11**)], 0.27 [achiral (?) 1,2-diferrocenyl-1,2-diphenylethanol (**10**)], 0.35 [2,2-diferrocenyl-1,2-diphenylethanone (**6**)], 0.60 [achiral–chiral 1,2-diferrocenyl-1,2-diphenylethane (**3**) and (**4**)], 0.66 [*trans*-1,2-diferrocenyl-1,2-diphenylethene (**5**)], and 0.76 [benzylferrocene (**2**)].

The reaction mixture was decanted and passed through a filter on which was collected a yellow solid. This material was washed with water and with ether. It (1.81 g) was subsequently recrystallized from hexane (1.10 g, mp 125–150°). This material was unstable in solution. It was shown (tlc, color change to red) to transform to a mixture of benzoylferrocene, chiral (?) 1,2-diferrocenyl-1,2-diphenylethanol (**11**, R_f 0.17), and benzylferrocene (**2**). Concentration of the filtrate (reaction mixture) gave another sample of yellow solid: 150 mg; mp 125–140°; tlc [hexane–benzene, 3:2 (v/v)] R_f 0.06 [benzoylferrocene (**1**)], 0.27 [achiral (?) 1,2-diferrocenyl-1,2-diphenylethanol (**10**)], and 0.76 [benzylferrocene (**2**)]. Each cleanly resolved spot (R_f 0.17 and 0.27, separated plates) was transformed into a mixture of itself, benzoylferrocene, and benzylferrocene in the course of about 15 min on tlc plates. The slower moving (R_f 0.17) and less soluble isomer appeared to undergo this transformation more rapidly. Material (*ca.* 100 mg) from the second crystallization (R_f 0.27) was used in repeated preparative tlc.[36] The material obtained (18 mg) was carefully recrystallized from hexane to give achiral (?) 1,2-diferrocenyl-1,2-diphenylethanol (**10**), 10 mg, mp 178–180°.

D. Aqueous Ether and Fast Stirrer at Room Temperature.—A mixture of benzoylferrocene (500 mg, 1.71 mmol), dissolved in ether (5 ml), amalgam (2 g, 0.2 g, 4 ml, 0.2 ml), and water (0.5 ml) was stirred (fast) at room temperature while concentrated hydrochloric acid (2 ml) was added dropwise. Although a yellow precipitate formed in the reaction mixture within 5 min after the acid addition was complete, the stirring was continued for a total time of 15 min before the yellow material was collected in a filter. The solid, a mixture of the achiral and chiral pinacols **8** and **9**, was very sensitive to air. It was quickly washed with small portions of water and with small portions of ether before it was dried and stored in an evacuated desiccator, 400 mg, mp 125–140°.

Tlc analysis [hexane–ether, 3:2 (v/v)] showed the solid to consist only of two components, R_f 0.54 [chiral 1,2-diferrocenyl-1,2-diphenyl-1,2-ethanediol (**9**)] and 0.61 [achiral isomer **8**]. When the developed tlc plate was exposed to air, these yellow spots turned red quite rapidly. The red spots were separately scraped from the plate, and the material from each was washed from the silicic acid and re-spotted on a fresh tlc plate along with an authentic sample of benzoylferrocene. Development of the plate showed all three spots to be identical, and that benzoylferrocene was the only substance present in the two reclaimed samples.

It was found that the rates of fragmentation of the pinacols are relatively slow in a moderately basic medium. Accordingly, a major portion of the orginal mixture of isomeric pinacols was dissolved in a mixture of ether (200 ml), water (50 ml), and potassium hydroxide (2 g). After the solution was carefully concentrated to a volume of about 100 ml and kept near 0° for 1 hr, then the initial crop of well-formed yellow crystals was collected in a filter, washed with cold ether, and dried *in vacuo* to provide the chiral pinacol **9**: 115 mg; mp 207–209° (oxygen-free, sealed capillary); single tlc spot, R_f 0.54. Evaporation of the ethereal supernatant liquid to a volume of about 50 ml provided a second crop of equally well-formed yellow crystals which, after recrystallization, gave the achiral pinacol **8**: 200 mg; mp 202–204° (oxygen-free, sealed capillary); single tlc spot, R_f 0.61. Thus, the combined yield of the unseparated pinacols was near 80%. The crude chiral:achiral ratio was approximated as 1:3. See Figures 1 and 2 for details of the high-frequency ir regions.

Independent Preparation of 2,2-Diferrocenyl-1,2-diphenylethanone (6) and 1,2-Diferrocenyl-2,2-diphenylethanone (7).—A mixture of benzoylferrocene (500 mg, 1.71 mmol), dissolved in absolute ethanol (4 ml), and zinc dust (500 mg) was stirred (fast) at room temperature while absolute ethanol (4 ml), previously saturated with hydrogen chloride gas, was added dropwise over a 5-min period before the whole was boiled under reflux for 2 hr. When the reaction mixture had cooled to room temperature, it was poured into water and extracted with benzene. The com-

(36) "Chrom-AR Sheet 500" (Mallinckrodt Chemical Works) was used. After each development the relevant band was cut out and eluted immediately so that the unstable alcohol, obtained by careful evaporation, could be stored and accumulated under inert conditions.

bined and dried ($MgSO_4$) extracts were evaporated to a residue which was chromatographed on alumina. Elution with hexane–benzene [3:1 (v/v)] gave benzylferrocene (2), 68 mg (14% yield), mp 73–75°. An orange solid (98 mg) was next eluted in hexane–benzene [1:1 (v/v)]. This material was shown by means of side-by-side tlc comparison with authentic compounds to be a mixture of *trans*-1,2-diferrocenyl-1,2-diphenylethene (5), achiral 3, and chiral 4. 2 2-Diferrocenyl-1,2-diphenylethanone (6), 242 mg (50.2% yield), mp 204–206°, was first eluted in benzene. It was followed by a red band from which was isolated the isomeric pinacolone, 1,2-diferrocenyl-2,2-diphenylethanone (7), 32 mg (6.6% yield), mp 245–250° dec.

Reductive Couplings of Ferrocenylphenylmethanol to Achiral and Chiral 1,2-Diferrocenyl-1,2-diphenylethanones (3 and 4). A. In Ether with Zinc Amalgam.—A mixture of ferrocenylphenylmethanol[37] (200 mg, 0.685 mmol), dissolved in ether (5 ml), amalgam (1 g, 0.2 g, 2 ml, 0.1 ml), and water (0.5 ml) was stirred (fast) at room temperature while concentrated hydrochloric acid (0.5 ml) was added dropwise (5 min). After 10 min, a tlc monitor [hexane–benzene, 3:1 (v/v)] showed the absence of starting material and indicated the presence of two components, R_f 0.35 (1,2-diferrocenyl-1,2-diphenylethane) and 0.58 (benzylferrocene). The ethereal phase was decanted, and the amalgam was washed with several portions of benzene which were combined with the original ether solution, and the whole mixture was washed with water and dried ($MgSO_4$). After the volume of the combined extracts was reduced to 5 ml, the concentrate deposited fluffy yellow crystals of chiral 1,2-diferrocenyl-1,2-diphenylethane (4), 51 mg (27% yield), mp 276–280°. The filtrate and ethereal washings were combined and evaporated to a solid which was carefully washed with several small portions of ether to dissolve the benzylferrocene. The residue gave achiral 1,2-diferrocenyl-1,2-diphenylethane (3), 92 mg (49% yield), mp 218–220°. The ether washings gave benzylferrocene (2), 27 mg (14% yield).

B. In (+)-(*S*)-1-Methoxy-2-methylbutane (12) with Zinc Dust.—Ferrocenylphenylmethanol[37] (200 mg, 0.685 mmol) was dissolved in (+)-(*S*)-1-methoxy-2-methylbutane[39] (2.5 ml) and added to a mixture of zinc dust (1 g) and water (0.5 ml). While this mixture was stirred (fast) at room temperature, concentrated hydrochloric acid (0.5 ml) was added dropwise. Within 5 min after the addition no starting material could be detected by tlc. The reaction mixture was worked up as described in the previous experiment (part A). The concentrated organic solution (10 ml) was kept at room temperature for 24 hr before collection of the initial yellow crystalline material which gave (+)-chiral-1,2-diferrocenyl-1,2-diphenylethane (4 or mirror image), 58 mg (31% yield), mp 276–278°, $[\alpha]^{22}_{546}$ 26.1 ± 1.7° (*c* 0.176, C_6H_6). The supernatant liquid and washings were evaporated to a final volume of 5 ml, giving a crystalline precipitate which provided pure achiral 1,2-diferrocenyl-1,2-diphenylethane (3), 35 mg (45% yield), mp 218–220°, $[\alpha]^{22}_{546}$ 1.70 ± 1.70° (*c* 0.176, C_6H_6). Evaporation of the supernatant liquid gave a solid which was shown by tlc to be benzylferrocene (2), 18 mg (95% yield).

Another run was carried out. It differed in that amalgam (1 g, 0.2 g, 0.5 ml, 0.05 ml) was used with ferrocenylphenylmethanol (250 mg, 0.856 mmol) and 5 ml of the optically active ether (12). That procedure gave (+)-chiral-1,2-diferrocenyl-1,2-diphenylethane (4) in higher optical yield {$[\alpha]^{22}_{546}$ 57.3 ± 5.5° (*c* 0.183, C_6H_5)} but in lower material yield (20 mg, 8.5% yield).

Reductive Coupling of Benzoylferrocene in the Presence of (+)-(*S*)-1-Methoxy-2-methylbutane (12).—A mixture of benzoylferrocene 2(50 mg, 0.862 mmol), dissolved in (+)-(*S*)-1-methoxy-2-methylbutane[39] (5 ml), zinc dust (1 g), and water (0.5 ml) was stirred (fast) at room temperature while concentrated hydrochloric acid (1 ml) was added dropwise. After the addition was complete and the reaction mixture was stirred for an additional 10 min, it was poured into a mixture of ether (100 ml) and 1.8 *M* aqueous potassium hydroxide (50 ml) and boiled gently during 5 min. The liquid was then decanted from the zinc and evaporated until the ether volume was about 25 ml. The crystalline yellow precipitate that developed was collected and purified to give (+)-chiral-1,2-diferrocenyl-1,2-diphenyl-1,2-ethanediol (9 or mirror image), 70 mg (28% yield), mp 207–209° (oxygen-free, sealed capillary), $[\alpha]^{21}_{546}$ 9.2 ± 1.0° (*c* 1.0, C_6H_6). The combined volumes of the supernatant liquid and washings were reduced to 10 ml, giving a yellow crystalline solid from which was obtained pure achiral 1,2-diferrocenyl-1,2-diphenyl-1,2-ethanediol (8), 80 mg (32% yield), mp 202–204° (oxygen-free, sealed capillary), $[\alpha]^{21}_{546}$ 0.80 ± 1.8° (*c* 0.50, C_6H_6).

Stereospecific Conversion of *trans*-1,2-Diferrocenyl-1,2-diphenylethene (5) to *threo*-1,2-Diferrocenyl-1,2-diphenylethane (4).—While a mixture of sodium borohydride (500 mg, 13.2 mmol) and *trans*-1,2-diferrocenyl-1,2-diphenylethene (50 mg, 0.091 mmol), dissolved in diglyme (50 ml), was stirred (magnetic) in a nitrogen atmosphere at room temperature, a solution of boron trifluoride etherate (2 ml) in diglyme (20 ml) was added dropwise during 30 min before the whole mixture was heated to, and maintained at, 100° for 2 hr. During this time the color of the reaction mixture changed from red to yellow. After the system was cooled to 30° and propionic acid (2.5 ml) was added dropwise over 15 min, the temperature was again raised to 100° and held there for 20 hr. The reaction mixture was then allowed to cool to room temperature when water (20 ml) was added slowly before the whole was poured into water (100 ml) and extracted with benzene. A tlc analysis [hexane–benzene, 3:2 (v/v)] of the combined, water-washed, and dried ($MgSO_4$) benzene extracts showed two components, R_f 0.60 (chiral 4) and 0.75 (benzylferrocene 2). Evaporation gave a yellow solid that was triturated with several small portions of methanol to remove the benzylferrocene. The residue gave chiral 1,2-diferrocenyl-1,2-diphenylethane (4), 29 mg (see below), mp 275–280°. The material obtained from evaporation of the combined methanol triturations was chromatographed carefully on alumina to give only benzylferrocene, 6.5 mg (26% yield), mp 74–76°, and an additional quantity of the chiral ethane 4, 6.7 mg [35.7 mg total (71% yield)], mp 275–278°.

Treatment of the Chiral and Achiral Diols with Lithium Aluminum Hydride and Aluminum Chloride.—1,2-Diferrocenyl-1,2-diphenyl-1,2-ethanediol (9) (50 mg, 0.086 mmol) was added to a stirred (magnetic) mixture of lithium aluminum hydride (15 mg, 0.40 mmol) and anhydrous aluminum chloride (150 mg, 1.13 mmol), contained in dry ether (15 ml) in a nitrogen atmosphere. After 10 min, the mixture was boiled under gentle reflux for 50 min before tlc examination [hexane–benzene, 3:1 (v/v)]: R_f 0.05 [2,2-diferrocenyl-1,2-diphenylethanol (10 and/or 11)], 0.12 [2,2-diferrocenyl-1,2-diphenylethanone (6)], 0.33 [*erythro*-1,2-diferrocenyl-1,2-diphenylethane (3)], and 0.60 [benzylferrocene (2)]. After the mixture was hydrolyzed and the hydrolysate extracted with ether, the combined ether extracts were washed with water and dried ($MgSO_4$) before being evaporated to dryness. The residue was chromatographed on alumina. Initial elution was with hexane–benzene [3:2 (v/v)] which gave benzylferrocene (2), 8.0 mg (17% yield), mp 73–75°. The yellow band eluted in hexane–benzene [1:1 (v/v)] gave achiral 1,2-diferrocenyl-1,2-diphenylethane (3), 24 mg (51% yield), mp 218–220°. Development of the material remaining on the column with benzene produced two bands. The faster moving one (red) was eluted in benzene and gave 2,2-diferrocenyl-1,2-diphenylethanone (6), 4 mg (8% yield), mp 203–205°. The slower moving band (yellow) was eluted with ether to give diferrocenylphenylmethanol,[40] 3 mg (7% yield), mp 197–199° (lit.[8,20] 195–197°).

Corresponding treatment of the achiral diol 8 (100 mg, 0.172 mmol, in 25 ml of ether) was carried out by dropwise addition of the solution (10 min) to a stirred (magnetic) mixture of lithium aluminum hydride (15 mg, 0.40 mmol) and aluminum chloride (150 mg, 1.13 mmol) in 15 ml of ether at room temperature (nitrogen atmosphere). After addition the reaction mixture was heated under reflux for 30 min before it was examined by tlc: R_f 0.15 [pinacolone (6)], 0.36 (achiral ethane 3), and 0.57 [benzylferrocene (2)]. Work-up and chromatography gave the three compounds: 8 mg (8% yield), 52 mg (55% yield), and 18 mg (19% yield), respectively.

Reductive Cleavage of Chiral and Achiral 1,2-Diferrocenyl-1,2-diphenyl-1,2-ethanediols with Raney Nickel.—A mixture of

(37) Prepared by reduction of benzoylferrocene with lithium aluminum hydride in ether, mp 80–81° (lit.[6,8,38] mp 80.3–80.5°).

(38) W. Kuan-Li, E. B. Sokolova, L. A. Leites, and A. D. Petrov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 887 (1962).

(39) Prepared by treatment of a mixture of (−)-(*S*)-2-methyl-1-butanol and sodium hydroxide with methyl iodide at 100°. The optically active ether, 12, was distilled from the reaction mixture. It was purified by an additional distillation, bp 90–92° (lit.[13] bp 91–94°), $\alpha^{21}D$ 0.302° (lit.[13] $\alpha^{18}D$ (0.29°).

(40) This material was shown to arise from cleavage of 2,2-diferrocenyl-1,2-diphenylethanol during alumina chromatography of the latter.

the chiral diol (50 mg, 0.086 mmol), dissolved in absolute ethanol (25 ml), and Raney nickel (freshly prepared[41] from 0.5 g of W-1 nickel–aluminum alloy) was stirred and boiled under reflux while contained under nitrogen. The reaction was periodically monitored by tlc [hexane–benzene, 3:2 (v/v)], which showed only a progressive increase in the formation of benzylferrocene (R_f 0.80). After 24 hr benzylferrocene was the only detectable compound present. Identical results were obtained when the experiment was repeated using the achiral diol.

(41) L. W. Convert and H. Adams, *J. Amer. Chem. Soc.*, **54**, 4116 (1932).

Registry No.—**1**, 1272-44-2; **3**, 1278-05-3; **4**, 1278-04-2; **5**, 12284-11-6; **6**, 12258-13-8; **7**, 12504-69-7; **8**, 12504-73-3; **9**, 12504-72-2; **10**, 12504-70-0; **11**, 12504-71-1.

Acknowledgments.—We wish to thank Dr. H. M. Fales of the National Heart Institute for mass spectra determined during the early stages of this work. Subsequent mass spectra were obtained with an instrument purchased in part with funds provided by a grant given by the National Science Foundation.

The Photochemistry of Aryl Alkyl Carbonates. I. The Chlorophenyl Ethyl Carbonates

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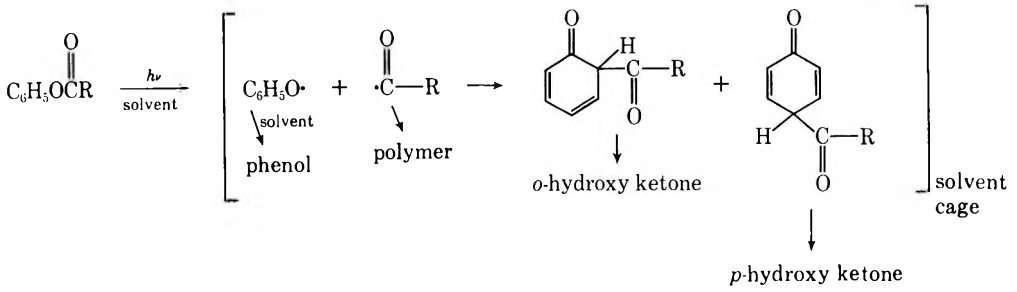
The photochemistry of the three chlorophenyl ethyl carbonates has been examined. The major process occurring is photodechlorination to give phenyl ethyl carbonate which subsequently undergoes a photo-Fries type of rearrangement. A minor process observed is the photosolvolysis of the chloride. The mechanisms of the reactions are discussed and the quantum yields are reported.

The Fries reaction is a well-known method for preparing aryl ketones from phenolic esters. The photo-Fries reaction is a less well-known but well-established method for effecting the same conversion.[2-7] The mechanism most often suggested for the reaction was proposed by Kobsa[4] and involves a homolytic cleavage of the carbonyl carbon–oxygen bond after the excitation of the ether molecule.



Pac and Tsutsumi[8] have reported that phenyl ethyl carbonate undergoes a photo-Fries type of reaction to give products analogous to those obtained in the photolysis of phenolic esters. Products that they identified were ethyl salicylate, ethyl *p*-hydroxybenzoate, and phenol. We have been investigating the photochemical reactions of a variety of aryl alkyl carbonates and can confirm Pac and Tsutsumi's results.

One way of investigating the mechanism of the photolysis of aryl alkyl carbonates is to examine the effect of placing various substituents on the aromatic ring. The type of substituent (electron attracting or electron repelling) and the position of the substituent relative to the reactive site have been shown to influence greatly the mode of photochemical reaction in aryl compounds.[9] Among the substituents chosen for this investigation was chlorine. In this paper we will discuss the observations that we made on the photochemical reaction of the chlorophenyl ethyl carbonates.

Results

The photolyses were performed by irradiating a solution of the chlorophenyl ethyl carbonate in isopropyl alcohol with a high-pressure mercury lamp using a Corex filter. The photolysis of the chlorophenyl ethyl carbonates (**1a–c**) gave phenyl ethyl carbonate (**2**) as the major product in each case. [The phenyl ethyl carbonate, as it was formed, was photolyzed to give phenol (**3**), ethyl salicylate (**4**), and ethyl *p*-hydroxybenzoate (**5**).] Two other products (**6** and **7**) were found; they appear to result from the interaction of the solvent with the chlorophenyl ethyl carbonate.

(1) Abstracted from the Ph.D. Thesis of I. Rosenberg, The George Washington University, 1969.

(2) J. Anderson and C. Reese, *Proc. Chem. Soc.*, 216 (1960).

(3) J. Anderson and C. Reese, *J. Chem. Soc.*, 1781 (1963).

(4) H. Kobsa, *J. Org. Chem.*, **27**, 2293 (1962), and references therein.

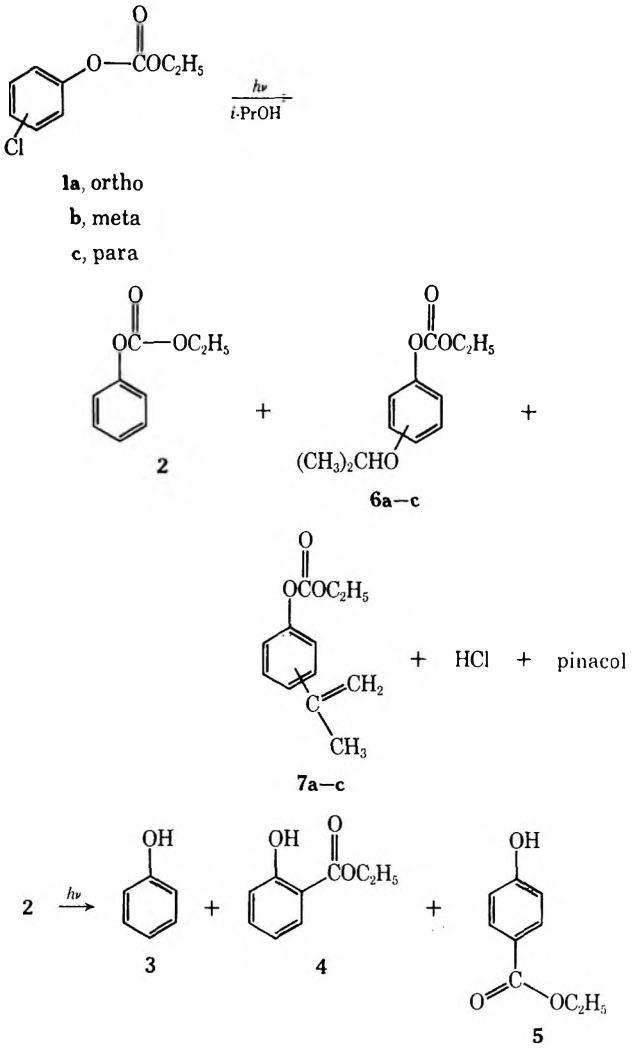
(5) H. Kobsa, Abstract of Papers, 148th National Meeting of the American Chemical Society, Chicago, Ill., 1964, 12E.

(6) V. Stenberg, "Organic Photochemistry," Vol. I, O. Chapman, Ed., Marcel Dekker, New York, N. Y., 1967, p 127–152.

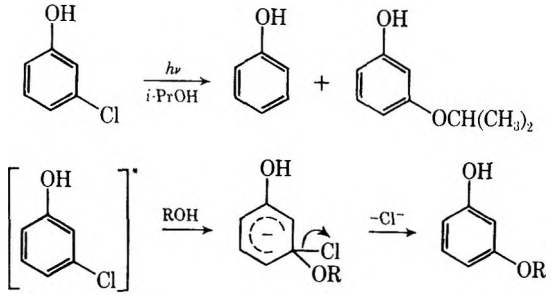
(7) R. Finnegan and D. Knutson, *J. Amer. Chem. Soc.*, **89**, 1970 (1967).

(8) C. Pac and S. Tsutsumi, *Bull. Chem. Soc. Jap.*, **37**, 1392 (1964).

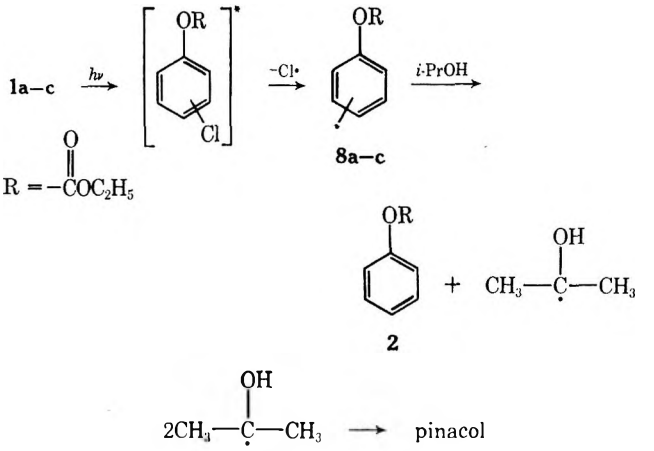
(9) R. Kan, "Organic Photochemistry," McGraw-Hill, New York, N Y., 1966, pp 255–260.



Pinhey and Rigby[10,11] have shown that *m*-chlorophenol on irradiation undergoes photoreduction and photosubstitution. They treat the substitution reaction as a solvolysis of the photoexcited chlorophenol.

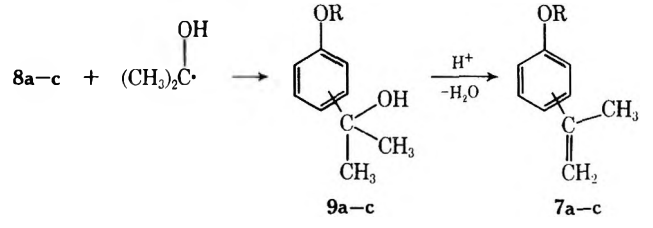


There appear to be two analogous processes occurring in the photochemical reaction of the chlorophenyl ethyl carbonates. The major process is the homolytic cleavage of the C–Cl bond to produce an aryl free radical and a Cl atom. The aryl radical then abstracts a H atom from the solvent to produce phenyl ethyl carbonate. The formation of substantial amounts of HCl and pinacol tend to substantiate the free-radical nature of this process.



The second process, and a minor one, is the displacement of chloride ion by a solvent molecule in a manner analogous to that shown above for *m*-chlorophenol. Thus we identified in each of the reaction mixtures a compound that has a molecular ion at *m/e* 224 which corresponds to the molecular weight of an isopropoxyphenyl ethyl carbonate, **6a–c**. The three compounds, in addition to having the same mass molecular ion, also had the same major peaks in their mass spectra. However, it is apparent from the relative abundance ratios of the peaks that these compounds are not identical but are most likely positional isomers. Pinhey and Rigby[10] have reported that the solvolysis occurs only with *m*-chlorophenol. We observed this reaction in all three chlorophenyl ethyl carbonates, although the percentage of the isopropoxyphenyl ethyl carbonate formed is larger in the meta isomer than it is in the other two isomers.

The isopropenylphenyl ethyl carbonates (**7**) probably form in the following manner.

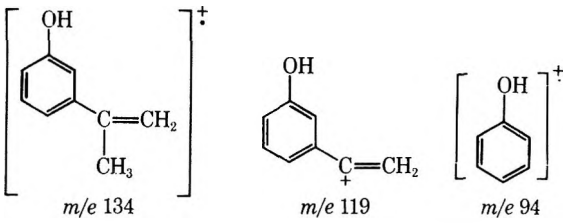


The alcohol (**9a–c**) which we postulate to form initially, dehydrates in the reaction solution to give the observed product, **7a–c**. The presence of **7** was determined by gas chromatography–mass spectroscopy, and it is possible that the alcohol could have dehydrated in this procedure which would make **7a–c** an artifact. The authors consider this to be unlikely, however, since a molecular ion has been reported in the mass spectrum of 2-phenyl-2-propanol.[12]

Structure of 6 and 7.—The structures of these compounds were determined by mass spectroscopy. Using the meta isomer as an example, the mass spectrum of **6b** had a M^+ 224, a M − 42, which is loss of $(CH_3)_2C^+$, and a base peak of *m/e* 110 which corresponds to a dihydroxybenzene ion. This evidence establishes the presence of the isopropyl group and the attachment of two oxygens to the aryl ring. The mass spectrum of **7b** has a molecular ion at *m/e* 206 and a base peak at *m/e*

(10) J. Pinhey and R. Rigby, *Tetrahedron Lett.*, 1267 (1969).
(11) J. Pinhey and R. Rigby, *ibid.*, 1271 (1969).
(12) E. Stenhagen, *et al.*, Atlas of Mass Spectral Data, Vol. 1, Interscience, New York, N. Y., 1969, p 696.

134. The latter peak corresponds to loss of carbon dioxide and ethylene which is always the major fragmentation pathway in aryl alkyl carbonates.[13] There are also major peaks at *m/e* 119 and 94 which are the loss of a methyl group from the *m*-isopropenylphenol ion and the phenol ion, respectively.



m/e 134 *m/e* 119 *m/e* 94

The ortho and para isomers of **6** and **7** give similar spectra except for variations in the intensity ratios of the peaks. This indicates that they are positional isomers and not the same compound nor are they in a mixture of constant composition such as might result from a photochemical process that permitted product isomerization.

Quantum Yields.—The quantum yields for the conversion of the chlorophenyl ethyl carbonates (**1a–c**) to phenyl ethyl carbonate (**2**) are as follows: **1a**, 0.83; **1b**, 0.68; **1c**, 0.33.[14] The decrease in quantum yield in going from the ortho to meta to para isomer is in keeping with the proposed mechanism for the formation of phenyl ethyl carbonate. The initial reaction step after activation is the loss of a chlorine atom to form the intermediate **8a–c**. An inductive effect appears to be adequate to explain the stabilization of the ortho isomer over the meta isomer over the para isomer.

Conclusion

The major photo process which takes place with the chlorophenyl ethyl carbonates is photodechlorination to form phenyl ethyl carbonate which subsequently undergoes a photo-Fries type of rearrangement. The evidence indicates that a homolytic cleavage of the chlorine–carbon bond to give an aryl radical is the major primary process. Abstraction of a hydrogen atom by the aryl radical from the solvent produces the phenyl ethyl carbonate, while reaction of the aryl radical with the solvent radical followed by dehydration produces the observed isopropenylphenyl ethyl carbonate. A minor primary process is believed to be a solvolytic displacement of chloride ion to produce the observed isopropoxyphenyl ethyl carbonate. The quantum yield measurements are consistent with this mechanistic hypothesis. The multiplicity of the excited state is not known but it is under active investigation.

Experimental Section

The gas chromatography (gc) was carried out on a Hewlett-Packard Model 700 gas chromatograph, equipped with a Model 240 temperature programming unit. The chromatograms were recorded on a Honeywell recorder equipped with a Disc integrator. The gc analytical measurements were made with a 6 ft by 1/8 in. column packed with 10% UC-W98 on Chromosorb A. The gc collections were made using a 3 ft by 0.25 in. column packed with 20% SE-52 on Chromosorb A. The detector and the injection port temperatures were 250° and the gas-flow rate was 30 ml/min. The mass spectra were obtained using a Perkin-Elmer Model 270 GC-DF mass spectrometer. This instrument has a gas chromatograph interfaced with the mass spectrometer.

TABLE I

PHOTOLYSIS OF *o*-CHLOROPHENYL ETHYL CARBONATE

Compd	Gc retention time, sec	Column temp, °C	%	Deviation, ±
Pinacol[a]	120	100	21	1.0
Phenol (**3**)	66	150	5	1.0
Phenyl ethyl carbonate (**2**)	216	150	66	1.3
Ethyl salicylate (**4**)	264	150	1.3	0.4
o-Chlorophenyl ethyl carbonate (**1a**)[b]	408	150	1.5	0.2
o-Isopropenylphenyl ethyl carbonate (**7a**)	474	150	3.2	0.1
o-Isopropoxyphenyl ethyl carbonate (**6a**)	686	150	1.4	0.2

[a] Separate run. [b] An unknown peak follows this one very closely. It represents 0.6 ± 0.1% of the mixture and is believed to be ethyl *p*-hydroxybenzoate (**5**).

TABLE II

PHOTOLYSIS OF *m*-CHLOROPHENYL ETHYL CARBONATE

Compd	Gc retention time, sec	Column temp, °C	%	Deviation, ±
Pinacol[a]	120	100	24.5	0.4
Phenol (**3**)	48	160	2.8	0.1
Phenyl ethyl carbonate (**2**)	180	160	62.0	1.3
Ethyl salicylate (**4**)	216	160	2.5	0.03
m-Chlorophenyl ethyl carbonate (**1b**)	336	160	3.2	0.3
Ethyl *p*-hydroxybenzoate	588	160	0.5	0.1
m-Isopropenylphenyl ethyl carbonate (**7b**)	654	160	3.5	0.4
m-Isopropoxyphenyl ethyl carbonate (**6b**)	1128	160	2.6	0.2

[a] Separate run.

Chlorophenyl Ethyl Carbonates (**1a–c**).—The chlorophenyl ethyl carbonates were prepared by the method of Smith and Kosters.[15] It was found that by allowing the reaction mixtures to stand for 24–48 hr longer than indicated, the yields could be increased over those reported. The boiling points, yields, and uv maxima are as follows: 1a (ortho) {bp 77–78° (0.1 Torr) [(lit.[13] 130–131° (15 Torr)]; 91%; 264 mμ (ε 9.37 × 10²), 273 (8.18 × 10²)}; 1b (meta) {bp 72° (0.01 Torr) [(lit.[13] 90–91° (1.6 Torr)]; 83%; 255 mμ (ε 3.24 × 10²), 263 (2.66 × 10²)}; 1c (para) {bp 75° (0.1 Torr) [(lit.[13] 149–151° (33 Torr)]; 84%; 267 mμ (ε 5.55 × 10²), 275 (4.64 × 10²)}.

Photolysis Conditions.—The chlorophenyl ethyl carbonate (5 ml, 5.8 g, 0.029 mol) was dissolved in 250 ml of Spectrograde isopropyl alcohol, and the solution was placed in a standard immersion-well type photochemical apparatus. The solution was stirred with a magnetic stirrer and purged with nitrogen for 15 min. The solution was then irradiated with a 450-W Hanovia[16] high-pressure mercury lamp through a Corex filter sleeve. The photolyses were carried out under a positive nitrogen pressure for the following lengths of time: **1a**, 24 hr; **1b**, 28 hr; **1c**, 26 hr. The composition of the reaction mixtures can be found in Tables I–III.

(13) H. Budzikiewitcz, *et al.*, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 484–493.

(14) The determination of the quantum yields was made by P. A. Tatem as part of her M.S. Thesis. The apparatus used was a Rayonet photochemical reactor equipped with a merry-go-round (The Southern New England Ultraviolet Co., Middletown, Conn.), and a benzophenone actinometer was used.

(15) G. Smith and B. Kosters, *Chem. Ber.*, **93**, 2403 (1960).

(16) Engelhard Hanovia, Inc., Newark, N. J.

TABLE III

PHOTOLYSIS OF *p*-CHLOROPHENYL ETHYL CARBONATE

Compd	Gc retention time, sec	Column temp, °C	%	Deviation ±
Pinacol[a]	120	100	10.3	0.5
Phenol (3)	65	150	1.2	0.1
Phenyl ethyl carbonate (2)	216	150	29.0	0.2
Ethyl salicylate (4)	264	150	1.3	0.1
p-Chlorophenyl ethyl carbonate (1c)[b]	360	150	55.9	0.1
p-Isopropenylphenyl ethyl carbonate (7c)[c]	900	150	1.2	0.2

[a] Separate run. [b] An unknown peak follows this peak very closely. It represents 1.1% (±0.1) of the mixture and is believed to be ethyl *p*-hydroxybenzoate (5). [c] Using gas chromatography–mass spectroscopy an additional peak was observed after this peak and was identified as *p*-isopropoxyphenyl ethyl carbonate (6c) from its mass spectrum.

A control reaction was carried out for each of the chlorophenyl ethyl carbonates and gc analysis showed that no dark reaction had occurred. The photolyses were monitored by gc and were stopped when it appeared that new products were not being formed. When the photolysis was ended, the solvent was evaporated under vacuum and the remaining solution analyzed by gc and by gc–mass spectroscopy. The principle products of the photolysis were collected as they eluted from the gas chromatograph and analyzed further by nuclear magnetic resonance (nmr) and by infrared (ir) spectroscopy.

Product Identification.—**Pinacol** was identified by comparing its retention time with that of an authentic sample.

Phenol (3) was identified by comparing its retention time and mass spectrum with those of an authentic sample.

Phenyl Ethyl Carbonate (2).—The retention time and mass spectrum of this compound were identical with those of an authentic sample. A pure sample of the material was obtained using preparative gc. The ir and nmr spectra of the material confirmed its identity as phenyl ethyl carbonate.

Ethyl Salicylate (4).—This compound was identified by comparing its retention time and mass spectrum with those of an authentic sample.

Ethyl *p*-hydroxybenzoate (5) was identified by its retention time. The identification is certain in the *m*-chlorophenyl ethyl carbonate reaction mixture and its reasonably certain in the other two reaction mixtures.

Isopropenylphenyl Ethyl Carbonate (7).—Identification was made from the mass spectra obtained by gc–mass spectroscopy. The mass spectral data in the case of the meta isomer are given in Table IV.

TABLE IV

m/e	% of base	*m/e*	% of base
	m-Isopropenyl Ethyl Carbonate		
207	2.5	162	7.5
206	11.0	135	11.8
134	100.0	115	14.2
133	32.0	94	58.0
119	24.0	91	34.2
117	14.2		
	m-Isopropoxyphenyl Ethyl Carbonate		
225	1.8	138	6.0
224	7.5	137	2.5
183	1.0	110	100.0
182	3.5	109	9.5
152	3.5		

Isopropoxyphenyl Ethyl Carbonate (6).—Identification was made from mass spectra obtained by means of gc–mass spectroscopy. The mass spectral data are given in Table IV in the case of the meta isomer.

Registry No.—1a, 1847-88-7; 1b, 1847-87-6; 1c, 22719-87-5.

Acknowledgments.—The authors thank the National Science Foundation (Grant P7 2164 E) for matching funds for the purchase of the nmr spectrometer and the mass spectrometer. The authors also wish to express their appreciation to the University Committee on Research for support of this work during the summers of 1968 and 1969.

The Reaction of Organometallic Reagents with Pyridinium Ions[1]

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Received February 11, 1970

The products of the reactions of methyl Grignard reagent with 1-methyl- and 1-benzyl-3-cyanopyridinium ions were shown to be mixtures of 1,2- and 1,6-dihydropyridines[3] resulting from nucleophilic addition at the ring carbons. From the reaction of these salts with aryl Grignards, only 6-aryl-1,6-dihydropyridines were detected. Comparable results were obtained from the reaction of methyl- and phenylcadmium reagents with 1-methyl- and 1-benzyl-3-methoxycarbonylpyridinium ions except that the phenylcadmium reagent with the 1-benzyl salt gave a mixture of products. The product of the reaction of 1-triphenylmethylpyridinium tetrafluoroborate with phenylmagnesium bromide gave 4-phenylpyridine on thermal decomposition. The structures of the products were based on spectral data.

The reactions of nucleophiles with pyridines occur to give 2- or 6-substituted pyridines presumably *via* 1,2- or 1,6-dihydropyridines[3] as intermediates.[4] The generality of this conclusion has been supported by the recent characterization of the organolithium adduct to pyridine.[5] In a few isolated examples, organometallic

(1) This research was presented in part before the Organic Division at the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970. The research was supported in part by a grant from the National Cancer Institute of the National Institutes of Health, CA-04143.

(2) The research was abstracted from the thesis of E. White V presented to the Graduate Faculty of the University of New Hampshire in partial fulfillment of the requirements of the Ph.D. Degree.

(3) The correct numbering system for these dihydropyridines would require that they both be 1,2-dihydropyridine; however, to facilitate the understanding of the results and to be in keeping with earlier papers, the 1,2- and 1,6-dihydropyridine convention will be used throughout this paper.

(4) R. A. Abramovitch and J. G. Saha, *Advan. Heterocycl. Chem.*, **6**, 229 (1966).

(5) (a) R. A. Abramovitch and G. A. Poulton, *J. Chem. Soc. B*, 901 (1969); (b) C. S. Giam and J. L. Strout, *Chem. Commun.*, 142 (1969); (c) G. Fraenkel and J. C. Cooper, *Tetrahedron Lett.*, 1825 (1968).

reagents[5] or complex metal hydrides[7] have given products of nucleophilic addition at the 4 position of the pyridine ring. These examples have all been with pyridines having one electron-withdrawing substituent at the 3 position or two such substituents at the 3 and 5 position.

Reactions of nucleophiles with pyridinium ions occur with even greater ease. The addition is similarly directed to the centers of low electron density, the 2, 4, and 6 positions;[8] however, the common site of reaction is adjacent to the positive nitrogen except with reduction by hydrosulfite ion,[9] thermodynamically controlled cyanide addition,[10] or hydride additions to pyridinium ions having a bulky nitrogen substituent.[11] The reaction of organometallic reagents with pyridinium ions has been limited to the reaction of 1-methylpyridinium salts and their alkyl derivatives with benzyl Grignards in the synthesis of morphinans and benzomorphans.[12] It seemed of interest to explore the reactivity of a series of pyridinium ions, having electron-withdrawing groups attached, with the Grignard reagent and some related organometallic derivatives. In particular it was desirable to determine whether the aromatic ring *or* the electron-withdrawing group would undergo reaction more rapidly with the reagent and, if the ring suffered addition, whether orientation would be affected by the electron-withdrawing substituent.

The cyano group was chosen as the electron-withdrawing substituent since it is less reactive than the carbonyl derivatives with organometallic derivatives. Attack at the cyano function would be unlikely since 3,5-dicyanopyridine undergoes only ring addition[13] and 3-benzoylpyridine gives about 50% ring addition with Grignard reagents.[6b]

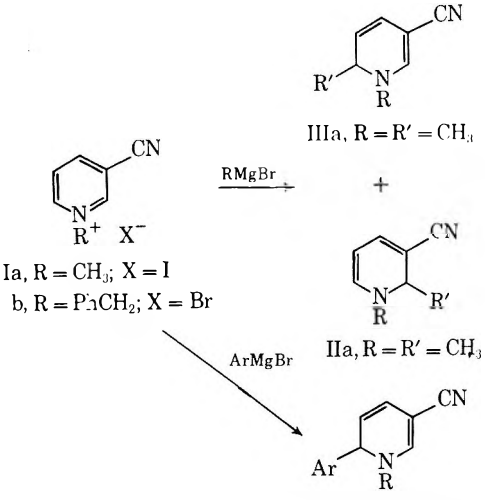
The reactions were carried out as heterogeneous processes in tetrahydrofuran. The reaction mixtures were decomposed with ammonium chloride solution, and the crude product was isolated by evaporation of the solvent. The dihydropyridines that were formed proved to be very unstable, and purification of the product by recrystallization, distillation, or chromatography was accompanied with great losses. In each instance a 1,6-dihydropyridine was isolated occasionally mixed with 1,2 isomer. Since the purification was accompanied by great losses, the presence of the 1,4-dihydropyridine could not be eliminated. It is worthy of note, however, in other series the 1,4-dihydropyridines have been shown to be more stable than the 1,2 or 1,6 isomers.[14]

The structures of the products were identified by ultraviolet, infrared, nuclear magnetic resonance, and mass spectroscopy.[15] The ultraviolet absorption spectra[16] provide the most reliable evidence for distinguishing between the three dihydro systems, for the 1,2-dihydropyridine with its conjugated cyano-dienamine system has a very low energy transition at about 400 nm while the 1,6-dihydropyridine has bands at 240 and 350 nm. The 1-methyl-3-cyano-1,4-dihydropyridine shows only a single absorption band at 340 nm, and this kind of spectrum was not observed in this study.

The nuclear magnetic resonance spectra were important for identification of the product but even more useful for quantitative analysis of the products which could not conveniently be separated. The distinction between the 1,2- and 1,6-dihydro system was immediately evident by noting whether or not the highest field signal was a doublet or singlet. This signal is from the proton attached to the sp^2 carbon adjacent to the nitrogen. If the product is the 1,2-dihydro derivative, this signal arises from the proton at the 6 position and will be split into a doublet by the proton at C-5. If the product is the 1,6-dihydropyridine, the proton at C-2 will be only weakly coupled with other hydrogens and appears as a singlet.

The infrared spectra also provided a means for the qualitative identification of the 3-cyano-1,2- and -1,6-dihydropyridines. These dihydropyridines have two bands due to vibrations of the dienamine function, one above and one below 1600 cm^{-1}. Both of these bands are at lower frequency in the 1,2-dihydropyridines near 1620 and 1525 cm^{-1} while the bands in the 1,6 isomer are near 1640 and 1585 cm^{-1}.

The reactions of 1-methyl-3-cyanopyridinium iodide (Ia) and 1-benzyl-3-cyanopyridinium bromide (Ib) with methylmagnesium bromide and *tert*-butylmagnesium chloride gave products which were very unstable and which failed to give correct analyses. The product from the methyl Grignard could be separated into two components which were shown by nmr, ir, and uv spectroscopy to be the 1,2-dimethyl-3-cyano-1,2-di-



IIIb, R = CH_3; Ar = C_6H_4
c, R = CH_3; Ar = p-$CH_3C_6H_4$
d, R = CH_3; Ar = o-$CH_3C_6H_4$
e, R = $PhCH_2$; Ar = C_6H_5
f, R = $PhCH_2$; Ar = p-$CH_3C_6H_4$

(6) (a) J. Kuthan, E. Janeckova, and M. Havel, *Collect. Czech. Chem. Commun.*, **29**, 143 (1964); (b) R. E. Lyle and D. A. Nelson, *J. Org. Chem.*, **28**, 169 (1963).

(7) J. Kuthan and E. Janeckova, *Collect. Czech. Chem. Commun.*, **30**, 3711 (1965).

(8) R. E. Lyle, *Chem. Eng. News*, **44**, 73 (1966).

(9) K. Wallenfels and H. Schüly, *Justus Liebigs Ann. Chem.*, **621**, 106, 215 (1959).

(10) R. E. Lyle and G. Gauthier, *Tetrahedron Lett.*, 4615 (1965).

(11) P. S. Anderson, W. E. Krueger, and R. E. Lyle, *ibid.*, 4011 (1965).

(12) (a) M. Freund and G. Bode, *Chem. Ber.*, **42**, 1746 (1909). (b) R. Grewe and A. Mondan, *ibid.*, **81**, 279 (1948). (c) A series by E. L. May and coworkers. See part XXXII: B. C. Joshi and E. L. May, *J. Med. Chem.*, **8**, 696 (1965). (d) J. Hellerbach, O. Schnider, H. Besendorf, and B. Pellmont, "Synthetic Analgesics," part IIa, Pergamon Press, Oxford, 1966; N. B. Eddy and E. L. May, *ibid.*, part IIb.

(13) J. Kuthan, *Collect. Czech. Chem. Commun.*, **30**, 2609 (1965); **31**, 3593 (1966).

(14) U. Eisner, *Chem. Commun.*, 1348 (1969).

(15) R. E. Lyle and E. White, *Tetrahedron Lett.*, 1871 (1970).

(16) R. E. Lyle and P. S. Anderson, *Advan. Heterocycl. Chem.*, **6**, 45 (1966).

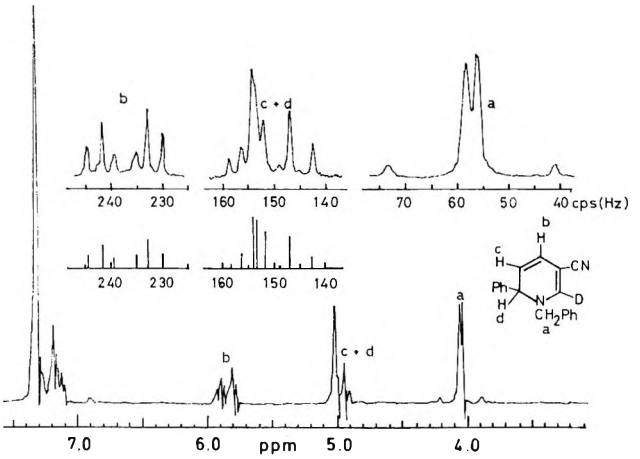
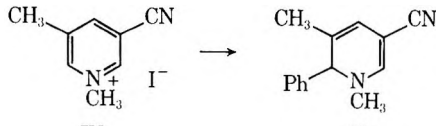
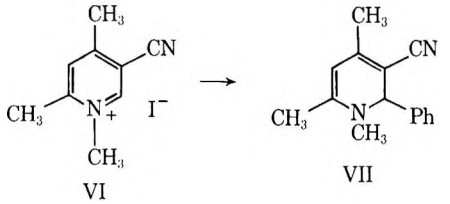


Figure 1.—The nmr spectrum of 1-benzyl-2-deuterio-6-phenyl-3-cyano-1,6-dihydropyridine (2-deuterio-IIIe). The calculated spectrum for the ABC pattern for the 4, 5, and 6 protons is shown under the observed signals.

hydropyridine (IIa) and 1,6-dimethyl-3-cyano-1,6-dihydropyridine (IIIa).

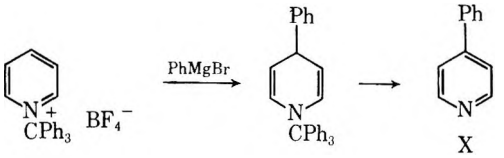
The products from the reactions of arylmagnesium halides were somewhat more stable and could be obtained in analytical purity, but only with great losses in yield. The reaction of Ia with phenyl Grignard reagent gave a product in which only 1-methyl-6-phenyl-3-cyano-1,6-dihydropyridine (IIIb) could be detected by nmr or glc or isolated. Similar results were obtained with a series of aromatic Grignard reagents with Ia and Ib. The major product in each case seems to result from addition of the Grignard reagent at the 6 position. This was true even when the steric interference to approach to this position was increased by introduction of a methyl substituent at the 5 position, for 1,5-dimethyl-3-cyanopyridinium iodide (IV) also gave the 1,6-dihydro derivative V. The 2 position was shown to be reactive to addition by blocking the 4 and 6 positions with methyl substituents. The reaction of 1,4,6-trimethyl-3-cyanopyridinium iodide (VI) with phenyl Grignard gave an addition product which was clearly the 1,2-dihydropyridine (VII) in view of the ultraviolet absorption at 404 nm.





The identification of the 6-aryl-1,6-dihydropyridines (IIIb–f) was confused by the nmr spectra which showed complex multiplets for the ring hydrogens. Only in the case of the *o*-tolyl adduct IIId did the complex pattern approach a first-order pattern. In order to support the structural assignment based on the ultraviolet absorption spectrum, a complete analysis of the nmr spectrum of 1-benzyl-6-phenyl-3-cyano-1,6-dihydropyridine was made.[17] The 100-MHz spectrum clearly indicated the diastereotopic nature of the benzyl protons which appeared as an AB quartet. This probably provided evidence for ruling out the 1,4-dihydropyridine, since the element of dissymmetry is too far removed from the benzyl substituent to be effective in causing magnetic anisotropy.[18] It was apparent that the ring hydrogens formed a four-spin system of the ABCM type. This conclusion was confirmed by double resonance experiments. To simplify the analysis to a three-spin system, the 2-deuterio-IIIe was prepared. This approximated a three-spin system involving the 4, 5, and 6 protons. The spectrum is shown in Figure 1. Following the method of Wiberg[19] and obtaining trial values for the chemical shifts and coupling constants as described by Bible[20] the resonance pattern was calculated. After making small variations in the spectral parameters, the calculated spectrum shown in Figure 1 was obtained using the following δ values: 4-H, 236.8 Hz; 5-H, 150.4 Hz; 6-H, 153.0 Hz ($J_{4,5}$ = 9.8 Hz, $J_{5,6}$ = 4.4 Hz, $J_{4,6}$ = −1.0 Hz).

The reaction of complex metal hydrides with pyridinium ions showed a sensitivity to the steric size of the 1-substituent,[11] a large group directing some addition to the 4 position. A similar experiment was tried with the Grignard reagent by studying the reaction of phenylmagnesium bromide and 1-triphenylmethylpyridinium fluoroborate (VIII). The product, a dihydropyridine (IX), was decomposed thermally to give 4-phenylpyridine (X) in 35% yield, purified. This reaction could not have occurred by initial addition of the phenyl group at the 2 position with subsequent rearrangement to the 4 position for 1-triphenylmethyl-2-phenyl-1,2-dihydropyridine has been shown to give 2-phenylpyridine on decomposition.[21]



The reaction of organocadmium reagents with pyridinium ions was studied to determine if the carbanion nature of the reagent would be sufficiently nucleophilic to add to the ring and to explore the possible uses of more reactive functional groups as the electron-withdrawing substituent. 1-Methyl- and 1-benzyl-3-methoxycarbonylpyridinium salts (XIa and b) were investigated with methyl- and phenylcadmium reagents; the results were very similar to those with the Grignard reactions. There was no evidence of addition to the carbonyl group of the ester, and addition of the organometallic carbanion occurred at the 6 position in all cases and

(17) The authors wish to express appreciation to Mrs. E. Richards of Dyson Perrins Laboratory, Oxford, England, and Dr. D. A. Nelson of the University of Wyoming for assistance with the double resonance experiments, and Dr. J. J. Uebel of the University of New Hampshire for assistance in calculating the spectrum of the three-spin system.

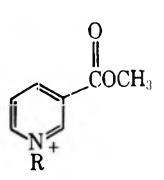
(18) R. E. Lyle and J. J. Thomas, *Tetrahedron Lett.*, 897 (1969).

(19) K. B. Wiberg, "Physical Organic Chemistry," Wiley, New York, N. Y., 1964, p 551.

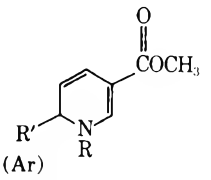
(20) R. H. Bible, Jr., "Interpretation of NMR Spectra—An Empirical Approach," Plenum Press, New York, N. Y., 1965, p 89.

(21) R. Grashey and R. Huisgen, *Chem. Ber.*, **92**, 2641 (1959).

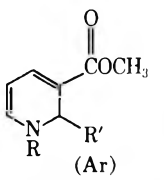
also at the 2 position with the methyl reagent and with the phenyl reagent on reaction with XIb. The success of the addition with organocadmium reagents provide a means for synthesis of otherwise difficultly prepared pyridines.



XIa, R = CH_3
b, R = $PhCH_2$



IIIg, R = R′ = Me
h, R = Me; Ar = Ph
i, R = $PhCH_2$; Ar = Ph



IIi, R = $PhCH_2$; Ar = Ph

The reaction of phenyllithium with 1-benzyl-3-cyanopyridinium bromide (Ib) was very vigorous and gave no isolable product. On the other hand diphenylmercury was found to be unreactive with a pyridinium salt even at the reflux temperature of tetrahydrofuran. Alkylation with ethyl cyanoacetate and ethyl acetoacetate occurred, but the highly colored solutions probably resulted from "anhydro bases" which were not isolated. Using an anion which could not form an "anhydro base," diethyl ethylmalonate, a product (XIII) could be isolated on reaction with 1-(2,6-dichlorobenzyl)-3-cyanopyridinium chloride (XII). The product appeared to be the 1,6-dihydropyridine based on the nmr spectrum.

Experimental Section[22]

General.—The preparation of organometallic compounds and operations involving dihydropyridines were conducted under an atmosphere of dry nitrogen. Dry tetrahydrofuran (THF) was prepared by distillation from calcium hydride and was stored over sodium. Evaporations were carried out under reduced pressure at temperatures below 40°.

1,2-Dimethyl-3-cyano-1,2-dihydropyridine (IIa) and 1,6-Dimethyl-3-cyano-1,6-dihydropyridine (IIIa).—A solution of the Grignard prepared from 5.84 g (0.240 g-atom) of magnesium and excess methyl bromide in a mixture of 150 ml of THF and 50 ml of ether was added dropwise in 3 hr to a stirred suspension of 49.4 g (0.200 mol) of 1-methyl-3-cyanopyridinium iodide (Ia)[23] in 300 ml of THF with cooling in an ice bath. After 1 hr the solid was collected and washed with benzene. The filter cake and the filtrate were hydrolyzed separately with aqueous ammonium chloride, and the resulting solutions were extracted with benzene and methylene chloride. The extracts were dried (K_2CO_3) and evaporated to give 10.0 and 8.6 g, respectively, of dark red oils which were mixtures of II and III in each case.

Distillation of the 8.6 g of material obtained from the filtrate gave 3.8 g (14%) of IIa as a yellow air-sensitive liquid, bp 130–139° (9.5 mm). The purity was 87% as determined by nmr spectroscopy and gas–liquid chromatographic analysis on Carbowax 20M on Chromosorb W at 150°. Correct elemental analyses could not be obtained since the material decomposed rapidly. The structure IIa was confirmed by the spectral data: uv λ_{max}^{EtOH} 397 nm; ir (film) ν 2185, 1620, and 1525 cm^{-1}; pmr δ 1.23 (CCH_3, d, J = 6.2 Hz), 3.00 (NCH_3, s), 4.20 [2 H, q (additional small coupling) J = 6.2 Hz], 4.76 (5 H, t, J = 6.5 Hz), 6.37 (C-4, d of d, J = 6.5, 1.0 Hz), 6.63 (6 H, d, J = 6.5 Hz).

The material obtained from the filter cake was distilled to give 7.6 g (26%) of IIIa, of 92% purity, bp 119–126° (1.25 mm), as a yellow liquid which darkened immediately on contact with air. A center cut, bp 122–124° (1.25 mm), mp 29–31°, was shown to be 98% pure by gas–liquid chromatography; however, the material underwent decomposition too rapidly to obtain an elemental analysis. The structure was evident from the spectral data: uv λ_{max}^{MeOH} 242.5 nm (log ϵ 3.90), 341.5 (3.72); ir (film) ν 2185, 1638, 1580 cm^{-1}; pmr δ 1.17 (CCH_3, d, J = 6.1 Hz), 2.97 (NCH_3, s), 4.17 (6 H, quintet, $J \cong 5.9$ Hz), 4.98 (5 H, d of d, J = 10.0 Hz, *ca.* 4.7), 5.78 (4 H, d with additional small coupling, J = 10 Hz), 6.83 (2 H, s, with additional coupling).

1-Methyl-3-cyano-6-phenyl-1,6-dihydropyridine (IIIb).—The Grignard reagent prepared from 37.7 g (0.240 mol) of bromobenzene and 5.59 g (0.230 g-atom) of magnesium in 180 ml of THF was added in 2.5 hr to a stirred suspension of 49.4 g (0.200 mol) of 1-methyl-3-cyanopyridinium iodide (Ia)[23] in 300 ml of THF in an ice bath. After the mixture was stirred for 2 hr, it was hydrolyzed by the addition of aqueous ammonium chloride. The THF was removed by evaporation and the mixture was diluted with 250 ml of water and extracted with a total of 550 ml of ether. The combined ether extracts were washed with an equal volume of water, dried (K_2CO_3), treated with charcoal, and evaporated to give 33.4 g of red oil. Distillation of the residual oil gave a fraction, bp 142–193° (0.05–0.1 mm), which on redistillation gave 9.55 g (25%) of IIIb as a yellow liquid, bp 182–186° (0.03 mm). From one reaction the product crystallized to give an yellow solid, mp 55–58°. The spectral data for IIIb: uv λ_{max}^{MeOH} 222 nm (log ϵ 4.23), 250 (sh, 3.85), 352 (3.65); ir ν 2185, 1645, 1575 cm^{-1}; pmr δ 2.7 (NCH_3, s), 5.0 (C-5 and C-6, multiplet), 5.9 (multiplet), 6.8 (C-2 broad singlet), 7.4 (Ph, s).

Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.28. Found: C, 79.76; H, 5.96; N, 14.29.

1-Methyl-3-cyano-6-*p*-tolyl-1,6-dihydropyridine (IIIc).—The reaction of the Grignard reagent prepared from 41.1 g (0.240 mol) of *p*-bromotoluene and 5.59 g (0.230 g-atom) of magnesium with 49.4 g (0.200 mol) of 1-methyl-3-cyanopyridinium iodide (Ia)[23] in a manner analogous to that for the preparation of IIIb was followed by a similar work-up. The residual oil was treated with hexane to give 39.5 g (94%) of crude IIIc, mp 85–93°. Two distillations gave 16.9 g (40%) of IIIc as a yellow liquid, bp 160–162° (0.03 mm), which slowly solidified on standing. The spectral data provide support for the structure: ir ν 2185, 1640, 1580 cm^{-1}; nmr δ 2.31 (CCH_3, s), 2.71 (NCH_3, s), *ca.* 5.0 (C-5 + C-6, m), *ca.* 5.8 (C-4, m), 6.80 (C-2, broad s), 7.22 (Ph, s).

Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71. Found: C, 79.97; H, 6.70.

1-Methyl-3-cyano-6-*o*-tolyl-1,6-dihydropyridine (IIId).—The reaction of the Grignard reagent prepared from 37.6 g (0.220 mol) of *o*-bromotoluene and 5.59 g (0.230 g-atom) of magnesium with 49.4 g (0.200 mol) of 1-methyl-3-cyanopyridinium iodide (Ia)[23] as above for the preparation of IIIb was followed by a similar work-up. The residue was washed with hexane to give 21.3 g (51%) of crude IIId, mp 124–145°. Recrystallization from ethanol and then from methanol gave 14.2 g (34%) of yellow crystals: mp 148–150.5° (open capillary), 149–150.5° (evacuated capillary); ir ν 2180, 1640, 1580 cm^{-1}; nmr δ 2.38 (CCH_3, s), 2.70 (NCH_3, s), 4.88 (C-5, d of d, J = 10, 3.8 Hz), 5.49 (C-6, d of d, J = 3.8, 1.5 Hz), 5.80 (C-4, d of m, J = 10 Hz), 6.88 (C-2, broad s), *ca.* 7.2 (Ph, m).

Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.32. Found: C, 79.91; H, 6.66, N, 13.50.

1-Benzyl-3-cyano-6-phenyl-1,6-dihydropyridine (IIIe).—The Grignard reagent from 37.7 g (0.240 mol) of bromobenzene and 5.6 g (0.23 g-atom) of magnesium was added to 55.0 g (0.200 mol) of 1-benzyl-3-cyanopyridinium bromide (Ib).[24] The reaction was run as for IIIb to give 25.1 g (46%) of IIIe, mp 142–145.5°, after two recrystallizations from methanol. Chromatography on Florisil with methylene chloride as eluent followed by crystallization from methanol gave an analytical sample: mp 144.5–146°; uv λ_{max}^{MeOH} 225 nm (sh, log ϵ 4.23), 252 (sh, 3.83), 353 (3.74); ir ν 2190, 1640, 1575 cm^{-1}; for nmr, see discussion.

(22) Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are corrected. Boiling points are uncorrected. The infrared spectra of all compounds were recorded on a Perkin-Elmer Model 337 spectrophotometer. Complete spectra are shown in the thesis from which the material is drawn.[2] Ultraviolet spectra were recorded on a Cary Model 15 spectrophotometer. Proton nuclear magnetic resonance spectra were determined in deuteriochloroform on a Varian Model A-60 nmr spectrometer. The chemical shifts are reported in parts per million shift downfield from tetramethylsilane as an internal standard. The coupling constants J are reported in hertz. Analytical gas chromatography was performed with a Perkin-Elmer Model 154 "Vapor fractometer." Microanalyses were determined by Drs. Weiler and Strauss, Oxford, England, and in these laboratories using an F & M Model 180 or Model 185 carbon, hydrogen, and nitrogen analyzer.

(23) K. Schenker and J. Druey, *Helv. Chim. Acta*, **42**, 1960 (1959).

(24) J. H. Supple Ph.D. Thesis, University of New Hampshire, 1963.

Anal. Calcd for $C_{19}H_{16}N_2$: C, 83.78; H, 5.92. Found: C, 83.78; H, 5.77.

1-Benzyl-2-deuterio-3-cyano-6-phenyl-1,6-dihydropyridine (2-deuterio-IIIe).—This material was prepared in the same manner as IIIe. From 7.7 g (0.021 mol) of 1-benzyl-2-deuterio-3-cyanopyridinium bromide[25] was obtained 3.0 g (52%) of the 1,6-dihydropyridine (2-deuterio-IIIe), mp 142–147°. Purification as above gave 2.7 g (47%) of pure 1,6-dihydropyridine, mp 144–146°.[15]

1-Benzyl-3-cyano-6-*p*-tolyl-1,6-dihydropyridine (IIIf).—The procedure followed was the same as that used for the preparation of IIIb. Addition of the Grignard reagent from 30.3 g of *p*-bromotoluene (0.230 mol) and 5.34 g (0.220 g-atom) of magnesium to 55.0 g (0.200 mol) of 1-benzyl-3-cyanopyridinium bromide (IIIb)[24] gave 28.8 g (50%) of crude IIIf, mp 89.5–98° after crystallization from methanol–hexane (1:1). Two further recrystallizations from methanol gave 23.8 g (42%) of IIIf, mp 96.5–98°.

A sample of IIIf was further purified by chromatography on Florisil using ether as eluent followed by crystallization from ether to give pure IIIf as large yellow crystals: mp 97.5–99°; uv λ_{max}^{MeOH} 232 nm (log ϵ 4.24), 352 (3.75); ir ν 2185, 1645, 1575 cm^{-1}; nmr δ 2.33 (CCH_3, s), 4.05 (CH_2, broad s), *ca.* 4.9 (C-5,6, m), *ca.* 5.8 (C-4, m), 6.88 (C-2, broad s), 7.19 (Ph, s), *ca.* 7.25 (Ar, m).

Anal. Calcd for $C_{20}H_{18}N_2$: C, 83.88; H, 6.33; N, 9.78. Found: C, 84.15; H, 6.18; N, 9.67.

1,5-Dimethyl-3-cyano-6-phenyl-1,6-dihydropyridine (V).—The Grignard reagent from 17.3 g (0.110 mol) of bromobenzene and 2.82 g (0.120 g-atom) of magnesium was added to 26.0 g (0.100 mol) of 1,5-dimethyl-3-cyanopyridinium iodide (IV).[26] Hydrolysis and work-up as above for IIIb gave 14.7 g (70%) of crude V as a solid, mp 105–120°. The solid was distilled twice to give 9.4 g (45%) of clear yellow liquid, bp 148–152° (0.02 mm), which solidified on standing: mp 118–124.5° (open capillary), mp 120–124.5° (evacuated capillary); uv λ_{max}^{MeOH} 220 nm (sh, log ϵ 3.85), 251 (3.85), 353 (3.69); ir ν 2180, 1650 (m), 1590 cm^{-1}; nmr δ 1.45 (CCH_3, d, $J \leqq 2$ Hz), 2.72 (NCH_3, s), 4.80 (C-6, broad s), 5.70 (C-4, m), 6.75 (C-2, broad s), 7.34 (Ph, s).

Anal. Calcd for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.32. Found: C, 80.07; H, 6.63; N, 13.45.

1,4,6-Trimethyl-2-phenyl-3-cyano-1,2-dihydropyridine (VII).—The reaction of the Grignard reagent prepared from 18.8 g (0.120 mol) of bromobenzene and 3.16 g (0.130 g-atom) of magnesium with 27.4 g of 1,4,6-trimethyl-3-cyanopyridinium iodide (VI)[27] was conducted in the same manner as for the preparation of IIIb. Two distillations through a short Vigreux column gave 5.35 g (24%) of VII as a deep yellow oil: bp 133–134° (0.02 mm); uv λ_{max}^{MeOH} 404 nm (log ϵ 3.88); ir ν 2180, 1615 (m), 1525 cm^{-1}; nmr δ 1.90 (CCH_3, s), 2.79 (NCH_3, s), 4.61 (C-5, s), 5.01 (C-2, s), 7.31 (Ph, s).

Anal. Calcd for $C_{15}H_{16}N_2$: C, 80.32; H, 7.19; N, 12.49. Found: C, 80.39; H, 7.18; N, 12.56.

4-Phenylpyridine (X) from Phenylmagnesium Bromide and 1-Triphenylmethylpyridinium Fluoroborate (VIII).—The Grignard reagent prepared from 17.3 g (0.110 mol) of bromobenzene and 2.92 g (0.120 g-atom) of magnesium in 75 ml of THF was added in 0.4 hr to a stirred suspension of 37.5 g (0.0918 mol) of VIII[28] in 100 ml of THF cooled with an ice bath. The mixture was stirred at room temperature for 0.3 hr and hydrolyzed by the addition of aqueous ammonium chloride.

The mixture was diluted with 500 ml of water and extracted with 250 ml of ether. The ether extract was washed twice with 500-ml portions of water, diluted with 100 ml of methylene chloride, dried (K_2CO_3), and evaporated to give a sticky yellow solid.

The solid was pyrolyzed at 8 mm under a water-cooled condenser in an air bath held at 200° for 1 hr. The material in the condenser and in the pot was dissolved in 200 ml of ether. Hydrogen bromide gas was bubbled into the ether solution until precipitation was complete. The precipitate was collected, washed with ether, and dried to give 16.2 g of brown powder. This solid was suspended in a mixture of 200 ml of ether and 20 ml of water. Solid potassium carbonate was added in large excess and the ether layer was decanted, dried (K_2CO_3), treated with charcoal, and evaporated to give a brown solid. Crystallization from 6 l. of water gave 5.03 g (35%) of X as white plates, mp 73–75.5°. The melting point was not depressed on mixing with authentic 4-phenylpyridine.

1,2-Dimethyl-3-carbomethoxy-1,2-dihydropyridine (IIg) and 1,6-Dimethyl-3-carbomethoxy-1,6-dihydropyridine (IIIg).—The Grignard reagent prepared from 11.63 g (0.480 g-atom) of magnesium and excess methyl bromide in 500 ml of THF was converted to the cadmium reagent by the addition of 87.8 g (0.480 mol) of dry cadmium chloride and 150 ml of THF and heating the mixture under reflux for 1 hr. To the stirred cadmium reagent, cooled by an ice bath, was added 92.8 g (0.400 mol) of 1-methyl-3-carbomethoxypyridinium bromide (XIa)[29] all at once. The mixture was stirred with cooling for 1 hr and then at room temperature for 16 hr. Hydrolysis with 200 ml of saturated aqueous ammonium chloride and dilution with 800 ml of water was followed by extraction with 1700 ml of methylene chloride. The organic layer was washed with water and dried (K_2CO_3), and the solvent was evaporated to give 32.8 g of a red liquid shown by glc to contain nearly equal amounts of IIg and IIIg.

Distillation of the crude mixture through a short Vigreux column gave 6.8 g (10%) of IIg as a yellow liquid (96% IIg by glc), bp 126–138° (9 mm), and 17.3 g (26%) of IIIg as a yellow liquid (92% IIIg by glc), bp 140–149° (9 mm).

Redistillation of IIg gave 3.6 g of pure IIg as a yellow air-sensitive liquid: bp 115–116.5° (8 mm); uv λ_{max}^{MeOH} 416 nm (log ϵ 3.92); ir ν 1685, 1620 (m), 1525 cm^{-1}; nmr δ 1.03 (CCH_3, d, J = 6.5 Hz), 3.00 (NCH_3, s), 3.63 (OCH_3, s), 4.50 q (2 H, q, J = 6.5 Hz), 4.71 (C-5, t, J = 6.5 Hz), 6.37 (C-4, d of t, J = 6.5 Hz), 6.97 (C-6, d, J = 6.5 Hz).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.66; H, 7.62; N, 8.74.

Redistillation of IIIg gave an 11.5-g sample of IIIg, bp 140.5–142° (8 mm), as a yellow, air-sensitive material with a purity of about 92% (estimated from the nmr since variable results arising from pyrolysis were obtained by glc). The sample for the ultraviolet spectrum and for analysis was redistilled immediately before use: uv λ_{max}^{MeOH} 257 nm (sh, log ϵ 3.95), 263 (4.00), 271 (sh, 3.90), 324 (3.83), 345 (sh, 3.77); ir ν 1680, 1640, 1575 cm^{-1}; nmr δ 1.15 (CCH_3, d, J = 5 Hz, 2.97 (NCH_3, s), 3.58 (OCH_3, s), 4.13 (C-6, quintet, $J \leqq 5.5$ Hz), 4.90 (C-5, d of d, J = 10, 5.0 Hz), 6.29 (C-4, d of d, J = 10, *ca.* 1 Hz), 7.24 (C-2, broad s).

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Foupd: C, 64.46; H, 7.96; N, 8.29.

1-Methyl-3-carbomethoxy-6-phenyl-1,6-dihydropyridine (IIIh).—To the Grignard reagent prepared from 18.82 g (0.120 mol) of bromobenzene and 2.92 g (0.120 g-atom) of magnesium in 150 ml THF was added 22.0 g (0.120 mol) of dry cadmium chloride and 50 ml of THF. The mixture was heated under reflux for 0.7 hr. The cadmium reagent was cooled to room temperature and, with stirring, 23.2 g (0.100 mol) of 1-methyl-3-carbomethoxypyridinium bromide (XIa)[29] was added all at once. The reaction mixture was stirred for 12 hr, cooled in an ice bath, and hydrolyzed by the addition of 50 ml of a saturated solution of ammonium chloride and 150 ml of water. The THF was evaporated and the residue was extracted with four 100-ml portions of ether. The combined ether extracts were washed with water, dried (K_2CO_3), and treated with charcoal. The ether was removed to leave an oil which solidified. Two recrystallizations from methanol gave 10.4 g (45%) of IIIh as light yellow crystals: mp 101–106°; ir ν 1670, 1630, 1565 cm^{-1}; nmr δ 2.73 (NCH_3, s), 3.68 (OCH_3, s), *ca.* 5.0 (C-5,6, m), 6.48 (C-4, m), 7.32 (Ph, s).

Samples of IIIh showed no improvement in melting point after either chromatography on Florisil or sublimation. Thin layer chromatography on silica gel gave no evidence for the presence of impurities.

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.64; H, 6.80; N, 6.22.

Mixture of 1-Benzyl-2-phenyl-3-carbomethoxy-1,2-dihydropyridine (IIi) and 1-Benzyl-3-carbomethoxy-6-phenyl-1,6-dihydropyridine (IIIi).—To the cadmium reagent prepared from 9.89 g (0.0630 mol) of bromobenzene, 1.46 g (0.0600 g-atom) of magnesium, and 11.0 g (0.0600 mol) of dry cadmium chloride was added to 15.4 g (0.050 mol) of 1-benzyl-3-carbomethoxy-

(25) The 1-benzyl-2-deuterio-3-cyanopyridinium bromide was prepared from the undeuterated salt Ib by repeated exchange with deuterium oxide at 100° in the presence of small amounts of potassium cyanide. The deuterium incorporation was determined by nmr and mass spectral[15] analysis.

(26) G. J. Gauthier, Ph.D. Thesis, University of New Hampshire, 1966.

(27) T. Kametani and M. Sato, *Yakugaku Kenku*, **34**, 112 (1962); *Chem. Abstr.*, **58**, 13910 (1963).

(28) R. E. Lyle and C. B. Boyce, unpublished results.

(29) D. A. Nelson, Ph.D. Thesis, University of New Hampshire, 1960.

pyridinium bromide (XIb).[30] Work-up in a manner similar to that for IIIb gave an oil from which no crystalline material could be obtained. Distillation provided 6.2 g of viscous yellow oil, bp 210–245° (0.06–1.0 mm), subsequently chromatographed on neutral alumina using benzene as eluent and redistilled to give 1.4 g (9%) of viscous yellow oil [bp 198–202 (0.03 mm); uv λ_{max}^{MeOH} 267.5 nm, 353, 427] shown by nmr spectroscopy to be 21% of the 1,2-dihydropyridine IIi and 79% of the 1,6-dihydropyridine IIIi: nmr δ 3.47 (IIi, OCH_3, s), 3.66 (IIIi, OCH_3, s), 4.05 (IIIi, NCH_2, s), 4.30 (IIi, NCH_2, s), 7.53 (IIIi, C-2, s), and other multiplets to be expected from this mixture.

Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.66; H, 6.45; N, 4.69.

1-(2,6-Dichlorobenzyl)-3-cyano-6-(1,1-dicarbethoxypropyl)-1,6-dihydropyridine (XIII).—Diethyl ethylmalonate, 1.87 ml, was added dropwise to a stirred suspension of 0.50 g of a 49.7% dispersion of sodium hydride in mineral oil in 20 ml of THF. The resulting solution was added dropwise to a stirred suspension of 3.0 g (0.010 mol) of 1-(2,6-dichlorophenyl)-3-cyanopyridinium chloride (XII)[26] in 20 ml of THF. The mixture was stirred for 0.5 hr, was filtered, and was concentrated. The residual oil was dissolved in ether and treated with charcoal. The solvent was removed and the residue crystallized on trituration with petroleum ether. Recrystallization from benzene–petroleum ether gave 0.8 g (18%) of crude XIII: mp 117–122° dec; uv λ_{max}^{MeOH} 363 nm, 310, 242 (sh). The nmr was consistent with the structure XIII. The triplets for two nonequivalent methyls of the ester and the methyl of the C-ethyl appear at about 1 ppm. The diastereotopic protons of the methylene of the C-ethyl give a multiplet at 2.0 ppm. The methylene protons of the ester groups appear at 4.1 ppm. The benzylmethylene appears at 4.64 ppm. The ring protons appear at 4.95 (C-5, d of d, J = 8.0, 4.5 Hz), 6.3 (C-4, d of d, J = 8.0, 1.5 Hz), 6.88 (C-2, d, J = 1.5 Hz). Recrystallization from 2-propanol and ether improved the melting point, 130.5–132.5°, but the nmr did not change.

Anal. Calcd for $C_{22}H_{24}Cl_2N_2O_4$: C, 58.54; H, 5.36; N, 6.21. Found: C, 58.28; H, 4.72; N, 6.25.

(30) G. Büchi, D. L. Coffen, K. Kocsis, P. E. Sonnet, and F. E. Ziegler, *J. Amer. Chem. Soc.*, **88**, 3099 (1966).

Registry No.—IIa, 27531-36-8; IIg, 27531-37-9; IIi, 27531-38-0; IIIa, 27531-39-1; IIIb, 27531-40-4; IIIc, 27531-41-5; IIId, 27531-42-6; IIIe, 27531-43-7; IIIe (2-deuterio), 27531-44-8; IIIf, 27531-45-9; IIIg, 27531-46-0; IIIh, 27531-47-1; IIIi, 27531-48-2; V, 27531-49-3; VIII, 27531-54-0; XIII, 27531-55-1; methylmagnesium bromide, 75-16-1; *tert*-butylmagnesium chloride 677-22-5; phenylmagnesium bromide, 100-58-3.

Quinazolines and 1,4-Benzodiazepines. XLVIII. Ring Enlargement of Some Chloromethylquinazolin-4-ones[1]

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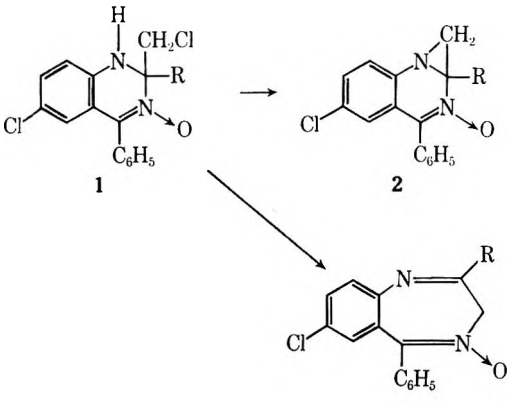
Treatment of 2-chloromethyl-1,2,3,4-tetrahydroquinazolin-4-ones with bases gives 1,4-benzodiazepin-5-ones. Aziridines are implicated as intermediates.

Reaction of 2-chloromethylquinazoline 3-oxide derivatives, such as **1**, with strong bases leads to ring expansion with formation of two types of compounds, benzodiazepines **3** and their structural isomers **2**.[2] One can consider this reaction to be an internal alkylation in which the chloromethyl group alkylates either the 1 nitrogen to produce **2** or the 3 nitrogen to produce ultimately **3**. Obviously, this reaction should be extendable to the synthesis of other heterocycles containing a seven-membered ring. However, since a change of the substituent R from hydrogen to methyl is enough to change the product from one type to the other, one might expect that other changes would also affect this delicate balance.[2] It therefore seemed of interest to study additional examples of this reaction.



We now report that 1,2,3,4-tetrahydro-4-oxoquinazolines,[3] *e.g.*, **5**, give only products derived by alkylation of the 1 nitrogen. The starting materials, **5**, **12**, and **17**, are easily prepared by the acid-catalyzed condensation of an anthranilamide with chloroacetone with azeotropic removal of the water formed. Treatment of **5** with potassium *tert*-butoxide in tetrahydrofuran, conditions which in the case discussed above favor formation of the aziridines **2**, yielded the benzodiazepinone **7**.

The nmr spectrum of **7** showed a singlet at δ 2.17 ppm for the methyl group, a band at δ 4.16 ppm for the methylene group, and a band at δ 8.5 for the NH. It absorbed 1 mol of hydrogen on hydrogenation over platinum to give the tetrahydrobenzodiazepinone **9**.[4] The structure of **7** was confirmed by its hydrolysis to an acetonyl anthranilamide (**8**) which on treatment with base gave 2-acetylindoxyl (**10**).[5] Alkylation of anthranilamide with chloroacetone in the presence of calcium carbonate also gave **8** (Scheme I).

Reaction of **5** with potassium methoxide in methanol, conditions which in the quinazoline 3-oxide series favor

(1) (a) Presented in part at the Middle Atlantic Regional Meeting of the American Chemical Society, New York, N. Y., Feb 1966. (b) Paper XLVII: R. Y. Ning, I. Douvan, and L. H. Sternbach, *J. Org. Chem.*, **35**, 2243 (1970).

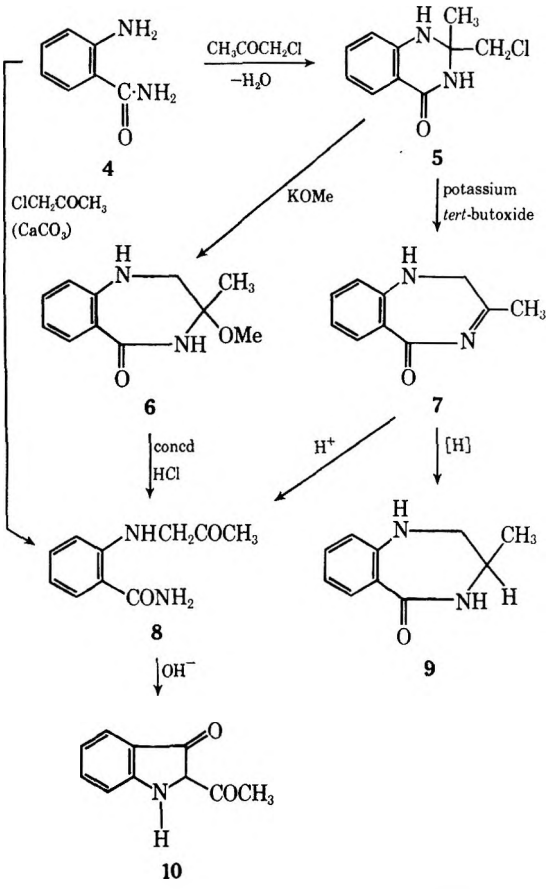
(2) G. F. Field, W. J. Zally, and L. H. Sternbach, *J. Amer. Chem. Soc.*, **89**, 332 (1967).

(3) H. Boehme and H. Boeing, *Arch. Pharm. (Weinheim)*, **293**, 1011 (1960); W. L. F. Armarego in "Fused Pyrimidines: Part I, Quinazolines," D. J. Brown, Ed., Interscience, New York, N. Y., 1967, pp 392–394.

(4) Similar compounds have been prepared by A. A. Santilli and T. S. Osdene, *J. Org. Chem.*, **31**, 4268 (1966).

(5) H. C. F. Su and K. C. Tsou, *J. Amer. Chem. Soc.*, **82**, 1187 (1960).

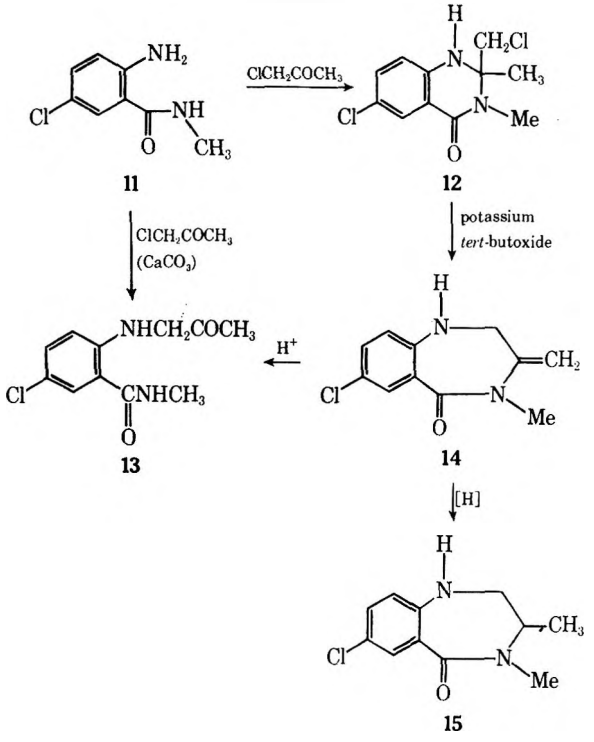
SCHEME I



alkylation at the 3 nitrogen to give products of structure 3,[2] gave the methoxy derivative 6, which also gave 8 on hydrolysis. Therefore, in both solvents, nitrogen 1 is alkylated.

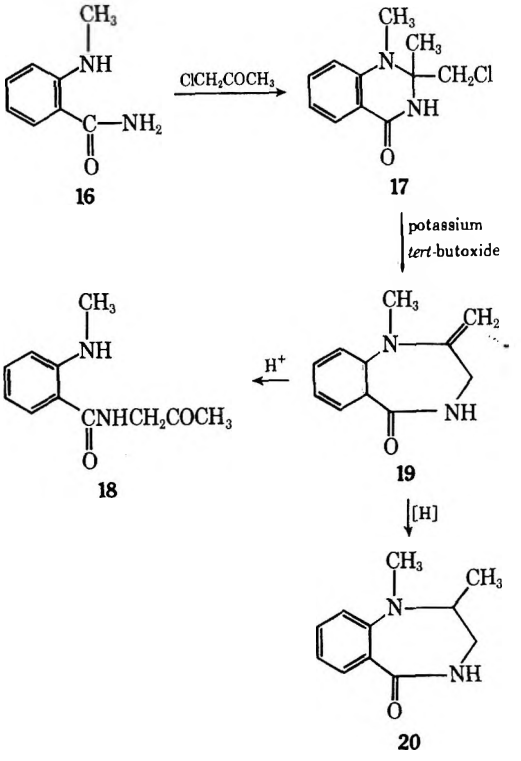
The *N*-methyl derivatives of 5 were also prepared and ring expanded. Reaction of 12 with potassium *tert*-butoxide in tetrahydrofuran gave a product to which structure 14 was assigned on the basis of the nmr spectrum. The double bond could be reduced to give 15. As with 7, acid hydrolysis gave an acetonyl compound 13 which was also obtained by alkylation of 11 with chloroacetone (Scheme II).

SCHEME II



Reaction of the 1-methylquinazolinone 17 with potassium *tert*-butoxide in tetrahydrofuran gave a product to which structure 19 was assigned on the basis of the nmr spectrum. Hydrolysis gave the acetonyl compound 18. Catalytic hydrogenation gave the tetrahydrobenzodiazepinone 20 whose nmr spectrum showed a doublet (J = 6 Hz) at δ 1.0 ppm for the *C*-methyl group (Scheme III).

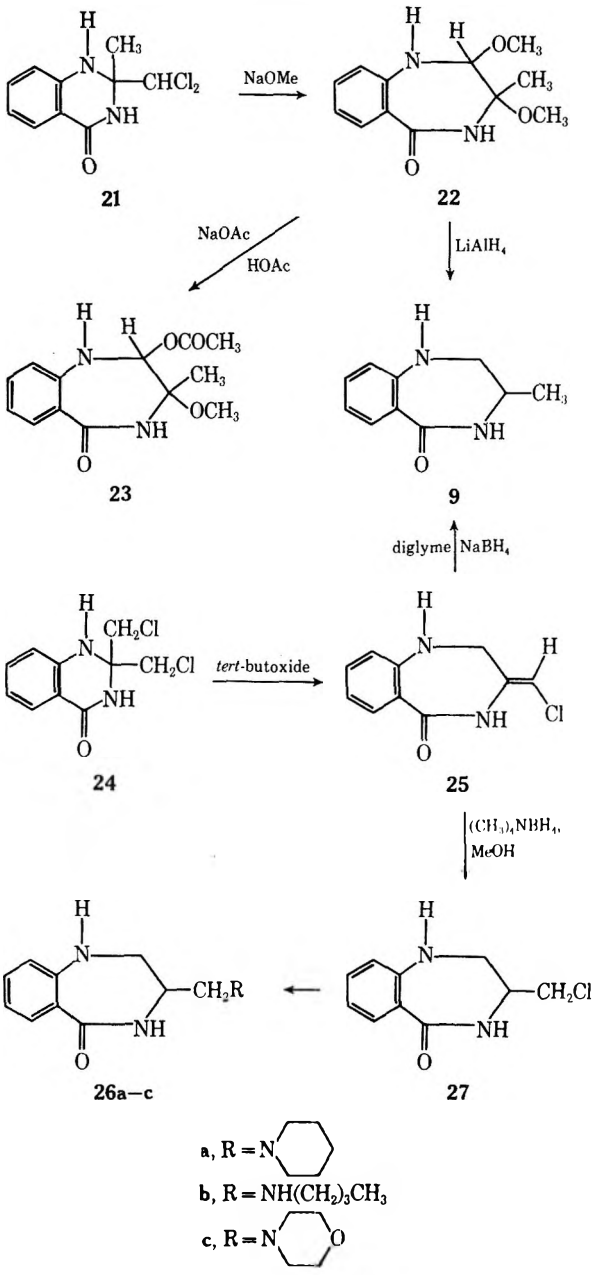
SCHEME III



The quinazolines 21 and 24 derived from symmetrical and unsymmetrical dichloroacetone were also studied. The dichloromethyl derivative 21 gave 22 with sodium methoxide in methanol. Reduction of 22 with lithium aluminum hydride gave 9 which confirms the presence of the benzodiazepine ring system. The disposition of the methoxy groups is shown by the nmr spectrum which contains a singlet at δ 1.47 ppm for the *C*-methyl and doublet at δ 4.23 ppm for the C-2 hydrogen which collapses to a singlet on exchange with D_2O. On treatment with sodium acetate in acetic acid, the 2-methoxy group is exchanged for acetate to give 23, demonstrating the nonequivalence of the two methoxy groups. The nmr spectrum of 23 shows that it is the 2-methoxy rather than the 3-methoxy which has been displaced, since the methine proton at C-2 shifts from δ 4.23 to 5.58 ppm.

Treatment of the bischloromethyl compound 24 with 1 equiv of potassium *tert*-butoxide caused the loss of 1 mol of hydrogen chloride and formation of 25. The gross structure of 25 was confirmed by reduction with sodium borohydride in diglyme to 9. The position of the double bond was shown by the nmr spectrum. The

SCHEME IV



methylene group at C-2 gives rise to a doublet (J = 4 Hz) at δ 3.85 (2 H). The vinyl hydrogen gave a singlet at δ 5.67 ppm, and the two exchangeable protons attached to the nitrogens are at δ 7.0 and 8.51 ppm. The presence of a chlorine atom apparently stabilizes the double bond in the exocyclic position. Reduction of **25** with tetramethylammonium borohydride in methanol gave the chloromethylbenzodiazepine **27**. This compound, on displacement of the chlorine with primary or secondary amines, gave the aminomethyl derivatives **26** (Scheme IV).

Discussion

Since there are two ionizable protons in **5**, there are two possible pathways by which the benzodiazepinones **6** and **7** could be formed. The products obtained from the *N*-methyl derivatives show that the N-1 proton is abstracted by the base to give the anion A as the first step to the reaction. The next step is ring closure to the aziridine B, which then isomerizes to the benzodiazepine **7**. This conclusion follows since the 3-methyl derivative, **12**, gave a similar product, **14**, while the 1-methyl derivative **17** gives a different type of product. If an alternative path through ions C and D was followed, the 1-methyl derivative **17** would have given a product similar to that of the original compound **5**, and the 3-methyl derivative **12** would have given the other type of product. (See Scheme V.)

This situation is much simpler than the case of the 1,2-dihydroquinazoline 3-oxides **1** which were studied previously.[2] Here only the path leading to the formation of aziridines is followed. There is no evidence for the formation of any intermediates in which the heterocyclic ring has opened.

Experimental Section[6]

2-Chloromethyl-1,2-dihydro-2-methyl-4(3*H*)-quinazolone (5).—A mixture of 2-aminobenzamide **4** (136.0 g, 1.0 mol), 2-chloropropanone (170 ml, 2.1 mol), and benzene (2.5 l.) was stirred under reflux for 4 hr; the water produced was collected with a Dean-Stark trap. The reaction mixture was cooled to 20°, and the precipitated crystals were filtered to give tan plates, mp 159–163° (198.1 g, 94%). An analytical sample was obtained as colorless plates after three recrystallizations from ethyl acetate: mp 165–168°; ir ($CHCl_3$) 1670 cm^{-1} (C=O).

Anal. Calcd for $C_{10}H_{11}ClN_2O$: C, 57.01; H, 5.26. Found: C, 57.19; H, 5.02.

1,2,3,4-Tetrahydro-3-methoxy-3-methyl-5*H*-1,4-benzodiazepin-5-one (6).—A solution of 4.2 g (20 mmol) of 2-chloromethyl-1,2-dihydro-2-methyl-4(3*H*)-quinazolone (**5**) and 2.24 g (20 mmol) of potassium *tert*-butoxide in 150 ml of methanol was stirred at room temperature for 4 hr. The precipitated inorganic material was removed by filtration through Celite, and the filtrate concentrated *in vacuo* to give 4.0 g of crude product, mp 168–172° dec. Two recrystallizations from methanol gave colorless prisms: mp 165–168° dec; ir ($CHCl_3$) 1635 cm^{-1} (CO); uv max 223 (ϵ 29,000), 255 (8500), and 340 (5000).

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84. Found: C, 64.01; H, 6.67.

1,2-Dihydro-3-methyl-5*H*-1,4-benzodiazepin-5-one (7).—Potassium *tert*-butoxide (22.4 g, 0.2 mol) was added to a cooled (10–15°) solution of 2-chloromethyl-1,2-dihydro-2-methyl-4(3*H*)-quinazolone (**5**) (42.1 g, 0.2 mol) in tetrahydrofuran (500 ml) with stirring. The reaction mixture was stirred at room temperature overnight and filtered through a bed of Celite, and the clear filtrate was concentrated to dryness *in vacuo*. The residue was crystallized from methylene chloride and the solids were filtered to give off-white plates, mp 143–149° (15.0–21.6 g, 43–63%). An analytical sample was obtained as off-white plates after four recrystallizations from ethanol: mp 156–159°; ir ($CHCl_3$) 1660 cm^{-1} (CO); uv max 215 mμ (ϵ 23,000), 255 (9000), and 341 (4050); nmr (DMSO) δ 2.17 (s, 3, CH_3), 4.16 (m, 2, CH_2), and 8.5 ppm (m, 1, NH).

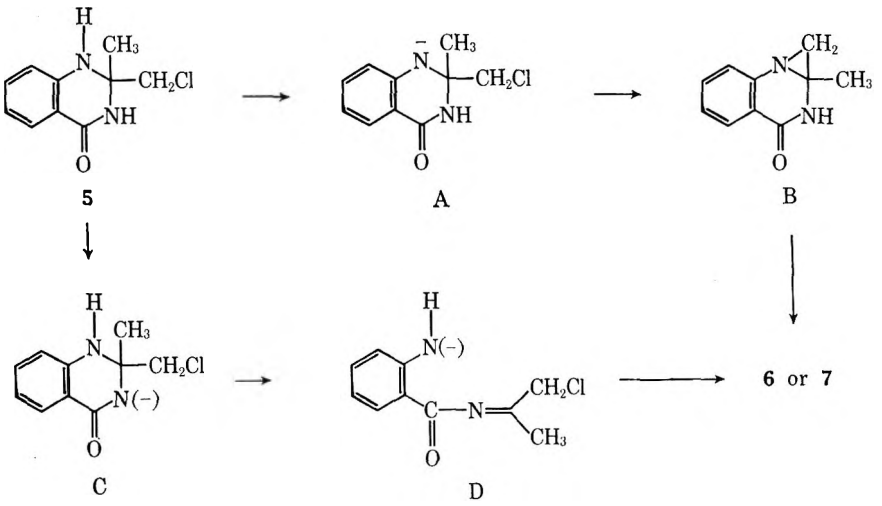
Anal. Calcd for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79. Found: C, 69.05; H, 5.79.

2-Acetonylamincbenzamide (8). A. From 7.—1,2-Dihydro-3-methyl-5*H*-1,4-benzodiazepin-5-one (**7**) (20.0 g, 0.115 mol) was dissolved in concentrated hydrochloric acid (300 ml) and stored at room temperature overnight. The solution was neutralized with 50% aqueous sodium hydroxide, diluted with water, and extracted with methylene chloride in five portions. The methylene chloride extracts were combined, dried over sodium sulfate, filtered, and concentrated to dryness. The solid residue was collected by filtration to give tan needles, mp 140–150° (15 g, 68.1%). An analytical sample was obtained as colorless needles after two recrystallizations from ethanol: mp 162–163.5°; ir (KBr) 3470 (NH), 3360 and 3310 (NH_2), 1780 (CO), 1640 and 1615 cm^{-1} (amide CO); nmr (DMSO) δ 2.14 (s, 3, CH_3), 4.06 (d, 2, J = 5 Hz, CH_2, and 8.45 ppm (t, 1, J = 5 Hz, NH).

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29. Found: C, 62.25; H, 6.11.

(6) Melting points were determined in capillaries and are corrected. The nmr spectra were determined on a Varian A-60 instrument. Alumina refers to Woelm grade I and petroleum ether to a fraction of bp 40–60°. The ultraviolet spectra were taken in 2-propanol.

SCHEME V



B. From 4.—A mixture of 2-aminobenzamide (4) (27.4 g, 0.2 mol), calcium carbonate (13.7 g, 0.137 mol), 2-chloropropanone (18.4 g, 0.2 mol), and water (200 ml) was stirred under reflux for 1 hr. The reaction mixture was cooled to room temperature and the precipitate collected to give 8 as tan needles, mp 162–165° (21.5 g, 54.7%), identified by mixture melting point and ir spectrum.

C. From 6.—A solution of 1,2,3,4-tetrahydro-3-methoxy-3-methyl-5*H*-1,4-benzodiazepin-5-one (6) (2.1 g, 10 mmol) in 75 ml of concentrated hydrochloric acid was allowed to stand overnight at room temperature. The solution was then diluted with water, neutralized with solid sodium bicarbonate, and extracted with methylene chloride in four portions. The extracts were dried over sodium sulfate and concentrated *in vacuo* to leave 1.2 g of solid, which on recrystallization from ethanol gave 1.0 g of 2-acetonylaminobenzamide (8), mp 161–163°. The infrared spectrum was identical with that of authentic material.

2-Acetylindoxyl (10).—A solution of 2-acetonylaminobenzamide (38.4 g, 0.2 mol) in 1 *N* aqueous sodium hydroxide (200 ml, 0.2 mol) was stirred under an atmosphere of nitrogen for several min. The internal temperature was gradually increased to 100° over a 45-min period and then maintained at this temperature for an additional 15 min. The solution was cooled to room temperature, filtered by gravity, and neutralized with 1 *N* aqueous hydrochloric acid. The precipitated solids were filtered and recrystallized from dilute methanol to give green needles, mp 157–162° (10.6 g, 30%). An analytical sample was obtained as greenish needles after three recrystallizations from dilute methanol: mp 158–159.5° (lit.[5] mp 161–161.5°); uv max 239 mμ (ε 15,000), 255 (sh) (9000), 316 (21,000), and 353 (7000).

Anal. Calcd for $C_{10}H_9NO_2$: C, 68.55; H, 5.17. Found: C, 68.38; H, 5.43.

1,2,3,4-Tetrahydro-3-methyl-5*H*-1,4-benzodiazepin-5-one (9).—1,2-Dihydro-3-methyl-5*H*-1,4-benzodiazepin-5-one (7) (21.5 g, 0.128 mol) was hydrogenated in ethyl acetate (240 ml) at room temperature and atmospheric pressure in the presence of platinum oxide (2.6 g, 0.0115 mol). After 2.5 hr, 3.4 l. (0.152 mol) of hydrogen had been absorbed and the uptake had stopped. The mixture was concentrated to a small volume *in vacuo* and filtered through a bed of Celite. The bed of Celite was slurried with hot ethanol and filtered through a second bed of Celite into the original filtrate. The combined filtrates were concentrated to dryness *in vacuo*, and the residue was crystallized from ethanol to give yellowish plates, mp 213–216° (14.0 g, 62.2%). An analytical sample was obtained as off-white plates after two recrystallizations from ethanol: mp 214–216°; ir (KBr) 1630 cm^{-1} (CO); uv max 222 mμ (ε 26,000), 258 (8000), and 338 (9500).

Anal. Calcd for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86. Found: C, 67.95; H, 7.09.

2-Amino-5-chloro-*N*-methylbenzamide (11).—To a solution of methylamine hydrochloride (6.7 g, 0.1 mol) in 100 ml of 1 *N* sodium hydroxide was added 6-chloroisatoic anhydride (7.9 g, 40 mol), and the mixture was stirred and heated under reflux for 0.5 hr. On cooling 11 (5.2 g, 70%), mp 131–133°, separated. Recrystallization from water gave colorless needles, mp 133–134°.

Anal. Calcd for $C_8H_9ClN_2O$: C, 52.04; H, 4.91. Found: C, 51.85; H, 5.00.

6-Chloro-2-chloromethyl-1,2-dihydro-2,3-dimethyl-4(3*H*)-quinazolone (12).—A mixture of 5-chloro-2-amino-*N*-methylbenzamide 11 (67.0 g, 0.363 mol), 2-chloropropanone (70.6 g, 0.76 mol), and benzene (1.2 l.) was stirred under reflux under a Dean-Stark trap for 4 hr. The reaction mixture was concentrated to dryness *in vacuo* and the residue triturated with ethyl acetate–hexane to give 12 as tan prisms, mp 186–192° (84.4 g, 89.8%). An analytical sample was obtained as colorless prisms after three recrystallizations from ethyl acetate: mp 198–200°; ir (KBr) 1635 cm^{-1} (CO); uv max 225 mμ (ε 32,000), 243 (sh) (12,000), 257 (7500), and 353 (3000).

Anal. Calcd for $C_{11}H_{12}Cl_2N_2O$: C, 50.98; H, 4.67. Found: C, 51.13; H, 5.05.

7-Chloro-1,2-dihydro-3-methylene-4-methyl-5*H*-1,4-benzodiazepin-5-one (14).—Potassium *tert*-butoxide (11.2 g, 0.1 mol) was added to a cooled (10–15°) solution of 6-chloro-2-chloromethyl-1,2-dihydro-2,3-methyl-4(3*H*)-quinazolone (12) (25.9 g, 0.1 mol) in tetrahydrofuran (600 ml) with stirring. The reaction mixture was stirred at room temperature for 4.5 hr and filtered through a bed of Celite, the clear filtrate concentrated to dryness *in vacuo*, and the residue crystallized from ethyl acetate–benzene to give 14 as off-white needles, mp 145–155° (15.5 g, 69.7%). An analytical sample was obtained as off-white needles after four recrystallizations from 2-propanol: mp 162.5–165°; ir ($CHCl_3$) 1620, 1600, and 1500 cm^{-1}; uv max 228 mμ (ε 21,000), 250 (18,000) and 357 (3500); nmr (DMSO) δ 3.23 (s, 3, NCH_3), 3.81 (d, 2, NCH_2), 4.67 (s, 1, C=CH_2), and 4.74 ppm (s, 1, C=CH_2).

Anal. Calcd for $C_{11}H_{11}ClN_2O$: C, 59.34; H, 4.98. Found: C, 59.67; H, 4.78.

7-Chloro-1,2,3,4-tetrahydro-3,4-methyl-5*H*-1,4-benzodiazepin-5-one (15).—Potassium *tert*-butoxide (33.6 g, 0.3 mol) was added to a cold solution (10–15°) of 6-chloro-2-chloromethyl-1,2-dihydro-2,3-dimethyl-4(3*H*)-quinazoline (12) (77.7 g, 0.3 mol) in tetrahydrofuran (1.6 l.) with stirring. After stirring overnight at room temperature, the reaction mixture was filtered through a bed of Celite.

The clear filtrate was hydrogenated at room temperature and atmospheric pressure in the presence of platinum oxide (4.0 g, 0.0176 mol). After 6 hr, 6.372 l. (0.2844 mol) of hydrogen had been absorbed and the uptake had stopped. The catalyst was filtered and the filtrate concentrated to dryness *in vacuo*. The residue was crystallized from ethanol to yield off-white needles, mp 165–178° (41.0 g, 60.9%). An analytical sample was obtained as colorless needles after four recrystallizations from ethanol: mp 190–192°; ir ($CHCl_3$) 1625 cm^{-1} (CO); nmr (DMSO) δ 1.1 ppm (d, J = 7 Hz, CH_3).

Anal. Calcd for $C_{11}H_{13}ClN_2O$: C, 58.80; H, 5.83. Found: C, 59.26; H, 6.01.

5-Chloro-2-acetonylamino-*N*-methylbenzamide (13). A. From 14.—7-Chloro-1,2-dihydro-3-methylene-4-methyl-5*H*-1,4-benzodiazepin-5-one (14) (5.0 g, 0.0225 mol) was dissolved in concentrated hydrochloric acid (75 ml). The solution was stirred at room temperature overnight, neutralized with 50%

aqueous sodium hydroxide, and diluted with water (3 vol) to give off-white needles, mp 164–167° (5 g, 92.6%) of **13**. An analytical sample was obtained as colorless needles after two recrystallizations from ethanol: mp 167–168°; ir ($CHCl_3$) 1730, 1625, 1520 cm^{-1}; uv max 260 mμ (ε 15,500) and 349 (4500).

Anal. Calcd for $C_{11}H_{13}ClN_2O_2$: C, 54.89; H, 5.44. Found: C, 54.89; H, 5.54.

B. From 11.—A mixture of 5-chloro-2-amino-*N*-methylbenzamide **11** (22 g, 0.119 mol), 2-chloropropanone (12.2 g, 0.132 mol), calcium carbonate (8.3 g, 0.083 mol), and water (200 ml) was stirred under reflux for 4 hr. After cooling to room temperature, the precipitated solids were filtered and recrystallized from ethanol to give off-white plates of **13**, mp 164–168° (17.2 g, 59.5%). The infrared spectrum was superimposable with that of the sample from method A.

2-Chloromethyl-1,2-dihydro-1,2-dimethyl-4(3*H*)-quinazolone (17).—A mixture of 2-methylaminobenzamide (**16**) (38 g, 0.253 mol), 2-chloropropanone (46.7 g, 0.506 mol), *p*-toluenesulfonic acid (1 g), and benzene (1.5 l.) was stirred under reflux overnight; the water produced was collected with a Dean-Stark trap. The reation mixture was chilled to 10° and the crystals filtered to give off-white needles of **17**, mp 165–170° (55 g, 96.8%). An analytical sample was obtained as colorless needles after three recrystallizations from ethyl acetate: mp 168–169.5°; ir ($CHCl_3$) 1675, and 1615 cm^{-1}; uv max 223 mμ (ε 36,000), 255 (5000), and 345 (3000).

Anal. Calcd for $C_{11}H_{13}ClN_2O$: C, 58.80; H, 5.83. Found: C, 59.09; H, 5.83.

2-Methylamino-*N*-acetonylbenzamide (18).—Potassium *tert*-butoxide (33.6 g, 0.3 mol) was added to a cold (10–15°) solution of 2-chloromethyl-1,2-dihydro-1,2-dimethyl-4(3*H*)-quinazolone (**17**) (67.3 g, 0.3 mol) in tetrahydrofuran (1.2 l.) with stirring. The reaction mixture was stirred at room temperature for 4.5 hr and filtered through a bed of Celite; the clear filtrate was concentrated to dryness *in vacuo*. The residue was stirred with water (1 l.) on the steam bath for 1 hr. The mixture was cooled to room temperature, diluted with water, and extracted with methylene chloride in four portions. The methylene chloride extracts were combined, dried over sodium sulfate, filtered, and concentrated to dryness *in vacuo*. The residue was crystallized from benzene–hexane to give **18**, mp 69–73° (43.4 g, 70.2%). An analytical sample was obtained as colorless prisms after four recrystallizations from benzene–hexane: mp 72–73°; ir ($CHCl_3$) 1730 and 1645 cm^{-1}; uv max 256 mμ (ε 11,000) and 345 (5000).

Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84. Found: C, 64.21; H, 6.50.

1,2-Dihydro-2-methylene-1-methyl-5*H*-1,4-benzodiazepin-5-one (19).—Potassium *tert*-butoxide (2.24 g, 0.02 mol) was added to a solution of 2-chloromethyl-1,2-dihydro-1,2-dimethyl-4(3*H*)-quinazolone (**17**) (4.49 g, 0.02 mol) in tetrahydrofuran (150 ml) at room temperature with stirring. The reaction mixture was stirred at room temperature for 4.5 hr and filtered through a bed of Celite; the clear filtrate was concentrated to dryness *in vacuo*. The residue was crystallized from benzene–hexane to give **19** as colorless plates, mp 120–129° (1.8 g, 47.9%). An analytical sample was obtained as colorless plates after three recrystallizations from benzene–hexane: mp 127–129°; ir ($CHCl_3$) 1665 cm^{-1}; uv max 240 mμ (sh) (ε 12,000), 260 (sh) (8000), 278 (4400), and 340 (5400); nmr (DMSO) δ 3.03 s, 3, NCH_3), 3.69 (d → s, 2, J = 6 Hz, $NHCH_2$), 3.76 (s, 1, $C{=}CH_2$), and 3.91 ppm (s, 1, $C{=}CH_2$).

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43. Found: C, 70.03; H, 6.69.

1,2,3,4-Tetrahydro-1,2-dimethyl-5*H*-1,4-benzodiazepin-5-one (20).—Potassium *tert*-butoxide (33.6 g, 0.3 mol) was added to a cold (10–15°) solution of 2-chloromethyl-1,2-dihydro-1,2-dimethyl-4(3*H*)-quinazolone (**17**) (67.3 g, 0.3 mol) in tetrahydrofuran (1.2 l.) with stirring. The reaction mixture was stirred at room temperature overnight and filtered through a bed of Celite.

The clear filtrate was hydrogenated at room temperature and atmospheric pressure in the presence of platinum oxide (4 g, 0.0176 mol). After 1.25 hr, 5.4 l. (0.241 mol) of hydrogen had been absorbed and the uptake had stopped. The catalyst was filtered off and the filtrate concentrated to dryness *in vacuo*. The residue was crystallized from ethyl acetate to yield **20**, mp 165–170° (26 g, 45.6%). An analytical sample was obtained as colorless prisms after three recrystallizations from ethyl acetate: mp 170–172.5°; ir ($CHCl_3$) 1660 cm^{-1}; uv max 262 mμ (ε 6000) and 322 (2000); nmr (DMSO) δ 0.97 (d, 3, J = 6 Hz, $CHCH_3$) and 2.79 ppm (s, 3, NCH_3).

Anal. Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42. Found: C, 69.36; H, 7.29.

2-Dichloromethyl-1,2-dihydro-2-methyl-4(3*H*)-quinazolinone (21).—A mixture of anthranilamide (13.6 g, 0.1 mol), 1,1-dichloro-2-propanone, (20 g, 0.158 mol), *p*-toluene sulfonic acid (1 g), and benzene (500 ml) was stirred and heated under reflux with azeotropic removal of water for 17.5 hr. At this time 2 ml of water had been collected. The reaction mixture was cooled and concentrated to dryness *in vacuo* to give 25 g of residue. This residue was dissolved in ethyl acetate and filtered through alumina (600 g). The filtrate was concentrated to dryness *in vacuo* and the residue recrystallized from ethyl acetate–hexane to give **21** (18.5 g, 75%), mp 178–184°. Recrystallization from ethyl acetate gave colorless prisms: mp 184–187° dec; ir ($CHCl_3$) 1680 cm^{-1}; uv max 222 mμ (ε 35,000), 250 (5000), and 340 (3000).

Anal. Calcd for $C_{10}H_{10}Cl_2N_2O$: C, 49.00; H, 4.11. Found: C, 49.02; H, 3.99.

1,2,3,4-Tetrahydro-2,3-dimethoxy-3-methyl-5*H*-1,4-benzodiazepin-5-one (22).[7]—A mixture of 2-dichloromethyl-1,2-dihydro-2-methyl-4(3*H*)-quinazolinone (**21**) (4.9 g, 20 mmol), methanol (100 ml), and sodium methoxide (4.32 g, 80 mmol) was heated under reflux for 2.5 hr. The reaction mixture was then cooled and concentrated to dryness. The residue was extracted with boiling ethyl acetate (200 ml); 1.5 g of product was deposited, mp 179–183° dec, on cooling. A further 2.3 g of product, mp 165–170° dec, was obtained on concentration of the ethyl acetate. Recrystallization from methanol gave colorless needles: mp 153–156° dec; ir ($CHCl_3$) 1640 cm^{-1}; uv max 220 mμ (ε 30,000), 250 (10,000), and 339 (5000); nmr (DMSO) δ 1.47 (s, 3, CCH_3), 3.04 (s, 3, OCH_3), 3.25 (s, 3, OCH_3), and 4.23 (d, 1, J = 7 Hz, CH).

Anal. Calcd for $C_{12}H_{16}N_2O_3$: C, 60.99; H, 6.82. Found: C, 61.08; H, 6.97.

Reduction of 22 to 9.—A solution of **22** (2.36 g, 10 mmol) in dry tetrahydrofuran (100 ml) was added to a suspension of lithium aluminum hydride (1 g, 26.4 mmol) in dry tetrahydrofuran (200 ml). The mixture was stirred and heated under reflux for 2.6 hr. Excess lithium aluminum hydride was destroyed by addition of ethyl acetate and ethanol. The mixture was then diluted with water, filtered through Celite, and extracted with methylene chloride in three portions. The extracts were combined, dried over sodium sulfate, and concentrated *in vacuo* to give 1.2 g of crude product, mp 205–215°. Recrystallization from ethanol gave pure **9**, mp 213–216°, identified by mixture melting point and infrared spectra.

2-Acetoxy-1,2,3,4-tetrahydro-3-methoxy-3-methyl-5*H*-1,4-benzodiazepin-5-one (23).[7]—A mixture of **22** (47.6 g, 0.2 mol), sodium acetate (32.8 g, 0.4 mol), and acetic acid (800 ml) was heated on the steam bath for 10 min, cooled, and concentrated *in vacuo*. The residue was partitioned between methylene chloride and water. The aqueous phase was washed with more methylene chloride in three portions. The methylene chloride extracts were combined, washed with 10% sodium bicarbonate solution and with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was crystallized from ethyl acetate to give **23** (22 g), mp 171–175°. The mother liquor was concentrated to dryness, dissolved in tetrahydrofuran, and filtered through a plug of alumina. The eluate was concentrated *in vacuo*, and the residue was crystallized from ethyl acetate to give a second crop of 6.5 g of **23**. The two crops were combined and recrystallized from ethyl acetate to give **23** (21 g, 40%), mp 179–182°. Further recrystallization from ethyl acetate gave off-white prisms: mp 180–183°; ir ($CHCl_3$) 1745 and 1670 cm^{-1}; uv max 223 mμ (ε 34,000), 250 (5000), and 344 (3300); nmr (DMSO) δ 1.40 (s, 3, $C{=}CH_3$), 2.02 (s, 3, $COCH_3$), 3.33 (s, 3, OCH_3), and 5.58 ppm (s, 1, CH).

Anal. Calcd for $C_{13}H_{16}N_2O_4$: C, 59.07; H, 6.11. Found: C, 59.29; H, 6.38.

2,2-Bis(chloromethyl)-1,2-dihydro-4(3*H*)-quinazolone (24).—A mixture of anthranilamide (13.6 g, 0.1 mol), 1,3-dichloro-2-propanone (19.1 g, 0.15 mol), and benzene (250 ml) was stirred and heated under reflux with azeotropic removal of water for 17 hr. The reaction mixture was then concentrated to dryness *in vacuo*, and the residue was crystallized from ether and washed with methanol to give **24** (16.4 g, 67%), mp 180–186°. Recrystal-

(7) The stereochemistry of this compound was not established.

lization from ethyl acetate gave **24** as off-white needles: mp 186–188°; ir ($CHCl_3$) 1650 cm^{-1}.

Anal. Calcd for $C_{10}H_{10}Cl_2N_2O$: C, 49.00; H, 4.11. Found: C, 49.21; H, 4.23.

3-Chloromethylene-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (25).—A solution of **24** (15 g, 61.2 mmol) in dry tetrahydrofuran (350 ml) was cooled in a Dry Ice–acetone bath. To the cold solution was added cautiously potassium *tert*-butoxide (6.7 g, 60 mmol), and the cooling bath was removed. The reaction mixture was then stirred for 17 hr and filtered through Celite. The residue left on concentrating the solution *in vacuo* was crystallized from ether–hexane to give 11 g of tacky solid. Recrystallization from ethyl acetate gave 7.7 g (60%) of **25**, mp 101–103° dec. Careful recrystallization from ethyl acetate gave **25** as off-white prisms: mp 107–108° dec; ir (KBr) 1610 cm^{-1}; nmr (DMSO) δ 3.85 (d, 2, J = 5 Hz, CH_2), 5.67 (s, 1, =CH), 7.00 (t, 1, J = 4 Hz, NH), and 8.51 ppm (s, 1, NH).

Anal. Calcd for $C_{10}H_9ClN_2O$: C, 57.56; H, 4.35. Found: C, 57.64; H, 4.20.

3-Chloromethyl-1,2,3,4-tetrahydro-5*H*-1,4-benzodiazepin-5-one (27).—A solution of **25** (23.5 g, 0.113 mol) in methanol (350 ml) was cooled in an ice bath and treated with tetramethylammonium borohydride (23.5 g, 0.258 mol). The mixture was removed from the ice bath and allowed to stand at room temperature for 20 hr. It was then diluted with several volumes of water, neutralized with glacial acetic acid, and cooled in an ice bath to give **26** (20.1 g, 85%), mp 177–184°. Recrystallization from ethanol gave colorless needles: mp 179–181°; ir ($CHCl_3$) 1635 cm^{-1}; uv max 223 mμ (ϵ 28,000), 250 (7600), and 337 (4200).

Anal. Calcd for $C_{10}H_{11}ClN_2O$: C, 57.02· H, 5.26. Found: C, 56.93 H, 5.15.

Reduction of 25 to 9.—To a solution of **25** (8.35 g) in diglyme (100 ml) which had been cooled to 10° was added sodium borohydride (8.35 g). The reaction mixture was allowed to stand at room temperature overnight, neutralized with acetic acid, diluted with water, and extracted with methylene chloride in four portions. The methylene chloride extracts were combined, dried over sodium sulfate, and concentrated *in vacuo*. The residue was crystallized from ethyl acetate to give crude **9** (5.2 g), mp 195–205°. Recrystallization from ethanol gave colorless plates, mp 210–215°, which had an infrared spectrum identical with that of authentic material.

1,2,3,4-Tetrahydro-3-piperidinomethyl-5*H*-1,4-benzodiazepin-5-one (26a).—A solution of **27** (2.1 g) in piperidine (100 ml) was heated under reflux for 5 hr and cooled. The piperidine hydrochloride was filtered, and the filtrate concentrated to dryness. Crystallization from ethanol of the residue left on evaporation of the solvent *in vacuo* gave **26a** (2 g), mp 174–176°. Recrystallization from ethanol gave colorless plates: mp 175–177° ir ($CHCl_3$) 1630 cm^{-1}.

Anal. Calcd for $C_{15}H_{21}N_3O$: C, 69.46 H, 8.16. Found: C, 69.28; H, 8.48.

1,2,3,4-Tetrahydro-3-*n*-butylaminomethyl-5*H*-1,4-benzodiazepin-5-one (26b).—A solution of **27** (2.1 g, 10 mmol) in *n*-butylamine (100 ml) was heated under reflux for 24 hr and then allowed to stand at room temperature for 24 hr. The reaction mixture was evaporated to dryness *in vacuo*. The residue was partitioned between water and methylene chloride, and the aqueous phase was washed with methylene chloride in three portions. The combined methylene chloride extracts were washed with 10% sodium bicarbonate and then with brine, dried over sodium sulfate, and concentrated *in vacuo* to leave a yellow residue which gave 1.7 g of **26b**, mp 135–147°, on crystallization from ethyl acetate–hexane. Recrystallization from ethyl acetate gave colorless lozenges: mp 145–147°; ir ($CHCl_3$) 1625 cm^{-1}.

Anal. Calcd for $C_{14}H_{21}N_3O$: C, 67.98; H, 8.56. Found: C, 68.36; H, 8.20.

1,2,3,4-Tetrahydro-3-morpholinomethyl-5*H*-1,4-benzodiazepin-5-one (26c).—A solution of **27** (2.1 g) in morpholine (50 ml) was heated under reflux overnight, and the reaction mixture was worked up as for the reaction with *n*-butylamine. This procedure gave crude **26c** (1.8 g), mp 145–150°. Recrystallization from ethyl acetate gave **26c** as off-white plates: mp 151–152.5°; ir ($CHCl_3$) 1630 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}N_3O_2$: C, 64.34; H, 7.33. Found: C, 64.47; H, 7.15.

Registry No.—**5**, 27545-02-4; **6**, 27545-03-5; **7**, 27610-05-5; **8**, 27545-04-6; **9**, 27545-05-7; **10**, 27545-06-8; **11**, 19178-37-1; **12**, 27545-08-10; **13**, 27545-09-1; **14**, 27545-10-4; **15**, 27545-15-9; **17**, 27545-16-0; **18**, 27545-17-1; **19**, 27610-13-5; **20**, 27545-18-2; **21**, 27545-19-3; **22**, 27545-20-6; **23**, 27545-21-7; **24**, 27545-22-8; **25**, 27545-23-9; **26a**, 27537-82-2; **26b**, 27537-83-3; **26c**, 27537-84-4; **27**, 27537-85-5.

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3-Amino-3,4-dihydroquinazolines[1]

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The reaction of hydrazine with the 2′-benzoyl-4′-chloroanilides **2** and **3** has been shown to yield the 3-amino-6-chloro-3,4-dihydro-4-hydroxy-4-phenylquinazolines **5** and **6**. Chemical transformations of these compounds to give both cyclic and ring-opened products are discussed.

Our interest in the reaction of amines with amides to give amidines[3] led us to investigate the reaction of hydrazine with amides. The *o*-benzoylanilides chosen for this study contained both amide and ketone functions and were expected to yield heterocyclic products on treatment with hydrazine.

Thus, 2′-benzoyl-4′-chloroformanilide (*2*) [prepared by formylation of the corresponding aminochlorobenzophenone **1** (Scheme I)] gave, on treatment with a 50% excess of hydrazine, a condensation product which was shown by elemental and mass spectral analyses to have lost only one molecule of water. Furthermore, the product did not retain the amide carbonyl group as evidenced by the ir spectrum. Of the possible structures **5**, **7**, **8**, and **9**, the quinazoline **5** seemed most reasonable on chemical and spectral grounds. Structure **7** was rejected since such a carbinolamine would be expected to undergo ready, if not spontaneous, dehydration. Attempts to dehydrate the product led only to a dimer of unknown structure (M^+ at m/e 510), and in no instance were we able to detect a dehydrated monomer. The mass spectral fragmentation pattern[1] of the product was

(1) A part of this work has been reported in preliminary form: M. E. Derieg, J. Blount, R. I. Fryer, and S. S. Hillery, *Tetrahedron Lett.*, 3869 (1970).

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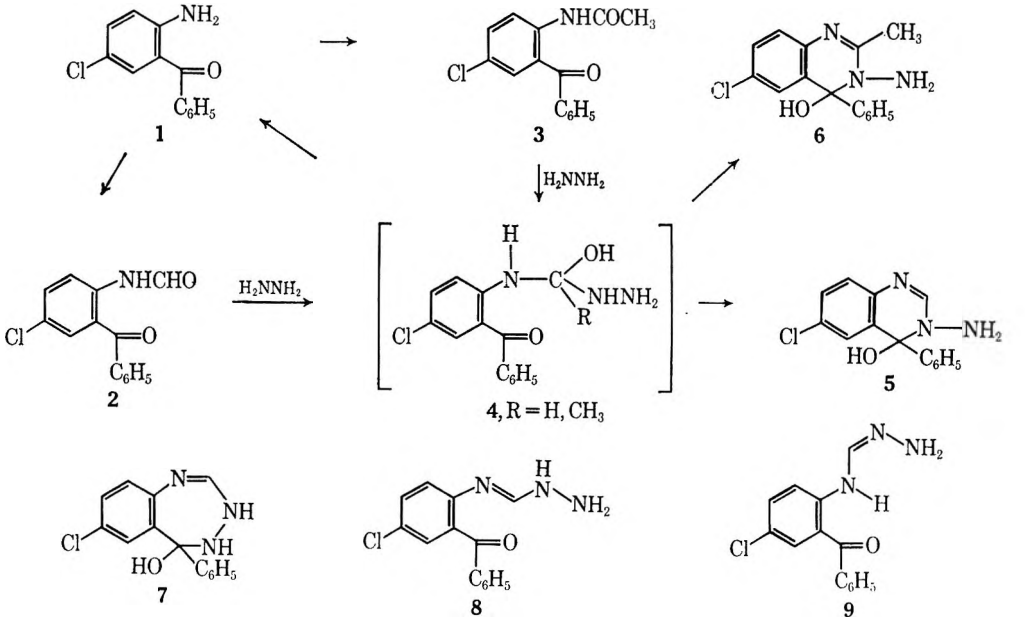
(3) M. E. Derieg, R. I. Fryer, R. M. Schweininger, and L. H. Sternbach, *J. Med. Chem.*, **11**, 912 (1968).

SCHEME I



incompatible with the open structures **8** and **9** but was quite consistent with that anticipated for the aminoquinazoline structure **5**.

Recently a publication[4] describing the use of diethylmalonate as a leaving group reported that the product of the reaction of hydrazine with 2-(2′,2′-biscarbethoxyvinylamino)-5-chlorobenzophenone was 5-hydroxy-5-phenyl-1,3,4-3*H*-4,5-dihydrobenzotriazepine (**7**).[5] The physical properties of the product were described, the major ir absorptions were presented, and a mechanism was suggested.

When the description of the compound reputed to be **7** was published, the melting point and ir spectral data were observed to be identical with that of the compound to which we had attributed structure **5**. Furthermore, both **5** and the compound purported to be **7** afforded a triacetylated product **25** which exhibited the same ir spectra and melting point.[4] This led us to conclude that the initial condensation products as well as the triacetates were in fact identical. Since an argument defending the assignment of structure **7** had been presented[6] and since the chemical and conventional spectral evidence allowed us little more than a rebuttal in support of structure **5**, X-ray analyses were performed.[1] The structures were thus defined as those depicted by **5** and **25**.

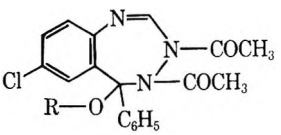
We next examined the products obtained by the treatment of **3**[7] with 1.5 equiv of hydrazine. Under the same conditions which had afforded a 92% yield of **5**, an intractable mixture of compounds **1** and **3** together with a new compound **6** was observed. However, when **3** was warmed in an excess of hydrazine, **6** was isolated in high yield. The ir and mass spectra[8] of **6** were similar to those of **5** and thus the assignment of structure **6** was made by analogy.

It was interesting to note that, in the formation of both **5** and **6**, 2-amino-5-chlorobenzophenone (**1**) was a minor by-product. In no case was the hydrazone of **1** observed nor were the hydrazones of compounds **2** and **3** detected. It thus seems probable that the initial attack of hydrazine occurred at the amide carbonyl of compounds **2** and **3** giving an intermediate of type **4** which could then dehydrate and cyclize to give compounds **5** and **6**, respectively. Podesva, *et al.*, encumbered by the incorrect assignment of structure **7** for compound **5**,[4] had postulated a mechanism for the attack of hydrazine on 2-(2′,2′-biscarbethoxyvinylamino)-5-chlorobenzophenone (**10**). They visualized the attack of hydrazine at the benzophenone carbonyl to yield a carbinol hydrazine intermediate. Since substituted methylene diethylmalonates are known to undergo the addition of hydrazine under these conditions and to subsequently expel diethylmalonate forming the hydrazone,[9] and since we have observed that the reaction of hydrazine with the carbonyl function of 2-aminobenzophenones under the conditions used by Podesva proceeds very slowly, we envisage the most probable mechanism to be the following.

(4) C. Podesva, G. Kohan, and K. Vagi, *Can. J. Chem.*, **47**, 489 (1969).

(5) The 1,3,4-benzotriazepine ring system is described in the literature. See, for example, O. Hromatka, F. Krenmüller, and M. Knollmüller, *Monatsh. Chem.*, **100**, 934 (1969), and references cited therein.

(6) Podesva, *et al.* (see ref 4), argued that solvolysis of the di- and triacetates, assigned by them structures A and B, to give *N,N′*-diacetylhydrazine and 6-chloro-4-phenylquinazoline clearly established those assignments. This is a tenuous argument. The *N,N*-diacetylhydrazone of



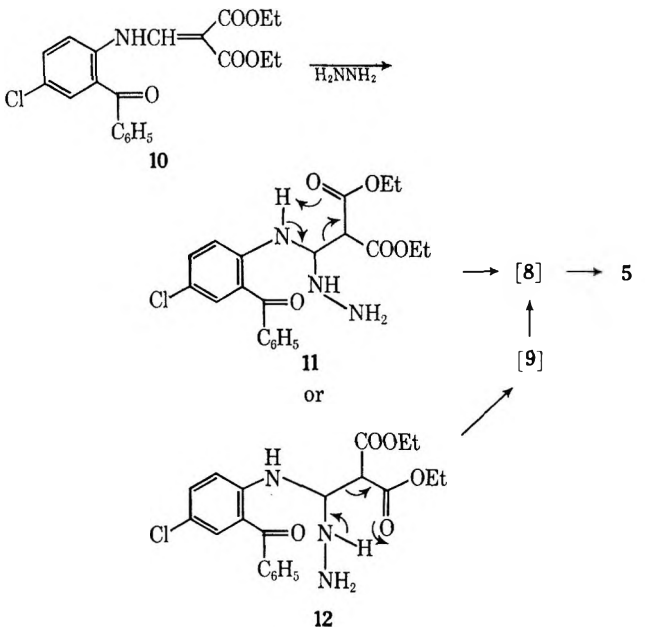
A, R = H
B, R = $COCH_3$

acetone is known to yield *N,N′*-diacetylhydrazine on hydrolysis: see R. A. Turner, *J. Amer. Chem. Soc.*, **69**, 875 (1947); M. H. Krackov and B. E. Christensen, *J. Org. Chem.*, **28**, 2677 (1963); H. Fever and J. D. Asunskis, *ibid.*, **27**, 4684 (1962). Thus, *N,N′*-diacetylhydrazine would be an explicable if not anticipated product of the *N,N*-diacetyl derivatives of **5**, **7**, **8**, and **9** as well as the *N,N*-diacetylhydrazone of **2**.

(7) F. D. Chattaway, *J. Chem. Soc.*, **85**, 344 (1904).

(8) Like compound **5**, compound **6** fragments in the mass spectrometer by way of the appropriate quinazoline (mol wt 254). The major ions are *m/e* 287, 254, 253, and 219.

(9) W. Wislicenus, *Justus Liebigs Ann. Chem.*, **279**, 23 (1894).



The cyclic structure of **5** in the crystalline state is now clearly established,[1] and, in the environment of the mass spectrometer, the presence of the cyclic species **5** and **6** is evident. Tautomerism in solution (*e.g.*, **5** ⇌ **8** ⇌ **9**) seems apparent from the isolation of both cyclic and noncyclic derivatives of compounds **5** and **6**.

When **6** was treated with hydrogen chloride in refluxing methanol, a new hydrochloride was obtained (Scheme II). The uv spectrum was only slightly changed from that of the hydrochloride of **6** and the weak ir absorption at 1650 cm^{-1} (C=N) was retained. Elemental analysis indicated that methylation had occurred, and methoxyl analysis showed that the product was an ether. Accordingly, the structure assigned was that of the expected carbinol ether amine **13**.

The reaction of *N*-amino compounds with nitrous acid is known to proceed *via* N–N cleavage.[10] Thus, the treatment of **6** with nitrous acid would be expected to lead to a 4-hydroxy-3,4-dihydroquinazoline intermediate which would then readily dehydrate to give the known quinazoline **15**.[11] When, in fact, **6** was treated with sodium nitrite in aqueous acetic acid, compound **15** was isolated together with the by-product **17**. The by-product demonstrated a strong ir absorption at 1675 cm^{-1} and had a molecular weight of 298 (mass spectrum). The elemental composition and spectral data suggested the tetrazolobenzophenone, structure **17**. Treatment of **17** with aqueous sodium hydroxide effected dehydration and gave compound **20**.[12] The alternate synthesis of **20** from the known dichloroquinoline **18**[13] confirmed the structural assignment.

The catalytic hydrogenolysis of carbinolamines is known to afford the corresponding amino derivatives.[14] Treatment of a solution of **6** in acetic acid with hydrogen over a platinum catalyst in the presence of hydrogen chloride gave the expected product **14**. Compound **14** was then treated with nitrous acid to give a product which was assigned structure **16**. This structural assignment was corroborated by the hydrogenation of **15** to give a compound identical in all respects with **16**.

The reactions of compound **5** also gave products derived from both open-chain and quinazoline forms. When **5** was treated with an excess of acetone at reflux, a compound was obtained to which structure **21** was assigned (Scheme III). This structural assignment was based largely on the mass spectral fragmentation pattern which exhibited ions characteristic of the aminobenzophenones,[15] rather than that of the quinazolines. Although the infrared absorption at 1620 cm^{-1} ($CHCl_3$) suggested that the benzophenone carbonyl was influenced by intramolecular hydrogen bonding[16] and that **22** might then best represent the structure of the product, the presence of an excess of triethylamine failed to effect a shift.[17] Thus, we believe that tautomer **21** is the more likely of the two possible structures.

Acetylation of **5** with acetic anhydride in pyridine gave a mixture of acetates in which the previously mentioned triacetate **25** was the major product. Thin layer chromatograms[18] of the reaction mixture indicated the presence of two major by-products. One of these was a diacetate which was much more conveniently prepared by carefully controlling the amount of acetic anhydride in the acetylation mixture. This diacetate exhibited mass spectral character[1] consistent with that of the aminobenzophenones. Upon further acetylation, the diacetate slowly yielded a new triacetate, very similar to, but spectrally nonidentical with, compound **25**. Accordingly, the remaining possible open triacetate structure **24** was assigned and **23** as the structure of the diacetate logically followed.

The remaining by-product of the acetylation of **5** proved to be identical with the compound obtained from the base hydrolysis of **25**. The treatment of compound **25** with methanolic potassium hydroxide gave a monoacetate, the mass spectrum[1] of which clearly indicated the quinazoline structure **26**.[19] The monoacetate **26** readily regenerated **25** under the original acetylation conditions.

Although the slow rate of reaction of acetic anhydride with **23** to give **24** is not surprising, the ease of formation of **25** from **26** under the same conditions merits comment.[20] Of the possible mechanisms[21] which would explain the accelerated formation of the imide **25**, we

(10) E. Fischer, *Justus Liebigs Ann. Chem.*, **199**, 314 (1879).

(11) S. C. Bell and P. H. L. Wei, *J. Org. Chem.*, **30**, 3576 (1965).

(12) The dehydration of *o*-benzoylacetanilides to give quinolones has been reported: R. I. Fryer, B. Brust, and L. H. Sternbach, *J. Chem. Soc.*, 3097, (1964).

(13) A. E. Drukker and C. I. Judd, *J. Heterocycl. Chem.*, **3**, 359 (1966).

(14) W. S. Emerson, *Org. React.*, **4**, 194 (1948).

(15) The mass spectrum of compound **21** was characterized by the following major ions: *m/e* 313, 298, 242, 230, and 105. The ions at *m/e* 242, 230, and 105 are typical of this class of aminobenzophenones.

(16) L. J. Bellamy in "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 144.

(17) N. B. Colthup, L. H. Daly, and S. E. Wiberley in "Introduction to Infrared and Raman Spectroscopy," Academic Press, New York, N. Y., 1964, p 190.

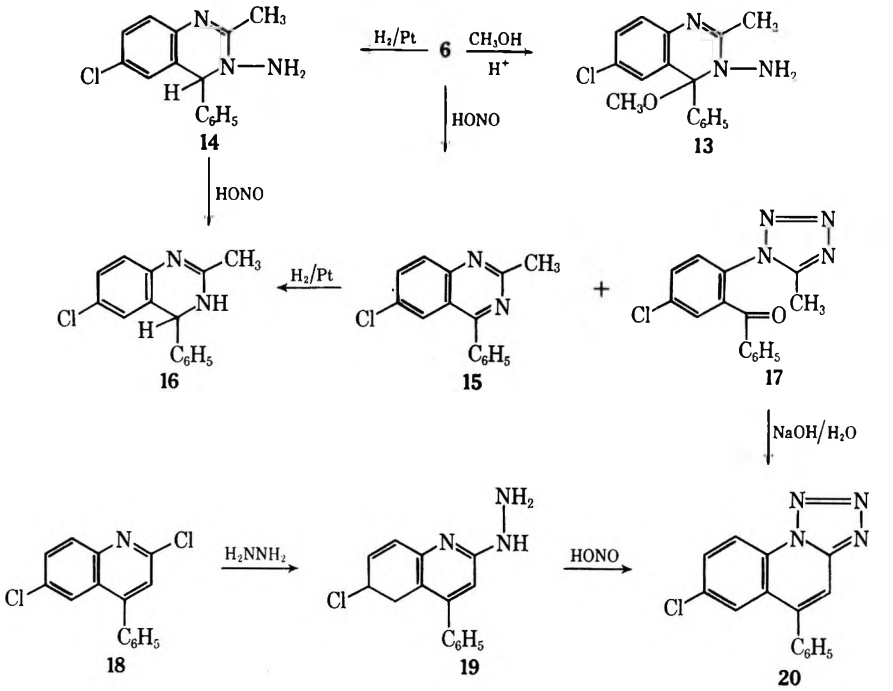
(18) The thin layer chromatograms were prepared as follows. A 1-cc aliquot was removed, mixed with 2 cc of water, and extracted with 1 cc of chloroform, which was washed with water, dried, and applied to a Brinkmann silica plate F 254. The eluent systems were 4:1 and 3:2 hexane–ethyl acetate. Determinations were made by visual comparisons.

(19) The quinazoline products are typified in the mass spectrum by the presence of major fragments at *m/e* 240, 239, and 205. Under these reaction conditions Podesva, *et al.*, reported the isolation of a diacetate.

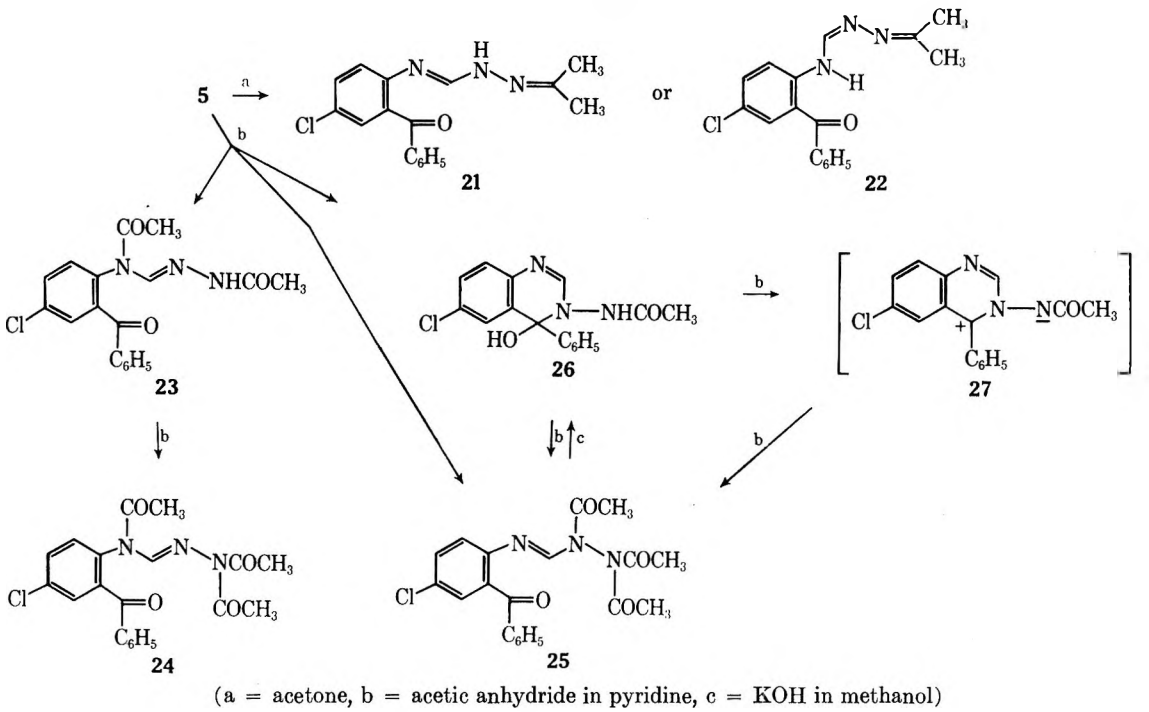
(20) See B. C. Challis and A. R. Butler in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, p 285, and references cited therein for comments on the introduction of a second acyl group on primary amines.

(21) An alternate mechanism was considered which involved the intramolecular attack of the hydroxy group of **26** at the amide carbonyl to yield a 1,3,4-oxadiazole intermediate. This might then be diacetylated and yield **25** by way of **30**.

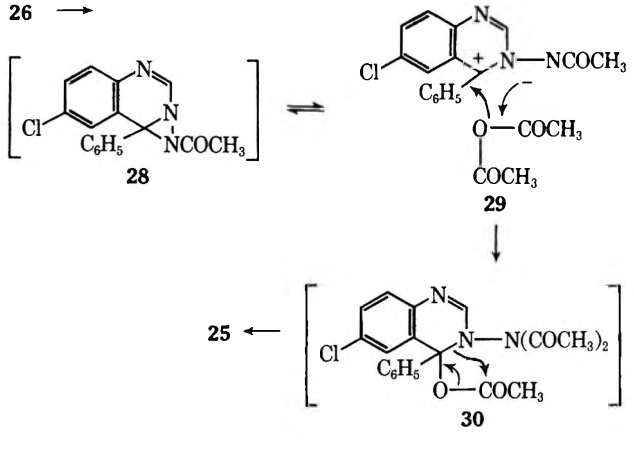
SCHEME II



SCHEME III



(a = acetone, b = acetic anhydride in pyridine, c = KOH in methanol)



favor that shown (28 → 30). In the dehydrating environment of the reaction conditions, the formation of the acetylated diaziridine 28 or its 1,3-dipolar isomer 29 might well result. Either 28 or 29 could react with acetic anhydride to give the triacetate 30, and rearrangement of the sterically crowded 30 to the open product 25 would not be unexpected.

Experimental Section

Melting points were determined microscopically on a hot stage and are corrected. The nmr spectra were determined on a Varian A-60 instrument, the ir spectra were determined on a Cary Model 14 spectrophotometer, and the mass spectra were determined by means of a CEC-21-110B instrument at 70 eV by

direct insertion. Solutions were dried over anhydrous magnesium sulfate. Petroleum ether (bp 30–50°) was used.

2′-Benzoyl-4′-chloroformanilide (2).—A solution of 100 g (0.43 mol) of 2-amino-5-chlorobenzophenone in 500 ml of formic acid (98–100%) was stirred at reflux overnight. The solvent was removed *in vacuo* and the oily residue was crystallized from methylene chloride–hexane to give 103.7 g (92.5%) of crystalline product, mp 85–92°. Recrystallizations from methylene chloride–hexane gave colorless prisms, mp 90–91°.

Anal. Calcd for $C_{14}H_{10}ClNO_2$: C, 64.75; H, 3.88; N, 5.39. Found: C, 64.65; H, 4.17; N, 5.51.

3-Amino-6-chloro-3,4-dihydro-4-hydroxy-4-phenylquinazoline (5).—A mixture of 26 g (0.1 mol) of **2** and 350 ml of ethanol at room temperature was vigorously stirred during the addition of 4.8 g (0.15 mol) of hydrazine. As the exothermic reaction began, solution was effected and the product then precipitated from solution. The reaction mixture was stirred overnight, chilled, and filtered. The precipitate was washed with ethanol and dried to give 25.2 g (92%) of product. Recrystallization from DMF gave colorless prisms: mp 196–198° dec; ir (KBr) 3325, 2780, 2600, 1640, and 1590 cm^{-1}; mass spectrum *m/e* (rel intensity) 273 (15), 254 (90), 240 (64), 239 (100), 205 (99).

Anal. Calcd for $C_{14}H_{12}ClN_3O$: C, 61.43; H, 4.42; N, 15.35. Found: C, 61.73; H, 4.17; N, 15.07.

Dehydration of 3-Amino-6-chloro-3,4-dihydro-4-hydroxy-4-phenylquinazoline (5).—**5** (10 g, 37 mmol) and 350 ml of dry xylene was heated at reflux for 65 hr. The xylene was removed *in vacuo* and the gummy residue was washed with ether, hot DMF, and methanol. The insoluble product, 2.8 g (30%) of orange prisms, mp >350°, was analyzed without further purification: mass spectrum (70 eV) *m/e* (rel intensity) 510 (17), 240 (52), 239 (100), 229 (79), 214 (58), 205 (94); ir (KBr) 1620 cm^{-1}.

Anal. Calcd for $C_{28}H_{20}N_6Cl_2$: C, 65.76; H, 3.94; N, 16.43. Found: C, 66.15; H, 4.06; N, 16.36.

3-Amino-6-chloro-3,4-dihydro-4-hydroxy-2-methyl-4-phenylquinazoline (6).—To 200 ml of 95% hydrazine was added 79 g (0.29 mol) of 2′-benzoyl-4′-chloroacetanilide (**3**). After 1.5 hr, the precipitate was removed by filtration and was washed with water and with ether. Recrystallization from methanol–chloroform gave 53.7 g (64%) of colorless prisms: mp 218–219° dec; ir (KBr) 3325, 2800, 2625, 1630, and 1580 cm^{-1}; mass spectrum *m/e* (rel intensity) 287 (7), 256 (57), 268 (7), 254 (46), 253 (80), 219 (100).

Anal. Calcd for $C_{15}H_{14}ClN_3O$: C, 62.61; H, 4.90; O, 5.56. Found: C, 62.31; H, 5.15; O, 5.72.

Compound **6** formed a salt in aqueous hydrochloric acid, which was recrystallized from aqueous methanol and ether to give colorless prisms, mp 216–220° dec, ir (KBr) 1660 cm^{-1}.

Anal. Calcd for $C_{15}H_{14}ClN_3O \cdot HCl$: C, 55.57; H, 4.66; Cl, 21.87. Found: C, 55.46; H, 4.61; Cl, 21.68.

3-Amino-6-chloro-3,4-dihydro-4-methoxy-2-methyl-4-phenylquinazoline Hydrochloride (13).—A methanolic solution of 8.3 g (29 mmol) of the hydrochloride of **6** was heated at reflux for 5 hr. The solution was concentrated *in vacuo*. Addition of ethereal hydrogen chloride yielded 5 g (58%) of colorless prisms, which after recrystallization from methanol melted at 210–212° dec, ir (KBr) 1650 cm^{-1}.

Anal. Calcd for $C_{16}H_{16}ClN_3O \cdot HCl$: C, 56.81; H, 5.07; Cl, 20.96; OCH_3, 9.18. Found: C, 56.83; H, 5.52; Cl, 20.82; OCH_3, 8.83.

3-Amino-6-chloro-3,4-dihydro-2-methyl-4-phenylquinazoline (14).—A mixture of 6 g (21 mmol) of **6**, 70 ml of acetic acid containing 0.4 g of hydrogen chloride, and 0.15 g of platinum oxide was shaken with hydrogen at room temperature and atmospheric pressure. After 24 hr, a total hydrogen uptake of 800 ml was measured, the catalyst was removed by filtration, and the filtrate was poured over ice and made basic with ammonium hydroxide. The aqueous mixture was extracted with methylene chloride; the extract was washed with water, dried, and concentrated *in vacuo*. Addition of ether gave 3.4 g (56%) of solid which was recrystallized from methylene chloride–ethanol to give colorless prisms: mp 202–207°; uv max (isopropyl alcohol) 227 mμ (ε 16,000), 302 (10,000), and 328 (4600).

Anal. Calcd for $C_{15}H_{14}ClN_3$: C, 66.30; H, 5.19; N, 15.46. Found: C, 66 62; H, 5.02; N, 15.73.

6-Chloro-2-methyl-4-phenylquinazoline (15) and 5-Chloro-2-(5-methyl-1*H*-tetrazol-1-yl)benzophenone (17).—To a solution of 6.34 g (22 mmol) of **6** in 50 ml of acetic acid was added a solution of 1.52 g (22 mmol) of sodium nitrite in 25 ml of water. A mildly exothermic reaction occurred, and after 30 min the reaction mixture was poured into ice and aqueous ammonia. The mixture was extracted with methylene chloride and the extract was washed with water, dried, and concentrated *in vacuo*. Addition of ether and petroleum ether gave 1.6 g (28.5%) of **17** as a crystalline solid which was recrystallized to give colorless prisms: mp 172–174°; ir ($CHCl_3$) 1675 cm^{-1}; uv max (isopropyl alcohol) 253 mμ (ε 18,500), 285 (4000); mass spectrum *m/e* 298, 270, 269, 229, 193, 105.

Anal. Calcd for $C_{16}H_{11}ClN_4O$: C, 60.31; H, 3.71; N, 18.75. Found: C, 60.22; H, 3.55; N, 18.78.

The combined mother liquors were evaporated to dryness *in vacuo* and dissolved in hot petroleum ether, and 0.65 g (10.9%) of **15** crystallized as colorless needles, mp 107–108° (lit.[22] 105–106°).

6-Chloro-3,4-dihydro-2-methyl-4-phenylquinazoline (16). A. From 15.—A solution of 4 g (16 mmol) of **15** in 60 ml of acetic acid was hydrogenated at 25° and 1 atm using 0.1 g of platinum oxide as catalyst. After the uptake of 20 mmol of hydrogen, the mixture was filtered, and the filtrate was poured over ice and made basic with sodium hydroxide. The crystalline precipitate was recrystallized from acetonitrile to give 3.3 g (82%) of colorless plates: mp 211–213°; ir ($CHCl_3$) 1620 cm^{-1}; uv max (isopropyl alcohol) 225 mμ (ε 18,000), 296 (9000), 330 (2000).

Anal. Calcd for $C_{15}H_{13}ClN_2$: C, 70.17; H, 5.10. Found: C, 70.32; H, 5.18.

B. From 14.—To a solution of 0.78 g (3 mmol) of the monohydrochloride of **14** in 25 ml of 2 *N* aqueous hydrochloric acid and 15 ml of acetic acid was carefully added 0.2 g (3 mmol) of sodium nitrite. After 1 hr, the mixture was filtered and the solid was partitioned between 3 *N* sodium hydroxide and ether. The organic phase was separated, washed with water, dried, and concentrated *in vacuo* to a residue which was recrystallized from acetonitrile to give a low yield of product (mp 208–213°) identical with that prepared from **15**.

6-Chloro-2-hydrazino-4-phenylquinoline (19).—A mixture of 4 g (15 mmol) of **18**[13] and 20 ml of hydrazine was heated under reflux for 10 min, cooled, and diluted with water to give 2.2 g (56%) of product, mp 160–163°. Recrystallization from tetrahydrofuran–hexane gave yellow prisms, mp 160–162°.

Anal. Calcd for $C_{15}H_{12}ClN_3$: C, 66.79; H, 4.48; N 15.58. Found: C, 66.79; H, 4.59; N, 15.34.

7-Chloro-5-phenyltetrazolo[1,5-*a*]quinoline (20). From 19.—To a stirred solution of 4 g (15 mmol) of **19** in 75 ml of 50% aqueous acetic acid was added dropwise a solution of 0.98 g (14 mmol) of sodium nitrite in 10 ml of water. The temperature was maintained at 20 ± 5° with an ice bath. The reaction mixture was stirred for 1 hr and filtered, and the solid partitioned between methylene chloride and water. The organic phase was washed with dilute ammonium hydroxide, water, and brine and dried. Evaporation of the solvent *in vacuo* gave 3.14 g (75%) of product, mp 192–196°. Recrystallization from chloroform–ether gave colorless rods, mp 206–209°.

Anal. Calcd for $C_{15}H_9ClN_4$: C, 64.18; H, 3.23; N, 19.96. Found: C, 64.09; H, 3.26; N, 19.96.

From 17.—A solution of 750 mg (2.5 mmol) of **17** in 50 ml of 2 *N* aqueous sodium hydroxide and 50 ml of methanol was heated at the reflux temperature for 15 min. When the solution was chilled, 350 mg (50%) of crystalline product precipitated. Recrystallization from methylene chloride–petroleum ether gave colorless rods, mp 194–195°, identical with **20** prepared from **19**.

5-Chloro-2-(2-isopropylidenehydrazomethyleneamino)benzophenone (21).—A mixture of 5 g (18 mmol) of **5** and 125 ml of acetone was heated at reflux. After 42 hr, the starting material **5** had totally dissolved in the yellow solution. The acetone was removed *in vacuo* and the residue was recrystallized from acetone to give 3.55 g (63%) of yellow crystalline **22**. Recrystallization from acetone gave yellow needles: mp 136–139°; ir (KBr) 1630, 1600 (broad), 1500 cm^{-1}; mass spectrum *m/e* (rel intensity) 313 (16), 300 (37), 298 (100), 242 (21), 230 (25), 105 (21).

Anal. Calcd for $C_{17}H_{16}ClN_3O$: C, 65.07; H, 5.14; N, 13.39. Found: C, 64.92; H, 5.17; N, 13.56.

2′-Benzoyl-4′-chloro-*N*-(2-acetylhydrazono)methylacetanilide (23).—A solution of 27 g (0.1 mol) of **5**, 10.2 g (0.1 mol) of acetic anhydride, and 225 ml of pyridine was stirred overnight at room temperature. The reaction mixture was evaporated *in vacuo* to an oily residue which was partitioned between chloroform and water. The organic layer was washed with 5% sodium bicarbon-

(22) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Amer. Chem. Soc.*, **82**, 475 (1960).

ate, water, 1.5 *N* hydrochloric acid, and again with water. The chloroform solution was dried and concentrated to 21.9 g of an oil which, when treated with ether, yielded 5 g (14%) of pale yellow prisms. Recrystallizations from methylene chloride–hexane gave colorless prisms: mp 164–166°; mass spectrum *m/e* (rel intensity) 357 (5), 315 (12), 273 (42), 242 (50), 231 (100), 230 (69), 105 (50).

Anal. Calcd for $C_{18}H_{16}ClN_3O_3$: C, 60.42; H, 4.51; N, 11.74. Found: C, 60.37; H, 4.60; N, 11.62.

2′-Benzoyl-4′-chloro-*N*-(2,2-diacetylhydrazono)methylacetanilide (24).—A solution of 800 mg (2 mmol) of **23**, 7 ml of acetic anhydride, and 10 ml of pyridine was stirred overnight at room temperature. The reaction mixture was poured over ice and extracted with chloroform. The organic extract was washed with water, dried, and concentrated *in vacuo*. The residue was washed with chloroform leaving 250 mg (44%) of the dimeric orange product from **5** (*vide supra*). The chloroform wash was treated with hexane and yielded 125 mg (14%) of colorless prisms: mp 134–136°; mass spectrum *m/e* (rel intensity) 399 (3), 357 (14), 315 (7), 298 (20), 273 (34), 242 (43), 231 (100), 230 (50), 105 (24).

Anal. Calcd for $C_{20}H_{18}ClN_3O_4$: C, 60.08; H, 4.54; N, 10.51. Found: C, 59.83; H, 4.58; N, 10.50.

5-Chloro-2-(1,2,2-triacetyl-1-hydrazinylmethyleneamino)benzophenone (25).—A mixture of 50 g (0.18 mol) of **5**, 100 ml of pyridine, and 200 ml of acetic anhydride was stirred at room temperature for 41 hr. The volatile materials were removed *in vacuo* leaving an oil which was partitioned between chloroform and water. The organic phase was washed with water, 5% sodium bicarbonate, water, 1.5 *N* hydrochloric acid, and again with water. The chloroform was removed *in vacuo* yielding an oily residue which was crystallized from ethanol to give 37.3 g (51.8%) of colorless crystals, mp 101–104°. Recrystallizations from ethanol gave colorless blocks: mp 105–107°; ir (KBr) 1730, 1672, 1647 cm^{-1}; mass spectrum *m/e* (rel intensity) 399 (18), 357 (22), 315 (29), 298 (57), 273 (76), 242 (86), 231 (100), 230 (80), 105 (55).

Anal. Calcd for $C_{20}H_{18}ClN_3O_4$: C, 60.08; H, 4.54; N, 10.51. Found: C, 60.13; H, 4.46; N, 10.52.

3-Acetamido-6-chloro-3,4-dihydro-4-hydroxy-4-phenylquinazoline (26).—A solution of 10% potassium hydroxide in methanol was added dropwise to a solution of 8 g (20 mmol) of **25** and 20 ml of methanol at 45°.

When the solution had maintained a pH of 10, it was allowed to stand for 30 min and was then diluted with 300 ml of water. The precipitate was removed by filtration, washed with water, and dried at 65–70° *in vacuo* (5 g, 79.3%). Recrystallizations from THF–ether gave colorless prisms: mp 160–162°; ir (KBr) 3240, 1670, 1610 cm^{-1}; nmr (DMSO) 1.60 (s, 3, $NCOCH_3$); mass spectrum *m/e* (rel intensity) 315 (2), 297 (35), 282 (36), 254 (70), 240 (33), 239 (55), 220 (100), 205 (44).

Anal. Calcd for $C_{16}H_{14}ClN_3O$: C, 60.86; H, 4.47; N, 13.31. Found: C, 60.75; H, 4.46; N, 13.19.

Registry No.—**2**, 10352-28-0; **5**, 27610-14-6; **6**, 27537-87-7; **6** HCl, 27537-88-8; **13** HCl, 27537-89-9; **14**, 27537-90-2; **16**, 17433-16-8; **17**, 27537-92-4; **19**, 27537-93-5; **20**, 27537-94-6; **21**, 27537-95-7; **23**, 27537-96-8; **24**, 27537-97-9; **25**, 27537-98-0; **26**, 27537-99-1.

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1,2,4-Triazines. IV. Synthesis and Characterization of 1,2,4-Triazine *N*-Oxides

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The N-oxidation of 1,2,4-triazines affords the 1-oxides when C_3 is either unsubstituted or is substituted by a methoxyl group. It has been shown that N-oxidation of 3-amino-1,2,4-triazines affords the 2-oxides as major products. This is in contrast to some of the reported data which suggested that oxidation of 3-amino-5,6-diphenyl-1,2,4-triazine yields the 1-oxide.

Recent developments of new syntheses of 1,2,4-triazines[1-3] have made this ring system readily available and permit its study in some detail.

We now wish to describe the preparation and structure elucidation of some 1,2,4-triazine *N*-oxides.

Several papers[4-7] have dealt with the N-oxidation of some 3-amino- and 3-methoxy-1,2,4-triazines with alkyl and aryl substituents in the 5 and 5,6 positions of the 1,2,4-triazine ring. The only all-alkyl or all-aryl substituted 1,2,4-triazine that has been N-oxidized is the 3,5,6-triphenyl compound,[8] where the 1-oxide is formed as the major product (33%) and the 2-oxide as the minor one (8%).

The N-oxidation of 1,2,4-triazines can, *a priori*, occur at either N-1, N-2, or N-4. In order to establish the position of N-oxidation one can, in theory, determine the dipole moments of these substances and thus elucidate their structures, or one can examine the differences in proton chemical shifts between the N-oxidized compounds and the appropriate bases themselves.

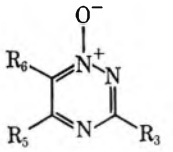
The oxidation with perbenzoic acid of compounds **1a–d** (see Scheme I) afforded mono-*N*-oxides in 15–40% yields after chromatography on neutral grade III alumina.

The mass spectra of these compounds clearly indicate the presence of an *N*-oxide function by the appearance of a P − 16 peak. In addition to this fragmentation process, all compounds (including those with no substituents at C-3) having a methyl or a phenyl group substituted at C-6 give rise to a P − 17 peak which is more abundant than the P − 16 ion. This observation suggests that we are dealing with the 1- rather than the 2-

(1) W. W. Paudler and J. M. Barton, *J. Org. Chem.*, **31**, 1720 (1966).
(2) W. W. Paudler and R. E. Herbener, *J. Heterocycl. Chem.*, **4**, 224 (1967).
(3) W. W. Paudler and T. K. Chen, *ibid.*, **7**, 767 (1970).
(4) T. Sasaki and K. Minamoto, *Chem. Pharm. Bull.*, **12**, 1329 (1964).
(5) T. Sasaki and K. Minamoto, *ibid.*, **13**, 1168 (1965).
(6) T. Sasaki and K. Minamoto, *J. Org. Chem.*, **31**, 3914 (1966).
(7) T. Sasaki and K. Minamoto, *ibid.*, **31**, 3917 (1966); *Chem. Abstr.*, **67**, 3102 (1967).
(8) C. M. Atkinson, D. A. Ibbitson, F. J. Rice, and J. P. B. Sandall, *J. Chem. Soc.*, 4209 (1964).

TABLE I

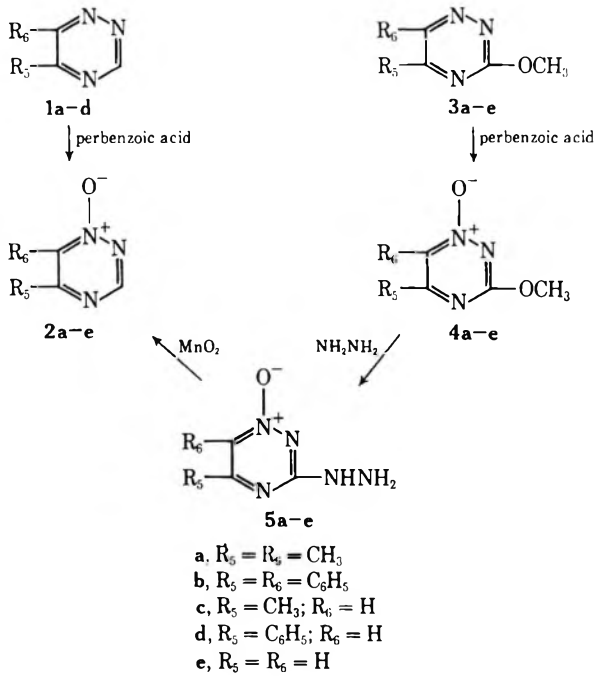
ANALYTICAL DATA FOR SOME 1,2,4-TRIAZINE 1-OXIDES



Pmr Data								Calcd, %			Found, %[b]		
Chemical shifts, τ[a]						Coupling constants, cps							
R_3	R_5	R_6	R_3	R_5	R_6	$J_{R_3R_6}$	$J_{R_5R_6}$	C	H	N	C	H	N
H	H	H	1.0	1.43	1.95[c]	1.8	3.3	37.11	3.09	43.30	37.41	3.20	43.52
OCH_3	H	H	5.94	1.63	2.17		3.3	37.80	3.94	33.07	37.87	3.89	33.04
H	CH_3	H	1.15	7.50	2.05	1.5		43.24	4.50	37.84	43.70	4.50	37.99
H	C_6H_5	H	1.0	1.97 (m)	1.52	1.5		62.43	4.05	24.28	62.19	4.05	23.67
				2.44 (m)									
H	CH_3	CH_3	1.26	7.40	7.51			48.00	5.60	33.60	48.17	5.12	33.85
H	C_6H_5	C_6H_5	1.02	2.68 (*ca.*)	2.68 (*ca.*)			72.79	4.42	16.87	72.85	4.67	17.08
OCH_3	CH_3	H	5.95	7.55	2.25			42.55	4.96	29.79	43.23	4.90	29.79
OCH_3	C_6H_5	H	5.85	1.97 (m)	1.70			59.11	4.43	20.69	58.81	4.60	20.57
				2.43 (m)									
OCH_3	CH_3	CH_3	5.99	7.48	7.60			46.40	5.80	27.10	47.04	5.87	26.48
OCH_3	C_6H_5	C_6H_5	5.86	2.68 (*ca.*)	2.68 (*ca.*)			68.82	4.66	15.05	68.87	4.18	14.96

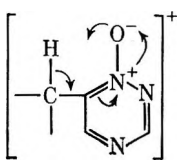
[a] All pmr spectra were obtained as 1% w/v solutions in $CDCl_3$. A Varian HA-100 spectrometer was used. The chemical shifts of the nonoxidized 1,2,4-triazines are reported in ref 3. [b] The mass spectrometric molecular weights of all compounds were obtained with a Hitachi Perkin-Elmer RMU-6E instrument and were found to be in agreement with the theoretical values. Elemental analyses were done by Mrs. P. Jones of this department. [c] The chemical shifts for H-3, H-5, and H-6 in 1,2,4-triazine are 0.12, 1.16, and 0.52, respectively, in $CDCl_3$.

SCHEME I



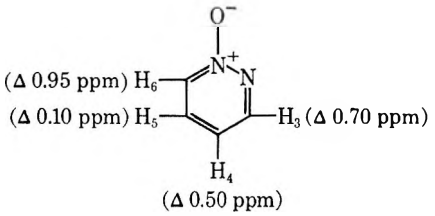
a, $R_5 = R_6 = CH_3$
b, $R_5 = R_6 = C_6H_5$
c, $R_5 = CH_3$; $R_6 = H$
d, $R_5 = C_6H_5$; $R_6 = H$
e, $R_5 = R_6 = H$

or 4-oxides since one can envision a McLafferty-type rearrangement to be operating which involves the following process.[9]

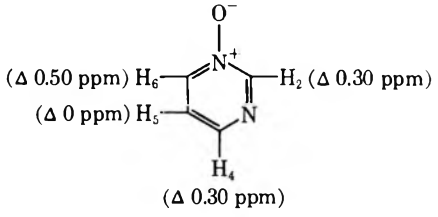


This implication is further supported by an analysis of the pmr spectra (see Table I) of pyrimidine and pyridazine *N*-oxides and a comparison of the proton chemical shift changes that occur in these compounds when they are transformed from their nonoxidized to their N-oxidized forms.

Thus H-3, H-4, H-5, and H-6 in pyridazine 1-oxide experience shielding (Δ) with respect to the corresponding proton chemical shifts in pyridazine itself,[10] by the following amounts.



Similarly, the various protons in pyrimidine *N*-oxides[10,11] are affected as follows.



A comparison of the chemical shift changes of the corresponding protons in the various 3-unsubstituted 1,2,4-triazines, with their counterparts in the *N*-oxides,

(9) T. Sasaki, K. Minamoto, M. Nishikawa, and T. Shima [*Tetrahedron*, **25**, 1021 (1969)] describe the mass spectra of various 3-amino- and 3-alkoxy-1,2,4-triazine 1- and 2-oxides and identify the abundant P − 17 fragment as arising from a McLafferty rearrangement involving the protons on the 3 substituent of the 2-oxide. Our results show that a C-6 substituent can also account for this OH loss in the 1-oxides. Detailed studies of these processes are in progress.

(10) E. Ochiai, "Aromatic Amine Oxides," Elsevier, Amsterdam, Netherands, 1967, p 101 ff.

(11) W. W. Paudler and S. A. Humphrey, *J. Org. Chem.*, submitted for publication.

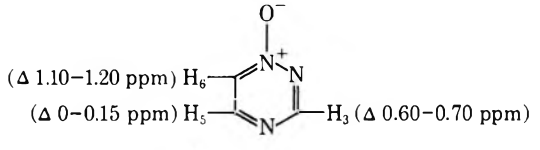
shows that H-3 is shielded by 0.6–0.7 ppm, H-5 by 0.15 ppm, and H-6 by 1.1–1.2 ppm.

If we are dealing with 2-oxides, we should expect, by analogy with H-3 in pyrimidine *N*-oxide, that H-3 be more shielded by about 0.3 ppm in the 1,2,4-triazine *N*-oxide. A similar effect would be anticipated if the 1,2,4-triazines had been oxidized at N-4. An analogous argument can be made for the chemical shift changes experienced by H-5 and H-6 of the 1,2,4-triazines upon N-oxidation.

On the other hand, if we assume that N-oxidation has occurred at N-1, then the similarity in the chemical shift changes at H-3 in 1,2,4-triazine upon oxidation at N-1 and at H-3 in the pyridazine 1-oxide are rather striking. The proton ortho to the *N*-oxide linkage, H-6, is also shielded (1.1–1.2 ppm) to the large extent observed for H-6 (0.95 ppm) in pyridazine 1-oxide.

The rather small change of the chemical shift of H-5 (0.15 ppm) in the 1,2,4-triazine 1-oxides as compared to the corresponding 1,2,4-triazines is also in accord with the small changes observed in the chemical shifts of H-5 in pyridazine (0.1 ppm) and in pyrimidine (0 ppm) upon oxidation at N-1.

Thus the following "composite" picture of the chemical shift changes of the various protons of different 1,2,4-triazines upon oxidation at N-1 can be drawn.



These data clearly establish that we are indeed dealing with 1,2,4-triazine 1-oxides.

Unfortunately, when an attempt was made to N-oxidize 1,2,4-triazine itself, no *N*-oxide could be isolated. This is perhaps not surprising since we have already shown[3] that the 5 position in 1,2,4-triazines is readily involved in covalent hydration in acidic media.

The oxidation of 3-methoxy-1,2,4-triazines (**3a–e**) also afforded the *N*-oxides in satisfactory yields. Since H-3 is no longer available for purposes of pmr analyses in order to establish the site of oxidation, it was necessary to convert those compounds where both C-5 and C-6 are substituted (**4a** and **4b**) into their 3-hydrazino derivatives and oxidize the latter compounds with MnO_2, by the procedure previously described,[3] to the 3-unsubstituted *N*-oxides. When this was done, the resulting compounds proved to be identical with the *N*-oxides obtained from the direct oxidation of the 3-unsubstituted compounds (**1a** and **1b**). Thus N-oxidation of 3-methoxy-5,6-diphenyl- and 3-methoxy-5,6-dimethyl-1,2,4-triazine also occurs at N-1. The 3-methoxy-5,6-diphenyl 1-oxide is identical with the compound described as the 2-oxide by Sasaki and Minamoto.[4]

An analysis of the pmr spectra of compounds **4c**, **4d**, and **4e**, in a manner analogous to that described for the 3-unsubstituted 1,2,4-triazines (**1a–d**) allows one to establish that these compounds also are 1-oxides.

Finally, the elusive parent 1,2,4-triazine 1-oxide itself was obtained by means of oxidation of the 3-hydrazino-1,2,4-triazine 1-oxide (**5e**). The pmr spectrum of this compound (see Table I) is in agreement with its assigned structure.

It has been well established[12,13] that the proton on a carbon atom adjacent to the *N*-oxide linkage is subject to base-catalyzed H → D exchange. When the 5-methyl-1,2,4-triazine 1-oxide was treated with dilute sodium deuterioxide in D_2O, the H-6 proton singlet disappears and the H-3 doublet becomes a singlet. Thus, this chemical evidence further confirms our structure assignments.

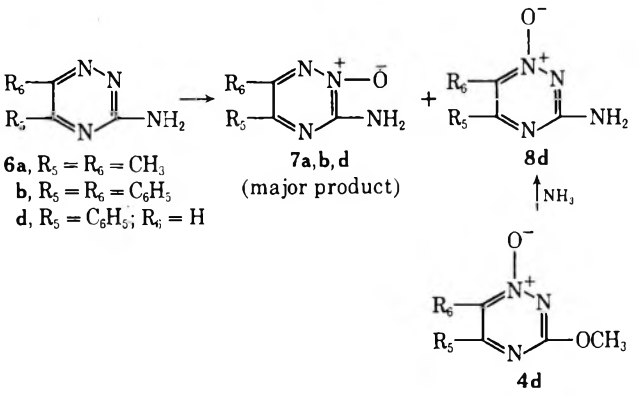
Sasaki and Minamoto[4] have described the N-oxidation of 3-amino-5,6-diphenyl-1,2,4-triazine and have concluded on the basis of dipole moment measurements in dioxane that N-oxidation occurs at N-1.

Since dipole moments determined in dioxane are notoriously inaccurate and the theoretical difference between the 1- and 2-oxides is only 0.22 D, it is not established whether this compound is the 1- or 2-oxide.

The same workers[4] converted their 3-methoxy-5,6-diphenyl-1,2,4-triazine *N*-oxide, now shown to be the 1-oxide (*vide supra*), to a 3-amino *N*-oxide which is different from that obtained by direct oxidation of 3-amino-5,6-diphenyl-1,2,4-triazine.

In order to bring all of this evidence into accord, we must conclude that the assignments made by Sasaki and Minamoto are in error and that, in fact, the oxidation of 3-amino-5,6-diphenyl-1,2,4-triazine affords the 2-oxide, in analogy with the results obtained by them upon oxidation of the 3-amino-5,6-dimethyl-1,2,4-triazine, and that the *N*-oxide obtained by treatment of the 3-methoxy-5,6-diphenyl-1,2,4-triazine *N*-oxide with ammonia is the 1-oxide. This interpretation also brings into harmony the observation of these workers, that the major product of oxidation of 3-amino-5-phenyl-1,2,4-triazine is the 2-oxide. In fact, when we treat the 3-methoxy-5-phenyl-1,2,4-triazine 1-oxide with ammonia, the resulting amino *N*-oxide is identical with the minor *N*-oxide obtained from the oxidation of 3-amino-5-phenyl-1,2,4-triazine as described by Sasaki and Minamoto.[4] These transformations are delineated in Scheme II. Finally, it should be mentioned that

Scheme II



the oxidation of 3-aminobenzo-1,2,4-triazine also yields the 2-oxide as the major product.[14] Thus, it appears that a 3-amino substituent facilitates oxidation at N-2 while oxidation at N-1 occurs when C-3 is either unsubstituted or is substituted by a methoxy or phenoxy group.

(12) J. A. Zoltewicz and G. M. Kaurrman, *J. Org. Chem.*, **34**, 1405 (1969).
(13) W. W. Paudler and S. A. Humphrey, *ibid.*, **35**, 3467 (1970).
(14) J. C. Mason and G. Tennant, *J. Chem. Soc. B*, 911 (1970).

TABLE II

EXPERIMENTAL VARIABLES FOR THE SYNTHESES OF VARIOUS TRIAZINE 1-OXIDES

Compd no.[a]	Procedure[b]	Reaction time, days	Reaction temp, °C	% yield	Mp, °C
2e	B	Step 1, 2 hr			
		Step 2, 4.5 hr	28	12[c]	61.5–64
4e	A	4	45	15	70.5–72
2c	A	4.5	28	27	65–67
	B	Step 1, 1 hr	28	11	
		Step 2, 6 hr			
2d	A	2	28	26	137.5–139.5
	B	Step 1, 6 hr	28	18[c]	
		Step 2, 6 hr			
2a	A	3.5	28	30	84–85.5
	B	Step 1, 3 hr	85	20[c]	
		Step 2, 4 hr	28		
2b	A	3	28	17	170–172
	B	Step 1, 12 hr	28	25[c]	
		Step 2, 4 hr			
4c	A	2.5	28	26	120–121.5
4d	A	3.5	28	39	127–128.5
4a	A	4	28	45	56–57.2
4b	A	3.5	28		
		0.5	45	23	156–158[d]

[a] See Schemes I and II for identification. [b] See Experimental Section for details. [c] Overall yield. [d] Lit.[6] 157.5–158.5.

Experimental Section

3-Methoxy-5-phenyl-1,2,4-triazine 1-Oxide (4d). General Procedure A.—To 1.094 g (0.00585 mol) of **3d** dissolved in 20 ml of chloroform was added 4 ml (0.00616 mol) of perbenzoic acid solution (0.00154 mol/ml). After standing at room temperature for 84 hr, the chloroform solution was washed with 40–50 ml of concentrated aqueous sodium carbonate. The aqueous layer was then extracted with chloroform (four 30-ml portions), and the concentrated chloroform extract was chromatographed on neutral alumina (grade III). The main fraction, when eluted with benzene, yielded a white solid. Sublimation at 100° (0.3 mm) afforded 0.46 g (38.7%) of **4d** (mp 127–128.5°).

1,2,4-Triazine 1-Oxide. General Procedure B. Step 1.—To 0.2 g of 3-methoxy-*as*-triazine 1-oxide in 4 ml of tetrahydrofuran was added 0.1 g of 95% hydrazine. Enough absolute methanol was added to dissolve all of the hydrazine. A yellow precipitate began to form within minutes. This solid was collected after 2 hr (0.185 g of shiny yellow crystals, mp 194° dec).

Step 2.—The hydrazine compound was then dissolved in a mixture of 200 ml of tetrahydrofuran and 15 ml of absolute methanol. To this solution was then added 5 g of activated MnO_2 and the slurry was stirred for 4.5 hr and filtered. Evaporation of the filtrate to dryness yielded a yellow oil which was sublimed at 40° (0.2 mm) to afford 18 mg of a 1,2,4-triazine 1-oxide (mp 61.5–64°).

Table II lists various triazine 1-oxides obtained by procedures A and B.

3-Amino-5-phenyl-1,2,4-triazine 1-Oxide.—3-Methoxy-5-phenyl-1,2,4-triazine 1-oxide (0.2 g) dissolved in 3 ml of 5% alcoholic ammonia was heated in a sealed tube on a steam bath for 8.5 hr. The cooled reaction mixture was filtered to yield 0.1 g of yellow needles (mp 228.5–230.5°, from ethyl alcohol).[7] An additional 0.5 g of product was obtained when the filtrate was concentrated further. This compound does not give a color test with aqueous $FeCl_3$ solution even after being warmed on a steam bath for 5 min.

Registry No.—**2a**, 27531-58-4; **2b**, 27531-59-5; **2c**, 27531-60-8; **2d**, 27513-61-9; **2e**, 27531-62-0; **4a**, 27531-63-1; **4b**, 27531-64-2; **4c**, 27531-65-3; **4d**, 27531-66-4; **4e**, 27531-67-5.

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Thiabenzenes. VII. Preparation and Properties of Some Substituted Thiabenzenes[1]

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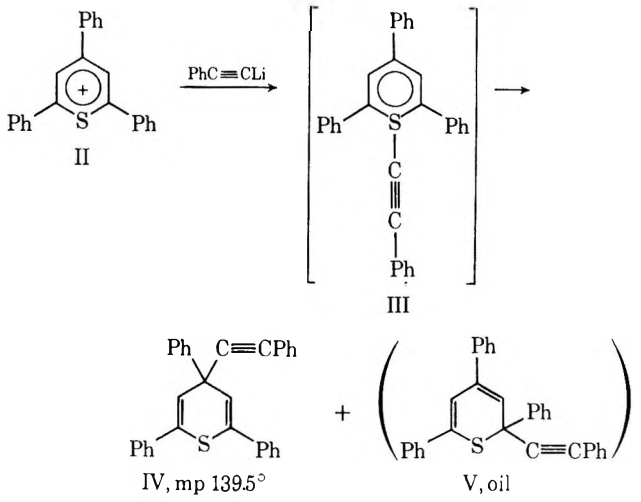
2,4,6-Triphenylthiopyrylium perchlorate coupled with phenylethynyllithium at carbon to give a mixture of 2- and 4-phenylethynyl-2,4,6-triphenylthiopyran rather than at sulfur to give the thiabenzene. 1-*p*-Tolyl-2,4,6-triphenyl- and 2-*p*-tolyl-1,4,6-triphenylthiabenzene have been prepared and shown to be distinct isomeric compounds which do not rapidly exchange the 1- and 2-aryl groups. 1-(*p*-Dimethylaminophenyl)-2,4,6-triphenylthiabenzene is more stable than the 1-phenyl and 1-tolyl analogs and is the first thiabenzene to give a crystalline X-ray powder diagram. Contrary to major fragmentation at the *S*-aryl bond for three other thiabenzenes on ionization in the mass spectrometer, the *p*-dimethylamino analog cleaved mainly to give the *p*-dimethylaminophenylmercaptide cation.

We wish here to report on further experiments to test hypotheses advanced[2] to explain the remarkable properties of the thiabenzenes and the altered color and stability of the hindered thiabenzene, 1,2,4,6-tetraphenylthiabenzene (I).

Efforts to make an ethynyl analog of I were prompted by the hypothesis that hindrance at the 1 position is largely responsible for the thermal, photo, and oxygen sensitivity of I. Furthermore, to date the only stable thiabenzenes isolated and identified have a phenyl group attached to sulfur.[3] We have therefore attempted to prepare an analog of I, introducing an ethynyl group between sulfur and the 1-phenyl with the expectation that this would relieve steric hindrance.[4] The desired thiabenzene III was not isolated although



it may have been an intermediate on the path to the two thiopyrans (IV and V) obtained.[5]

The structure of IV was confirmed by its uv spectrum, λ_{max} (log ϵ) 240 nm (4.77), and by its nmr spectrum, δ 6.0 (s, 2 H) and 7–8 ppm (20 H), in agreement with values reported for 2,4,4,6-substituted thiopyrans.[5,6] While pure V was not isolated, the content of V in crude product was estimated from the nmr singlets appearing at δ 5.9 and 6.8 ppm[6] in an intensity indicating that the crude product contained an ~7:4 ratio of IV and V. The structure assigned to IV was further supported by its conversion to the sulfone, mp 151°, a characteristic of 2,4,4,6- but *not* 2,2,4,6-tetrasubstituted thiopyrans.[5]

We remain without an adequate explanation of the remarkable difference in coupling of thiopyrylium salts to various metal alkyls, but it does appear that phenylethynyllithium resembles alkyllithiums rather than aryllithiums in this regard.

Observations recorded earlier[7] indicated that the rearrangement of I to a mixture of thiopyrans could be reversible in sunlight. We have now carried out experiments to see whether such a rearrangement was so labile a process that phenyl groups on sulfur and carbon could be rapidly exchanged. This was accomplished by making the isomeric methyl homologs, VI and XI.

Like I, VI and XI are purple amorphous solids, with slightly higher softening points. Like I, they rearrange at room temperature, especially when exposed to light, to give mixtures of thiopyrans from which the crystalline 2,4,4,6 isomers, VII and XII, were isolated and characterized. The nmr and uv spectra are especially useful in identifying their structure. Like I, VI and XI are both rapidly decolorized by oxygen in ether solution. These solutions on treatment with ethereal hydrogen chloride liberate aryl mercaptan (VIII and XIII) and the oxypyrylium zwitterions (IX and XIV). These observations indicate that the tolyl and phenyl groups in VI and XI are not rapidly exchanged (Scheme I).

Coupling of II with *p*-dimethylaminophenyllithium proved successful and, in fact, produced the thiabenzene, 1-(*p*-dimethylaminophenyl)-2,4,6-triphenylthiabenzene (XV), in much better yields than did phenyl- or tolyllithium.

Like the *S*-phenyl analog, XV is a deep purple compound. Unlike any of its analogs, XV proved to have a beautifully sharp X-ray powder diagram with at least 32 readily discernible rings. As yet, we have not succeeded in growing large enough crystals for single

(1) From the doctoral dissertation of M. Siskin and the master's thesis of J. Follweiler, University of Pennsylvania, 1968; supported in part by National Science Foundation Grant No. GP 5269.

(2) See C. C. Price and D. M. Follweiler, *J. Org. Chem.*, **34**, 3202 (1969).

(3) A. G. Hortmann and R. L. Harris, *J. Amer. Chem. Soc.*, **92**, 1803 (1970), report the preparation of solutions of 1-methyl-3,5-diphenylthiabenzene.

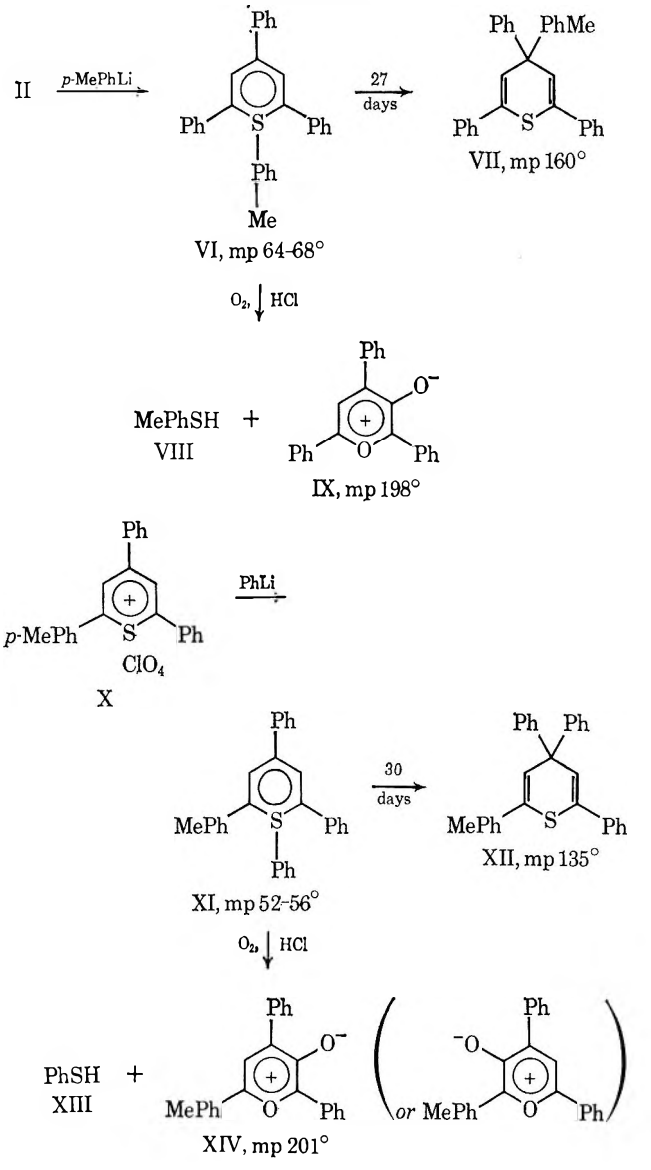
(4) See P. D. Bartlett and L. J. Rosen, *ibid.*, **64**, 543 (1942).

(5) G. Suld and C. C. Price, *ibid.*, **84**, 2090 (1962), have reported that several Grignard reagents and alkyllithiums react with II to give isomeric thiopyrans rather than thiabenzenes, although a transient purple color characteristic of the hindered thiabenzenes suggested that the latter may have been intermediates.

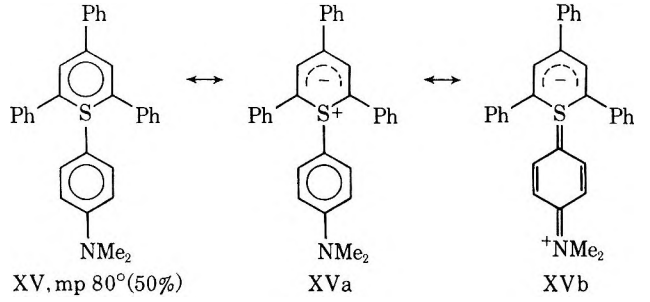
(6) T. Parasaran and C. C. Price, *J. Org. Chem.*, **29**, 946 (1964).

(7) G. Suld, Ph.D. Dissertation, University of Pennsylvania, 1960, reports that solutions of pure crystalline 2,4,4,6-tetraphenylthiopyran, on exposure to sunlight and air, produced 3-oxy-2,4,6-triphenylpyrylium zwitterion and phenyl mercaptan, a characteristic reaction of 1,2,4,6-tetraphenylthiabenzene.

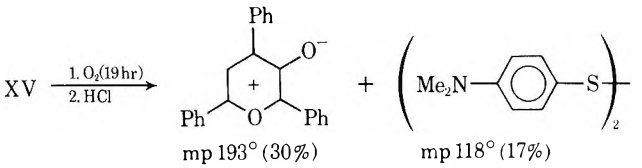
SCHEME I



crystal X-ray structure measurements. The crystallinity is also reflected in a markedly diminished solubility in ether.

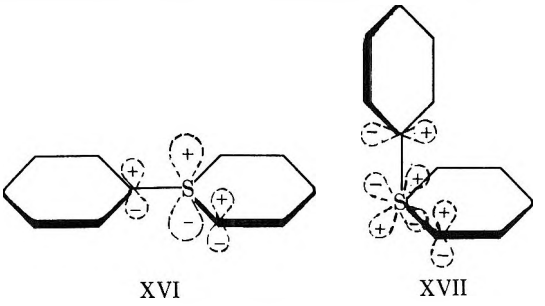


Enhanced stability for XV, as compared to its *S*-phenyl analog I, is demonstrated by the much slower rate of reaction of XV with oxygen in ether. Rather than losing its purple color in a few minutes by such treatment, XV requires many hours. When then treated with hydrogen chloride, it did indeed give the same type of decomposition as observed earlier for the simpler analog.



Like the *S*-phenyl analog, solutions of XV were decolorized on exposure to light. So far, we have not isolated or identified any pure compounds from the gummy mixture of compounds produced. Treatment of XV with HCl in ether also decolorized the solution and addition of aqueous alkali did not regenerate the purple color. These products are being investigated further.

We have earlier proposed that unhindered thiabenzenes have a very low barrier to bending at the *S*-phenyl bond, with virtually no barrier between conformers XVI and XVII. For each, one can construct a



continuous π-molecular orbital, conjugating the aromatic rings through sulfur and permitting a cyclic aromatic ring current in the thiabenzene ring.[8] We suggest that this involves using the $3p_z$ orbital on sulfur for XVI and a single $3d_{xz}$ orbital for XVII. The importance of the through conjugation as represented by XVI and XVII may also be of significance in view of our failure to isolate *S*-alkylthiabenzenes[5] and the recent report of Hortmann and Harris[3] on the possible nature of an *S*-methylthiabenzene.

Since our hypothesis and the higher dipole moment for I than for other thiabenzenes suggest greater ylide character for the bent conformer, and since the positive charge on sulfur in the ylide structure would be stabilized by the *p*-dimethylamino group in XV, the crystalline nature of XV may indeed be due to a marked preference for the bent conformer, leading to a more rigid geometry. We had also postulated that the characteristic "long tail" absorption out into the visible without a maximum was due to the very low barrier between conformers XVI and XVII.[2] The fact that XV has a strong maximum at 534 nm would also be in accord with a "fixed" conformation and thus a "fixed" excitation energy. The importance of electron donor character for the group attached to sulfur may indeed offer an explanation for our failure to obtain phenylethynylthiabenzene, since the ethynyl group is electrophilic.

The mass spectrum of XV proved to have some significant differences from other analogs. Unfortunately, the thermal instability of I seemed to preclude obtaining mass spectral data for this compound uncomplicated by the isomeric thiopyrans. For comparison, we report the mass spectra of 1-phenylthiabenzene (XVIII),

(8) This contrasts to the conjugated system proposed by M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, N. Y., 1969, pp 430–436.

9-phenyl-9-thiaanthracene (XIX), and 9,10-diphenyl-9-thiaanthracene (XX). Fragmentation of the latter three compounds occurs principally at the *S*-phenyl bond, producing the corresponding thiopyrylium ions as major peaks in the spectra.

In contrast, 2,4,6-triphenylthiopyrylium ion was a minor peak in the spectrum of XV. The two major peaks were identified as dimethylaminomercaptide and II less sulfur. Thus both the increased chemical stability and the mass spectral fragmentation indicate a stronger *S*–aryl bond as a result of introducing the *p*-dimethylamino group. This would seem quite reasonable in view of the significant contribution XVb would make to the structure of XV.

One feature of the mass spectra of XVIII, XIX, and XX is the pattern of evidence for ion–molecule reactions. In all three cases, a number of peaks are explicable by reaction of the parent molecule with the major cations observed. For XVIII, three such peaks are diphenyl sulfide, C_6H_5, and biphenyl, all of which could arise from reaction of XVIII with phenyl. For XIX, the peaks at 350, 470, and 546 correspond to reaction of XIX with phenyl, thioxanthyl, and 9-phenylthioxanthyl, respectively. For XX, the peaks at 427, 546, and 623 correspond to reaction of XX with the same three fragments.

Experimental Section

2,4,6-Triphenylthiopyrylium perchlorate (II), mp 121–122°[9] (4.2 g, 9.8 mmol), was stirred in 75 ml of ether under nitrogen while 37 ml of 0.94 *M* phenylethynyllithium[10] was added. The reaction mixture slowly turned a dark brown-green color. After 18 hr the mixture was quenched with 50 ml of saturated aqueous ammonium chloride. The brown ether layer appeared insensitive to oxygen. Washing, drying, and evaporation left a brown oil which was put on an alumina column in hexane. A diffuse green band was eluted with ether–hexane (1:3), which left 2.9 g (69%) of a green oil on evaporation. White crystals of 4-phenylethynyl-2,4,6-triphenylthiopyran (IV) separated from ethanol: mp 139–139.5°; λ_{max} (log ϵ) 240 nm (4.77); nmr ($CDCl_3$) δ 6.1 (s, 2 H), 7.1–7.9 (m, 20 H). Analytical data indicated that some oxidation occurred before combustion.

Anal. Calcd for $C_{31}H_{22}S \cdot {}^1/_4O$: C, 86.46; H, 5.15; S, 7.44; O, 0.93. Found: C, 86.38; H, 4.99; S, 7.53; O, 1.12.

The green oil also showed two additional singlets in the nmr at δ 5.9 and 6.8, characteristic of 2,2,4,6-tetrasubsituted thiopyrans.[6] The ratio of the δ 6.1 to 5.9 and 6.8 peaks was 7:2:2. The same green oil was produced in the same yield when the reaction was carried out in THF.

IV sulfone was prepared from a hot solution of 50 mg of IV in 4 ml of acetic acid to which 6 drops of 70% hydrogen peroxide was added. Addition of 10 ml of water precipitated a white solid which was recrystallized from ethanol to give 30 mg (54.5%) of IV sulfone: mp 150–151°; ir sulfone bands, 1130 and 1295 cm^{-1}.

Anal. Calcd for $C_{31}H_{22}SO_2 \cdot {}^1/_2C_2H_5OH$: C, 79.64; H, 5.43; S, 6.64. Found: C, 79.80; H, 5.31; S, 6.61.

1-*p*-Tolyl-2,4,6-triphenylthiabenzene (VI).—The procedure of Suld[7] was modified by design of a reaction vessel[1] which permitted manipulation with minimum exposure to air. To a stirred suspension of 5.0 g of II under nitrogen was added 35 ml of 1.3 *M* *p*-tolyllithium in ether. An intense purple color developed and the suspended II disappeared. The reaction mixture was quenched with 50 ml of saturated aqueous ammonium chloride, washed with water, and dried over potassium carbonate, all under nitrogen and with minimum exposure to light. The ether solution was added to 50 ml of petroleum ether (bp 30–60°) which had been percolated through alumina and was cooled in a Dry Ice–acetone bath. Filtration removed some white impurity. Evaporation left a purple resin which was redissolved in 30 ml of dry ether which was again added to 150 ml of petroleum ether at −78°. The purple precipitate formed was collected by filtration and vacuum dried to give 1.1 g of VI as a red-violet electrostatic powder: mp 64–68°; λ_{max} (log ϵ) 218 nm (4.49), 296 (4.23) (ether); nmr (CCl_4) δ 2.2 (s, 3 H), 6.6–7.7 (m, 21 H).

When the original ether solution above, after quenching and washing, was allowed to stand under nitrogen for 27 days exposed to daylight, the solution had turned from purple to dark orange. Evaporation and recrystallization from ethanol gave a 35% yield of 4-*p*-tolyl-2,4,6-triphenylthiopyran (VII) as white crystals: mp 158–160°; λ_{max} (log ϵ) 236 nm (4.56); nmr ($CDCl_3$) δ 2.3 (s, 3 H), 6.25 (s, 2 H), 7.2–7.7 (m, 19 H).

Anal. Calcd for $C_{30}H_{24}S$: C, 86.49; H, 5.81; S, 7.70. Found: C, 86.47; H, 5.85; S, 7.53.

When oxygen was bubbled through a purple solution of VI, a clear dark red solution was formed in 12 min. Hydrogen chloride was then bubbled in for 1 min, immediately precipitating an orange solid. Two recrystallizations gave 1 g (31%) of IX as red crystals with a bronze sheen: mp 195–198° (lit.[2] 195°); nmr ($CDCl_3$) δ 7.5 (m, 9 H), 7.8 (m, 3 H), 8.1–8.4 (m, 2 H), 8.7–9.0 (m, 2 H).

The filtrate from the oxidation was washed with 5% NaOH. Acidification of the alkaline extract, extraction with ether, and evaporation left an oil with a disagreeable thiol odor. Treatment with 2,4-dinitrochlorobenzene in ethanol[11] gave yellow crystals of 2,4-dinitro-4′-methyldiphenyl sulfide, mp 99–102° (lit.[11] 103°).

2,4-Diphenyl-6-*p*-tolylthiopyrylium perchlorate (X) was prepared from 2,4-diphenyl-6-*p*-tolylpyrylium perchlorate, mp 224–225° (lit.[12] 224°), by treatment with sodium sulfide in water and then perchloric acid.[9] Three recrystallizations from 2-propanol gave a 50% yield of orange crystals of X: mp 174–175°; λ_{max} (log ϵ) 227 nm (4.20), 243 (4.17) (in CH_3OH); nmr (CF_3COOH) δ 2.5 (s, 3 H), 7.5–8.3 (m, 14 H), 8.9 (s, 2 H).

Anal. Calcd for $C_{23}H_{19}SClO_4$: C, 65.67; H, 4.36; S, 7.30; Cl, 8.07. Found: C, 65.53; H, 4.33; S, 7.14; Cl, 8.08.

2-*p*-Tolyl-1,4,6-triphenylthiabenzene (XI) prepared from X and phenyllithium in ether (as for VI) was a red-violet, electrostatic powder, in 15.7% yield: mp 52–56°; λ_{max} (log ϵ) 233 nm (4.36), 303 (4.10) (ether); nmr (CCl_4) δ 2.25 (s, 3 H), 6.7–7.6 (m, 30 H).

A purple ether solution turned orange after 30 days at room temperature. Recrystallization from ether gave a 19% yield of colorless crystals of XII: mp 134–136°; λ_{max} (log ϵ) 238 nm (4.56) (ethanol); nmr ($CDCl_3$) δ 2.3 (s, 3 H), 6.2 (s, 2 H), 7–7.6 (m, 19 H).

Anal. Calcd for $C_{30}H_{24}S$: C, 86.49; H, 5.81; S, 7.70. Found: C, 86.47; H, 5.93; S, 7.45.

When oxygen and then hydrogen chloride were passed through a purple ethereal solution of XI, a red precipitate formed. It was recrystallized from acetone–water or acetonitrile to give 7.4% of XIV as red crystals with a bronze sheen: mp 198–201°; λ_{max} (log ϵ) 217 nm (4.09), 263 (3.99), 315 (3.85) (ethanol); nmr ($CDCl_3$) δ 2.4 (s, 3 H), 7.2 (d, 1 H), 7.3–7.5 (m, 7 H), 7.7 (s, 1 H), 7.8 (s, 2 H), 8.0–8.3 (m, 2 H), 8.6–8.9 (m, 2 H).

Anal. Calcd for $C_{24}H_{18}O_2 \cdot {}^1/_8H_2O$: C, 84.61; H, 5.41. Found: C, 84.48; H, 5.42.

The filtrate from the oxidation reaction mixture was extracted and treated with 2,4-dinitrochlorobenzene[11] to give yellow crystals of 2,4-dinitrodiphenyl sulfide, mp 117–120° (lit.[11] 121°).

1-(*p*-Dimethylaminophenyl)-2,4,6-triphenylthiabenzene (XV).—A suspension of 6.36 g (15 mmol) of 2,4,6-triphenylthiopyrylium perchlorate[9] in 120 ml of dry ether in the dark under nitrogen at −60° was treated with 57 ml of 1.03 *M* ethereal *p*-dimethylaminophenyllithium[13] (59 mmol) with stirring over a 5-min period. The reaction turned deep purple immediately. After another 5 min of stirring at −60°, the mixture was warmed to 0° for 10 min, quenched with 100 ml of cold saturated aqueous ammonium chloride, and stirred for 2 hr. Filtration gave a deep purple precipitate[14] which was washed thoroughly with distilled water

(9) R. Wizinger and P. Ulrich, *Helv. Chim. Acta*, **39**, 207 (1956).

(10) H. Gilman and R. Young, *J. Org. Chem.*, **1**, 315 (1936).

(11) S. M. McElvain, "The Characterization of Organic Compounds," MacMillan, New York, N. Y., 1945, pp 277–278.

(12) K. Dimroth, G. Neubauer, and G. Osterloo, *Chem. Ber.*, **90**, 1668 (1957).

(13) R. G. Jones and H. Gilman, "Organic Reactions," Collect. Vol. VI, Wiley, New York, N. Y., 1967, p 353; H. Gilman, E. A. Zoellner, and W. M. Selby, *J. Amer. Chem. Soc.*, **55**, 1252 (1933).

(14) The purple ether layer of the filtrate gave 1.2 g of tan solid when treated with 500 ml of cold petroleum ether. This filtrate, on evaporation and vacuum distillation, gave 2.67 g of *N,N*-dimethylaniline, and then vacuum sublimation gave 1.1 g of *p*-bromo-*N,N*-dimethylaniline and 650 mg of brown resinous residue.

and dried. Half of this crude product was dissolved in 1.2 l. of dry 0° ether under N_2 in the dark, and 900 ml of −20° petroleum ether (bp 30–60°) was added. After standing 1 hr at −20°, 20 mg of purple-brown solid was removed by filtration. Rotoevaporation of the filtrate at 5–10° in the dark gave, after washing with −30° petroleum ether, 3.35 g (50%) of deep purple shiny microcrystalline 1-(*p*-dimethylaminophenyl)-2,4,6-triphenylthiabenzene: mp 78–80° (changing to orange-brown at 82°); λ_{max} (log ϵ) 231 nm (4.31), 271 (4.40), 311 (4.42), 357 (4.13), and 534 (4.05) (cyclohexane);[15] nmr (CCl_4, 0°) δ 2.9 (s, 6 H), 6.5 (d, J = 8 Hz, 2 H), ~7.3 (m, 19 H); ir (KBr) (% absorbed) 3048 (56), 3020 (56), 2915 (53), 2845 (49), 2800 (45), 1588 (94), 1490 (84), 1440 (88), 1420 (88), 1358 (68), 1249 (81), 1192 (67), 1070 (63), 892 (37), 874 (32), 808 (55), 755 (78), 712 (50), 692 (78), 598 (31), 532 (26), 511 cm^{-1} (27); X-ray powder pattern (vacuum-sealed capillary, chromium K_α, V filter, 40 kV, 20 mA, 16 hr) Å (rel intensity) 10.18 (vs), 9.32 (vs), 7.05 (vw), 6.68 (s), 6.26 (w), 5.72 (m), 5.34 (vs), 5.09 (m), 4.71 (vs), 4.59 (vs), 4.44 (vs), 4.36 (vs), 4.14 (vs), 3.95 (mw), 3.78 (mw), 3.70 (s), 3.56 (w), 3.49 (s), 3.41 (w), 3.23 (mw), 3.14 (m), 3.02 (mw), 2.93 (m), 2.84 (w), 2.77 (mw), 2.68 (w), 2.58 (mw), 2.50 (mw), 2.39 (w), 2.35 (mw), 2.30 (vw), 2.26 (mw).

Anal. Calcd for $C_{31}H_{27}NS$: C, 83.59; H, 6.07; N, 3.15; S, 7.19. Found: C, 83.35; H, 6.17; N, 3.15; S, 7.18.

When oxygen was bubbled through 500 mg of the thiabenzene in 600 ml of ether, the solution was still purple after 3.5 hr, orange after 8.5 hr, and yellow after 19 hr. Hydrogen chloride gave a yellow precipitate which on recrystallization proved to be 2,4,6-triphenyl-3-oxypyrylium zwitterion, 110 mg (30%), mp 191–193° (lit. 193.5–195°), with ir and uv spectra the same as reported earlier. Alkaline extraction of the ethereal mother liquor gave the mercaptan, which oxidized in air[16] to disulfide, recrystallized from ethanol to give bis(*p*-dimethylaminophenyl) disulfide (28 mg, 17%), mp 117–118° (lit.[16] 118°).

The mass spectra were carried out on Consolidated Electrodynamics Corp., Model 21-30, or Associated Electrical Industries, Ltd., Model MS-9023, mass spectrometers.

The preparation of the **1-phenylthiabenzene**[17] (**XVIII**) has been described elsewhere: *m/e* (rel intensity) 186 (12), 154 (3), 97 (100) for inlet at 90°; 186 (27), 154 (100), 97 (11) for inlet at 130°, 70 eV.

9-Phenyl-9-thiaanthracene (**XIX**), softening at 123–128°, was prepared from thioxanthylium perchlorate and phenyllithium in 8% yield:[18] *m/e* (rel intensity) 546 (1), 470 (2), 350 (4), 274 (100), 197 (87), 154 (42) for inlet at 150–200°, 70 eV.

9,10-Diphenyl-9-thiaanthracene (**XX**), softening at 142–145°, was obtained in 43% yield from 9-phenylthioxanthylium perchlorate and phenyllithium:[18] *m/e* (rel intensity) 623 (10), 546 (20), 426 (10), 350 (39), 273 (93), 197 (100), 154 (31) for inlet at 150–200°, 70 eV.

XV, obtained as described above, had the following mass spectrum: *m/e* (rel intensity) 445 (14), 368 (10), 325 (4), 294 (24), 153 (52), 152 (100) for inlet at 120°; 445 (9), 368 (7), 325 (4), 294 (20), 153 (16), 152 (32) for inlet at 90°, 50 eV. Using the Hitachi Perkin-Elmer RMH-2 mass spectrometer with biphenyl as internal standard, the 152 peak was shown to consist of 84% of $Me_2NC_6H_4S$ (*m/e* 152.0537; calcd, 152.05340) and 16% of $C_{12}H_8$ (calcd, 152.06260). The major intensity at *m/e* 153 was found due to $Me_2NC_6H_4SH$ (*m/e* 153.06129; calcd, 153.06123).

Registry No.—IV, 28278-42-4; IV sulfone, 28278-43-5; VI, 28278-44-6; VII, 28278-45-7; X, 28278-46-8; XI, 28278-47-9; XII, 28278-48-0; XIV, 28264-15-5; XV, 28278-49-1.

(15) G. Suld, Ph.D. Dissertation, University of Pennsylvania, 1960, has reported for 1,2,4,6-tetraphenylthiabenzene λ_{max} 244, 265, 273, 524 (isooctane).

(16) C. S. Argyle and G. M. Dyson, *J. Chem. Soc.*, 1629 (1937).

(17) M. Polk, M. Siskin, and C. C. Price, *J. Amer. Chem. Soc.*, **91**, 1206 (1969).

(18) C. C. Price, M. Hori, T. Parasaran, and M. Polk, *ibid.*, **85**, 2278 (1963).

Thiabenzenes. VIII. One-Electron Reductions and Disproportionations of Thioxanthylium and 9-Phenylthioxanthylium Ion and a Bithiabenzene Analog

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In inert media, thioxanthylium perchlorate (I) is converted by a number of reducing agents, such as zinc, cobaltocene, dithionite, and potassium and phosphonium iodide, to bithioxanthyl (II). The reaction evidently proceeds through one-electron reduction to a free radical (Ia) and oxygen and nitric oxide divert Ia to thioxanthone as the main product. Although 9-phenylthioxanthyl (VIa) was once reported to be a stable free radical, one-electron reduction of 9-phenylthioxanthylium perchlorate (VI) gave a nearly quantitative yield of a pale green oily S–S dimer (VII). On heating, this S–S dimer rearranged to the colorless crystalline C–C dimer, 9,9′-diphenylbithioxanthyl (VIII). Both dimers II and VIII are reconverted to I and VI, respectively, by perchloric acid while with hydrogen peroxide in acetic acid they form the dimeric disulfones. Disproportionation reactions involving I, VI, and the corresponding thioxanthenes (III and XI) can be explained by ready hydranion exchange and by condensation of I and III to form the dimer II.

There have been many reports of the one-electron reductions of aromatic cations, such as tropylium,[3] pyrylium,[4] and pyridinium[5] salts. In a few cases, the free radical initially formed could be isolated as a stable entity,[5b] but more frequently the carbon-to-carbon dimer was the product.

We[6] have reported such a dimer (bithioxanthyl, II) as a by-product in the formation of 9-phenyl-9-thiaanthracene from thioxanthylium perchlorate (I) and phenyllithium. Since II may indeed have resulted from a one-electron reduction of I by phenyllithium,[7,8] we have undertaken a more systematic investigation of the one-

(1) From the Ph.D. Dissertation of M. Siskin, University of Pennsylvania, 1968, which contains details of infrared and mass spectra.

(2) Supported in part by National Science Foundation, Grant No. GP 5269.

(3) W. v. E. Doering and L. H. Knox, *J. Amer. Chem. Soc.*, **76**, 3206 (1954); **79**, 351 (1957).

(4) A. T. Balaban, C. Bratu, and C. N. Rentea, *Tetrahedron Lett.*, No. 20, 265 (1964).

(5) (a) A. W. Hofmann, *Chem. Ber.*, **14**, 1503 (1881); K. Wallenfels and M. Gellrich, *Justus Liebigs Ann. Chem.*, **621**, 198 (1959). (b) E. M. Kosower and E. J. Poziomek, *J. Amer. Chem. Soc.*, **86**, 5515 (1964); M. Itoh and S. Nagakura, *Tetrahedron Lett.*, 417 (1965).

(6) C. C. Price, M. Hori, T. Parasaran, and M. Polk, *J. Amer. Chem. Soc.*, **85**, 2280 (1963).

(7) K. Ziegler and C. Ochs, *Chem. Ber.*, **55**, 2257 (1922), have reported the reduction of 9-phenylxanthylium perchlorate to a stable free radical by phenylmagnesium chloride.

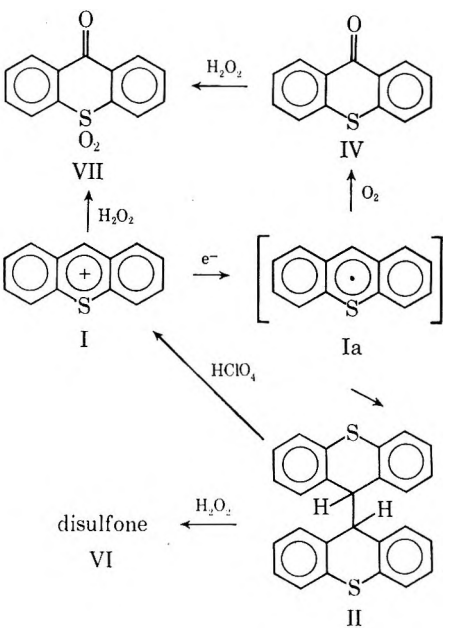
(8) See also C. C. Price and D. M. Follweiler, *J. Org. Chem.*, **34**, 3202 (1969).

electron reduction of thiopyrylium salts. We wish to report here some studies of one-electron reductions of I and its 9-phenyl analog (VI) and some characteristics of the processes and products.

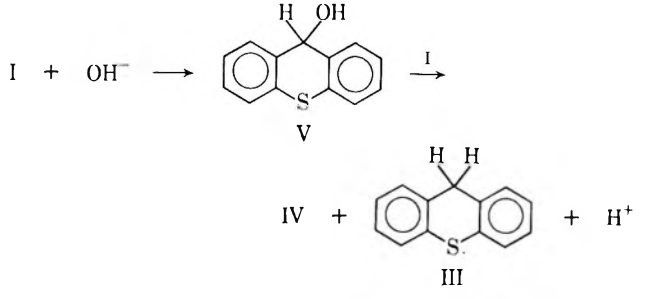
Results

Reductions.—The major conversions observed for thioxanthylium perchlorate (I) are summarized in Scheme I.

SCHEME I



In diglyme solution under nitrogen or *in vacuo*, with zinc dust, sodium dithionite, cobaltocene, or phosphonium iodide, the yields of II were essentially quantitative. With the alkali metals, thioxanthene and thioxanthone were obtained as well, presumably by the following sequence.



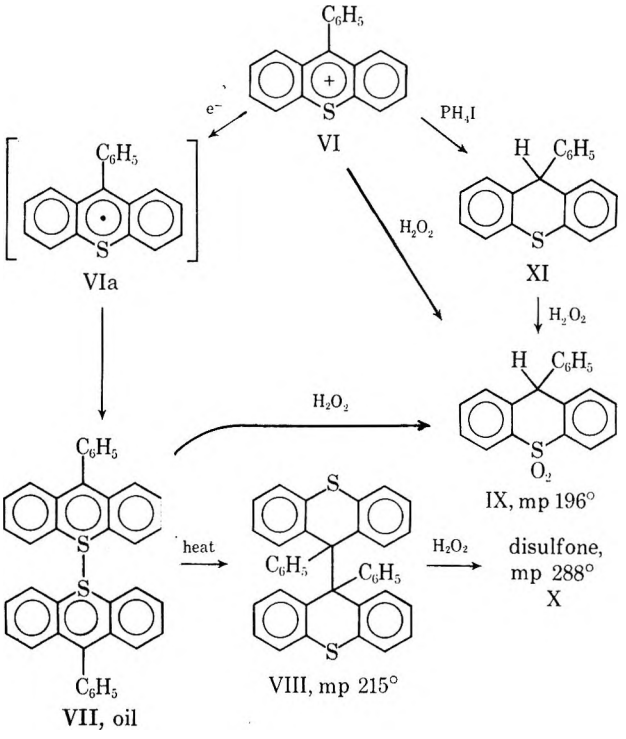
The reaction of I with hydroxyl ion adventitiously present with the alkali metal would give V. Hydranion exchange to I would produce thioxanthene (III) and protonated IV.[9]

Since III was not formed when water was added to a zinc reduction, it may be concluded that the reduction proceeds by one-electron addition to give the radical Ia, rather than by two electrons to form an anion intermediate. Presumably this addition would put an electron in the lowest unfilled anthracene-like orbital of I, a process enhanced in I as compared to anthracene by the formal positive charge in I.

(9) E. K. Fields and S. Meyerson, *J. Org. Chem.*, **30**, 937 (1965), have reported III and IV as the products from treatment of thioxanthylium perbromide with aqueous sodium hydroxide.

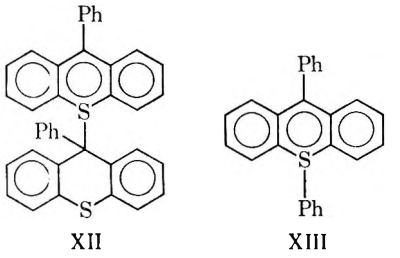
The major conversions observed for 9-phenylthioxanthylium perchlorate (VI) are summarized in Scheme II.

SCHEME II



Reduction of VI with sodium dithionite, zinc, or sodium gave a viscous oil, obtained in excellent yield after passing a benzene solution through a neutral alumina column. Molecular weight determination, both by mass spectrometry and cryoscopically, showed the material to be a dimer, rather than the stable triaryl free radical VIa.[10]

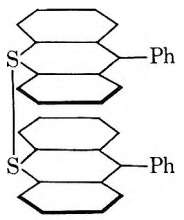
The failure of the radical VIa to couple at the 9 position is not so unexpected in view of the added hindrance of the 9-phenyl group as compared to Ia. The sulfur–sulfur coupling would, of course, be much less hindered and indeed the coupling of simple sulfur radicals from oxidation of mercaptans to form disulfide bonds is common. The evidence that the oil is in fact the dimer VII is supported by (1) its molecular weight, (2) its mass spectra, and (3) its failure to give a disulfone (as does IX). We believe the carbon–sulfur dimer XII is excluded since this would be a thiaanthracene analogous to XIII and since XIII and its analogs are deeply colored amorphous solids with softening points above 125°.



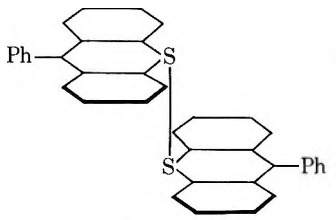
The amorphous nature of thiabenzenes has been ascribed to a very low barrier to bending at the S–C_6H_5

(10) The original claim to have obtained this free radical [W. Schklenk and J. Renning, *Justus Liebigs Ann. Chem.*, **394**, 190 (1912)] was discounted by M. Gomberg and W. Minnis, *J. Amer. Chem. Soc.*, **43**, 1940 (1921).

bond.[6,8] Similar behavior in VII would allow a remarkable degree of flexibility at the S–S bond. We postulated a 180° bending in thiabenzenes, *i.e.*, from orthogonal above to orthogonal below the plane defined by the sulfur ring. In VII this bending may extend another 90° in each direction, permitting a geometry with the two rings parallel, one above the other (VIIa). In addition to freedom of bending at the S–S bond, there



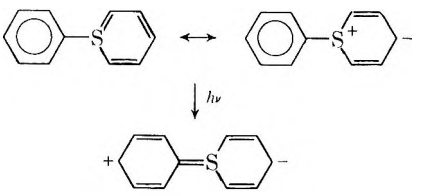
VIIa



VIIb

is the likely possibility of low barriers to rotation at the S–S bond, as indicated by VIIb.[11] It may be this extreme flexibility which permits this molecule to be an oil at room temperature. Certainly some remarkable and unique structural feature must be invoked to explain how a molecule of this size and structure could exhibit such a property.

The other surprising feature of this molecule, as compared to *S*-phenylthiabenzenes, is the lack of intense color. One of the possible electronic excitations responsible for the color of thiabenzenes is electron transfer from the phenyl group to a molecular orbital involving increased participation of the vacant orbitals on the sulfur atom. This could be represented as electron transfer from phenyl to the partially positive sulfur atom. In the case of VII, neither ring would serve so readily as



XIV

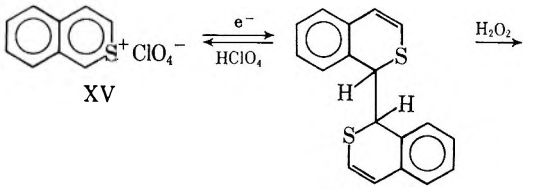
an electron donor; so the type of excitation depicted by XIV[12] may not occur in the visible region or may be forbidden.

Although the reduction of I and VI by zinc and dithionite are very similar, there is a remarkable contrast with phosphonium iodide. While this reagent gave II, the one-electron reduction product in 1 min from I, with VI, the reduction to a colorless state required 50 min of reflux in 1-butanol and the product was XI, the result of two-electron reduction. Actually the bright red color of VI rapidly turned to bright yellow, which only slowly faded to colorless. This suggests the possibility that the bright yellow color was due to VIa, which couples only slowly to VI but can be reduced by phosphonium iodide to XI.

The mass spectrum fragmentation patterns of VII and VIII deserve brief comment. Cleavage back to the stable 9-phenylthioxanthylium ion (VI, *m/e* 273) represents the most intense peak for either compound, but the sulfur–sulfur dimer obviously undergoes this cleavage more readily since the parent peak (*m/e* 546) is observed readily at 19.9 eV but not at 70 eV. While the spectra of VII at 19.9 eV and VIII at 70 eV are generally similar, a major difference is the presence of peaks from VII at *m/e* 350 (4.6%), 349 (11.6%), and 348 (25.6%) entirely absent from VIII. These three peaks could be cations related to 9,9-diphenylthioxanthene. One could envision a ready cleavage of conformation VIIa by simultaneous breaking of the S–S bond and phenyl transfer to give thioxanthylium ion (*m/e* 197, 44.5%) and the ions of *m/e* 350 to 348 (total abundance, 41.8%). Another major difference is the peaks at *m/e* 288 (32.1%) and 287 (30.7%) from VII, absent from VIII. These two peaks formally correspond to I plus CH_2 and CH_3. A third difference is the formation of *m/e* 239 (9.3%, 9-phenylfluorenyl cation?) from VIII but not from VII. Both give substantial peaks at *m/e* 165 (fluorenyl cation).

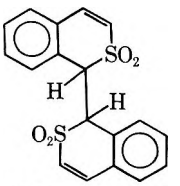
The mass spectrum fragmentation of the disulfone X gave a much more complex pattern perhaps partly due to the fact that simple cleavage of one or two bonds could not produce stable thioxanthylium cations. Symmetrical cleavage to *m/e* 305 (100%) does represent the most prominent ion formed except for *m/e* 44 (384%, CO_2), although this ion less one oxygen (*m/e* 289, 57.4%) and two oxygens (*m/e* 273, 15.4%) is also observed, as well as *m/e* 321 (29.7%) which represents addition of one oxygen. The thioxanthylium ion [*m/e* 197 (17.4%), 196 (26.7%)] is prominent as are a series of small ions which appear to represent analogs of thiopyrylium ion ($C_5H_5S^+$, *m/e* 97, 93%) appearing at *m/e* 111 (54%, $C_6H_5S^+$), 99 (49.7%, $C_5H_7S^+$), 85 (98.2%, $C_4H_5S^+$), 73 (93.4%, $C_3H_5S^+$), 71 (96.5%, $C_3H_3S^+$). There is also a strong peak at *m/e* 64 (94.8%, SO_2) and at 57 (215%) which is the correct mass for the *tert*-butyl cation.

We have also reduced 2-thianaphthalenium perchlorate (XV) by zinc dust, cobaltocene, sodium dithionite, and, coincidentally, *tert*-butylmagnesium chloride.[8] From the first three reducing agents the product isolated was the dimer XVIa (mp 230°), while the Grignard reagent also gave about an equal amount of the diastereoisomer XVIb (mp 200°). We have not determined which isomer is *dl* and which is *meso;* that coupling oc-



XV

XVIa, mp 230°
b, mp 200°



XVII, mp 262°

(11) As compared to conventional disulfides, RSSR, which have a strongly preferred 90° dihedral angle at the S–S bond, there are in VII no unshared electrons on sulfur in p orbitals, believed to be the major source of the fixed conformation for disulfides and peroxides.

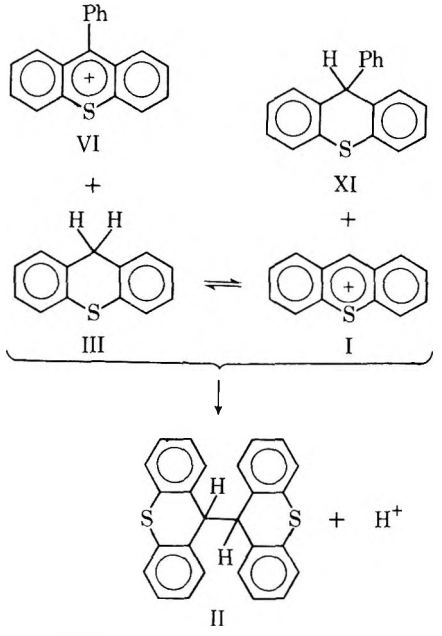
(12) We have found that a methyl or especially a dimethylamino group in the para position of the phenyl ring enhances the stability of 1,2,4,6-tetraphenylthiabenzene: J. Follweiler, M.S. Thesis, Department of Chemistry, University of Pennsylvania, 1968; C. C. Price, J. Follweiler, H. Pirelahi, and M. Siskin, *J. Org. Chem.*, **36**, 791 (1971).

curs at the 1 position is supported by the 2-thiochromene-like uv, ir, and nmr spectra of XVIa and XVIb.

Oxidation of XVIa occurs in good yield by perchloric acid to regenerate XV. With hydrogen peroxide in acetic acid, the product is the disulfone XVII.

Disproportionations.—The ready one-electron[8] and two-electron[6,13] reduction of thiopyrylium salts, as well as extensive studies of reversible one- and two-electron reductions of analogous pyridinium systems,[5,14] has suggested to us the possibility of redox disproportionations between thioxanthenes and thioxanthylium salts. We have therefore studied reactions of the four possible combinations of thioxanthylium (I) and 9-phenylthioxanthylium (IV) ions with thioxanthene (III) and 9-phenylthioxanthene (XI).

The reactions observed in dry diglyme can be summarized in the following reaction scheme.



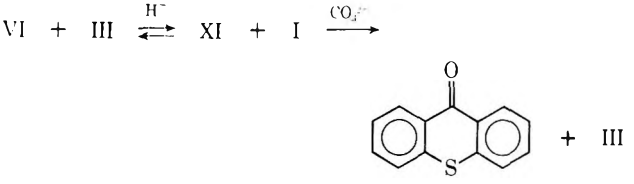
Reactions between I and III, I and XI, or VI and III all produced the bithioxanthyl II and titratable acid was liberated.

For I and III, the disproportionation gave a 27% conversion to II with 80% of III recovered unchanged. When this reaction was not carried out in the dark, the reaction mixture turned black and the yield of II decreased but more III was recovered than added.[15]

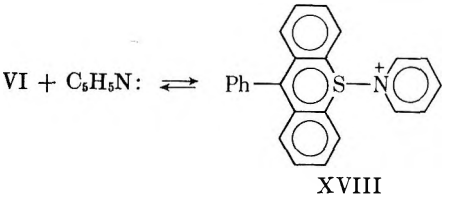
In every case above, the product II crystallized from the reaction mixture and its low solubility may indeed by a major factor pushing the disproportionations. When VI and XI were mixed, no reaction occurred. In this case, one-electron disproportionation would produce a radical (VIa) which undergoes S–S coupling nearly quantitatively to give a soluble, oily dimer. The failure to obtain the dimer of VIa argues against radical intermediates for the generation of II.

The addition of pyridine (to react with perchloric acid produced) did not seem to substantially alter the course of the reaction between I and III although a good yield of pyridinium perchlorate was isolated. However, for the reaction of VI and III, addition of 1 equiv of pyridine blocked disproportionation and led to recovery of reactants.

The use of magnesium carbonate as a base diverted the reaction to a new course, producing from I and III thioxanthone IV and more III than initially added, presumably through the same intermediate thioxanthol as mentioned above for the alkali metal reduction of I. Of somewhat more interest is the formation of thioxanthone from VI and III in the presence of magnesium carbonate. This must involve a prior hydranion transfer.

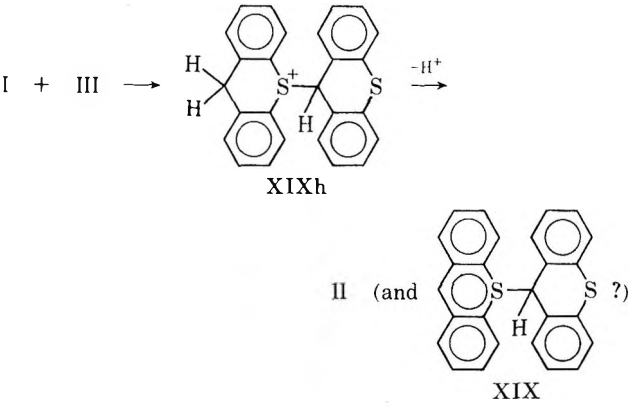


The disproportionation products observed can be accounted for by two types of reaction. One is simply a hydranion exchange such as that between VI and III giving XI and I, or its reverse. The second is the reaction of I with III to give dimer II. The presence of pyridine may block hydranion exchange to VI, by reversibly coupling with II to form the thiaanthracene analog XVIII. It is reasonable to assume that phenyllithium coupling to form thiabenzenes proceeds through



analogous coupling of the electronically similar phenyl anion at sulfur of a thiopyrylium salt. Phenyl anion couples to sulfur in VI in much better yield than to I.

The failure to isolate any dimer of VIa leads us to propose a nonradical mechanism for the formation of II from I and III. Structures XIX and XIXh are an *S*-



alkylthiabenzene and its protonated form, analogous to the *S*-alkylthiabenzene recently reported by Hortmann and Harris[16] to be reversibly protonated. We had earlier evidence[13] that ortho-unsubstituted *S*-alkylthiabenzenes rearranged to isomeric thiopyrans which in this instance would be II. The species XIXh could represent part of the titratable acid observed.

(13) G. Suld and C. C. Price, *J. Amer. Chem. Soc.*, **84**, 2093 (1962).

(14) See, *e.g.*, N. O. Kaplan, "The Enzymes," Vol. III, Academic Press, New York, N. Y., 1960.

(15) We have not carried out independent tests to see whether, in fact, II is photoreducible to III.

(16) A. G. Hortmann and R. L. Harris, *J. Amer. Chem. Soc.*, **92**, 1803 (1970).

The failure to observe dimeric coupling products from VI and XI or VI and III could be due to enhanced resonance stabilization of the cationic center of VI as well as increased steric hindrance to coupling at the 9 carbon of VI. The failure to observe dimeric coupling products from I and XI could be due to steric restrictions arising from the p^3 geometry at a sulfonium center and an adverse inductive effect from the 9-phenyl group in XI.

The poor yields of dimer II obtained may be due in part to oxidation of II by the perchloric acid formed, since 70% aqueous perchloric acid has been shown to produce an 80% yield of I from II.[8] This cannot be the sole reason for the poor yield of II, however, since the yield of acid formed was consistently greater than that of II. In the reaction mixture of I and III containing pyridine, a quantitative yield of "crude" dimer was obtained, which yielded only 30% of the dimer II. The large loss on recrystallization may be due to our failure to recover the dimer XIX.

Experimental Section

Reduction of I[6] was carried out in diglyme dried by vacuum distillation from calcium hydride or lithium aluminum hydride, either in a vacuum system or under nitrogen. On stirring 1 g of I with 4 equiv of zinc dust for 1 hr, the red color faded and a white precipitate of II formed in quantitative yield. On recrystallization from xylene, it melted at 330–332° (lit.[17] 325°). Addition of 0.2 ml of water gave 91% of II in 45 min. When oxygen was bubbled through the diglyme, no precipitate of II formed. The solvent was removed by vacuum distillation and the yellow residue recrystallized from benzene yielding 207 mg (30%) of thioxanthone (IV), mp 216–218° (lit.[18] 209°). A similar experiment with nitrogen dioxide in place of oxygen gave 53% of IV and no II. With sulfur dioxide, 87% of II and 6% of IV were isolated.

Reduction of 1 g of I with 1 equiv of sodium dithionite in diglyme gave 90% of II in 6 hr; at 60° with 4 equiv, the yield was 96% in 30 min. When 500 mg (1.68 mmol) of I in dry 1-butanol was treated with 550 mg (3.40 mmol) of phosphonium iodide, shiny white crystals of II separated in quantitative yield in 1 min. A 10% solution of cobaltocene in benzene (2 equiv, Aldrich Chemical Co.) was added to 1 g of I in 50 ml of diglyme and stirred for 48 hr giving II in quantitative yield.

Reduction with 1 equiv of alkali metal in diglyme for 4–7 days gave the following yields of II: Li, 9%, Na, 22%; K, 66%.

Oxidation of II (250 mg) was accomplished by heating to 100° in 10 ml of 70% perchloric acid. The dark red solution was rapidly chilled to 0° and poured into 150 ml of ether at 0°, precipitating 277 mg (80%) of I, mp 226–229°.

When 250 mg of II was suspended in 3 ml of acetic acid, heated under reflux, and treated dropwise with 4 ml of 50% H_2O_2, a vigorous reaction occurred. After addition and 30 min of further reflux, cooling, filtration, and recrystallization from acetic acid, II gave 235 mg (82%) of 9,9′-bithioxanthyl disulfone (VI): white plates; mp 416–417°; ir sulfone bands at 1285 and 1155 cm^{-1}; uv (CH_3OH) λ_{max}, nm (log ϵ), 271.5 (4.01), 278.5 (3.95); nmr (CF_3CO_2H) δ 8.2 (d, 2 H), 7.7 (t, 2 H), 7.6 (t, 2 H), 6.7 (d, 2 H, J = 7 Hz), and 5.0 (s, 1 H). *Anal.* Calcd for $C_{26}H_{18}S_2O_4$: C, 68.10; H, 3.96; S, 13.99. Found: C, 68.17; H, 3.89; S, 13.94.

Oxidation of I (500 mg) by hydrogen peroxide in acetic acid in a similar manner gave an immediate change from red to colorless. Addition of water and ether, followed by evaporation of the ether layer and recrystallization from acetic acid, gave 289 mg (81%) of thioxanthone sulfone (VII), white needles, mp 190.5–191.5° (lit.[19] 187°). The same product was obtained by a similar oxidation of thioxanthone (IV, Aldrich).

Oxidation of III in the same manner gave white needles of thioxanthene sulfone (85%) on cooling: mp 169° (lit.[20] 170°); uv (CH_3OH) λ_{max}, nm (log ϵ), 232.5 (3.39), 268 (2.70), 276.5 (2.78).

Reduction of VI[6] (2.00 g) by 1 equiv of sodium dithionite (or zinc dust or sodium) in 100 ml of stirred diglyme was carried out under vacuum. The bright red solution turned dark red in 30 min. After 48 hr the solvent was removed by vacuum, leaving an oily red residue. The organic material was extracted therefrom with benzene and evaporation left a red oil, which was placed neat on a neutral alumina column and eluted with benzene. A green band was washed through the column and evaporation left 1.69 g of pale green oil.[21] This material was homogeneous on silica gel and alumina tlc plates: λ_{max}, nm (log ϵ), 254 (3.98), 267 (4.12), and 370 (2.97) (in acetonitrile and dioxane), 255 (4.04), 270 (4.21), 359 (2.92), and 377 (2.99) (in cyclohexane); nmr broad aromatic multiplet at δ 6.7–7.5 ppm; mol wt, 544 (cryoscopic in benzene). The mass spectrum at 70 eV gave a "parent" peak at 273.0719 (calcd 273.0738).[22] By reducing the ionizing potential to 19.9 eV, the true parent peak of m/e 546 appeared at nearly the same intensity as the 273 peak: mass spectrum (19.9 eV) m/e (rel intensity), 547 (42), 546 (98), 545 (54), 469 (45), 348 (25), 288 (32), 287 (31), 274 (54), 273 (100), 197 (45), 78 (293), 77 (261), 52 (84), 51 (84), 50 (61); mass spectrum (70 eV) 274 (95), 273 (100), 198 (44), 197 (68), 165 (35), 78 (52), 77 (84), 51 (21).

When 1.4 g of VII was heated to 200° (0.04 mm), a violet solid, mp *ca.* 65°, was formed. A benzene eluate from neutral alumina was recrystallized several times slowly from petroleum ether–ethanol to give 61.2 mg of white powder, mp 212–215° and analyzing correctly for VIII: mol wt, 528 (cryoscopic in benzene); uv (CCl_4) λ_{max}, nm (log ϵ), 276 (4.30); mass spectrum (70 eV) m/e (rel intensity) 547 (21) 546 (86), 469 (53), 274 (92), 273 (100), 271 (52), 197 (65), 97 (17), 91 (21), 83 (23), 77 (16), 71 (31), 69 (38), 58 (41), 57 (43), 56 (31), 55 (45). *Anal.* Calcd for $C_{38}H_{26}S_2$: C, 83.48; H, 4.79; S, 11.73. Found: C, 83.22; H, 4.74; S, 11.70.

Reduction of VI (500 mg) in 50 ml of dry 1-butanol by 919 mg of phosphonium iodide turned from red to bright yellow as it was heated to reflux. After refluxing for 50 min, the solution turned colorless. After cooling, the 1-butanol was removed *in vacuo*, leaving white crystals which were dissolved in benzene, washed with water, dried, and evaporated. The residue was recrystallized from methanol to give 9-phenylthioxanthene (XI), white needles, mp 99° (lit.[6] 99°).

Oxidation of VII (195 mg) in 2 ml of acetic acid (wine red on heating) by dropwise addition of 2 ml of 50% H_2O_2 gave a white precipitate which redissolved on refluxing. On cooling to 0°, white crystals separated and were recrystallized from acetic acid to give 123 mg of 9-phenylthioxanthene sulfone (IX): mp 194–196° (lit.[23] 193–194°); uv (CH_3OH) λ_{max}, nm (log ϵ), 270 (3.40) and 277 (3.35); nmr (CF_3CO_2H) δ 8.2 (m, 3 H), 7.4 (m, 10 H), 5.4 (s, 1 H).

Oxidation of VI or XI similarly gave IX in 68 and 55% yields, respectively.

Oxidation of VIII (6.2 mg) suspended in 0.5 ml of boiling acetic acid by dropwise addition of 1 ml of 50% H_2O_2 gave 1.6 mg of disulfone (X): mp 285–288°; ir sulfone bands at 1300 and 1155 cm^{-1}; mass spectrum m/e (at 70 eV) 610.1251 (calcd for $C_{38}H_{26}O_4S_2$, 610.1272),[22] other peaks m/e (rel intensity) 610 (14), 484 (17), 471 (16), 455 (39), 355 (22), 321 (30), 305 (100), 289 (57), 281 (34), 273 (15), 267 (16), 257 (49), 241 (86), 239 (49), 226 (15), 207 (52), 196 (27), 181 (21), 165 (27), 151 (33), 125 (26), 111 (54), 105 (57), 99 (50), 97 (93), 85 (98), 77 (43), 73 (93), 64 (95), 57 (215), 44 (384).

1,1′-Dihydro-2,2′-dithia-1,1′-binaphthyl (XVIa) was prepared by reducing 1.00 g (40 mmol) of 2-thianaphthalenium perchlorate in 75 ml of benzene with 20 ml of 10% cobaltocene (80 mmol, Aldrich Chemical Co.) with stirring under reflux for 4 hr. After cooling the benzene was washed and dried. Evaporation gave colorless needles which, after recrystallization from benzene, weighed 300 mg (50%): mp 230–231°; uv λ_{max} (log ϵ) 241 (4.84), 253 (4.61), and 330 (4.44) nm; nmr δ 7.2–7.4 (m 8 H), 6.9 and 6.3 (d, 2 H each, J = 10 Hz), and 3.8 (s, 2 H).

Anal. Calcd for $C_{18}H_{14}S_2$: C, 73.47; H, 4.76; S, 21.77. Found: C, 73.62; H, 4.90; S, 21.67.

(17) A. Schonberg and A. Mustafa, *J. Chem. Soc.*, 657 (1945).

(18) E. G. Davis and S. Smiles, *ibid.*, **97**, 1296 (1910).

(19) E. T. Kaiser and D. H. Eargle, Jr., *J. Amer. Chem. Soc.*, **85**, 1821 (1963).

(20) C. Graebe and O. Schultess, *Justus Liebigs Ann. Chem.*, **263**, 8 (1891).

(21) Since the theoretical yield is 1.47 g, this material evidently was not free of residual benzene, also indicated by the relatively strong m/e 78 peaks in the mass spectra at both 19.9 and 70 eV.

(22) Using an Associated Electrical Industries, Ltd., Model MS9023, high resolution mass spectrometer, matching the m/e 273 peak with perfluoro-*n*-butylamine.

(23) M. Gomberg and E. C. Britton, *J. Amer. Chem. Soc.*, **43**, 1946 (1921).

The same isomer (XVIa) was obtained in 50% yield by reduction with 4 equiv of sodium dithionite in acetonitrile at room temperature for 1 hr. In diglyme, the yield was 64% after 3 hr. Stirring with zinc dust (4 equiv) in benzene under nitrogen for 12 hr gave 51% while in diglyme the yield was 68%.

Reaction of XV with *tert*-butylmagnesium chloride has been reported[3] not only to give XVIa in 12% yield, but also the stereoisomer XVIb, mp 199–200°, in 10% yield, with the same uv and nmr spectra.

Anal. Found: C, 73.12; H, 4.60; S, 21.95.

Oxidation of XVIa (100 mg) in 6 ml of 2:1 70% perchloric acid–acetic acid by heating to boiling gave a dark red-green solution which was quickly cooled to 0° and then 20 ml of ether, precooled to −78°, was added slowly to give 136 mg (72%) of dark green crystals of XV, mp 192–195°.

Oxidation of XVIa[3] (339 mg) in 4 ml of boiling acetic acid by dropwise addition of 1 ml of 50% H_2O_2 gave, on cooling, pale yellow crystals. Recrystallization from acetic acid yielded 317 mg (77%) of the disulfone XVII: mp 261–262°; sulfone bands at 1290 and 1112 cm^{-1}; uv λ_{max} (log ϵ) 284 (4.06) nm.

Anal. Calcd for $C_{18}H_{14}S_2O_4$: C, 60.32; H, 3.94; S, 17.86. Found: C, 60.57; H, 4.13; S, 17.90.

Disproportionations.—All disproportionation reactions were carried out under vacuum at 40–50° in diglyme first dried over calcium hydride and then distilled from a 5:1 potassium–sodium alloy into an evacuated flask containing the reactants and a Teflon-coated magnetic stirring bar. Some reactions involving thioxanthene were carried out in the dark to avoid its possible photodimerization.[24]

A solution of 1.00 g of I and 655 mg of III (protected from light) turned red-violet after 5 days. Filtration yielded 355 mg (27%) of II, mp 330–332°, after recrystallization from xylene.[2] Evaporation of the diglyme, benzene extraction of the black residue, benzene elution from a neutral alumina column, and recrystallization from $CHCl_3$–ethanol recovered 534 mg of III, mp 126–128°. Duplicate reactions not protected from light turned black within 3 days and yielded 181 mg (126 mg) of II and 674 mg (818 mg) of III. An aliquot of this reaction mixture (0.500 g, 1.68 mequiv of I, 0.333 g, 1 mequiv of III) was added to distilled water and titrated with 0.01 *N* NaOH, indicating the formation of 1.33 mequiv (79%) of free perchloric acid.

A similar reaction of 500 mg of I and 333 mg of III carried out in the presence of 1 equiv of pyridine (to neutralize perchloric acid formed) gave a pale pink reaction mixture in 4 hr. The white precipitate (670 mg) was collected. The acetone-soluble fraction gave, after addition of benzene, 233 mg (75%) of pyridinium perchlorate: mp 299–300°; uv (MeOH) λ_{max}, nm (log ϵ), 250 (4.69), 255 (4.73), 262 (4.56).

Anal. Calcd for $C_5H_6ClNO_4$: C, 33.42; H, 3.37; N, 7.79. Found: C, 33.66; H, 3.40; N, 7.66.

The acetone-insoluble solid gave 204 mg (30%) of II on recrystallization from xylene.

A solution of 378 mg of I and 600 mg of XI was red-violet after 5 days. Filtration gave 110 mg (45%) of II. Evaporation of the diglyme solvent, extraction with chloroform, charcoal treatment, filtration, evaporation, and recrystallization recovered 230 mg of XI.

A solution of 500 mg of VI and 531 mg of III gave a red-violet solution in 4 days, either in the light or dark. Filtration gave 184–190 mg (69–71%) of II. Vacuum evaporation of solvent, benzene extraction, benzene elution from neutral alumina, evaporation, and recrystallization from methanol gave 307–328 mg (86–93%) of XI, mp 99°. A similar reaction mixture containing 1 equiv of pyridine to neutralize perchloric acid formed gave no reaction; both starting materials were recovered unchanged.

Reaction of 500 mg of I, 330 mg of III, and 71 mg of $MgCO_3$ in diglyme gave a red reaction mixture which faded to a clear pale yellow overnight. After vacuum distillation of the solvent, the residue was placed on a neutral alumina column and eluted with CCl_4 to give 436 mg of III after recrystallization from ethanol, mp 126–128°. Methanol elution gave 250 mg (71%) of thioxanthone after recrystallization from ethanol as pale yellow needles, mp 216–217°.

Reaction of 250 mg of VI, 134 mg of III, and 28.5 mg of $MgCO_3$ turned from red to colorless overnight. Similar work-up gave 293 mg of what appeared to be a mixture of III and XI (by its infrared spectrum) and 59 mg (22%) of thioxanthone, mp 216–218°.

Registry No.—I, 26401-81-0; II, 10496-86-3; VI disulfone, 26430-92-2; VII, 3166-15-2; VIII, 26430-88-6; IX, 26430-89-7; X disulfone, 26430-90-0; XV, 7432-88-4; XVIa, 25548-01-0; XVIb, 26372-65-6; XVII, 26438-45-9; pyridinium perchlorate, 15598-34-2.

(24) A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 657 (1945).

Chemistry of the Sulfur–Nitrogen Bond. I. Thermal Reactions of Nitrobenzenesulfenanilides[1,2]

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2-Nitrobenzenesulfenanilides undergo an unusual thermal rearrangement to give *o*- and *p*-amino-2-nitrodiphenyl sulfides, phenothiazines, and 2-aminobenzenesulfonanilides. 3-Nitrobenzenesulfenanilide when heated gave only *o*- and *p*-amino-3-nitrodiphenyl sulfides.

Compounds which contain the sulfur–nitrogen bond are of considerable importance both from a practical as well as theoretical standpoint. Compounds which contain this bond have been reported to be useful as antiradiation drugs, antioxidants, and accelerators in the vulcanization of rubber. Factors which may contribute to the sulfur–nitrogen bond's activity, such as steric interactions, coulombic repulsion between nitrogen and sulfur lone-pair electrons, and p–d π bonding, have only recently been investigated in connection with studies of rotation about the S–N bond.[4]

Moore and Johnson investigated the thermal reactions of arylsulfenanilides.[5] They reported that when 2-nitrobenzenesulfenanilide (**1a**) was heated at 160° in aniline for 6 hr a 70% yield of 4′-amino-2-nitrodiphenylsulfide (**2a**) was obtained.[5a] Similar results were obtained with 2-nitrobenzenesulfen-*p*-toluide (**1b**) which gave 2′-amino-5′-methyl-2-nitrobenzene sulfide (**2b**) on heating in *p*-toluidine.[5a] When **1a** was heated in *p*-to-

(1) Reported in part at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969.

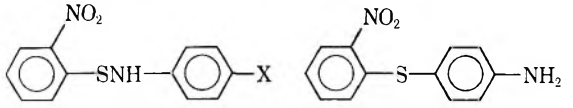
(2) For a preliminary communication, see F. A. Davis, R. B. Wetzel, T. J. Devon, and J. F. Stackhouse, *Chem. Commun.*, 678 (1970).

(3) National Science Foundation Undergraduate Research Participant, 1968.

(4) (a) J. M. Lehn and J. Wagner, *Chem. Commun.*, 1298 (1968); (b) M. Raban and F. B. Jones, Jr., *J. Amer. Chem. Soc.*, **91**, 2180 (1969); (c) M. Raban, G. W. J. Kenney, Jr., and F. B. Jones, Jr., *ibid.*, **91**, 6677 (1969).

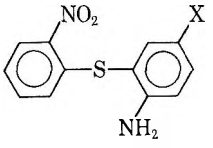
(5) (a) M. L. Moore and T. B. Johnson, *ibid.*, **57**, 1517 (1935); (b) *ibid.*, **57**, 2234 (1935); (c) *ibid.*, **58**, 1091 (1936); (d) *ibid.*, **58**, 1960 (1936).

luidine, **2b** was obtained, and **1b** in aniline gave **2a**.[5a] Products were isolated by treating the reaction mixture with dilute hydrochloric acid, dissolving the resulting precipitate in ethanol, and neutralizing to give the aminonitrodiphenyl sulfide.[5a]



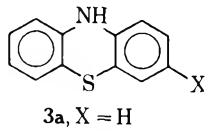
1a, X = H
b, X = CH_3

2a

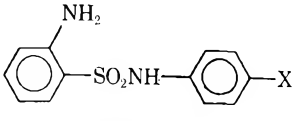


2b, X = CH_3
c, X = H

In a reinvestigation of this thermal rearrangement, we observed quite different results. Heating **1a** in a sealed tube with an excess of aniline for 15 hr at 195° gave, in addition to a 12% yield of **2a**,[6] phenothiazine (**3a**),[7] 3%, 2′-amino-2-nitrodiphenyl sulfide (**2c**),[8] 5%, and 2-aminobenzenesulfonanilide (**4a**),[9] 37%. Sulfenamide **1b** in *p*-toluidine gave **2b**, 18%, 3-methylphenothiazine (**3b**),[10] 14%, and 2-aminobenzenesulfon-*p*-toluidine (**4b**),[11] 55%. Sulfenamide **1a** in *p*-toluidine gave **2b**, **3b**, and **4b**. Sulfenamide **1b** in aniline gave **1a**, **2a**, **2c**, **3a**, and **4a**. No products from the original sulfenamides were isolated. Products were separated by column chromatography and identified by comparison with authentic samples. At lower temperatures the reaction failed to precede to any significant degree. These results are summarized in Table I.



3a, X = H
b, X = CH_3



4a, X = H
b, X = CH_3

TABLE I
THERMAL REACTIONS OF SULFENAMIDES

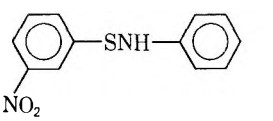
Sulfenamide	Solvent	Temp, C°	Time, hr	Products (% yield)
1a	Aniline	195	15.6	**1a** (34), **2a** (12), **2c** (5), **3a** (3), **4a** (37)
	p-Toluidine	195	15.2	**2b** (20), **3b** (12), **4b** (53)
	p-Toluidine	110	12	**1b** (90)
1b	*p*-Toluidine	195	15.2	**2b** (18), **3b** (14), **4b** (55)
	Aniline	195	15.6	**1a** (36), **2a** (14), **2c** (7), **3a** (3), **4a** (35)
	Aniline	110	12	**1a** (88), **1b** (10)
1b[a]	*p*-Toluidine	195	16	**2b** (21), **3b** (8), **4b** (60)
5	Aniline	195	15	**6a** (22), **6b** (60)

[a] Degassed.

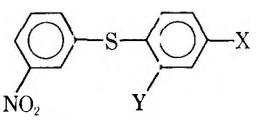
(6) H. H. Hodgson and W. Rosenberg, *J. Chem. Soc.*, 181 (1930).
(7) A. Bernthsen, *Ber.*, **16**, 2896 (1883).
(8) A. Levi, L. A. Warren, and S. Smiles, *J. Chem. Soc.*, 1492 (1933).
(9) F. Ullmann and C. Gross, *Ber.*, **43**, 2694 (1910).
(10) H. Gilman and D. A. Shirley, *J. Amer. Chem. Soc.*, **66**, 888 (1944).
(11) J. H. Freeman and E. C. Wagner, *J. Org. Chem.*, **16**, 815 (1951).

Moore and Johnson reported the melting point of sulfide **2b** as 108°,[5a] whereas the compound isolated by us had mp 87°. The structure of sulfide **2b** is supported by elemental analysis, its infrared spectrum, nmr spectrum, and independent synthesis. The infrared spectrum of **2b** showed doublet absorption centered at 3400 cm^{-1} (primary amine) and strong absorption at 812, 802, and 740 cm^{-1} characteristic of 1,2- and 1,2,5-substituted benzene.[12] The proton nmr spectrum showed absorption at δ 2.25 (singlet), 4.2 (broad singlet), and 7.0 and 8.25 (relative areas 3:2:6:1) in agreement with proposed structure. Sulfide **2b** was prepared independently by condensation of the sodium salt of 2-amino-5-methylbenzenethiol, prepared by zinc reduction of 2-nitro-5-methylphenyl disulfide, with 2-chloronitrobenzene to give a greater than 70% yield of **2b**.

3-Nitrobenzenesulfenanilide (**5**), prepared from 3-nitrobenzenesulfenyl chloride[13] and aniline, when heated in aniline gave only rearrangement products 2′-amino-3-nitrodiphenyl sulfide (**6a**) and 4′-amino-3-nitrodiphenyl sulfide (**6b**). The structure of sulfenamide **5** was supported by elemental analysis, its infrared spectrum, and nmr spectrum. The infrared spectrum of **5** showed absorption at 3350 cm^{-1} (secondary amine) and a medium band at 908 cm^{-1}. This absorption was present in all of the sulfenamides investigated and is presumably the S–N stretching vibration. This absorption was not present in the sulfides. The proton nmr spectrum of **5** showed absorption at δ 5.25, 7.1, and 7.95 (relative areas 1:7:2) in agreement with the proposed structure.

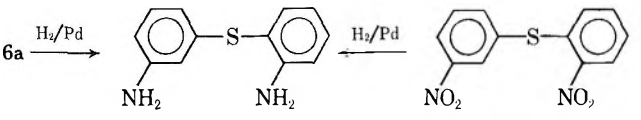


5



6a, X = H; Y = NH_2
b, X = NH_2; Y = H

The structure of **6a** is supported by elemental analysis, infrared spectrum, and reduction to 2,3′-diaminodiphenyl sulfide (**7**). Diamine **7** was prepared independently by reduction of 2,3′-dinitrodiphenyl sulfide (**8**).



7 **8**

The infrared spectrum of **6a** showed doublet absorption centered at 3420 cm^{-1} (primary amine) and strong absorption at 875, 755, 750, and 730 cm^{-1}, characteristic of 1,3- and 1,2-disubstituted benzenes.[12]

Structural proof of **6b** was based upon elemental analysis, infrared and proton nmr spectra, and conversion with iodomethane to 4-*N*,*N*-dimethylamino-3′-nitrodiphenyl sulfide.[13] The infrared spectrum of **6b** showed doublet absorption centered at 3410 cm^{-1} (primary amine) and at 875, 825, 800, and 735 cm^{-1}, characteristic of 1,3- and 1,4-disubstituted benzenes.[12] The nmr spectrum of **6b** showed absorption at δ 3.8, 6.6, 7.3, and 7.8 (relative areas 2:2:4:2).

Phenothiazines **3a** and **3b** apparently formed from rearrangement products **2c** and **2b**, respectively. Under

(12) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Inc., Boston, 1966, Chapter 5.
(13) H. Z. Lecher and E. M. Hardy, *J. Org. Chem.*, **20**, 475 (1955).

the reaction conditions sulfide **2c** in aniline gave a 25–30% yield of **3a**, and **2b** in *p*-toluidine gave a 42% yield of **3b**. Products were separated by column chromatography and identified by comparison with authentic samples. These results are summarized in Table II.

TABLE II
REARRANGEMENT OF 2,2′-AMINONITRODIPHENYL SULFIDES AT 195° FOR 15 HR

Diphenyl sulfide	Solvent	Products (% yield)
2c	Aniline	**3a** (29), **2c** (61)
2b	*p*-Toluidine	**3b** (42), **2b** (45)

Substitutions on the S–N bond in sulfenamides by the solvent take place under relatively mild conditions. At 110°, **1a** in *p*-toluidine gave a greater than 90% yield of **1b**, and **1b** in aniline gave an 88% yield of **1a**. Furthermore, at 195° when **1b** was heated in aniline, a 36% yield of **1a** was isolated (see Table I).

Discussion

Apparently three reactions take place when 2-nitrobenzenesulfenanilides are heated in primary aromatic amine solvents. They rearrange to give *o*- and *p*-amino-2-nitrodiphenyl sulfides, with the para isomer predominating. They undergo an unusual oxidation–reduction in which the nitro group is reduced and the sulfur oxidized, and they undergo facile exchange with the solvent.

Recently we have established that **2c** rearranges to phenothiazine (**3a**) *via* a thermal Smiles rearrangement,[14] and this mechanism undoubtedly applies to the arrangement of **2b** to **3b**.

The rearrangement of nitrobenzenesulfenanilides to *o*- and *p*-aminonitrodiphenyl sulfides may be inter- or intramolecular. The photolysis of 2,4-dinitrobenzenesulfenyl acetate in benzene to give 2,4-dinitrodiphenyl sulfide[15] and the thermal rearrangement of aryl 2-nitrobenzenesulfenates to give the corresponding hydroxy diphenyl sulfides[16] have both been shown to be intermolecular.

On the basis of present information, no definitive answer as to the inter- or intramolecularity of the rearrangement of sulfenamides can be made because exchange may occur prior to rearrangement.

The ability of an *o*-nitro group to transfer its oxygens to an adjacent group is well known and has been reviewed.[17] The pyrolysis of *tert*-butyl 2-nitrobenzenesulfenate gave, among other products, aniline.[18] The photolysis of 2,4-dinitrobenzenesulfen-*N*-methylaniline gave 2-amino-4-nitrobenzenesulfonyl-*N*-methylaniline, but **1a** under the same conditions gave azobenzene.[15] Brown has recently demonstrated the intramolecular transfer of oxygens in the base-catalyzed rearrangement of **1a** to 2-azobenzenesulfenate.[19]

Formation of 2-aminobenzenesulfonamides **4a** and **4b** probably proceeds in several steps, but attempts to isolate intermediates have thus far failed. However, the lack of sulfonamide formation for sulfenamide **5** and the fact that the absence of molecular oxygen has no effect on the formation of **4b** strongly suggest that the oxygens are transferred by an intramolecular process from the nitro group to the sulfur.

(14) F. A. Davis and R. B. Wetzel, *Tetrahedron Lett.*, 4483 (1969).
(15) D. H. R. Barton, T. Nakano, and P. G. Sammes, *J. Chem. Soc. C*, 322 (1968).
(16) D. R. Hogg, J. H. Smith, and P. W. Vipond, *ibid.*, 2713 (1968).
(17) J. D. Loudon and G. Tennant, *Quart. Rev.*, **18**, 389 (1964).
(18) D. R. Hogg and P. W. Vipond, *J. Chem. Soc. C*, 60 (1970).
(19) C. Brown, *J. Amer. Chem. Soc.*, **91**, 5832 (1969).

Experimental Section

Sulfenamide **1a**[5b] and **1b**[5a] were prepared according to procedures given in the literature. Solvents were purified by standard methods. Melting points were obtained on a Fisher-Johns apparatus and are uncorrected. Proton nmr spectra were measured on a Varian A-60A instrument, and infrared spectra were measured on a Perkin-Elmer 457 spectrometer.

General Procedure for Thermal Rearrangement of Sulfenamides.—Sulfenamides were heated in an oil bath with an excess of amine in a sealed tube for 12–16 hr. Excess solvent was removed under vacuum (oil pump) and the dark residue chromatographed on Florisil. Samples isolated from the column were washed with pentane or methanol and dried under high vacuum for at least 12 hr.

2-Nitrobenzenesulfenanilide (1a).—Sulfenamide **1a** (0.1553 g, 0.00063 mol) in aniline gave, on elution with pentane–benzene (1:1), 0.0038 g (3%) of a white solid, mp 183° (lit.[7] mp 180°), identified as **phenothiazine (3a)** by comparison of its properties with an authentic sample. Elution with pentane–benzene (2:3) gave 0.0529 g (34%) of a red solid, mp 94° (lit.[20] mp 94.5°), identified as sulfenamide **1a** by comparison of its properties with an authentic sample. The proton nmr spectrum of **1a** ($CDCl_3$) showed absorption at δ 5.1 (s, 1 H), 7.2 (m, 8 H), and 8.2 (d, 1 H). Elution with benzene–chloroform (4:1) gave 0.0078 g (5%) of a yellow solid, mp 86° (lit.[8] mp 85°), identified as **2′-amino-2-nitrodiphenyl sulfide (2c)** by comparison of its properties with an authentic sample. Diphenyl sulfide **2c** had the following properties: infrared (KBr) 3450 (s), 3330 (s), 3060 (w), 1610 (s), 1590 (s), 1560 (m), 1500 (s), 1480 (s), 1450 (m), 1330 (s), 1300 (s), 1250 (w–m), 1150 (w), 1100 (m), 1055 (m), 1050 (m), 1040 (m), 1020 (m–w), 850 (m), 780 (m), 765 (s), 730 (s), 710 (m), 680 (w), and 500 cm^{-1} (m); nmr ($CDCl_3$) δ 4.2 (s, 2 H), 6.8 (complex d, 3 H), 7.3 (m, 4 H), and 8.2 (d, 1 H). Further elution with benzene–chloroform (1:1) gave 0.0188 g (12%) of a brown-yellow solid, mp 102° (lit.[5] mp 102–103°), identified as **4′-amino-2-nitrodiphenyl sulfide (2a)** by comparison of its properties with an authentic sample. Diphenyl sulfide **2a** had the following properties: infrared spectrum (KBr) 3400 (m–w), 3320 (m), 3210 (w), 1645 (w), 1595 (s), 1560 (m), 1510 (s), 1450 (w–m), 1340 (s), 1305 (s), 1290 (m), 1250 (m–w), 1180 (m), 1100 (m), 1040 (w), 840 (m–w), 786 (w–m), and 730 cm^{-1} (s); nmr ($CDCl_3$) δ 4.05 (s, 2 H), 6.8 (m, 3 H), 7.25 (m, 4 H), and 8.2 (d, 1 H). Elution with chloroform gave a brown oil which was alternately washed with 5% sodium hydroxide solution and water (three 50-ml portions). The aqueous washings were carefully neutralized with 5% hydrochloric acid solution and on cooling overnight gave 0.0542 g (37%) of white crystals, mp 119–120° (lit.[9] mp 119°), identified as **2-aminobenzenesulfonanilide (4a)** by comparison of its properties with an authentic sample. Sulfonamide **4a** had the following properties: infrared (KBr) 3470 (s), 3380 (s), 3310 (s), 1630 (s), 1610 (s), 1490 (s), 1460 (m), 1420 (m), 1330 (m), 1290 (m), 1290 (s), 1230 (m), 1155 (s), 1100 (m), 1070 (m–w), 1040 (m–w), 930 (s), 820 (w), 760 (s), 730 (m) 700 (s), 630 (w), and 600 cm^{-1} (s); nmr ($CDCl_3$) δ 4.7 (s, 2 H), 6.7 (t, 2 H), (s, 7 H), and 7.5 (m, 1 H).

2-Nitrobenzenesulfen-*p*-toluidine (1b).[5a]—Sulfenamide **1b** had the following properties: infrared (KBr) 3450 (m), 1600 (m), 1510 (s), 1340 (s) 1300 (m–s), 1290 (m), 1240 (m), 1100 (w), 1030 (w), 910 (m), 960 (w), 815 (s), 790 (m), and 735 cm^{-1} (s); nmr ($CDCl_3$) δ 2.25 (s, 3 H), 6.8 (m, 3 H), 7.2 (m, 3 H), and 8.2 (m, 1 H). Sulfenamide **1b** (0.1448 g, 0.00056 mol) in *p*-toluidine gave, on elution with pentane–benzene (4:1), 0.0172 g (14%) of white crystals, mp 167–168 (lit.[10] mp 168°), identified as **3-methylphenothiazine (3b)** by comparison of its properties with an authentic sample. Compound **3a** had the following properties: infrared (KBr) 3340 (m), 1600 (w), 1470 (s), 1430 (m), 1310 (m), 1300 (m–w), 1260 (m), 920 (w), 810 (s), 740 (s), and 640 cm^{-1} (w); nmr (acetone-d_6) δ 2.18 (s, 3 H), 6.8 (t, 7 H), and 7.6 (s, 1 H). Elution with benzene–chloroform (4:1) gave

(20) M. P. Cava and C. E. Blake, *ibid.*, **78**, 5444 (1956).

0.026 g (18%) of red crystals, mp 87°, identified as **2'-amino-5'-methyl-2-nitrodiphenyl sulfide** (**2b**) by comparison of its properties with an authentic sample (see below). Elution with chloroform gave a brown oil which was alternately washed with 5% sodium hydroxide solution and water (three 50-ml portions). The aqueous washings were carefully neutralized with 5% hydrochloric acid solution and on cooling overnight gave 0.0795 g (55%) of white crystals, mp 124–126° (lit.[11] mp 124°), identified as **2-aminobenzenesulfon-*p*-toluidide** (**4b**) by comparison of its properties with an authentic sample. Sulfonamide **4b** had the following properties: infrared (KBr) 3460 (m), 3380 (m), 3250 (m), 1625 (m–s), 1600 (m), 1560 (w), 1510 (m–s), 1480 (s), 1450 (m), 1390 (m–w), 1320 (m), 1300 (m), 1225 (m), 1135 (s), 915 (m), 850 (m), 810 (m), 760 (s), 730 (m), 700 (m), and 600 cm^{-1} (s); nmr ($CDCl_3$) δ 2.25 (s, 3 H), 4.82 (s, 2 H), 6.7 (t, 2 H), 6.95 (s, 5 H, and 7.3 (m, 2 H).

2'-Amino-5'-methyl-2-nitrodiphenyl Sulfide (**2b**).—3-Chloro-4-nitrotoluene (20.5 g, 0.12 mol) in 100 ml of alcohol was added dropwise to a solution of sodium disulfide (prepared from 23 g of sodium sulfide 9-hydrate and 3.75 g of sulfur) in 150 ml of alcohol in a 500-ml three-necked flask equipped with reflux condenser, dropping funnel and mechanical stirrer. After addition, the reaction mixture was refluxed for 6 hr and cooled, and the precipitated salt and disulfide were removed by filtration. The solid was washed with alcohol (two 50-ml portions) and with water (two 50-ml portions). After air drying, 9.0 g (45%) of the crude disulfide was obtained and used without further purification. The crude disulfide, 4.0 g, was dissolved in 350 ml of glacial acetic acid in a 500-ml three-necked flask equipped with magnetic stirring bar, reflux condenser, and thermometer. The reaction mixture was warmed to 100°, 20.0 g of zinc dust added over 0.5 hr, and the reaction mixture refluxed for 1 hr. The solution was filtered while hot and the residue washed with hot acetic acid (two 50-ml portions) and hot water (100 ml). Hot water (800 ml) was added to the filtrate and on cooling gave 1.3 g of the zinc salt of 2-amino-5-methylbenzenethiol. The zinc salt (1.3 g, 0.00382 mol) was placed in 100 ml of absolute ethanol in a 250-ml three-necked flask equipped with mechanical stirrer and reflux condenser. Metallic sodium (0.175 g, 0.0076 g-atom) was slowly added to the reaction mixture, the solution was refluxed for 0.5 hr at which time 1-chloro-2-nitrobenzene (1.16 g, 0.0076 mol) was added, and the reaction mixture was refluxed for 10 hr. The solution was cooled and filtered, and the solvent was removed to give a dark oil which was redissolved in ether, washed with 5% sodium hydroxide solution (two 50-ml portions), treated with charcoal (Norit A), and dried over anhydrous magnesium sulfate. Removal of solvent under vacuum gave a yellow oil which solidified under high vacuum. Crystallization from ether–pentane gave 1.4 g (71%) of bright red-orange plates, mp 87°.

Anal. Calcd for $C_{13}H_{12}N_2O_2S$: C, 59.98; H, 4.65. Found: C, 60.29; H, 4.52.

Diphenyl sulfide **2b** had the following properties: infrared (KBr) 3440 (s), 3360 (s), 3100 (w), 3030 (w), 3010 (w), 1630 (m), 1610 (m), 1525 (s), 1495 (s), 1460 (m), 1435 (m), 1415 (w), 1350 (s), 1310 (m–w), 1270 (s), 1210 (s), 1180 (w), 1125 (w), 1035 (s), 875 (m), 800 (m–w), 745 (s), 730 (s,) and 665 cm^{-1} (m); nmr ($CDCl_3$) δ 2.25 (s, 3 H), 4.2 (broad s, 2 H), 6.8 (t, 2 H), 7.3 (m, 6 H), and 8.2 (m, 1 H).

2-Nitrobenzenesulfen-*p*-toluidine (**1b**).—**1b** (0.1603 g, 0.000627 mol) in aniline gave, on elution with pentane–benzene (1:1), 0.0040 g (3%) of **3a**; elution with pentane–benzene (2:3) gave 0.0555 g (36%) of **1a**; elution with benzene–chloroform (4:1) gave 0.0108 g (7%) of **2c**; elution with benzene–chloroform (4:1) gave 0.0219 g (14%) of **2a**; elution with chloroform gave an oil which when treated with 5% sodium hydroxide followed by neutralization and cooling gave 0.0578 g (38%) of **4a**.

3-Nitrobenzenesulfenanilide (**5**).—3-Nitrobenzenesulfenyl chloride,[12] prepared from 3-nitrophenyl disulfide (Aldrich Chemical Co.) (52.6 g, 0.171 mol) and dry chlorine gas in 100 ml of dry chloroform, was added dropwise over 0.5 hr to aniline (62.2 g, 0.680 mol) in 100 ml of dry ether cooled to −78° in a Dry Ice–acetone bath in a 1000-ml three-necked flask equipped with dropping funnel, mechanical stirrer, and nitrogen inlet tube. After addition, the yellow reaction mixture was stirred for an additional 0.5 hr at −78° at which time 700 ml of dry pentane, cooled to −78°, was added followed by 50 ml of water, and the reaction mixture was allowed to warm to room temperature. The yellow sulfenamide which had precipitated out was collected by filtration, dissolved in ether, washed with water (three 50-ml portions) and 5% sodium hydroxide solution (two 50-ml portions), and dried over anhydrous magnesium sulfate. Removal of solvent under vacuum gave a yellow solid which was crystallized from pentane–ether at −50° to give 34 g (40%) of yellow needles, mp 93–94°.

Anal. Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09; N, 11.4; S, 13.0. Found: C, 58.79; H, 3.97; N, 11.57; S, 13.17.

Sulfenamide **5** had the following properties: infrared (KBr) 3400 (m), 1600 (s), 1510 (s), 1490 (s), 1400 (m), 1320 (s), 1300 (m), 1290 (m), 1220 (m), 1110 (m), 1060 (w), 1010 (w), 995 (w), 910 (m–s), 870 (s), 830 (w–m), 800 (m), 745 (s), 720 (s), and 690 cm^{-1} (s); nmr ($CDCl_3$) δ 5.25 (broad s, 1 H), 7.1 (m, 7 H), and 7.95 (m, 2 H). Sulfenamide **5** (0.1650 g, 0.00067 mol) in aniline gave, on elution with pentane–ether, an oil which on sublimation at 40° (0.5 mm) gave 0.0363 g (22%) of yellow needles, mp 63–64°, identified as **2'-amino-3-nitrodiphenyl sulfide** (**6a**) by reduction to **7**.

Anal. Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.09. Found: C, 58.51; H, 4.39.

Diphenyl sulfide **6a** had the following properties: infrared (KBr) 3465 (m), 3370 (m), 1615 (s), 1525 (s), 1480 (m), 1460 (w), 1445 (w), 1350 (s), 1310 (w), 1275 (w), 1250 (w), 1155 (w), 1120 (w), 1070 (w), 1020 (w), 885 (w–m), 875 (m), 850 (w), 800 (m), 755 (s), 750 (s), 730 (s), and 668 cm^{-1} (m); nmr ($CDCl_3$) δ 4.2 (s, 2 H), 6.8 (t, J = 8 Hz, 2 H), 7.4 (m, 4 H), and 8.0 (s, 2 H). Further elution with pentane–ether gave 0.099 g (60%) of yellow plates, mp 130–131°, identified as **4-amino-3-nitrodiphenyl sulfide** (**6b**) by conversion with iodomethane to 4-*N*,*N*-dimethylamino-3'-nitrodiphenyl sulfide.[13]

Anal. Calcd for $C_{12}H_{10}N_2O_2S$: C, 58.52; H, 4.06; N, 11.4; S, 13.0. Found: C, 58.46; H, 4.11; H, 11.29; S, 12.80.

Diphenyl sulfide **6b** had the following properties: infrared (KBr) 3450 (m), 3370 (m), 1625 (m), 1595 (m), 1510 (m–s), 1490 (m–s), 1450 (w), 1420 (w), 1345 (s), 1300 (m), 1270 (m), 1190 (m), 1110 (w–m), 1100 (w), 875 (m), 825 (m), 810 (w), 800 (m), 745 (m), 735 cm^{-1} (s), nmr ($CDCl_3$) δ 3.3 (broad s, 2 H), 6.6 (d, J = 8 Hz, 2 H), 7.3 (m, 4 H), and 7.8 (m, 2 H).

Reduction of 6a with Hydrogen.—Compound **6a** (0.1199 g, 0.00049 mol) in 50 ml of absolute ethanol at 40 psi over 100 mg of 10% palladium on charcoal for 6 hr gave a oil which was sublimed at 110° (0.1 mm). The resulting clear oil, 0.074 g (70%), was identified as **2,3'-diaminodiphenyl sulfide** (**7**) by comparison of its properties with an authentic sample (see following discussion).

Treatment of 6b with Iodomethane.—In a 100-ml one-necked flask equipped with an efficient reflux condenser was placed sulfide **6b** (0.2612 g, 0.00106 mol) in 50 ml of absolute methanol and 1.0 g of iodomethane. The reaction mixture was refluxed for 48 hr, solvent removed under vacuum, and the resulting oil dissolved in benzene. The benzene solution was washed with 5% potassium hydroxide (two 50-ml portions) and dried over anhydrous magnesium sulfate. The solvent was removed after drying. The oil dissolved in 50 ml of methanol and 1.0 g of iodomethane, and the reaction mixture refluxed for 24 hr. The solvent was removed, and the dark oil was dissolved in xylene and heated at 138° for 4 hr in an oil bath. Removal of solvent under vacuum gave a greenish oil which when chromatographed on Florisil (elution with benzene) gave 0.101 g (34%) of yellow plates, mp 116–118°(lit.[13] mp 115–116°), identified as 4-*N* *N*-dimethylamino-3'-nitrodiphenyl sulfide[13] by comparison of its properties with an authentic sample. 4-*N*,*N*-Dimethylamino-3'-nitrodiphenyl sulfide had the following properties: infrared (KBr) 3100 (w), 2900 (w), 1595 (s), 1502 (s), 1445 (m), 1365 (m–s), 1350 (s), 1310 (w), 1275 (w–m), 1230 (m), 1200 (s), 1125 (m), 1100 (w), 1070 (m), 1000 (w), 880 (s), 815 (s), 765 (w), 750 (m–s), 735 (s), and 670 cm^{-1} (m); nmr ($CDCl_3$) δ 3.05 (s, 6 H), 6.7 (d, J = 9 Hz, 2 H), 7.3 (m, 4 H), and 7.82 (m, 2 H).

2,3'-Dinitrodiphenyl Sulfide (**8**).—In a 250-ml three-necked flask equipped with mechanical stirrer and reflux condenser was placed 3-nitrodiphenyl disulfide (2.0 g, 0.0065 mol) and sodium (0.312 g, 0.013 g-atom) in 100 ml of absolute ethanol. The reaction mixture was refluxed for 0.5 hr, and 2-chloronitrobenzene (2.054 g, 0.012 mol) was added slowly with stirring. The reaction mixture was heated at reflux for an additional 12 hr and filtered while hot. The solvent was removed under vacuum to give a dark oil which was taken up in ether, filtered, washed with 5% potassium hydroxide (two 50-ml portions) and water (two 50-ml portions), treated with charcoal (Norit A), and dried over anhydrous magnesium sulfate. Removal of the ether solvent gave an orange solid which was crystallized from ethanol to give 2.8 g (85%) of yellow-orange needles, mp 137–138°.

Anal. Calcd for $C_{12}H_8N_2O_4S$: C, 52.17; H, 2.95. Found: C, 52.26; H, 2.95.

Diphenyl sulfide **8** had the following properties: infrared (KBr) 3010 (w), 1590 (m), 1520 (s), 1450 (w), 1325 (s), 1340 (m), 1310 (w), 1260 (w), 1100 (w), 1055 (w), 1040 (w), 915 (w), 880 (w), 810 (w), 790 (m), 750 (w), 735 (s), and 680 cm^{-1} (w); nmr ($CDCl_3$) δ 6.9 (m, 1 H), 7.3 (m, 2 H), 7.8 (m, 2 H), and 8.4 (m, 3 H).

2,3'-Diaminodiphenyl Sulfide (7).—Hydrogenation of sulfide **8**, prepared above (0.20 g, 0.000725 mol) in 100 ml of absolute ethanol at 40 psi over 200 mg of 10% palladium on charcoal for 6 hr, yielded an oil which was distilled at 110° (0.1 mm). The resulting clear oil, 0.102 g (65%), failed to crystallize. An analytical sample of **7** was obtained by preparative glc.

Anal. Calcd for $C_{12}H_{12}N_2S$: C, 66.63; H, 5.59. Found: C, 66.76; H, 5.70.

Aminodiphenyl sulfide **7** had the following infrared and nmr properties: infrared (thin film) 3410 (m), 3320 (m), 2980 (w), 1620 (s), 1590 (s), 1520 (m), 1480 (s), 1450 (w), 1410 (w), 1380 (w), 1330 (w), 1305 (w), 1145 (m), 1070 (w), 1020 (w), 990 (m), 940 (w–m), 855 (w–m), 835 (m), 815 (w–m), 770 (s), 750 (s), 685 cm^{-1} (m–s); nmr ($CDCl_3$) δ 3.6 (broad s, 2 H), 4.25 (s, 2 H), and 6.8 (m, 8 H).

General Procedure for Rearrangement of 2,2'-Aminonitrodiphenyl Sulfides.—Sulfides were heated in an oil bath at 195° with an excess of amine in a sealed tube. Excess solvent was removed under vacuum and the dark residue chromatographed on Florisil. Samples isolated from the column were washed with pentane and placed under vacuum for at least 8 hr.

Phenothiazine (3a).—Sulfide **2c** (0.1554 g, 0.000632 mol) in aniline gave, on elution with benzene–pentane (3:2), 0.0357 g (29%) of a white solid, mp 183° (lit.[7] mp 180°), identified as **3a** by comparison of its properties with an authentic sample. Elution with pentane–benzene (1:1) gave 0.0948 g (61%) of a yellow-orange solid, mp 86° (lit.[8] mp 85°), identified as **2c** by comparison of its properties with an authentic sample.

3-Methylphenothiazine (3b).—Sulfide **2b** (0.1596 g, 0.000614 mol) in *p*-toluidine gave, on elution with pentane–benzene (4:1), 0.0557 g (42%) of a white solid, mp 167–168° (lit.[10] mp 168°), identified as **3b** by comparison of its properties with an authentic sample. Elution with benzene gave 0.0723 g (45%) of a red solid, mp 87°, identified as **2b** by comparison of its properties with an authentic sample.

Registry No.—**1a**, 4837-33-6; **1b**, 4837-32-5; **2a**, 1144-81-6; **2b**, 27332-17-8; **2c**, 19284-81-2; **3b**, 3939-47-7; **4a**, 27332-20-3; **4b**, 27384-96-9; **5**, 27332-21-4; **6a**, 27332-22-5; **6b**, 27332-23-6; **7**, 27332-24-7; **8**, 27332-25-8; 4-*N*,*N*-dimethylamino-3'-nitrodiphenyl sulfide, 27332-26-9.

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Reduction of Aromatic Nitro Compounds with Sodium Borohydride in Dimethyl Sulfoxide or Sulfolane. Synthesis of Azo or Azoxy Derivatives

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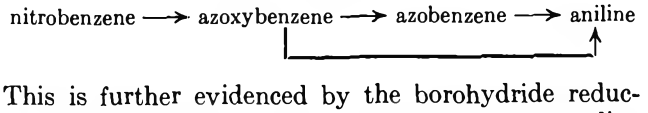
The reduction of aromatic nitro compounds with sodium borohydride in the polar aprotic solvents, DMSO and sulfolane, has been investigated. The reactions involve initial production of azoxy compounds which, in most cases, are subsequently reduced to the corresponding azo derivatives and amines. Other functional groups including cyano and amido are not reduced under the reaction conditions. Electron-withdrawing substituents facilitate both the initial production of azoxy compounds and the further reduction to azobenzenes and anilines. Electron-releasing groups slow the reductions of the azoxy compounds to the extent that these derivatives may be obtained in reasonable yields.

During a recent investigation of the reduction of aliphatic halides and tosylates with sodium borohydride in polar aprotic solvents,[2] we observed that reduction of aromatic nitro groups proceeded slowly at mild temperatures (*i.e.*, 25°) enabling benzylic halides to be selectively removed in their presence; the same results have also been obtained independently by Bell and coworkers.[3] However, at higher temperatures (*i.e.*, 85°) we have observed the ready reduction of aromatic nitro groups by borohydride in dimethyl sulfoxide or sulfolane to initially afford azoxy compounds which may be further reduced to mixtures of the corresponding azo derivatives and amines. As part of our exploratory investigations of the synthetic utility of borohydride in polar aprotic solvents,[2] we wish to report the scope of such reductions as convenient procedures for preparing azoxy and/or azobenzenes.

In order to determine the timing of production of the various observed products and thus aid in obtaining the best experimental procedures, the reduction of nitrobenzene in DMSO was monitored using gas chromatography to simultaneously measure the disappearance of nitrobenzene and appearance of azoxybenzene, azobenzene, and aniline. To conveniently accomplish this, an internal standard was added at the beginning of the reaction. Small aliquots of the reaction mixture were removed at appropriate time intervals, quenched in water, and extracted with chloroform, and the organic solution was analyzed. The results of such studies at 55 and 85° are plotted in Figure 1. Several noteworthy features of the reaction are evident from these plots. First, both cases suggest that the overall reduction occurs in three sequential steps.



This is further evidenced by the borohydride reduction of *p,p'*-dichloroazoxybenzene to the corresponding azo and amine derivatives (entry 24, Table I). Furthermore, the rate of formation of azoxybenzene is very much faster than is subsequent reduction at 85°; the

(1) (a) National Science Foundation Undergraduate Research Participant, (b) Undergraduate Research Participant, 1969–present.

(2) R. O. Hutchins, D. Hoke, J. Keogh, and D. Kobarski, *Tetrahedron Lett.*, 3495 (1969).

(3) H. M. Bell, C. W. Vanderslice, and A. Spehar, *J. Org. Chem.*, **34**, 3923 (1969).

TABLE I

REDUCTION OF AROMATIC NITRO COMPOUNDS WITH SODIUM BOROHYDRIDE IN DIMETHYL SULFOXIDE OR SULFOLANE

Entry	Compd	Registry no.	Solvent	T, °C	Time, hr	Yields, %[a] Amine	Azo	Azoxy	Other
1	Nitrobenzene	98-95-3	DMSO	85	1.5	22.4	74.6		
2			DMSO[b]	85	2.0	9.8	77.6		
3			Sulfolane	100	8.5	50.3	26.3	Trace	
4			Sulfolane	110	7.0	53.9	20.0	Trace	
5	*p*-Nitrotoluene	99-99-0	DMSO	85	1.5				*c*
6			Sulfolane	100	2.5	18.7	18.6	44.2	
7			Sulfolane	100	12	21.7	28.3	30.3	
8			Sulfolane	100	44	45.5	34.0		
9	*m*-Nitrotoluene	99-08-1	DMSO	85	1.5	*Ca.* 3	40.9	49.0	
10			DMSO	85	12.0	22.9	76.1		
11	*o*-Nitrotoluene	88-72-2	DMSO	85	1.5	10.5	1.4	48.3	10.5[d]
12			DMSO	85	5	14.2	5.2	53.9	
13	*p*-Nitroanisole	100-17-4	DMSO	85	1.5	*Ca.* 5	7.0	77.8	
14			DMSO	85	34	11.0	8.4	69.9	
15	*p*-Nitrophenetole	100-29-8	DMSO	85	5	*Ca.* 4	*Ca.* 3	90.0	
16	*m*-Nitroanisole	555-03-3	DMSO	85	1.5	13.3	75.9		
17	*o*-Nitroanisole	91-23-6	DMSO	85	34	63.1	22.3		
18	*o*-Nitrobiphenyl	86-00-0	DMSO	85	1.5	22.6		71.5	
19	*p*-Nitroaniline	100-01-6	DMSO	85	1.5				89.5[d]
20			DMSO	85	31				25.6[d]
21	*p*-Nitrobenzonitrile	619-72-7	DMSO	85	1.5	24.4	58.4[e]		
22	*p*-Nitrobenzamide	619-80-7	DMSO	85	1.5	*f*	50[g]		
23	*p*-Chloronitrobenzene	100-00-5	DMSO	85	1.5	38.3	41.0		
24	*p,p'*-Dichloroazoxybenzene	614-26-6	DMSO	85	1.5	32.6	56.1		
25	*o,o'*-Dinitrobiphenyl	2436-96-6	DMSO	85	1.5				79[g,h]
26	Nitrosobenzene	586-96-9	DMSO	85	1.5	12.1	78.8	Trace	
27	Phenylhydroxylamine	100-65-2	DMSO	85	1.5	7.8	82.8	Trace	

[a] Final solution 2.4 *M* in sodium borohydride, 0.4 *M* in nitro compound; yields determined by gpc analysis using standard solutions of the products (average of three to five determinations) and/or by isolation. [b] Conducted under nitrogen. [c] Orange-red highly insoluble material. [d] Starting material. [e] Mp 275° (reported[4b] mp 250°). *Anal.* Calcd for $C_{14}H_8N_4$: C, 72.40; H, 3.47. Found: C, 72.38; H, 3.76. [f] Not analyzed for. [g] Isolated yield. [h] *o,o'*-Dinitrosobiphenyl.

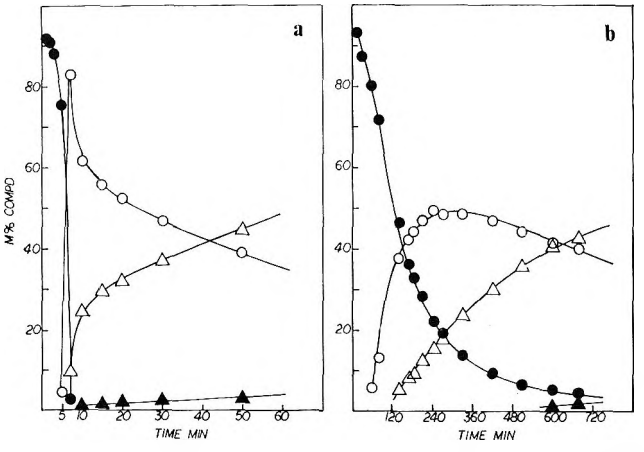


Figure 1.—Reduction of nitrobenzene with $NaBH_4$ in DMSO (concentrations determined by glpc; *N*-ethyl-*N*-methylaniline used as internal standard): nitrobenzene (●), azoxybenzene (○), azobenzene (△), aniline (▲). (a) $T = 85°$. (b) $T = 55°$.

concentration of nitrobenzene falls to zero after only 7.0 min; and the concentration of azoxybenzene attains its maximum (83%).[4] Complete reduction to azobenzene requires an additional 190 min. At 55° all the reductive steps are much slower, but the same general features are observed; as the nitrobenzene concentration decreases, the azoxybenzene concentration increases and then decreases again as azobenzene appears. Complete reduction is not obtained even after 48 1/4 hr (concentrations 75.7% azobenzene, 3.6% aniline, 5.9% azoxybenzene). At both temperatures aniline does not appear in measurable quantities until a substantial amount of azobenzene is present, which suggests that this product may arise from the known reduction of azobenzene by borane.[5]

The mechanism for the formation of azoxybenzene probably involves initial reduction of nitrobenzene (possibly through nitrobenzene radical anion)[6,7] to nitrosobenzene and phenylhydroxylamine which are known to form the nitrosobenzene radical anion with bases in DMSO and eventually lead to azoxybenzene.[7] This is evidenced by the observations that nitrosobenzene or phenylhydroxylamine furnish similar mixtures of azobenzene and aniline as nitrobenzene upon borohydride

(4) The sharp drop in nitrobenzene concentration which occurred between the 5- and 7-min reaction time (from 76 to 3%) suggested that the reaction was exothermic and the generated heat was not dissipated adequately enough to keep the reaction temperature at 85° until all the nitrobenzene was consumed.

(5) H. C. Brown and B. C. Subba Rao, *J. Amer. Chem. Soc.*, **82**, 681 (1960). Borane formation in DMSO or sulfolane has been reported (ref 2 and 3). The situation is complicated by the observation that treatment of azobenzene with $NaBH_4$ in DMSO at 85° for extended periods of time (*i.e.*, 24 hr) affords some hydrazobenzene which partially disproportionates under our glc conditions to a mixture of aniline and hydrazobenzene. Consequently, part of the observed aniline may arise from hydrazobenzene formation which escapes detection by glc. In addition, borane is known to reduce nitroso compounds to amines: H. Feuer and D. M. Braunstein, *J. Org. Chem.*, **34**, 2024 (1969). The origin of aniline in our reduction is therefore open to question and may arise from competition between all three of the above mentioned reductions. We are pursuing this point at present.

(6) M. G. Swanwich and W. A. Waters, *Chem. Commun.*, 63 (1970).

(7) G. A. Russell, E. J. Geels, F. J. Smentowski, K. Y. Chang, J. Reynolds, and G. Kaupp, *J. Amer. Chem. Soc.*, **89**, 3821 (1967).

reduction (compare entries 1 and 2 with 26 and 27, Table I). We are currently investigating the detailed mechanistic aspects of the reduction by esr spectroscopy and kinetic studies.

The data in Figure 1 suggested that a temperature of about 85° was adequate for preparative applications in DMSO; at higher temperatures the reduction of nitrobenzene became very vigorous and difficult to control. Preliminary experiments in sulfolane indicated that reduction occurred less readily and 100° seemed appropriate for this solvent. The experimental procedures were simple and straightforward. The nitro compound was added directly or as a solution in dimethyl sulfoxide or sulfolane to a stirred solution of sodium borohydride in the appropriate solvent maintained at the desired temperature. Progress of the reductions were followed by gas chromatography and the reaction mixtures were worked up by pouring into water and extracting into chloroform. Yields were determined in most cases by gas chromatography. Table I presents conditions and results for a variety of representative nitro compounds. The use of sulfolane appears to require longer reaction times and affords greater quantities of amines (compare entries 1–4).[8] For the preparation of azo compounds, the amines are easily removed by extraction of the chloroform solution with dilute hydrochloric acid. There appears to be no advantage to conducting the reactions under nitrogen (compare entries 1 and 2).

Several interesting features of the reductions are apparent from Table I. First, electron-withdrawing substituents enhance both the initial reduction to azoxy compounds and the further reduction to azo derivatives and amines.[9] For such cases the reactions provide relatively rapid and convenient methods for preparing azo compounds, especially since other reducible functional groups such as cyano and amido are not affected (entries 21 and 22). The corresponding azoxy compounds are also converted to the azo derivatives and amines under the reduction conditions (entry 24). Electron-releasing groups, on the other hand, retard the reactions to varying degrees dependent upon their donating ability.[9] Thus, *m*-nitrotoluene (entries 9 and 10) required 12 hr for conversion to *m*-azotoluene and *m*-toluidine; *p*-nitroanisole and *p*-nitrophenetole (entries 13–15) afforded good yields of the azoxy derivatives which were quite resistant to further reduction; *p*-nitroaniline (entries 19 and 20) was not reduced to any indentifiable product. Reduction of *p*-nitrotoluene in dimethyl sulfoxide gave an orange-red, highly insoluble solid, probably arising from base-promoted coupling of the methyl groups[10] in addition to reduction of the nitro groups. The reaction in sulfolane afforded normal reduction products (entries 6–8). The reduction of 2,2′-dinitrobiphenyl to the corresponding dinitroso derivative (entry 25) was anomalous, which probably reflects a difficulty in generating two nitroso radical anions on the same molecule (*i.e.*, a singlet dianion may be produced).

In summary, sodium borohydride in DMSO or sulfolane provides convenient systems for the preparative reduction of aromatic nitro compounds to azoxy or azo compounds especially when other reducible functions such as cyano or amido are present. The method complements the procedure of Shine and Mallory (KBH_4 in pyridine or ethanol) in that compounds bearing electron-withdrawing substituents afford azo derivatives by our procedure while that of Shine and Mallory gives good yields of the corresponding azoxy compounds. Furthermore, most rings bearing electron-releasing substituents (except NH_2) afford azoxy derivatives using $NaBH_4$ in DMSO but are inert to KBH_4 in pyridine or ethanol.

Experimental Section[11]

Materials.—The aromatic nitro compounds used in this study were commercial samples repurified by recrystallization or distillation. The products used as standards were either obtained commercially, prepared by independent methods, or isolated from the reduction reactions. In all cases, physical constants of starting materials and products agreed satisfactorily with literature values. Fisher Scientific Co. reagent dimethyl sulfoxide was either distilled from calcium hydride and stored over 4A molecular sieves or, since the commercial material contains very little water, just stored over molecular sieves. Phillips Petroleum Co. commercial sulfolane was distilled from calcium hydride and stored over 4A molecular sieves.

Reduction of Nitroaromatics. General Procedure.—A solution of sodium borohydride in dimethyl sulfoxide or sulfolane was prepared in a three-necked flask maintained at the desired temperature (Table I) and equipped with a mechanical stirrer, condenser, and drying tube. The aromatic nitro compound (0.01–0.03 mol) was then either added directly or dropwise as a solution in the appropriate solvent. The latter technique was usually followed for those nitro compounds bearing electron-withdrawing substituents since the reactions were often quite vigorous. The amounts of reagents and solvent were chosen so that the final solution was 2.4 *M* in sodium borohydride and 0.4 *M* in the nitro compound. Progress of the reactions was followed in several cases by removing small aliquots of the reaction mixture, quenching with water, extracting with a few drops of chloroform, and analyzing the chloroform solution for starting material and products by gas–liquid chromatography. After the appropriate reaction time listed in Table I, the mixtures were worked up by diluting with water and extracting into chloroform. In most cases, the chloroform solution was diluted to a constant volume and analyzed by glpc using standard solutions of the products to determine yields. In most cases (see Table I) the azo and/or azoxy compounds were isolated by washing the chloroform solution with dilute hydrochloric acid and water and drying over anhydrous magnesium sulfate followed by concentration at reduced pressure. A typical reduction procedure is given below for *m*-nitroanisole. The reaction progress data presented in Figure 1 were obtained by following the disappearance of nitrobenzene and appearance of products by gas chromatography in a similar manner as described above except that a weighed amount of *N*-methyl-*N*-ethylaniline was added as an internal standard at the beginning of the reaction. At the appropriate time intervals, 1.0-ml aliquots were removed, quenched with 5 ml of water, extracted with 0.5 ml of chloroform, and analyzed. In this manner, the concentrations of nitrobenzene, azoxybenzene, azobenzene, and aniline could be determined simultaneously using predetermined detector response factors for each compound.

(8) The production of much larger quantities of aniline (entries 3 and 4, Table I) in sulfolane may occur because borane is essentially inert toward this solvent and thus is free to react with azobenzene. On the other hand, dimethyl sulfoxide suffers reduction by borane (ref 5) and, because of its relatively high concentration, competes very effectively with azobenzene for any borane produced.

(9) (a) H. J. Shine and E. Mallory, *J. Org. Chem.*, **27**, 2390 (1962). These authors observed that reduction of aromatic nitro compounds with potassium borohydride in ethanol or pyridine gave azoxy derivatives only if the ring substituent had a positive σ constant; otherwise, no reduction was obtained. (b) G. Otani, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.*, **16**, 1840 (1968). (c) The use of sodium borohydride in combination with palladium on carbon gives only the corresponding aniline from aromatic nitro derivatives with no evidence for azo or azoxy formation; see T. Neilson, H. Wood, and A. Wylie, *J. Chem. Soc.*, **371** (1962).

(10) G. A. Russell and E. G. Janzen, *J. Amer. Chem. Soc.*, **89**, 300 (1967).

(11) Gas chromatographic analyses were performed using a Hewlett-Packard Model 5250B gas chromatograph coupled to an L & N Model W recorder equipped with a Disc integrator. For all analysis, either a 6 ft × 1/8 in. 10% OV-1 on 60–80 Chromosorb W or a 1/8 in × 12 ft 10% UC-W98 on 80–100 Chromosorb W column was used. Microanalysis were performed by Midwest Microlab, Inc., Indianapolis, Ind., or by A. Bernhardt Microanalytical Laboratory, West Germany. Melting points are uncorrected.

Reduction of *m*-Nitroanisole with Sodium Borohydride in Dimethyl Sulfoxide.—To a stirred solution of sodium borohydride (3.405 g, 0.09 mol) in 25 ml of DMSO maintained at 85° was added dropwise a solution of *m*-nitroanisole (2.297 g, 0.015 mol) in 12 ml of DMSO over a 10-min period. After 1.5 hr, the solution was poured into 150 ml of water and extracted with three 25-ml portions of $CHCl_3$. The $CHCl_3$ solution was diluted to 100 ml and analyzed for yields of *m*-anisidine and *m*-azoanisole by glpc using standard solutions of the products (13.2 and 75.9% *m*-anisidine and *m*-azoanisole, respectively). The solution was washed with dilute HCl, then with water, and dried ($MgSO_4$). Removal of solvent on a rotary evaporator gave a red oil which solidified (1.96 g). A 208-mg sample was chromatographed on Florisil. Elution with 1:1 pentane–benzene afforded an orange-red solid, mp 75–76° (111.1 mg, representing a 61% yield). The ir and nmr spectra were consistent with *m*-azoanisole. One sublimation at reduced pressure gave the analytical sample.

Anal. Calcd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.65; H, 5.73; N, 11.56.

***p,p'*-Azobenzamide.**—In a similar manner as above, *p,p'*-azobenzamide was obtained from *p*-nitrobenzamide in 49% yield. Three recrystallizations from DMF afforded the analytical sample, mp 360–363° (dec).

Anal. Calcd for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.68; H, 4.42; N, 20.86.

Registry No.—Sodium borohydride, 16940-66-2; *m*-azoanisole, 6319-23-9; *p,p'*-azobenzamide, 27332-13-4.

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Reactions of 2,2-Dinitroalkyl Tosylates with Nucleophiles

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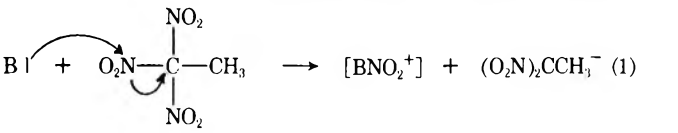
Some reactions of 2-fluoro-2,2-dinitroethyl tosylate (1) and 2,2-dinitropropyl tosylate (2) with nucleophiles were investigated. Weak bases lead to tosylate displacement, in some instances in preparatively useful yields. With strong bases side reactions such as nitrous acid elimination prevail. The reactivity of these tosylates is discussed, and some properties of 2,2-dinitroalkyl azides prepared from them are given.

The effects of β substituents on the SN2 reactivity of alkyl halides and sulfonates have been the subject of extensive studies. No completely unequivocal rationalization of these effects in terms of steric and electronic properties of the substituents has been achieved. It seems clear, however, that β substitution generally decreases reaction rates rather strongly due to steric crowding in the transition state; if the β substituent is electron withdrawing (*e.g.*, halogen), a further smaller decrease is frequently observed.[1] A combination of these factors has been invoked, for example, to account for the observation that 1,1-di-*H*-perfluoroalkyl halides and tosylates are much less reactive toward KI in acetone or NaI in alcohols than the corresponding unsubstituted alkyl substrates.[2]

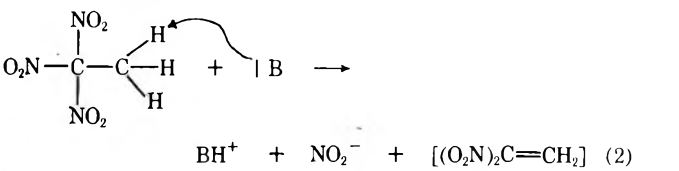
If this trend were to continue with bulkier and still more electron-withdrawing substituents such as nitro, it could result in 2-nitroalkyl sulfonates being essentially unreactive in SN2 displacement reactions. The extent of our knowledge on this subject appeared confined to a single statement to the effect that "2,2-dinitropropyl benzenesulfonate is unreactive toward LiCl and KOAc in boiling ethanol."[3] We therefore investigated the reactions of several nucleophiles with some 2,2-dinitroalkyl tosylates which became available to us in the course of other studies with 2,2-dinitroalkanols.[4]

This paper deals primarily with the course of such reactions of 2-fluoro-2,2-dinitroethyl tosylate (**1**) and, to a lesser extent, of 2,2-dinitropropyl tosylate (**2**); quantitative rate data regarding their relative reactivities will be presented elsewhere. That these tosylates are, in fact, surprisingly reactive is demonstrated by the following experiment. Refluxing **1** with LiBr in acetone for 5 hr results in precipitation of *ca.* 90% of the theoretical amount of lithium tosylate, most of which deriving from a direct displacement reaction (see below), while trifluoroethyl tosylate is recovered unchanged after a reaction time of 150 hr.

Displacement reactions on 2,2-dinitroalkyl tosylates are likely to be complicated by the fact that polynitroalkanes themselves are subject to attack by nucleophiles. Thus, 1,1,1-trinitroethane undergoes two general reactions with nucleophiles under relatively mild conditions:[5] (1) attack by the nucleophile on one of the nitro groups with displacement of the 1,1-dinitroethane



anion, and (2) abstraction by the nucleophile of a β-hydrogen atom resulting in elimination of nitrous acid and formation of 1,1-dinitroethene as an intermediate. 1-



Halo-1,1-dinitroalkanes react similarly. When hal = Cl or Br, dinitrocarbanion formation occurs (reaction 1);[5] with hal = F, fluoronitroethene intermediates are formed (reaction 2).[6] Simple *gem*-dinitroalkanes with nonterminal dinitromethylene groups are more resistant to attack by nucleophiles. In particular, proton ab-

(1) A. Streitweiser, Jr., *Chem. Rev.*, **56**, 691 (1956); J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 163 ff.

(2) G. V. D. Tiers, H. A. Brown, and T. S. Reid, *J. Amer. Chem. Soc.*, **75**, 5978 (1953); E. T. McBee, R. D. Battershell, and H. P. Braendlin, *ibid.*, **84**, 3157 (1962).

(3) L. W. Kissinger, T. M. Benziger, H. E. Ungnade, and R. K. Rohwer, *J. Org. Chem.*, **28**, 2491 (1963).

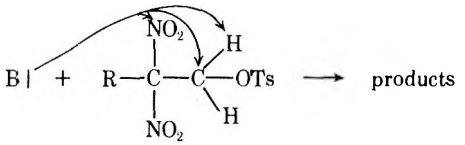
(4) H. G. Adolph and M. J. Kamlet, *ibid.*, **34**, 45 (1969).

(5) L. Zeldin and H. Shechter, *J. Amer. Chem. Soc.*, **79**, 4708 (1957).

(6) L. A. Kaplan, this laboratory, private communication.

straction from the adjacent carbon does not occur readily. For example, no deuterium uptake (or any other change) was detected by nmr over a period of 5 days when 2,2-dinitropropane was allowed to react with CD_3O^- in CD_3OD at room temperature.

One must therefore expect, at least in the reactions of **1** with nucleophiles, that denitrosation (2) and other side reactions resulting from proton abstraction at C_1 by the nucleophile or from its initial attack on the dinitromethylene group may come into play.



1, R = F
2, R = CH_3

The results of the reactions of **1** and **2** with several nucleophiles are listed in Table I. It is seen that the reaction conditions vary considerably, and interpretation of the results is further complicated by the possibility that the tosylate displacement products may be unstable to varying extents under the reaction conditions. Further reaction of the primary products with the nucleophile by paths 1 or 2 could lead to a decrease in yield or, possibly, to a complete disappearance from the product mixture. Except for the reaction with potassium fluoride, a distinct effect of the basicity of the nucleophile on the course of the reaction is nevertheless evident. The weakest base, bromide ion, gives the best yield of tosylate displacement product. The considerably stronger base, azide ion, yields much less of it. Finally, the strongly basic cyanide and methoxide ions give no substitution products at all. There is also strong indication that C_1-proton abstraction by the nucleophile either in the substrate or in the product does occur. Thus, in the fluorodinitroethyl system which should be more vulnerable to such attack, the yield of dinitroalkyl azide is much lower than in the dinitropropyl series. In addition, the reaction of **1** with $KOCH_3$ and, under certain conditions with NaN_3, gave products which probably in the latter and definitely in the former case arise from a denitrosation reaction (see below).

Table I
Reaction of 2,2-Dinitroalkyl Tosylates with Nucleophiles

Substrate	Nucleophile	Reaction conditions	Products, yield
1	Br^-	LiBr/acetone, 5 hr at 55°	2-Fluoro-2,2-dinitroethyl bromide (**3**), 75%
1	F^-	KF/DMSO, 15 hr at 75–80°	1 recovered, 20%; no other products isolated
1	N_3^-	NaN_3/80% aq DMSO, 15 hr at 25–30°	1 recovered, 30%; 2-fluoro-2,2-dinitroethyl azide (**4**), 20–25% of reacted **1**
2	N_3^-	NaN_3/80% aq DMSO, 48 hr at 60°	2 recovered, 35%; 2,2-dinitropropyl azide (**5**), 73% reacted **2**
1	CN^-	NaCN/80% aq DMSO, 24 hr at 25–30°	1 recovered, 50%; no other products
2	CN^-	NaCN/80% aq DMSO, 48 hr at 50–60°	2 recovered, 57%; no other products
1	CH_3O^-	2 KOH/MeOH, 15 min at 0°	No **1** recovered; major product, 1-fluoro-1-nitro-2,2-dimethoxyethane (**8**), 30%

No other evidence was obtained during this work as to the fate of that portion of the substrate that was consumed but not converted to a tosylate displacement product. It is clear that for synthetic purposes the results of the attempted displacement reactions are not encouraging in the case of **1** but do suggest some usefulness of the reaction for 2,2-dinitroalkyl sulfonates such as **2**. A more detailed discussion of some of the reactions and products listed in Table I follows.

2-Fluoro-2,2-dinitroethyl bromide (**3**), the product of the reaction of **1** with lithium bromide in acetone, was also prepared from 2-fluoro-2,2-dinitroethanol by reaction with triphenylphosphine dibromide in acetonitrile.[7]

$$CF(NO_2)_2CH_2OH + (C_6H_5)_3P + Br_2 \xrightarrow[40\%]{\text{reflux in MeCN}} CF(NO_2)_2CH_2Br$$

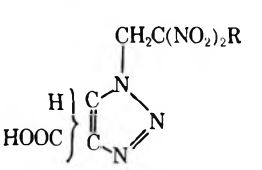
3

The structure of 2-fluoro-2,2-dinitroethyl azide followed from its ir spectrum (azide band at 2150 cm^{-1}, asymmetric and symmetric nitro stretching frequencies at 1595 and 1315 cm^{-1}, respectively) and from analytical and spectral data for its adduct to propiolic acid, 1-(2-fluoro-2,2-dinitroethyl)-4- (or 5-) carboxy-1,2,3-triazole (**6**). **4** was also obtained in *ca.* 10% yield from 2-fluoro-2,2-dinitroethyl mesylate in 80% aqueous DMSO. When the reaction between **1** and sodium azide was conducted in anhydrous DMSO, no **4** was obtained at all. Instead, a small amount of a material was isolated which, from comparison of its ir and nmr spectra with those of **8**, is believed to be a fluoromononitro species of the partial structure $HCF(NO_2)CHN_3$. The formation of this structure would seem to lend further support to the view that increased basicity of the nucleophile, here due to decreased solvation of the azide ion, favors the denitrosation reaction.

2,2-Dinitropropyl azide (**5**) also added to propiolic acid in essentially one direction to give **7** in excellent yield.

$$RC(NO_2)_2CH_2N_3 + HC{\equiv}CCOOH \longrightarrow$$

4, R = F
5, R = CH_3



6, R = F (90%)
7, R = CH_3 (90%)

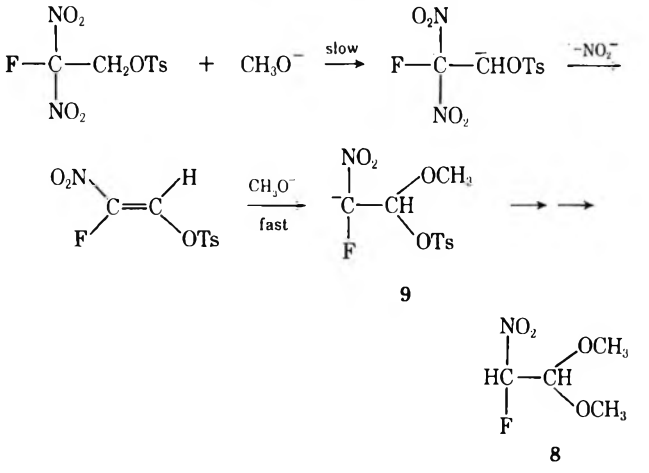
2-Nitroalkyl azides such as **4** and **5** have apparently not been described in the literature. It is noteworthy that these compounds are surprisingly stable in view of the facile conversion to furoxanes of the structurally

(7) G. A. Wiley, R. L. Hershkowitz, B. M. Rein, and B. C. Chung, *J. Amer. Chem. Soc.*, **86**, 964 (1964).

similar *o*-nitrophenyl azides.[8] Thus, *o*-nitrophenyl azide readily loses nitrogen on heating to 100° in toluene solution. In contrast, when **4** was refluxed in toluene for 5 hr or heated neat or in acetic acid to 110–115° for 5 hr, no change was detected by glpc. Heating for 1 hr at 150° also had little effect; on prolonged heating at this temperature **4** did decompose, but no furoxane was formed. Apparently this conversion does not take place in the aliphatic series.

The reaction of **1** with methanolic potassium hydroxide was comparatively rapid. When equimolar amounts were allowed to react, half of the tosylate was recovered unchanged. Two equivalents of base consumed all of the starting material. The products were the same in both cases and consisted of a mixture of at least five compounds with a main component amounting to about 80% of the isolated material. This was shown to be 1-fluoro-1-nitro-2,2-dimethoxyethane (**8**) on the basis of elemental analyses and uv, ir, and nmr spectral data. None of the minor products were identified, but it was shown that the product of a direct displacement of the tosyloxy group, fluorodinitroethyl methyl ether, was not among them by comparison of the glpc retention times with that of an authentic sample of the latter.[9]

The formation of **8** very likely involves initial denitrosation of **1**. The fact that with 1 mol of base only half of the tosylate was converted suggests that a slow, base-consuming step is followed by a rapid one which consumes a second equivalent of base. **9** might lose a tosylate ion and add methanol to give the final product.



9

8

Attempts to obtain a dinitrophenylhydrazone from **8** failed, neither were we able to obtain the parent aldehyde by acid hydrolysis. **8** was stable in aqueous acids but decomposed completely in concentrated sulfuric acid.

Experimental Section

General.—*Caution:* Some of the materials described here are explosives of moderate to considerable sensitivity to initiation by impact, shock, friction, and other means and should be handled with *care*. 2-Fluoro-2,2-dinitroethanol is also a strong skin irritant.

Microanalyses and molecular weight determinations were by Professor M. H. Aldridge, American University, Washington, D. C., and by Mr. D. J. Glover of this laboratory. Melting and boiling points are uncorrected. Nmr spectra were obtained on a Varian HA-100 spectrometer; chemical shifts are in parts per million relative to TMS (δ 0.00) as internal standard.

(8) P. A. S. Smith and J. H. Boyer, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 75.

(9) M. J. Kamlet and H. G. Adolph, *J. Org. Chem.*, **33**, 3073 (1968).

2,2-Dinitropropyl Tosylate (**2**).—To a solution of 15 g of 2,2-dinitropropanol and 38 g of *p*-toluenesulfonyl chloride in 100 ml of chloroform was added 19 g of pyridine *N*-oxide, and the mixture was heated to a gentle reflux for 5 hr. After cooling, the solids were filtered off and washed with methylene chloride. The filtrate was washed with dilute sulfuric acid, water, and dilute $NaHCO_3$ solution, and concentrated to *ca.* 100 ml. Hexane was added to the cloud point and the solution was chilled to give 26.0 g (85%) of crude **2** in two crops. The analytical sample was obtained from CCl_4, mp 84–85°.

Anal. Calcd for $C_{10}H_{12}SN_2O_7$: C, 39.48; H, 3.98; N, 9.21; mol wt, 304.28. Found: C, 39.57; H, 3.70; N, 9.15; mol wt ($CHCl_3$), 297.

2-Fluoro-2,2-dinitroethyl Bromide (**3**) **from 1 and LiBr.**—A solution of 10 g of anhydrous lithium bromide and 19.5 g of **1**[4] in 100 ml of dry acetone was refluxed for 5 hr. A precipitate of lithium tosylate appeared soon. The mixture was poured into ice–water, the product extracted into methylene chloride, and the extract washed once with water, dried, and distilled to give 10.3 g (75%) of **3**, bp 46–48° (2 mm).

Anal. Calcd for $C_2H_2BrFN_2O_4$ (216.96): N, 12.91; F, 8.76; Br, 36.83. Found: N, 12.90; F, 8.81; Br, 36.94.

2-Fluoro-2,2-dinitroethyl Bromide (**3**) **from 2-Fluoro-2,2-dinitroethanol and Triphenylphosphine Dibromide.**—To a suspension of 17 g of triphenylphosphine in 80 ml of acetonitrile was added with ice cooling a solution of 10.4 g of bromine in 20 ml of acetonitrile. To this mixture was added within a few minutes and without further cooling 10 g of 2-fluoro-2,2-dinitroethanol[4] dissolved in 20 ml of acetonitrile. After 2 hr of stirring at room temperature, the mixture was refluxed for 5 hr and then stirred into 150 ml of water. The lower organic phase was separated and washed once with water. At 0.2 mm and a bath temperature rising gradually to 100°, the volatile material was distilled into a trap immersed in ice–water. The product thus collected weighed 5.6 g (40%) and was found to be **3** of excellent purity. It was identical with material prepared from **1** as evidenced by superimposable ir spectra and identical glpc retention times.

2-Fluoro-2,2-dinitroethyl Azide (**4**).—A solution of 12.5 g of sodium azide in 100 ml of 50% aqueous DMSO was added at room temperature to a solution of 40 g of **1** in 150 ml of DMSO, and the mixture was stirred for 15 hr. After pouring the mixture into ice–water, the organic material was extracted into methylene chloride, the extract was washed once with water, concentrated to about 50 ml, washed again with water to remove residual DMSO, and dried ($MgSO_4$), and the solvent was distilled off. The azide **4** was distilled from the residue at 0.2 mm and a bath temperature up to 90–100°, and the distillate collected in a receiver cooled with ice–water. Obtained was 3.5 g of **4** of good purity; refractionation gave a material of bp 35° (0.25 mm) showing no impurities in the glp chromatogram. It was analyzed as its propiolic acid adduct. Upon recrystallization of the distillation residue from methanol, 12.5 g of unreacted **1** was recovered; the yield of **4** was thus 22%.

Reaction of 1 with Sodium Azide in Anhydrous DMSO.—Sodium azide, 6 g, was dissolved in 70 ml of warm DMSO, and the solution was cooled to room temperature (partial reprecipitation of NaN_3). **1** (8 g) was added and the mixture was stirred at 25–30° for 20 hr. Drowning the reaction mixture in 250 ml of ice–water gave a clear solution, indicating the absence of unreacted **1**. The drowning liquors were extracted with methylene chloride, and the extracts were concentrated, washed with water to remove DMSO, dried ($MgSO_4$), and freed from the remaining solvent *in vacuo*. The residual oil was partially distilled at 0.01 mm to a bath temperature of 60°. About 1 g of an oil was collected which had the following spectral characteristics: ir 2140 (azide), 1585 cm^{-1} (asymmetric mononitro stretch); nmr ($CHCl_3$) δ 5.28 (double d J_{HF} = 51, J_{HH} = 5 cps, FCHCH). Attempts to isolate a pure material from this oil were not successful.

2,2-Dinitropropyl Azide (**5**).—A solution of 4.05 g of sodium azide in 26 ml of 50% aqueous DMSO was added to 13 g of **2** in 49 ml of DMSO, the mixture was stirred for 48 hr at 60° and drowned in ice–water, and the products were extracted into methylene chloride. The extracts were washed with water and concentrated to 50 ml, and hexane was added to the cloud point. Upon cooling 3.2 g of **2** was recovered. The filtrate was washed with water and dried ($MgSO_4$), and the solvents were removed *in vacuo*. The residue was distilled at 0.1 mm, bath temperature up to 90°, to give 3.6 g of **5** of excellent purity (glpc). Crystallizing the distillation residue from methylene chloride–hexane

gave an additional 1.3 g of unreacted 2. The yield of crude 5 is thus 73.5% of the reacted 2, bp 60° (0.5 mm). It showed the expected azide and nitro absorption in the ir and was analyzed as the adduct to propiolic acid.

1-(2-Fluoro-2,2-dinitroethyl)-4- (or 5-) carboxy-1,2,3-triazole (6).—To 2.15 g of 4 in 10 ml of chloroform was added 0.9 g of propiolic acid, and the mixture was allowed to stand at room temperature for 3 days. The solid was filtered off and washed with a small amount of chloroform, and a second crop was obtained by chilling the filtrate. After recrystallization from acetonitrile–carbon tetrachloride (1:1), there was obtained 2.65 g (88.5%) of 6: mp 160° with gassing (decarboxylation); nmr (acetone-d_3) δ 8.73 (s), 6.37 (d, J_{HF} = 16 cps), 4.64 (s, COOH); relative areas, 1:2:1.

Anal. Calcd for $C_5H_4FN_5O_6$: N, 28.11; F, 7.63; mol wt and neut equiv, 249.12. Found: N, 27.91; F, 7.80; mol wt (acetonitrile), 242; neut equiv, 242.[10]

1-(2,2-Dinitropropyl)-4- (or 5-) carboxy-1,2,3-triazole (7).—Azide 5, 0.75 g, was reacted with propiolic acid in chloroform as described for 4. 7 (0.95 g, 90.5%) was obtained: mp (after recrystallization from acetonitrile) 157–158° dec; nmr (acetone-d_6) δ 8.67 (s), 5.89 (s), 4.21 (s, COOH); relative areas, 1:2:1.

Anal. Calcd for $C_6H_7N_5O_6$ (245.15): C, 29.40; H, 2.88; N, 28.57. Found: C, 29.71; H, 2.84; N, 28.39.

Reaction of 1 with Potassium Hydroxide in Methanol.—Tosylate 1, 50 g, was dissolved in 500 ml of warm methanol, the solution was cooled in an ice bath, and a precooled solution of 25 g of potassium hydroxide in 150 ml of methanol was added rapidly with stirring. Potassium tosylate precipitated immediately. The mixture was stirred for 15 min with continued cooling, the precipitate filtered off, and the filtrate freed from most of the methanol at 50° (25 mm). The residue and the previously obtained filter cake were triturated with 500 ml of water, the resulting two-phase mixture was extracted with methylene chloride, the extract was dried ($MgSO_4$), and the solvent was distilled off. A glp chromatogram of the remaining oil showed the presence of at least five compounds. The material was distilled at 0.1 mm and 8.3 g went over at 38–43°. The distillate was a 9:1 mixture of two components which were separated readily by chromatography on silica (G. F. Smith, Columbus, Ohio) with methylene chloride as the eluent. The impurity was eluted first. Thus obtained was 7.4 g (30%) of 8 of good purity: ir 1585, 1355 cm^{-1} (asym and sym NO_2 stretch); nmr (CCl_4) δ 5.64 (double d, J_{HF} = 49, J_{HH} = 4.5 cps), 4.73 (double d, J_{HF} = 10.6, J_{HH} = 4.5 cps), 3.50 (s), 3.47 (s); relative areas, 1:1:3:3; uv λ_{max} (0.01 *N* NaOH) 232.5 nm (ϵ 10,200) [compare 1-chloro-1-nitroethane, λ_{max} (0.1 *N* NaOH) 237 nm (ϵ 10,000)].[11]

Anal. Calcd for $C_4H_6FNO_4$: N, 9.15; F, 12.41. Found: N, 8.90; F, 12.71.

(10) Base was consumed rapidly past the point of neutralization which was therefore difficult to determine.

Registry No.—1, 18138-91-5; 2, 27396-49-2; 3, 27396-50-5; 4, 27396-51-6; 5, 27396-52-7; 6, 27378-67-2; 7, 27378-68-3; 8, 27396-53-8.

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(11) M. F. Hawthorne, *J. Amer. Chem. Soc.*, **78**, 4980 (1956).

Nuclear Magnetic Resonance Anisotropic Effects of the Epoxy Group and Averaging of Coupling Constants in *trans*- and *cis*-4,5-Epoxy-*trans*-2-(*p*-chlorophenyl)nitrocyclohexane and Derivatives

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The long-range anisotropic effects of the epoxy group in *trans*- (1) and *cis*-4,5-epoxy-*trans*-2-(*p*-chlorophenyl)-nitrocyclohexane (2) cause deshielding of both axial hydrogens cis to the epoxy group and have little effect on the chemical shift of the axial hydrogen trans to, and two carbons removed from, the epoxy group. The deshielding of the cis axial hydrogen, two carbons removed, is of the same magnitude as the deshielding of the same hydrogen caused by the anisotropic effect of the double bond in the parent alkene. The nmr spectra establish the presence of very high populations of the half-chair conformations with the substituents in equatorial orientations for both epoxides and for the parent alkene. The configurational assignment of the isomeric epoxides has been verified from the nmr spectra of the derived diols, monoacetates, and diacetates from the difference between the spatial 1,3-diaxial deshielding effects of hydroxyl and acetoxy groups. Anisotropic deshielding effects of the epoxy, hydroxyl, and acetoxy groups are responsible for significant averaging of coupling constants, involving geminal hydrogens, observed in the spectra of the epoxides and their derivatives.

Epoxidation of *trans*-4-(*p*-chlorophenyl)-5-nitrocyclohexene (3)[2] with *m*-chloroperbenzoic acid in ethyl ether yielded the isomeric epoxides *trans*- (1) and *cis*-4,5-epoxy-*trans*-2-(*p*-chlorophenyl)nitrocyclohexane (2) with a much larger proportion of the trans isomer 1. The nmr spectra of 1 and 2, Figure 1, are significantly different. Analysis of the spectra shows that the observed differences are not due to conformational differences, as might be suspected, but result from long-range shielding effects of the epoxy group and from averaging of coupling constants caused by these effects. Complications resulting from averaging of coupling constants due to strong coupling effects in ABX (or higher spin) systems, in which A and B are geminal hydrogens with small chemical shift differences, have been fully described.[3-6] The important thing to keep in mind is that in such systems strong coupling effects tend to average the individual values of J_{XA} and J_{XB}, thus causing changes in the pattern of the signal involved, but the sum of the coupling constants and, therefore, the width of the signal are not affected.[3]

Conformation of Epoxides, Anisotropic Effects, and Averaging of Coupling Constants.—Figure 1 gives portions of the 60-MHz spectra of the two epoxides measured in chloroform-*d*. The width of the signal of H-1 (27.2 Hz at δ 4.89, spectrum A) of the major epoxide 1 and the widths of the signals of H-1 (29 Hz) and H-2 (27.9 Hz) of the minor epoxide at δ 4.68 and 3.34, re-

(1) NSF Undergraduate Participant, 1968.

(2) A. C. Huitric and W. D. Kumler, *J. Amer. Chem. Soc.*, **78**, 614 (1956).

(3) W. F. Trager, B. J. Nist, and A. C. Huitric, *J. Pharm. Sci.*, **56**, 698 (1967).

(4) R. J. Abraham and H. J. Bernstein, *Can. J. Chem.*, **39**, 216 (1961).

(5) J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).

(6) T. Schaefer, *Can. J. Chem.*, **40**, 1679 (1962).

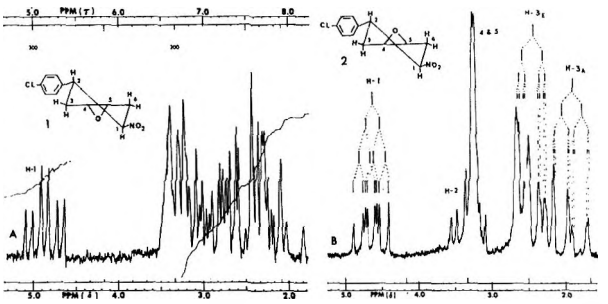


Figure 1.—Portions of the 60-MHz nmr spectra of the major 1 (spectrum A) and minor 2 (B) epoxides in chloroform-*d* at about 33–35° with TMS as internal reference.

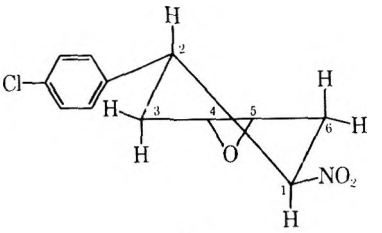
spectively, spectrum B, establish that each of these compounds has a very high population of the half-chair conformation with the nitro and aromatic groups in equatorial orientations as depicted by structures **1** and **2**. These signal widths (the sum of the coupling constants) are consistent with H-1 and H-2 having axial orientations and each being coupled with two adjacent axial and one equatorial hydrogens. In these mobile systems, any contribution from the other half-chair conformation (substituents axial) or any other flexible conformations would decrease the width of the signals of H-1 and H-2. In the other half-chair conformation H-1 and H-2 have equatorial orientations and the width of their signals would be in the order of 9–12 Hz. In compound **1** the signal of H-1 gives an essentially first-order triplet of doublets, $J_{12} \simeq J_{16a} \simeq 11.2$ and $J_{16e} \simeq 4.8$ Hz, but the signal of H-2, which is partially overlapped by the signals of H-4 and H-5, gives a more complex pattern. In the minor epoxide the signal of H-2 at δ 3.34, which is partially overlapped by signals of H-4 and H-5, gives essentially a first-order triplet of doublets, $J_{21} \simeq J_{23a} \simeq 11.6$ and $J_{23e} \simeq 4.6$ Hz, but the signal of H-1 is complicated by averaging of coupling constants and does not yield true coupling constants by first-order approximation. The widths of the signals of the hydrogens on the nitro- and aromatic-bearing carbons of the parent alkene **3** in chloroform-*d* are 26.7 and 27.5 Hz, respectively, indicating a similar high population of the half-chair conformation depicted by structure **3**. For the corresponding alkane **4**, the width of the signal of H-1 is 26 Hz in chloroform-*d*. This compound has been shown to exist essentially in the chair conformation with both substituents in equatorial orientations.[7]

The chemical shifts of the hydrogens on the nitro- and aromatic-bearing carbons of the parent cyclohexene, the corresponding cyclohexane, and the isomeric epoxides are given in Table I. In the parent cyclohexene **3**, in the conformation depicted by structure **3**, H-4 and H-5 have identical geometrical relationships to the double bond and should therefore experience analogous deshielding effects from the magnetic anisotropy of the double bond. This is substantiated by comparison of chemical shifts of these hydrogens with those of the corresponding hydrogens of the saturated compound **4**. Differences of 0.29 and 0.28 ppm are seen for the hydrogen on the nitro- and aromatic-bearing carbons, respectively, between compounds **3** and **4**. In the two isomeric epoxides, when in their established favored conformations, H-1 of **1** and H-2 of **2** have analogous cis geometrical relationships to the epoxy group, and likewise H-2 of **1** and H-1 of **2** have similar trans relationships to the epoxy group. It is interesting to note that the chemical shifts of H-1 in **1** and H-2 in **2** are about identical with those of the corresponding hydrogens in the parent alkene and that the chemical shift of H-1 in **2** is very close to that of H-1 in the corresponding saturated compound **4**.[8] This indicates that when measured in chloroform-*d* the epoxy group in a six-membered ring existing in a given half-chair conformation causes a deshielding of about 0.20 to 0.26 ppm of a cis axial hydrogen two carbons removed from the epoxy group, and that it has little effect on the chemical shift of a trans

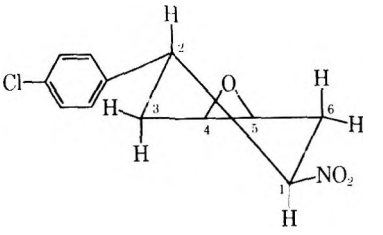
TABLE I

CHEMICAL SHIFTS IN CHLOROFORM-*d* IN δ UNITS (PARTS PER MILLION), INTERNAL TMS

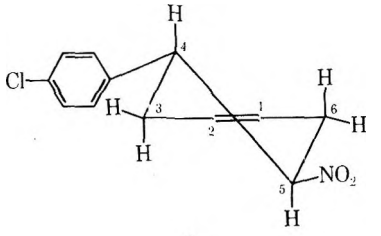
	O_2NCH	ArCH
Parent cyclohexene **3**	4.89	3.36
Major epoxide **1**	4.89	
Minor epoxide **2**	4.68	3.34
Cyclohexane **4**	4.60	3.08



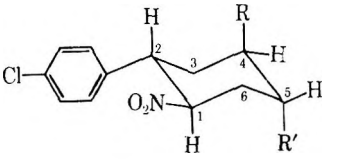
1



2



3



4, R = R′ = H
5, R = R′ = OH
6, R = R′ = OAc
7, R = OAc; R′ = OH
8, R = OH; R′ = OAc

(7) W. F. Trager, F. F. Vincenzi, and A. C. Huitric, *J. Org. Chem.*, **27**, 3006 (1962).

(8) A similar relationship seems to hold between H-2 of **1** and H-2 of the saturated compound **4**, but the chemical shift of H-2 in **1** cannot be determined with certainty.

axial hydrogen two carbons removed.[9] Spectra A and B indicate that there is also deshielding of the adjacent cis pseudoaxial hydrogens H-6a in **2** and H-3a in **1**. There is apparently little effect on the chemical shift of the adjacent trans pseudoaxial H-3a in **2**. At least, the observed difference of 0.52 ppm between the chemical shifts of the equatorial and axial hydrogens on C-3 is normal. First-order treatment of the signals of H-3a centered at δ 1.93, H-3e at 2.45, and H-2 at 3.34, in spectrum B gives the following apparent coupling constants: $J_{3a3e} \simeq 15.5$, $J_{23a} \simeq J_{21} \simeq 11.6$ Hz; $J_{23e} \simeq 4.6$, $J_{3a4} \simeq J_{3e4} \simeq 1.5$ Hz. The signal of H-2, although partially overlapped with the signals of H-4 and H-5, shows essentially a first-order triplet of doublets, as expected from coupling with axial H-1, axial H-3a, and equatorial H-3e, providing that there is a sufficient difference between the chemical shifts of geminal H-3a and H-3e. In contrast to H-2, the signal of H-1 gives an eight-peak multiplet. The complexity of the signal arises from averaging of coupling constants J_{16a} and J_{16e} because of the small difference in chemical shifts between geminal H-6a and H-6e. The signals of the geminal hydrogens on C-6 appear as a pair of complex components, about 8–9 Hz apart, centered at about δ 2.60. They partially overlap the signal of H-3e. The observed pattern is explainable on the basis of a small difference in chemical shift between the two geminal hydrogens and an averaging of their coupling constants with H-1. The outer components of the highly skewed doublets resulting from geminal coupling are not discernible. The signal of H-1 gives $J_{12} \simeq 11.7$ Hz, and averaging of J_{16a} and J_{16e} to yield separations of 9.7 and 7.7 Hz, respectively. The computer reproduced spectrum[10] of H-1 matched the observed spectrum exactly when the difference of 4 Hz was used between the chemical shifts of H-6a and H-6e with the equatorial hydrogen at lower field. The other values used were $J_{gem} = -15.5$, $J_{aa} = 11.7$, and $J_{ae} = 5.7$ Hz.[11] Decoupling of H-1, by double resonance, caused a partial merging of the two components of the C-6 hydrogens without causing any change in the signals of the hydrogens on C-3. Strong irradiation in the region of the C-6 hydrogens caused a collapse of the signal of H-1 essentially into a doublet with separation of about 11.5 Hz. Clean decoupling becomes more difficult the larger the coupling constants with the hydrogen being decoupled (the wider its signal). The near equivalence of chemical shifts of H-6a and H-6e is attributed to a deshielding effect of H-6a by the *cis*-epoxy group. The anisotropy of the nitro group may also play a role, but the fact that the signals of H-1 in **4** and in **1** are essentially first-order, six-peak multiplets indicates that the role of the epoxy group is the most important. The fact that the signal of H-2 in **1** appears to be complicated by averaging of coupling constants is consistent with a deshielding of axial H-3a by the adjacent *cis*-epoxy group.

Proof of Configuration.—The configurations of the epoxides **1** and **2** were established from the nmr spectra of their diol, diacetate, and monoacetate derivatives by taking advantage of the spatial 1,3-diaxial deshielding effects of a hydroxyl group on ring hydrogens[12–16] and of the larger deshielding effect of a hydroxyl group compared to the corresponding acetoxy group.[13,15,17] The diol was obtained by acid-catalyzed hydrolysis of either epoxide or from a mixture of the two. The monoacetates were prepared by treating each epoxide with potassium acetate in acetic acid, and the diacetate was prepared from the diol or the monoacetates. The relevant portions of the 60-MHz spectra of the four derivatives, in pyridine, are given in Figure 2. The widths of the signals of H-1 or H-2, or both when discernible, are of the order of 27–28 Hz, consistent with H-1 and H-2 having axial orientations and being coupled with two axial and one equatorial hydrogens. This establishes a high time-average population of the chair conformation with the nitro and aromatic group in equatorial orientations for each derivative. The narrow signals of H-4 and H-5 indicate that these hydrogens have the equatorial orientation and establish that in each derivative the hydroxyl and acetoxy group have the trans-diaxial relationship while the nitro and aromatic groups have the trans-diequatorial orientations. The structures of these products indicate that the epoxide opening occurred *via* a transition state which can be visualized as having the aromatic and nitro groups essentially

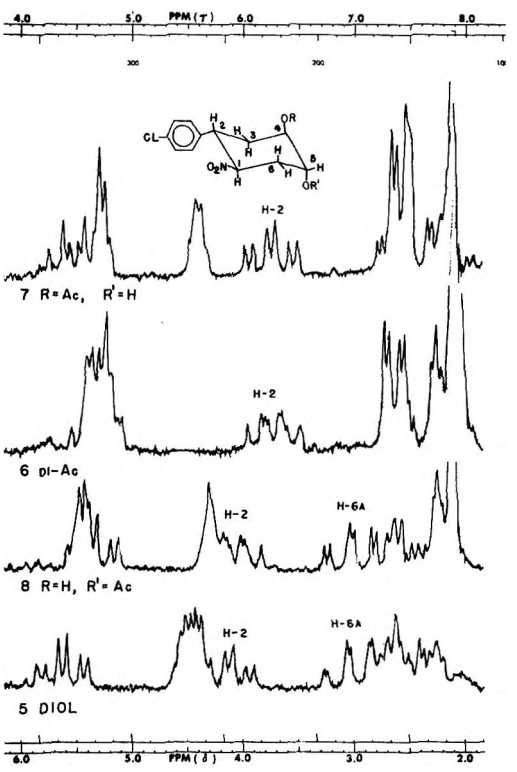


Figure 2.—Portions of the 60-MHz nmr spectra of the diol **5**, the diacetate **6**, and the major **7** and minor **8** monoacetates in pyridine at about 33–35° with TMS as internal reference.

(9) The assumption is made that there is little difference in the time-average populations of rotamers of the nitro and aromatic groups between the epoxides, the cyclohexene, and the cyclohexane in the conformations described, with both substituents in equatorial orientations.

(10) K. B. Wiberg and B. J. Nist, "The Interpretation of NMR Spectra," W. Benjamin, New York, N. Y., 1962.

(11) The theoretical value of 5.7 Hz for J_{ae} exceeds observed J_{23e} by about 1 Hz. It was obtained by difference from the width of the signal of H-1, with the assumption that J_{12} and J_{16a} are equal. This assumption may not be exactly correct, but the results clearly demonstrate the complications by averaging of coupling constants.

(12) A. C. Huitric, J. B. Carr, and W. F. Trager, *J. Pharm. Sci.*, **55**, 211 (1966).

(13) D. B. Roll and A. C. Huitric, *ibid.*, **55**, 942 (1966).

(14) K. Tori and T. Komeno, *Tetrahedron*, **21**, 309 (1965).

(15) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 19, 185.

(16) P. V. Demarco, E. Farkas, D. Doddrell, B. L. Mylari, and E. Wenkert, *J. Amer. Chem. Soc.*, **90**, 5480 (1968).

(17) K. Tori and Y. Kondo, *Steroids*, **4**, 713 (1964).

equatorial. A transition state involving the other half-chair conformation, with the aromatic and nitro groups axial, would yield a diol which would differ from structure **5** by having the trans-diequatorial hydroxyl groups. Similar all-equatorial products would be obtained from such transition states in the formation of the monoacetates, but in addition the relative skeletal positions of the hydroxyl and acetoxy groups would be inverted in the product from a given epoxide. There is no evidence that any such products were formed.

The determination of the direction of epoxide opening also establishes that epoxides **1** and **2** yield the monoacetates **7** and **8**, respectively. The monoacetates were characterized by comparing the chemical shifts of H-1 and H-2 with those of the diol and diacetate in pyridine. The monoacetate obtained from the major epoxide gives spectrum **7**. The similarity in chemical shifts of H-2 with that of the diacetate (spectrum **6**) and of H-1 with that of the diol (spectrum **5**) establishes that this monoacetate has the acetoxy group at C-4, structure **7**. This characterizes the major epoxide as structure **1**. The monoacetate obtained from the minor epoxide gives spectrum **8**. The similarity in chemical shifts of H-2 with that of the diol and of H-1 with that of the diacetate establishes that the compound has the acetoxy group at C-5. This characterized the minor epoxide as structure **2**.

TABLE II

CHEMICAL SHIFTS IN PYRIDINE IN δ UNITS (PARTS PER MILLION), INTERNAL TMS

	H-1	H-2	H-6a
Diol **5**	5.62	4.12	3.04
Di-Ac **6**	5.32	3.72	
Monoacetate **7** (from major epoxide)	5.52	3.75	
Monoacetate **8** (from minor epoxide)	5.35	4.08	3.02
Cyclohexane **4**	4.87	3.12	

Averaging of Coupling Constants in the Acetates.—Spectrum **5**, of the diol, gives essentially first-order signals for H-1 and H-2 with observed coupling constants of $J_{12} \simeq J_{16a} \simeq J_{23a} \simeq 11.6$ Hz, $J_{16e} \simeq 4.5$ Hz, and $J_{23e} \simeq 4.2$ Hz. Comparison of the chemical shifts of H-1 and H-2 of the diol with the alkane **4** shows a deshielding of 1.0 ppm of H-2 by the axial C-4 hydroxyl group and of 0.75 ppm of H-1 by the axial C-5 OH group. Similar deshielding effects will be experienced by axial H-3a and axial H-6a, and the chemical shifts of these axial hydrogens are expected to be at lower field than those of their geminal equatorial partners. The signal (triplet of doublets) centered at δ 3.04 is attributed to H-6a. The observed pattern results from the geminal coupling with H-6e being about equal to $J_{6a1} \simeq$ 11–13 Hz, and $J_{6a5} \simeq$ 3–4 Hz.[18] When an acetoxy replaces an axial OH group, the 1,3-diaxial deshielding is reduced such that an acetoxy group at C-5 will cause the chemical shifts of the geminal hydrogens at C-3 to be more closely equivalent; an axial acetoxy at C-4 will have a similar effect on the geminal C-6 hydrogens. The complex patterns of the signals of H-2 in the diacetate **6** and monoacetate **8** are attributed to averaging of J_{23a} and J_{23e} because of small differences in the chemical shifts of the C-3 geminal hydrogens.[19] Similarly, the small difference in chemical shifts of the geminal C-6 hydrogens in **7** causes the complex pattern of H-1. The similarity in chemical shifts of H-6a of the minor acetate and the diol further substantiates that the minor acetate has the OH group at C-4.

Experimental Section[20]

***trans*-4,5-Epoxy-*trans*-2-(*p*-chlorophenyl)nitrocyclohexane (1) and *cis*-4,5-Epoxy-*trans*-2-(*p*-chlorophenyl)nitrocyclohexane (2).**—A solution of 10 g (0.042 mol) of *trans*-4-(*p*-chlorophenyl)-5-nitrocyclohexene (**3**)[2] and 17.1 g of 85% *m*-chloroperbenzoic acid (0.084 mol) in 200 ml of anhydrous ethyl ether was kept at room temperature, and the progress of the reaction was followed by thin layer chromatography (tlc) on silica gel. A solvent mixture of equal volumes of chloroform and hexane gave good separation of the alkene from the epoxides, with the alkene having the largest R_f value. There was no evidence of starting alkene after 4 days. The ether solution was then washed successively with aqueous 20% sodium bisulfite, water, saturated sodium bicarbonate solution, and water. Removal of the solvent gave 6.5 g of colorless solid, mp ~103–107°. The nmr spectrum indicated a mixture of epoxides with a large predominance of isomer **1** which could be obtained by recrystallization of the mixture in 2-propanol, mp 107.5–109°. Tlc on silica gel (ethyl ether) showed separation of the isomers. The minor isomer **2** was obtained in pure form by ascending dry-column chromatography using silica gel (0.05–0.2 mm) deactivated to Brockmann activity II[21] and equilibrated with 5% ethyl ether. Anhydrous ethyl ether was used as solvent. A mixture of epoxides (5.7 g) which had been enriched in **2** by crystallization of **1** was deposited on 20 g of silica gel, and this material was placed at the bottom of 5 × 95 cm nylon tubing column equipped for ascending chromatography. The solvent was brought to 8 cm from the top in 5 hr. Positions of the compounds on the column were approximated with the aid of a uv lamp;[22] the column was sliced in sections and the compounds were eluted by soaking in ether. Three 6-cm sections, with R_f values[23] of 0.49, 0.55, and 0.62, contained pure **2** (analyzed by tlc and nmr). The next section contained a mixture of **1** and **2**, and pure **1** was found in the upper part of the column. The separated isomers were recrystallized from 2-propanol, mp 107.5–109°, for the major epoxide **1**, and 108.5–109.5° for **2**. A mixture of the two epoxides gives a depression in the melting point.

Anal. Calcd for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.77; N, 5.52. Found (**1**): C, 56.61; H, 4.87; N, 5.50. Found (**2**): C, 56.83; H, 4.92; N, 5.51.

***trans*-2-(*p*-Chlorophenyl)-*cis*-4-acetoxy-*trans*-5-hydroxynitrocyclohexane (7) and *trans*-2-(*p*-Chlorophenyl)-*cis*-4-hydroxy-*trans*-5-acetoxynitrocyclohexane (8).**—The monoacetates were prepared by allowing a solution of about 500 mg of the epoxide and 650 mg of potassium acetate in 10 ml of glacial acetic acid to stand at room temperature for 3 or 4 days. The solution was

(18) The assignment of H-6a has been verified by decoupling of H-1 at 100 MHz. The 100-MHz spectrum also gives distinct signals for H-4 and H-5 at δ 4.38 and 4.50, respectively. Differentiation between H-4 and H-5 was done by decoupling of H-6a, causing a narrowing of the signal at δ 4.50 without affecting the signal at 4.38. The 100-MHz spectrum also shows the signal of equatorial H-3a as a six-peak multiplet (doublet of triplets, $J_{gem} \simeq 13$, $J_{3e2} \simeq J_{3e4} \simeq 3.5$ Hz) centered at δ 2.13. Decoupling of H-2 causes a decrease in the multiplicity of this signal and does not affect the signal assigned to H-6a.

(19) The near equivalence of the geminal C-3 hydrogens of the minor monoacetate **8** is clearly seen in the 100-MHz spectrum where the signals of these two hydrogens overlap to give a signal centered at δ 2.15 (also overlapped by the acetoxy methyl hydrogens). At 100 MHz the signal of equatorial H-6e appears as a six-peak multiplet ($J_{gem} \simeq 13$, $J_{6e1} \simeq J_{6e3} \simeq 3.5$ Hz) centered at δ 2.51. Decoupling of H-1 changes the multiplicities of the signals of H-6a and H-6e, while irradiation at the position of H-2 causes changes in the pattern of the overlapping H-3a and H-3e signals without causing any changes in the signals of H-6a and H-6e.

(20) Melting points were determined on a Kofler micro hot stage. The nmr spectra were obtained with a Varian A-60 spectrometer, unless otherwise stated, in the solvents reported, with TMS internal standard, at an operating temperature of about 33–35°.

(21) B. Loev and M. M. Goodman, *Chem. Ind.* (*London*), 2026 (1967).

(22) About 0.5% of G.E. Electronic Phosphor, type 118-2-7, was blended with the silica gel as a fluorescent indicator.

(23) These values are taken from the center of the sections.

then added to 100 ml of water, the mixture extracted with ether, the ethereal extract washed with sodium bicarbonate solution and dried (Na_2SO_4), and the solvent removed. The product was recrystallized from a mixture of benzene and hexane. Epoxide **1** yielded the monoacetate **7**, mp 161–162°, and the minor epoxide **2** gave monoacetate **8**, mp 168.5–170°.

Anal. Calcd for $C_{14}H_{16}ClNO_5$: C, 53.59; H, 5.14; N, 4.46. Found (**7**): C, 53.39; H, 5.14; N, 4.41. Found (**8**): C, 53.80; H, 5.21; N, 4.45.

***trans*-2-(*p*-Chlorophenyl)-*cis*-4-*trans*-5-dihydroxynitrocyclohexane (5).**—A mixture of 1.5 g of epoxide **1** (or a mixture of the two epoxides), 7.5 ml of H_2O, and 2 drops of concentrated H_2SO_4 in 15 ml purified dioxane was allowed to stand for 2 days. The mixture was added to 60 ml of water and extracted with ether. The product was recrystallized from a mixture of benzene and hexane, mp 204–205°.

Anal. Calcd for $C_{12}H_{14}ClNO_4$: C, 53.03; H, 5.19; N, 5.16. Found: C, 52.96; H, 5.51; N, 5.09.

The diacetate **6** was prepared from **5** with acetic anhydride in dry pyridine by the usual manner and recrystallized from a mixture of benzene and hexane, mp 162–163°.

Anal. Calcd for $C_{16}H_{18}ClNO_6$: C, 54.02; H, 5.10; N, 3.94. Found: C, 53.91; H, 5.14; N, 3.78.

Registry No.—**1**, 27390-71-2; **2**, 27390-72-3; **4**, 17321-89-0; **5**, 27390-74-5; **6**, 27390-75-6; **7**, 27390-76-7; **8**, 27390-77-8.

Orientation in the 1,3-Dipolar Cycloaddition Reactions of Heteroaromatic Nitrogen Methylides with Dipolarophiles[1]

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The orientation in the 1,3-dipolar cycloaddition reactions of several ring-substituted nitrogen methylides with dipolarophiles was investigated. The cycloaddition reactions of 3-substituted pyridazinium methylides with dimethyl acetylenedicarboxylate (DAC) and cyanoacetylene afforded the corresponding cycloadducts. In reactions of 3,6-dialkoxypyridazinium methylides with DAC, one of two alkoxyl groups was expelled in the formation of the adducts. A mixture of isomeric adducts was obtained in the reactions of 3-substituted pyrazinium methylides and 3-substituted pyridinium methylides, in which the major product was produced by cyclization at the C-2 position. An isomeric mixture of the adducts was also obtained by the reaction of 3,4-dimethylpyridinium methylide; however, the major product was afforded by cyclization at the C-6 position. Although the thermal addition of 4-carbomethoxypyridinium methylide to DAC afforded the cycloadduct, the methylide was photochemically too stable to undergo the photocycloaddition.

Indolidines and polyazaindolidines of the 10-π-electron system are of interest for the studies on azulene heteroanalogs, and recent studies[2,3] have focused on the convenient one-step synthesis of these aromatic heterocycles by 1,3-dipolar cycloaddition reactions.

Although the mechanism of 1,3-dipolar cycloaddition reactions has been extensively discussed by Huisgen and Firestone,[4] little is known about the orientation in 1,3-dipolar cycloaddition reactions of ring-substituted heteroaromatic nitrogen methylides with dipolarophiles. Recent results[3,5] in the 1,3-dipolar photocycloaddition reactions of isoelectronic 3-methyl-1-carbethoxyiminopyridinium ylide disclose significant differences between ground state and the excited state properties. In continuation of these studies,[3,5] this paper deals with an extension of the 1,3-dipolar cycloaddition of a series of ring-substituted heteroaromatic nitrogen methylides with dipolarophiles.[6]

Results and Discussion

Pyridazine (**1**), substituted pyridazine derivatives (**2–6**), and β-substituted pyridine derivatives (**26** and **27**) reacted with tetracyanoethylene oxide (TCNEO) to give crystalline compounds **7**, **8–12**, **30**, and **32**, respectively. Their compositions corresponded to 1:1 adducts of the base and dicyanomethylene. The infrared spectra of these compounds exhibit common strong nitrile absorptions at 2225 and 2220 cm^{-1}, indicating a high degree of ionic character in the dicyanomethylides.[7] Pyrazinium *N*-phenacylide (**22**) and pyridinium *N*-phenacylides (**31**, **33–35**) were prepared by treatment of the corresponding phenacyl bromides with aqueous potassium carbonate.[3] The structures of these ylides are based on the structural elucidation of 1,3-dipolar cycloaddition products as discussed below. The physical data of the dicyanomethylides **7–12** and **32** are summarized in Table I.

1,3-Dipolar Cycloaddition of Pyridazinium Methylides with DAC and Cyanoacetylene.—The 1,3-dipolar cycloaddition reactions of pyridazinium dicyanomethylide (**7**) and 3-substituted pyridazinium dicyanomethylides **8** and **10** with DAC afforded the cycloadducts **13–15**, respectively, in 50–70% yields. The spectrum of **13** shows a doublet at τ 1.87 (1 H, H_4, $J_{4,3}$ = 6.0 Hz),[8] double doublets at τ 2.74 (1 H, H_3, $J_{2,3}$ = 6.0 Hz, $J_{3,4}$ = 3.0 Hz), a doublet at τ 1.90 (1 H, H_2, $J_{2,3}$ = 3.0 Hz),[8] and singlet signals of two methyl protons at τ 5.88 and 5.99. In contrast, the spectra of **14** and **15** exhibit two ring proton signals at τ 1.70–1.80 (1 H) and τ 2.93–3.35 (1 H) as each doublet with the coupling constant of 9–10 Hz. Since the coupling constants of compound **13** are considerably different from those of compounds **14** and **15**, the structural elucidation of **13** was

(1) Studies of Heteroaromaticity. XLIII.

(2) For a recent review, see V. Boekelheide and N. A. Fedoruk, *J. Amer. Chem. Soc.*, **90**, 3830 (1968), and references cited therein.

(3) T. Sasaki, K. Kanematsu, and Y. Yukimoto, *J. Chem. Soc. C*, 481 (1970).

(4) (a) R. Huisgen, *J. Org. Chem.*, **33**, 2291 (1968); (b) R. A. Firestone, *ibid.*, **33**, 2285 (1968).

(5) T. Sasaki, K. Kanematsu, A. Kakehi, I. Ichikawa, and K. Hayakawa, *ibid.*, **35**, 426 (1970).

(6) Contrary to extensive studies on the 1,3-dipolar cycloaddition reactions of the zwitterionic methylides with DAC, the same reactions of 1-alkoxycarbonyliminopyridinium ylides will be presented later [see Studies of Heteroaromaticity. LI (submitted for publication in *J. Org. Chem.*)].

(7) W. J. Linn, O. W. Webster, and R. E. Benson, *J. Amer. Chem. Soc.*, **87**, 3651 (1965).

(8) The assignment of the H_3 and H_4 signals is based on the magnitude of $J_{4,3}$ in **13** and of $J_{3,4}$ in **14** and **15**; it may be the reverse of that given.

TABLE I

PHYSICAL AND SPECTRAL DATA OF THE HETEROAROMATIC *N*-DICYANOMETHYLIDES[a,b]

Compd no.	Mp, °C	Yield, %	Ir $\nu_{C\equiv N}^{KBr}$, cm^{-1}	Uv λ_{max}^{EtOH} (log ϵ)
7	210	75	2225	427 (4.22)
			2220	
8	217–219	80	2225	428 (4.34)
			2220	330 (3.39)
				265 (3.44)
9	178–180	70	2250	454 (4.25)
			2225	310 (3.43)
				265 (3.57)
10	206–208	70	2225	429 (4.28)
			2220	330 (3.31)
				260 (2.96)
11	182–184	60	2230	460 (4.14)
			2220	326 (3.88)
12	182–183	72	2240	424 (4.33)
			2200	
32	255–257	15	2280	413 (4.18)
			2180	250 (3.73)
			2160	

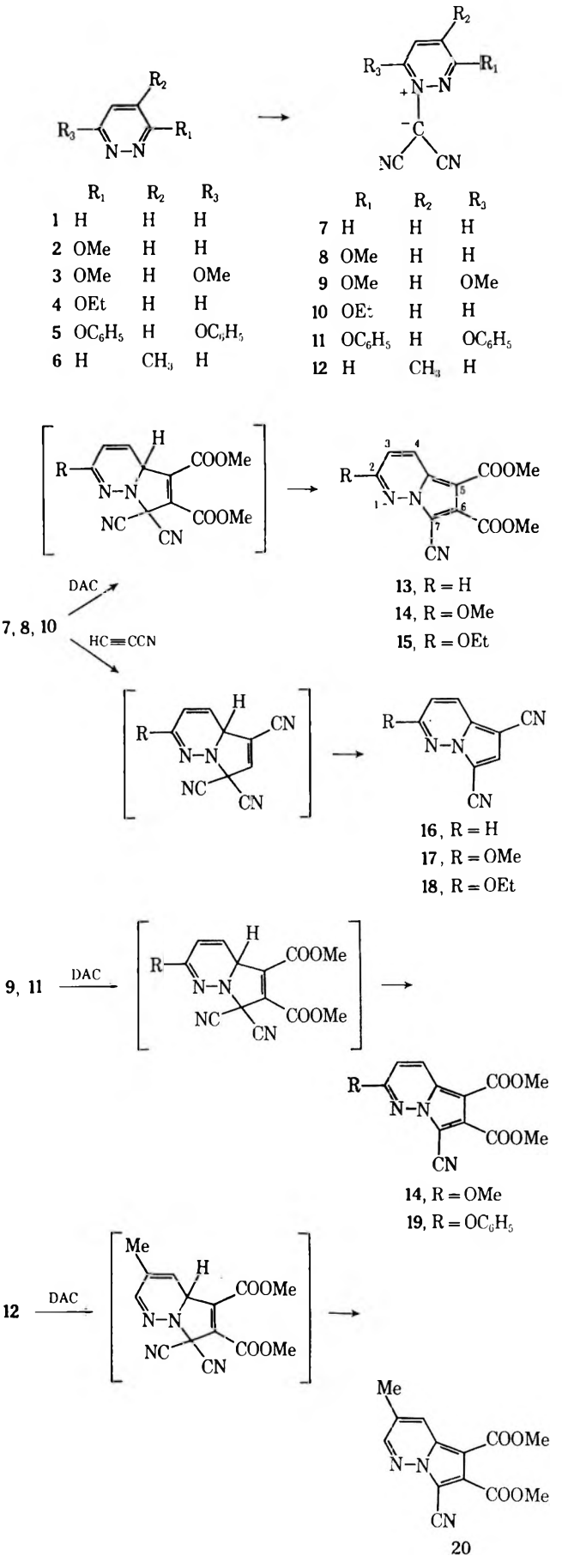
[a] Compound **30**, mp 214° (lit.[7] 213.5–214°). [b] Satisfactory analytical data (±0.25% for C, H, and N) were reported for all compounds in the table: Ed.

accomplished by chemical degradation. Treatment of **13** with refluxing methanolic hydrogen chloride (20%) for 10 hr gave 5,6,7-tricarbomethoxypyrrolo[1,2-*b*]pyridazine in 50% yield, which was identical with an authentic sample prepared by independent synthesis[9] by 1,3-dipolar addition of the pyridazinium–methyl bromoacetate adduct and DAC. Treatment of dicyanomethylides **7**, **8**, and **10** with cyanoacetylene afforded the expected 5,7-dicyano compounds **16**–**18**.

Surprisingly, in the reactions of 3,6-dialkoxypyridazinium methylides **9** and **11** with DAC, an alkoxy and a cyano group must be expelled to give the 2-alkoxy derivatives **14** and **19**; the nmr spectra contained only one characteristic alkoxy resonance at τ 5.94 (3 H, s, OCH_3) and 2.70 (5 H, m, OC_6H_5), respectively (*cf.* Table II). A formally similar aromatization, with loss of methane, was observed in the reaction of 3,6-dimethylpyridazinium methylide with DAC.[9] Treatment of dicyanomethylide **12** with DAC afforded 3-methyl-5,6-dicarbomethoxy-7-cyanopyrrolo[1,2-*b*]pyridazine (**20**); the nmr spectrum of the latter established the N-1 position of the dicyanomethylene group in **12**. These results are summarized in Tables II and III and Scheme I.

1,3-Dipolar Cycloaddition of β-Substituted Pyrazinium and Pyridinium Methylides with DAC.—The reaction of 3-methylpyrazinium *N*-phenacylide (**22**) with DAC in acetonitrile at room temperature gave 4% yield of 1,2-dicarbomethoxy-3-benzoyl-8-methyl-7-azaindolidine (**23**). However, the same reaction in refluxing chloroform gave *ca.* 8.5% yield of a mixture of **23** and 1,2-dicarbomethoxy-3-benzoyl-6-methyl-7-azaindoline (**24**) in the ratio of 2:1 (by nmr analysis); the ratio of the integrated areas for each peak at τ 2.14 and 1.14 (each doublet, J = 5.5 Hz) attributable to the ring protons of **23**, and those at τ 0.91 and 0.41 (each singlet) due to the ring protons of **24** was 2:1. Since an isomeric mixture was obtained, an alternative structure

SCHEME I



25, which would arise from the 2-methylpyrazinium ylide, could be ruled out. (See Scheme II.)

(9) D. G. Farnum, R. J. Alamino, and J. M. Dunston, *J. Org. Chem.*, **32**, 1130 (1967).

TABLE II

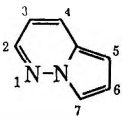
PHYSICAL AND SPECTRAL DATA OF THE CYCLOADDUCTS

Compd no.	Reaction conditions: Temp	Time, hr	Yield, %	Mp, °C	Uv: λ_{max}^{EtOH}, mμ (log ε)	M+, m/e	Formula	Calcd, %: C	H	N	Found, %: C	H	N
13	Room temp	12	50	141–143	348 (3.63) 302 (3.70) 290 (3.71) 260 (4.14) 246 (4.51) 217 (4.30)	259	$C_{12}H_9N_3O_4$	55.60	3.50	16.21	55.76	3.56	16.10
14	Room temp Reflux	12 15	70[a] 10[b]	155–156	330 (3.78) 260 (4.31) 243 (4.45) 236 (4.45) 220 (4.34)	289	$C_{13}H_{11}N_3O_5$	53.98	3.83	14.53	54.02	3.67	14.55
15	Room temp	15	50	170–171	340 (3.73) 262 (4.24) 245 (4.37) 240 (4.36) 220 (4.24)	303	$C_{14}H_{13}N_3O_5$	57.44	4.29	29.77	57.47	4.19	30.00
16	Reflux	4	30	202–204	343 (3.53) 298 (3.71) 286 (3.73) 245 (4.62)	168	$C_9H_4N_4$	64.28	2.40	33.32	64.34	2.38	33.46
17	Room temp	12	70	233–235	324 (3.76) 257 (4.48) 248 (4.52) 216 (4.60)	198	$C_{10}H_6N_4O$	60.60	3.05	28.27	60.57	2.85	28.09
18	Room temp	12	80	166–168	325 (3.65) 258 (4.37) 249 (4.30) 217 (4.41)	212	$C_{11}H_8N_4O$	62.25	3.80	26.40	62.28	3.96	26.54
19	Room temp	15	10	155–157	334 (3.78) 240 (4.50) 220 (4.46)	351	$C_{18}H_{13}N_3O_5$	61.54	3.73	11.96	61.42	3.77	12.13
20	Reflux	16	66	164–167	348 (3.53) 300 (3.79) 290 (3.77) 245 (4.48) 216 (4.23)	273	$C_{13}H_{11}N_3O_4$	57.14	4.06	15.38	57.20	4.10	15.40

[a] It was obtained from the reaction of compound 8 and DAC. [b] It was obtained from the reaction of compound 9 and DAC.

TABLE III

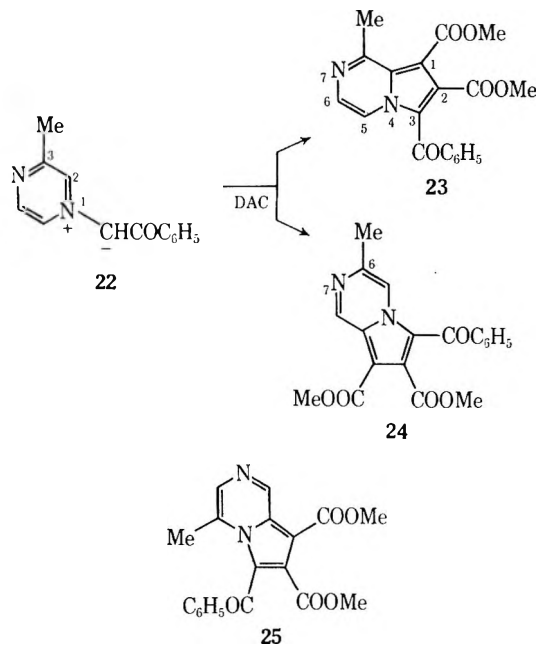
NMR SPECTRA OF PYRROLO[1,2-*b*]PYRIDAZINE DERIVATIVES IN $CDCl_3$ AT 60 MHz



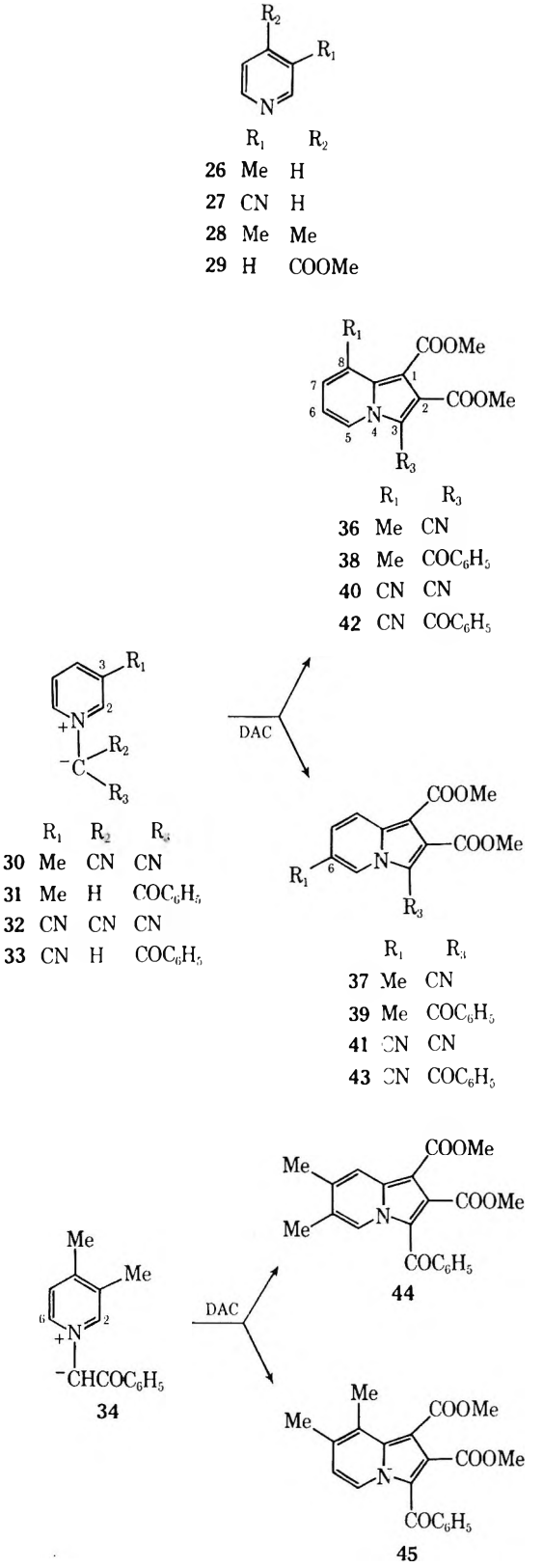
Compd no.[a]	Chemical shifts (τ) and coupling constants (J in Hz): C_2	C_3	C_4	C_5	C_6
13	1.87 (d), J = 6.0	2.74 (dd), J = 6.0, 3.0	1.90 (d), J = 3.0	5.99 (s) 5.88 (s)	$2COOCH_3$
14	5.94 (s, OCH_3)	3.35 (d), J = 9.0	1.80 (d), J = 9.0	6.10 (s) 6.02 (s)	$2COOCH_3$
15[b]	5.6 (q), 8.59 (t), J = 7.0 (OC_2H_5)	2.93 (d), J = 10.0	1.70 (d), J = 10.0	6.14 (s) 6.09 (s)	$2COOCH_3$
17	5.0 (s, OCH_3)	2.88 (d), J = 10.0	1.70 (d), J = 10.0		1.92 (s)
18	5.52 (q), 8.52 (t), J = 6.8 (OC_2H_5)	3.25 (d), J = 9.0	2.18 (d), J = 9.0		1.65 (s)
19	2.6~2.8 (OC_6H_5) (complex m)	3.02 (d), J = 10.5	1.56 (d), J = 10.5	6.10 (s) 6.03 (s)	$2COOCH_3$
20	1.69[c] (m, overlapping with ring protons)	7.46 (s, CH_3)	1.69[c] (m, overlapping with ring protons)	6.03 (s) 5.93 (s)	$2COOCH_3$

[a] Compound 16 is insoluble for nmr measurement. [b] In DMSO-d_6. [c] This signal is assigned by integrating to 2 H.

SCHEME II



SCHEME III



Treatment of 3-methyl- and 3-cyanopyridinium methylides (**30**–**33**) with DAC gave a mixture of 8-substituted (**36**, **38**, **40**, and **42**) and 6-substituted indolizine derivatives (**37**, **39**, **41**, and **43**) in the ratio of *ca.* 3:1 by the nmr analysis. The isomeric mixture from the reaction of **33** and DAC was separated by column chromatography to give **42** and **43**. However, the isomeric mixtures **36**–**37**, **38**–**39**, and **40**–**41** could not be separated by column chromatography or by repeated recrystallization. The ring protons in compound **42** exhibit signals at τ 0.35 (double doublet, 1 H, H_5, $J_{5,6}$ = 7.5 Hz, $J_{5,7}$ = 1.0 Hz), 2.10 (double doublet, 1 H, H_7, $J_{7,6}$ = 7.5 Hz, $J_{7,5}$ = 1.0 Hz), and 2.85 (triplet, 1 H, H_6, $J_{6,7}$ = 7.5 Hz), and those in compound **43**, at τ 0.05 (doublet, 1 H, H_5, $J_{5,7}$ = 1.0 Hz), 1.50 (doublet, 1 H, H_8, $J_{7,8}$ = 9.0 Hz), and 2.45 (1 H, H_7, m, overlapping with phenyl protons). The isomeric adducts were assigned on the basis of the nmr spectra of **42** and **43** in Table IV. The anisotropy of a benzoyl group is sufficient to account for the low-field displacement of C-5 indolizine ring proton in **38**, **39**, **42**, and **43**. The reaction of 3,4-dimethylpyridinium-*N*-phenacylide (**34**) with DAC yielded a mixture of isomeric adducts **44** and **45** in the ratio of 2:1, in which the major product was produced by cyclization at C-6 in contrast to the above reactions. The reasons underlying these differences in orientation are not yet resolved. (See Scheme III.)

1,3-Dipolar Cycloaddition of γ-Substituted Pyridinium Methylide with DAC.—Recently Snieckus, *et al.*,[10] suggested that the photochemical stability of 1,4-dicarbethoxy-1-iminopyridinium ylide might be associated with the negative charge on the exocyclic nitrogen. In an attempt to compare the reactivities of 4-carboalkoxypyridinium methylide (**35**) and the isoelectronic iminopyridinium ylide, in the ground state and the excited state, it was found that compound **35** was photochemically too stable to undergo the photocycloaddition in our present experimental data, while the reaction of **35** with DAC in acetonitrile at the refluxing temperature afforded the expected cycloadduct **46** in 38% yield, indicating that the betaine forms might be predominant in the resonance contribution at the ground state as shown in Scheme IV.

(10) A. Balasubramanian, J. M. McIntosh, and V. Snieckus, *J. Org. Chem.*, **35**, 433 (1970).

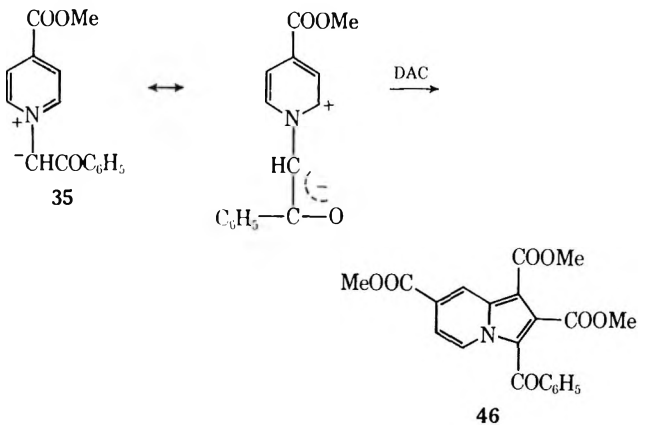
TABLE IV

RATIOS OF ISOMERIC CYCLOADDUCTS AND THEIR SPECTRAL DATA

Compd no.	Reaction conditions—Temp	Time, hr	Total yield, %	Ratio	M⁺, m/e	Nmr at 100 MHz (DMSO-d_6), τ, J in Hz[a] at C-5 H
36 + 37	Room temp	4	40	3.0:1.0[b]	272	2.0 (dd, J = 7.0, 1.0), 1.8 (d, J = 1.0)
38 + 39	Reflux	12	20	2.5:1.0	351	0.72 (dd, J = 7.0, 1.0), 0.65 (d, J = 1.0)
40 + 41	Room temp	4	80	3.1:1.0	283	1.14 (dd, J = 7.0, 1.0), 0.57 (d, J = 1.0)
42 + 43	Room temp	5	15	2.5:1.0	362	0.35 (dd, J = 7.5, 1.0), 0.05 (d, J = 1.0)
44 + 45	Room temp	5	12	2.0:1.0	365	0.61 (s), 0.93 (d, J = 7.5)

[a] $J_{5,6} = J_{6,7} = J_{7,8} = 7.0\sim7.5$ Hz; $J_{5,7} = J_{6,8} = 1.0$ Hz (Scheme III). [b] The ratio was also determined by the integrated areas for the methyl proton signals appeared at τ 7.50 in **36** and τ 7.55 in **37**.

SCHEME IV



Experimental Section[11]

Preparation of the Dicyanomethylides.—The dicyanomethylides were prepared by a modified method of Linn, *et al.*[7] To a stirred and cooled (ice bath) solution of 0.3 mol of the base [1–6, 3-methylpyridine (26), and 3-cyanopyridine (27)] in 100 ml of tetrahydrofuran was added slowly a solution of 0.1–0.15 mol of TCNEO in 50 ml of tetrahydrofuran over 1 hr. The mixture was stirred for an additional hour at room temperature or under gentle reflux condition and filtered. The ylides were purified by recrystallization from methanol. The yields, analyses, and spectral data of the dicyanomethylides (7–12 and **32**) are given in Table I.

Preparation of the Phenacylides.—The phenacylides were prepared by a modified method of Kröhnke[3] as follows. A mixture of 0.11 mol of the base (**1**, **21**, **26**, **27**, **28**, and **29**) and 0.1 mol of phenacyl bromide in 20 ml of chloroform or acetonitrile was stirred at room temperature for 1 hr. The mixture was warmed for an additional hour at 50° for complete crystallization. The resulting slurry was filtered and recrystallized from methanol. Subsequent treatments of these phenacyl salts with 10% potassium carbonate in 20 ml of water afforded the phenacylides **22**, **31**, **33**, **34**, and **35**, which are slightly hygroscopic, and directly used to 1,3-dipolar cycloaddition reactions without further purification.

1,3-Dipolar Cycloaddition Reactions of the Pyridazinium Dicyanomethylides with Dipolarophiles.—A suspension of 0.1 mol of the dicyanomethylides (**7–12**) and 0.1 mol of DAC or cyanoacetylene in 20 ml of acetonitrile was stirred at room temperature or at the refluxing temperature for 4–16 hr. The solvent was removed under reduced pressure and the residue was purified on a silica gel column with benzene as an eluent to give the corresponding adducts (**13–20**). The yields and analytical and spectral data are given in Tables II and III.

Methanolysis of Compound 13.—A mixture of **13** (0.1 g) and 20% methanolic hydrogen chloride solution (30 ml) was refluxed at 100° in an oil bath for 15 hr. The solvent was removed *in vacuo*, the residue was dissolved in water (50 ml), and the solution was adjusted to pH 7 with 10% sodium hydroxide solution. Then the solution was concentrated under reduced pressure to give a 50% yield of 5,6,7-tricarbomethoxypyrrolo[1,2-*b*]-pyridazine as a colorless solid, mp 160–161° (lit.[9] 163°).

1,3-Dipolar Cycloaddition Reaction of 3-Methylpyrazinium *N*-Phenacylide (22) with DAC. 1.—A solution of **22** (0.9 g, 0.004 mol) and DAC (0.6 g, 0.004 mol) in acetonitrile (100 ml) was stirred at room temperature for 17 hr. The solvent was then removed under reduced pressure and the residue was purified by silica gel chromatography with chloroform as an eluent to give a yellow crystal **23** (0.06 g, 4%): mp 141–142°; τ ($CDCl_3$) 7.16 (s, CH_3), 6.75 (s, $COOCH_3$), 6.09 (s, $COOCH_3$), 2.46 (m, C_6H_5), 2.14 (d, J = 5.5 Hz, 1 H, ring proton), 1.14 (d, J = 5.5 Hz, 1 H, ring proton).

Anal. Calcd for $C_{19}H_{16}O_5N_2$: C, 64.77; H, 4.58; N, 7.95. Found: C, 64.50; H, 4.60; N, 7.90.

2.—A solution of **22** (4.35 g, 0.02 mol) and DAC (5.83 g, 0.04 mol) in chloroform (20 ml) was refluxed for 17 hr. The solvent was then removed under reduced pressure, and the residue was purified by silica gel chromatography with chloroform as an eluent to give a yellow crystal (0.062 g, 8.5%), mp 120–135°, which was identified as a 2:1 mixture of **23** and **24** by nmr. A mixture of **23** and **24** was separated by repeated recrystallization from methanol: **23** had mp 185–188° [τ ($CDCl_3$) 7.41 (s, CH_3), 6.69 (s, $COOCH_3$), 6.09 (s, $COOCH_3$), 2.46 (m, C_6H_5), 0.91 (s, 1 H, ring proton), 0.41 (s, 1 H, ring proton)], and **24** had mp 141–142°.

Anal. Calcd for $C_{19}H_{16}O_5N_2$: C, 64.77; H, 4.58; N, 7.95. Found for **23**: C, 64.61; H, 4.55; N, 7.92. Found for **24**: C, 64.70; H, 4.49; N, 7.89.

1,3-Dipolar Cycloaddition Reactions of Substituted Pyridinium Ylides (30–34) with DAC. 1.—A solution of 0.1 mol of the dicyanomethylides (**30** and **32**) and 0.1 mol of DAC in 50 ml of acetonitrile was stirred at room temperature or under the refluxing conditions for 4–12 hr, and the solvent was then removed under reduced pressure. The residue was found to be a mixture of isomeric adducts. However, the isomers could not be separated from the mixture by column chromatography. The ratios of the isomeric adducts and their spectral data are given in Table IV.

2.—A solution of 0.1 mol of the phenacylides (**31**, **33**, and **34**) and 0.2 mol of DAC in 50 ml of acetonitrile was treated as described above to give an isomeric mixture of the adducts (Table IV). A mixture of adducts **42** and **43** was separated by column chromatography with benzene as an eluent: **42** had mp 190–196° [ν_{max}^{KBr} 2280 (C≡N), 1745 ($COOCH_3$), 1710 ($COOCH_3$), 1640 cm^{-1} (COC_6H_5)], and **43** had mp 210–218° [ν_{max}^{KBr} 2280 (C≡N), 1745 ($COOCH_3$), 1710 ($COOCH_3$), 1640 cm^{-1} (COC_6H_5)].

Anal. Calcd for $C_{20}H_{14}O_5N_2$: C, 66.29; H, 3.89; N, 7.73. Found for **42**: C, 66.31; H, 3.90; N, 7.80. Found for **43**: C, 66.29; H, 3.85; N, 7.70.

A mixture of adducts (**38** + **39**, **44** + **45**) could not be separated from the mixture either by column chromatography or by repeated recrystallization.

1,3-Dipolar Cycloaddition Reaction of 4-Methoxycarbonylpyridinium-*N*-phenacylide (35) with DAC.—A solution of **35** (1.2 g) and DAC (1.5 g) in acetonitrile (30 ml) was refluxed for 21 hr. The solvent was removed under reduced pressure to give yellow powder. Recrystallization from methanol gave **46** (0.7 g, 40%): mp 189–191°; τ ($CDCl_3$) 6.63 (s, $COOCH_3$), 6.03 (s, $COOCH_3$), 5.97 (s, $COOCH_3$), 2.37 (m, 6 H, C_6H_6, and 1 H of H_6, ring proton), 0.83 (d, J = 1.0 Hz, 1 H, H_8, ring proton), 0.16 (d, J = 7.0 Hz, 1 H, H_6 ring proton).

(11) The melting points were measured with a Yanagimoto micromelting point apparatus and are uncorrected. Microanalyses were determined with a Perkin-Elmer 240 elemental analyzer. The uv spectra were taken with a JASCO Model ORD/UV-5 analyzer. The nmr spectra were taken with a Jeolco Model C-60-XL and a Minimer-100 nmr spectrometers with tetramethylsilane as an internal standard. The chemical shifts are expressed in τ values. The ir spectra were taken with a JASCO Model IR-S spectrophotometer. The mass spectra were obtained on a Hitachi RMU-D double-focusing mass spectrometer operating at an ionization potential of 70 eV.

Anal. Calcd for $C_{21}H_{17}O_7N$: C, 63.79; H, 4.33; N, 3.54. Found: C, 63.81; H, 4.40; N, 3.50.

Registry No.—**7**, 27391-06-6; **8**, 27391-07-7; **9**, 27391-08-8; **10**, 27391-09-9; **11**, 27391-10-2; **12**, 27391-11-3; **13**, 27425-46-3; **14**, 27425-47-4; **15**, 27425-48-5; **16**, 27391-12-4; **17**, 27391-13-5; **18**, 27391-14-6; **19**, 27425-49-6; **20**, 27415-61-8; **23**, 27415-62-9; **24**, 27415-63-0; **32**, 27415-64-1; **36**, 27371-68-2; **37**, 27415-66-3; **38**, 27415-67-4; **39**, 27425-50-9; **40**, 27415-68-5; **41**, 27415-69-6; **42**, 27415-70-9; **43**, 27415-71-0; **44**, 27415-72-1; **45**, 27415-73-2; **46**, 27415-65-2.

The Synthesis of 1-Fluorocycloalkenes

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Contribution No. 1713 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

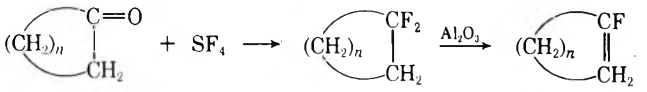
Received August 24, 1970

The reaction of anhydrous, neutral alumina, activity grade I, with a 1,1-difluorocycloalkane produces the corresponding 1-fluorocycloalkene in 20–70% yield. In this way, 1-fluorocyclopentene, 1-fluorocyclohexene, 1-fluorocycloheptene, 1-fluorocyclooctene, 1-fluorocyclododecene, and 4-methoxy-1-fluorocyclohexene were prepared and characterized, principally by proton and fluorine nmr and infrared spectra. The starting difluoro compounds were obtained by the action of sulfur tetrafluoride on the cyclic ketone. Thus, a facile, two-step entry into this elusive class of vinyl fluorides is provided.

Although linear vinyl fluorides are a well-known class of organic compounds, their cyclic counterparts are little described in the chemical literature. To our knowledge, the only example reported is 1-fluorocyclohexene (**6**).[1] We wish to report that the action of anhydrous, neutral alumina on a *gem*-difluorocycloalkane is a convenient, general route to cyclic vinyl fluorides. The difluoro compounds are obtained readily from the corresponding cyclic ketone and sulfur tetrafluoride[2] and this synthetic approach is outlined in Scheme I.

SCHEME I

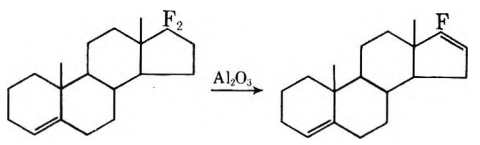
SYNTHESIS OF 1-FLUOROCYCLOALKENES



1, $n = 3$	**2**, $n = 3$	**3**, $n = 3$
4, $n = 4$	**5**, $n = 4$	**6**, $n = 4$
7, $n = 5$	**8**, $n = 5$	**9**, $n = 5$
10, $n = 6$	**11**, $n = 6$	**12**, $n = 6$
13, $n = 10$	**14**, $n = 10$	**15**, $n = 10$

Results and Discussion

Initially, the model reaction **16** → **17**[3] was chosen for study in order to establish optimum conditions of solvent, temperature, and type of alumina. This reaction proceeded under very mild conditions[4] and no side reactions were observed. In addition, integration of H-4 *vs.* H-16, which are well resolved in the 60-MHz nmr spectrum of **17**, provided accurate quantitative data. By this method, it was established that hydrocarbon solvents gave high yields of **17**, whereas polar solvents, *e.g.*, acetonitrile, ethyl acetate, and dimethyl sulfoxide, gave essentially no product under identical reaction conditions. The source of the alumina was critical. Several samples were tested but only Woelm or Guilini[5] neutral alumina,[6] activity grade I, gave good results. Woelm basic alumina gave lower yields and Woelm acidic alumina and other samples of alumina from various commercial sources returned only unchanged **16**. The reactivity of an alumina sample probably is a function of available Lewis acid and base sites on the alumina surface, since we have shown that blocking the former sites with pyridine *or* the latter sites with tetracyanoethylene[7] completely inhibited the above reaction. Additional evidence in support of active sites is the fact that alumina is required in stoichiometric amount. No more than about 1 mmol of difluoro compound per 5 g of alumina can be dehydrofluorinated under the conditions used; and, if this ratio is exceeded, a mixture of starting material and product is obtained.



16 **17**

When alumina was suspended in a hexane solution of 1,1-difluorocyclohexane (**5**) at reflux temperature, starting material was consumed completely, and a single volatile product was formed as evidenced by gas–liquid chromatography. However, it was not possible to separate product from solvent by careful distillation, and essentially all the product was lost in fractions over the boiling range of 80–92°. To circumvent this difficulty, neat **5** was admixed with alumina without solvent and heated in an oil bath in a nitrogen atmosphere after which the reaction vessel was evacuated through a cold trap. The volatile material in the trap was shown to be a mixture of 96% of **6** and 4% of cyclohexene by nmr, mass spectrum, and glc analysis. The yield was 63% compared to 66%[8] in the solvent-mediated reaction

(1) (a) G. N. Valkanas and H. Hopff, U. S. Patent 3,093,692 (1963); *Chem. Abstr.*, **59**, 11291e (1963). (b) G. Wittig and B. Mayer, *Ber.*, **96**, 329 (1963).

(2) (a) W. R. Hasek, W. C. Smith, and V. A. Engelhardt, *J. Amer. Chem. Soc.*, **82**, 543 (1960); (b) D. G. Martin and F. Kagan, *J. Org. Chem.*, **27**, 3164 (1962).

(3) The preparation of steroid vinyl fluorides will be the subject of a separate communication from this laboratory.

(4) In hexane at room temperature, yields of **17** were 50 and 60% after 1 and 18 hr, respectively. At reflux temperature, the yield was 95–98% in 1 hr.

(5) Supplied by Bodman Chemical Co., Narberth, Pa.

(6) Hereafter designated as alumina.

(7) F. Figueras Roca, A. Nohl, L. de Mourges, and Y. Trambourze, *C. R. Acad. Sci.*, **266**, 1123 (1968).

(8) Gas–liquid chromatographic analysis.

described above. Similarly, pure 1-fluorocyclopentene (**3**) was obtained from 1,1-difluorocyclopentane (**2**) in 67% yield.

However, when this technique was applied to 1,1-difluorocycloheptane, no volatile products collected in the cold trap. A complex mixture of nonvolatile products was removed from the alumina with ether and a mixture of ether and methanol, from which cycloheptanone was isolated in 40% yield. The residual 35–40% of products was not identified, but spectral evidence indicated that, in part, they were condensation products of cycloheptanone.[9] Ketones were formed in all dehydrofluorination reactions reported herein, presumably by hydrolysis of the difluoro compound on the alumina surface but only the seven-membered ring gave ketone as the major product. The desired product **9** was finally obtained in 20% yield along with 42% of cycloheptanone by use of hexane solvent at reflux temperature.

The action of sulfur tetrafluoride on cyclooctanone gave pure 1,1-difluorocyclooctane in about 0.5% yield, and our studies of this substance were limited. In pentane solution at room temperature, **11** was consumed rapidly by alumina, and at least three volatile products were formed as shown by glc analysis. By use of a combined gas chromatograph–mass spectrometer, the most abundant of the three products was shown to be the only one which contained fluorine. A small sample was collected by preparative glc. An exact mass measurement gave the formula $C_8H_{13}F$, and in pentane solution the fluorine resonance was a triplet (J_{FCCH} = 22.5 Hz) of doublets ($J_{FC=CH}$ = 18.0 Hz) centered at 99.1 ppm. The vinyl proton was a doublet (J_{HF} = 18.0 Hz) of triplets (J_{HH} = 8.6 Hz) which confirmed strong coupling between fluorine and the vinyl proton. These data are most consistent with the *cis*-1-fluorocyclooctene structure.[10]

Finally, treatment of 1,1-difluorocyclododecane with alumina in hexane solution under conditions similar to those used for **9** revealed that vinyl fluorides are also dehydrofluorinated by alumina. The major product was cyclododecyne contaminated with one or more cyclic dienes.[11] 1-Fluorocyclododecene was prepared by increasing the amount of **14** per gram of alumina and was obtained in 46% yield as a colorless oil contaminated with starting difluoro compound. Since the product was characterized by infrared, nmr, and mass spectra, preparative glc was not carried out and **15** was not obtained in pure form.

Spectral Data.—The main features of the nmr spectra of the 1-fluorocycloalkenes are presented in Table I.[12] Although the spectra of 1-fluorocyclopentene are not well resolved, the spectra of the remaining members of the series essentially define the structure. It is difficult to interpret the strong doublet coupling between the fluorine atom and vinyl proton as the result of other than a vinyl fluoride. The magnitude of $J_{(FC=CH)}$ is consistent with the expected cis stereochemistry at the carbon–carbon double bond of the cyclopentene through cyclooctene compounds; the $J_{(FC=CH)}$ = 37 Hz of 1-fluorocyclododecene suggests a trans structure. Unfortunately, the more intriguing aspects of the nmr spectra, such as the large variation of fluorine chemical shift *vs.* ring size, cannot be explained at this time.

Table I

Nmr Parameters for 1-Fluorocycloalkenes[a]

Ring size	Chemical shift, F, ppm	Chemical shift, Vinyl H, δ	J, Hz, CH=CF	J, Hz, CH_2CF=	J, Hz, CH_2CH=
5	122.7	4.92	*b*	*b*	*b*
6	101.1	5.14	17	*c*	*c*
d	103.1	5.00	16	*e*	3.5
7	91.9	5.35	21.5	11.5	6.0
8	99.1	5.10	18.0	22.5	8.6
12	112.5	4.53	37.0	16.0	7.5

[a] Additional nmr data for these compounds are given in the Experimental Section. [b] *J* values are small. Proton and fluorine resonances are narrow (10 Hz) multiplets. [c] Pattern is too complex to analyze. [d] 4-Methoxy-1-fluorocyclohexene. [e] Not resolved.

Each of the fluoroenes gave a molecular ion as the most important feature in the low-resolution mass spectrum and the molecular weight of the dehydrofluorination products was confirmed in this way. However, the fragmentation patterns were of little use for determination of structure. It should be noted that the mass spectra of a 1-fluorocycloalkene and the corresponding 1,1-difluorocycloalkane are very similar. The difluoro compounds lose the elements of hydrogen fluoride and give M − 20 as the ion of highest mass in the spectrum. Some of our initial, small-scale studies were confused by this fact.

Experimental Section

General Methods.—Proton (60 MHz) and fluorine (56.4 MHz) nmr spectra were recorded as solutions in deuteriochloroform with tetramethylsilane and fluorotrichloromethane as internal references. Fluorine chemical shifts are in ppm upfield from the reference. The notation s, d, t, q, and m refers to singlet, doublet, triplet, quartet, and multiplet, respectively. Gas–liquid chromatography was carried out with a 6 ft × 0.25 in. column of Dow Corning silicone oil, FS 1265, 20% on Gas-Chrom R (60–80 mesh). Infrared spectra were recorded on neat films. Mass spectra were obtained on a Bendix time-of-flight mass spectrometer which was equipped to sample from a glc unit. Mass measurements were confirmed with higher resolution instruments when necessary.

Materials.—Cyclic ketones were commercial samples used without purificaton except 4-methoxycyclohexanone, which was obtained by catalytic reduction of *p*-methoxyphenol to 4-methoxycyclohexanol followed by dichromate oxidation to the ketone, bp 78–79° (11 mm) [lit.[13] bp 84–85° (14 mm)]. Hexane was ACS grade and Woelm or Guilini[5] neutral alumina, activity grade I, was used.

1,1-Difluorocyclopentane (2).—Literature procedures[2] were used with slight modification. A mixture of **1** (1.0 mol), hydrogen fluoride (1.0 mol), sulfur tetrafluoride (1.0 mol), and 150 ml of dichloromethane was agitated for 120 hr in a Hastelloy C pressure vessel at 30° and autogenous pressure. The vessel was opened and the reaction mixture was washed with water, 10% sodium bicarbonate solution, and water. The organic layer was dried ($CaSO_4$) and was flash-distilled on a rotary evaporator. The flash distillate was dried again and was fractionated carefully through a spinning-band column to give 39% of **2**: bp 69–70°; $n^{25}D$ 1.3612; fmr was a quintet at 93.4 ppm, J_{HF} = 14.0 Hz.

Anal. Calcd for $C_5H_8F_2$: C, 56.61; H, 7.60; F, 35.82. Found: C, 57.8; H, 7.75; F, 35.7.

1,1-Difluorocyclohexane (5).—The above procedure was used with **4** (2.5 mol), hydrogen fluoride (3.0 mol), sulfur tetrafluoride

(9) A. T. Nielsen and W. J. Houlihan, *Org. React.*, **16**, 1 (1968).

(10) The low-temperature fluorine nmr of this substance is the subject of a separate communication from this laboratory: F. J. Weigert and D. R. Strobach, *Org. Magn. Resonance*, **2**, 303 (1970).

(11) The elimination of 2 mol of hydrogen fluoride was also noted with linear systems such as 2,2-difluorooctane, which gave 2-octyne as a major product.

(12) For comparison, the nmr spectra of the series, cyclopropene through cyclooctane, have been recorded and discussed: K. B. Wiberg and J. Nist, *J. Amer. Chem. Soc.*, **83**, 1226 (1961).

(13) N. A. Milas and C. P. Priesing, *ibid.*, **79**, 6295 (1957).

(2.0 mol), and 300 ml of dichloromethane with a reaction time of 48 hr. The yield of **5** was 70%: bp 99–100°; n^{25}D 1.3904 (lit.[2a] values are bp 98–99°, n^{25}D 1.3890); fmr was a quintet at 96.0 ppm, J_{HF} = 14.0 Hz.

1,1-Difluoro-4-methoxycyclohexane.—As above, 4-methoxycyclohexanone (0.195 mol), hydrogen fluoride (0.50 mol), sulfur tetrafluoride (0.37 mol), and dichloromethane (50 ml) were agitated for 18 hr. The yield of product was 57%, bp 65–67° (45 mm). Fmr was an AB quartet at 93.2 ppm (equatorial) and 101.7 ppm (axial), J_{FF} = 236 Hz.

Anal. Calcd for $C_7H_{12}F_2O$: C, 55.98; H, 8.05; F, 25.30. Found: C, 56.6; H, 8.08; F, 25.9.

1,1-Difluorocycloheptane (**8**).—As above, **7** (0.45 mol), hydrogen fluoride (1.0 mol), sulfur tetrafluoride (0.56 mol), and dichloromethane (100 ml) were agitated for 24 hr. The yield of **8** was 79%: bp 130–131°; n^{25}D 1.4058; fmr was a quintet at 85.3 ppm, J_{HF} = 16.0 Hz.

Anal. Calcd for $C_7H_{12}F_2$: C, 62.65; H, 9.02; F, 28.33. Found: C, 62.7; H, 9.09; F, 28.3.

1,1-Difluorocyclooctane (**11**).—As above, **10** (0.60 mol), hydrogen fluoride (2.25 mol), sulfur tetrafluoride (1.20 mol), and dichloromethane (150 ml) were agitated for 18 hr. An impure product was collected by distillation, 1.24 g (1.6%), bp 62–65° (35 mm). This was purified by preparative glc on a 6-ft column of 25% fluorosilicone on Gas-Chrom R. Column temperature was 75° and He flow rate was 500 ml per min. The product had 93.9-min retention time. Fmr was a quintet at 88.0 ppm, J_{HF} = 15.0 Hz (lit.[14] values are a quintet at 89.0 ppm, J_{HF} = 15.1 Hz in propene as solvent).

Anal. Calcd for $C_8H_{14}F_2$: F, 25.64. Found: F, 24.9.

1,1-Difluorocyclododecane (**14**).—As above, **13** (0.41 mol), hydrogen fluoride (0.50 mol), sulfur tetrafluoride (0.56 mol), and dichloromethane (150 ml) were agitated for 120 hr. The crude product could not be distilled and was passed over a column (4.8 × 43 cm) of Florisil with hexane as eluent. Fractions (50 ml) were collected and monitored by gravimetric analysis and tlc on silica gel. Appropriate fractions were combined, solvent was removed, and the residue was sublimed (bath temperature 60°, 0.10 mm) to give 19.2 g (23%) of colorless, crystalline, waxy solid, mp 42–44°. Fmr was a quintet at 91.7 ppm, J_{HF} = 14.5 Hz.

Anal. Calcd for $C_{12}H_{22}F_2$: C, 70.54; H, 10.86; F, 18.60. Found: C, 70.9; H, 10.89; F, 18.7.

1-Fluorocyclopentene (**3**).—1,1-Difluorocyclopentane (10.0 g, 0.094 mol) was added to a freshly opened, 500-g can of Woelm alumina and mixed for 15 min. The contents of the can were transferred to a flask which was heated in an oil bath (70°) for 15 hr under nitrogen. The flask was evacuated slowly to 5-mm pressure through a Dry Ice–acetone trap. The bath temperature was raised rapidly to 150°, and, after 1 hr, 5.40 g (66%) of colorless liquid was removed from the trap and dried ($CaSO_4$). The dried product was analytically pure, n^{25}D 1.400, and had infrared bands at 2980 (s), 2870 (s), 1680 (s, CH=CF), 1450 (w), 1340 (s), 1160 (s), 950 (m), 870 (m), and 800 cm^{-1} (m, broad). Pmr was δ 2.00, m, 6 H. A small sample was distilled, bp 56°.

Anal. Calcd for C_5H_7F: C, 69.75; H, 8.19; F, 22.06. Found: C, 69.9; H, 8.29; F, 22.1.

1-Fluorocyclohexene (**6**).—The procedure used to prepare **3** was repeated with 1,1-difluorocyclohexane (10.4 g, 0.087 mol). The liquid in the trap weighed 5.46 g (63%) and was dried over $CaSO_4$, n^{25}D 1.4251. The product gave a molecular ion (*m/e* 100) in the mass spectrum and was contaminated with 4% of cyclohexene, which was identified by mass spectrum (*m/e* 82) and glc retention time: infrared bands at 2970 (s), 2860 (s), 1700 (s, CH=CF), 1440 (m), 1360 (s), 1330 (m), 1140 (s), 970 (m), 920 (m), 910 (m), 860 (m), 840 (m), 800 (m), and 780 cm^{-1} (m); pmr resonance at δ 1.65 m, 4 H and 2.06, m, 4 H (CH_2C=).

4-Methoxy-1-fluorocyclohexene.—A stirred mixture of 375 g of alumina, 500 ml of hexane, and 8.0 g (0.053 mol) of 4-methoxy-1,1-difluorocyclohexane was refluxed for 16 hr under nitrogen when starting material was consumed (glc). The mixture was cooled and solids were removed and washed with hexane. The filtrates were concentrated on the water pump to give 3.00 g (43%) of colorless oil which was pure by glc analysis: infrared bands at 2920 (s), 2850 (s), 1700 (s, CH=CF), 1450 (s), 1360 (s), 1240 (m), 1190 (s), 1180–1080 (s, broad), 1030 (m), 1000 (m), 915 (m), 875 (m), 840 (s), 830 (s), 805 (m), 780 (m), and 710 cm^{-1} (m); pmr resonances at δ 1.88, m, 2 H (CCH_2COMe), 2.18, m, 4 H (CH_2C=), 3.28, s with m buried underneath, 4 H ($HCOCH_3$).

Anal. Calcd for $C_7H_{11}FO$: C, 64.57; H, 8.52; F, 14.60. Found: C, 64.8; H, 8.44; F, 14.1.

1-Fluorocycloheptene (**9**).—Using the amounts and procedure described above for the methoxy compound, 10.4 g (0.077 mol) of 1,1-difluorocycloheptane was agitated for 25 hr. The hexane solution and washes were concentrated by distillation, and the residues was distilled to give 2.0 g (20%) of **9**: bp 54° (60 mm); n^{25}D 1.4359; infrared bands at 2920 (s), 2850 (s), 1700 (s, CH=CF), 1450 (s), 1370 (s), 1210 (m), 1150 (m), 1110 (m), 1090 (s), 1070 (s), 1010 (m), 840 (m), 815 (m), 800 (m), and 725 cm^{-1} (m); pmr resonance at δ 1.68, m, 6 H (ring CH_2 groups), 1.8–2.7, broad m, 4 H (CH_2C=).

Anal. Calcd for $C_7H_{11}F$: C, 73.62; H, 9.71; F, 16.64. Found: C, 73.7; H, 10.2; F, 16.0.

***cis*-1-Fluorocyclooctene** (**12**).—A mixture of approximately 0.3 ml of 1,1-difluorocyclooctane, 18.8 g of alumina, and 25 ml of pentane was shaken occasionally for 4 hr at room temperature. Glc indicated that **11** had been consumed and three new peaks were present. The mass spectrum of each peak showed that only the major product contained fluorine. A small sample was collected from the analytical gas chromatograph and the molecular formula was established by exact mass measurement (Calcd for $C_8H_{13}F$: 128.1001. Found: 128.0997.). The sample was not completely free of impurities and only the fmr spectrum and vinyl region of the pmr spectrum were recorded (Table I).

***trans*-1-Fluorocyclododecene** (**15**).—A mixture of 3.0 g (0.015 mol) of 1,1-difluorocyclododecane (**14**), 37.5 g of alumina, and 50 ml of hexane was agitated overnight at room temperature. The mixture was filtered, solvent was removed, and the residue was distilled to give 1.82 g of colorless liquid, bp 46–50° (0.25 mm). Glc and fmr analysis indicated that about 1.24 g (46% based on **14**) of **15** was present in the product mixture, the remainder being **14**. Strong bands at 2980, 1710 (CH=CF), and 1460 cm^{-1} were present in the infrared spectrum.

Registry No.—**2**, 1120-70-3; **3**, 27415-42-5; **5**, 371-90-4; **6**, 694-51-9; **8**, 27371-42-2; **9**, 27415-45-8; **11**, 23170-87-8; **12**, 27390-78-9; **14**, 27415-48-1; **15**, 27390-79-0; 1,1-difluoro-4-methoxycyclohexane, 27371-43-3; 4-methoxy-1-fluorocyclohexene, 27415-47-0.

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Use of Acetyl Chloride–Triethylamine and Acetic Anhydride–Triethylamine Mixtures in the Synthesis of Isomaleimides from Maleamic Acids

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Procedures for preparing N-substituted isomaleimides by reacting N-substituted maleamic acids with acetyl chloride–triethylamine and acetic anhydride–triethylamine mixtures are described. In contrast to reports by others, isomaleimides can be prepared in good yield with these reagents, provided reaction conditions are carefully controlled. The influence of temperature, amine concentration, dehydrating agent, and solvent on the preparation of *N*-(*n*-propyl)isomaleimide, *N*-(*n*-butyl)isomaleimide, *N*-(*sec*-butyl)isomaleimide, *N*-(*tert*-butyl)-isomaleimide, and *N*-phenylisomaleimide was investigated. At least 2 mol of amine per mol of maleamic acid should be used to obtain good yields of most *N*-alkylisomaleimides, but no more than 1 mol of amine per mol of maleamic acid should be used when *N*-arylisomaleimides are prepared. A mechanism is proposed to rationalize these results.

A number of papers[1-10] have appeared recently which describe the preparation and reactions of N-substituted isomaleimides, bis(isomaleimides), and cyclic isoimidium salts. These materials are generally prepared by dehydration of maleamic acids under kinetically controlled conditions. They often rearrange in the presence of catalytic amounts of base at elevated temperatures to form the N-substituted maleimides, which are usually the thermodynamically more stable isomers.

Trifluoroacetic anhydride, ethyl chloroformate, and *N*,*N*′-dicyclohexylcarbodiimide are the reagents currently favored for use in dehydrating maleamic acids to obtain isomaleimides; their high reactivity favors the formation of kinetically controlled products, and the relatively weak bases which result as by-products from these reagents are not efficient catalysts for isoimide isomerization. Acetyl chloride and acetic anhydride have also been used in isomaleimide preparations,[6] but some workers[2,3] have suggested that these reagents are not satisfactory for this purpose. It seems that reaction conditions have a significant influence on the nature of the products obtained from reactions involving these reagents.

The purpose of the present paper is to show that acetyl chloride or acetic anhydride can be used to prepare isomaleimides and related compounds in high yield and good purity, provided that reaction conditions are controlled carefully. We have found that acetyl chloride–triethylamine under the appropriate conditions behaves just like trifluoroacetic anhydride in producing isomaleimides from corresponding maleamic acids.

Cotter, *et al.*,[3] reported that the reactions of *N*-(*n*-butyl)maleamic acid with acetic anhydride–triethylamine or acetyl chloride–triethylamine mixtures yielded *N*-(*n*-butyl)maleimide. When we repeated these reactions, the principal product was *N*-(*n*-butyl)isomaleimide. When this material was refluxed (100°) for 3 hr and then redistilled, pure *N*-(*n*-butyl)maleimide was obtained. It appears that Cotter and coworkers[3] obtained *N*-(*n*-butyl)isomaleimide as the major initial product but that it rearranged to *N*-(*n*-butyl)maleimide under their work-up conditions.

The reaction of *N*-(*n*-butyl)maleamic acid at −20° with acetyl chloride–triethylamine in methylene chloride gave almost pure (97%) *N*-(*n*-butyl)isomaleimide in 61% yield. This result was comparable to that obtained in the reaction of the maleamic acid with trifluoroacetic anhydride–triethylamine at 25°. The reactions of other *N*-alkylmaleamic acids with acetyl chloride–triethylamine or acetic anhydride–triethylamine mixtures also yielded isomaleimides in high purity and reasonable yield (Table I) when the reactions were conducted at low temperature with 2 mol of triethylamine per mol of maleamic acid. The use of smaller amounts of amine resulted in lower product yields, probably due to acid-catalyzed hydrolysis of isomaleimides during work-up.[3]

In most cases, the yields obtainable by this procedure were comparable to those obtained when trifluoroacetic anhydride was the dehydrating agent. The yields obtained in the preparation of *N*-(*sec*-butyl)isomaleimide and *N*-(*tert*-butyl)isomaleimide with acetyl chloride or acetic anhydride were less than were obtained with trifluoroacetic anhydride, but this difference is probably due to differences in the reactivities of the reagents and not to differences in selectivity; both *N*-(*sec*-butyl)isomaleimide and *N*-(*tert*-butyl)isomaleimide were stable to the reaction conditions employed. In fact, we failed to prepare *N*-(*tert*-butyl)maleimide and *N*-(*sec*-butyl)maleimide by the general method of heating the maleamic acids in excess acetic anhydride–sodium acetate. These maleimides could only be obtained in low yields (2%) by fusing the amic acids for 0.5 hr, followed by distillation.[11,12] It seems that sterically hindered isomaleimides are difficult to rearrange to isoimides.

The reaction of *N*-phenylmaleamic acid with acetyl chloride in the presence of 1 equiv of triethylamine at −22° yielded *N*-phenylisomaleimide in 63% yield. The recrystallized product did not absorb at ~1730

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TABLE I

RESULTS OF REACTION OF SOME N-ALKYLMALEAMIC ACIDS WITH ACETIC ANHYDRIDE, ACETYL CHLORIDE, OR TRIFLUOROACETIC ANHYDRIDE IN THE PRESENCE OF TRIETHYLAMINE[a]

Maleamic acid	Dehydrating agent	T, °C	Time, hr	Overall yield, %	Composition of product: % imide	% isoimide
N-(n-Propyl)maleamic acid	CH_3COCl	−20	1	61	3	97
	$(CF_3CO)_2O$	25	0.5	65		100
N-(n-Butyl)maleamic acid	CH_3COCl	5	16	40	17	83
	CH_3COCl	−20	1	61	3	97
	Ac_2O	5	3	38	20	80
	$(CF_3CO)_2O$	25	0.5	62		100
N-(sec-Butyl)maleamic acid	CH_3COCl	0	1	25	Trace	~100
	$(CF_3CO)_2O$	25	1	48		100
N-(tert-Butyl)maleamic acid	CH_3COCl	25	5	32	Trace	~100
	CH_3COCl	−15	5	31	Trace	~100
	Ac_2O	60	1	31	Trace	~100
	Ac_2O	−15	5	31	Trace	~100
	$(CF_3CO)_2O$	25	5	47		100
1,2-Bis(3-carboxyacrylyl) hydrazine	CH_3COCl	25	3	50		100
	$(CF_3CO)_2O$[b]	Reflux	5	60		100

[a] Two equivalents of triethylamine was used in each experiment. [b] Imide was detected by hydrolysis of product, followed by infrared spectroscopic examination of a CCl_4 extract of the hydrolysate.

TABLE II

PRODUCTS OBTAINED FROM THE REACTION OF N-PHENYLMALEAMIC ACID WITH ACETYL CHLORIDE–TRIETHYLAMINE UNDER VARIOUS CONDITIONS

Temp, °C	Solvent	Mol Et_3N/mol acid	Time, hr	Overall yield, %	Composition of product[a]: % imide	% isoimide
−22	CH_2Cl_2	1	1	63		100
−20	$CHCl_3$	2	1	62	99	Trace
25	CH_2Cl_2	1	1	60	77	23
25	CH_2Cl_2	2	1	60	92	8
38	C_6H_6	1	1	55	68	32
38	C_6H_6	2	1	51	99	Trace
80	C_6H_6	1	2	40	100	

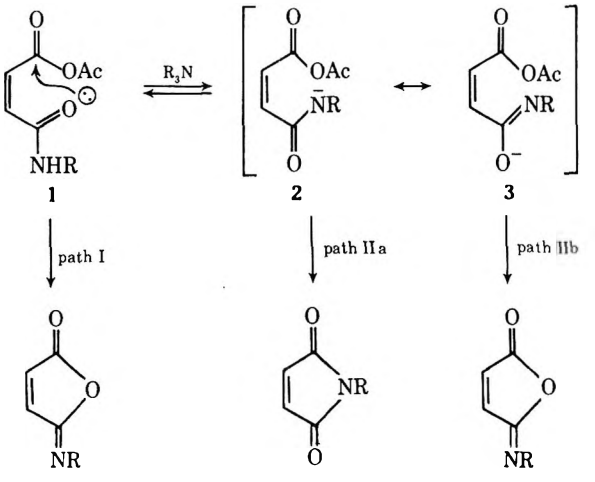
[a] Product compositions were determined by infrared analysis of product mixtures in CCl_4. The relative intensities of the carbonyl absorptions of both isomers were easily measured.

cm^{-1}, indicating that no N-phenylmaleimide was present. Use of 2 equiv of triethylamine caused N-phenylmaleimide to be the major product of the reaction. This result is interesting because N-phenylisomaleimide did not rearrange to the imide during a 6-hr treatment with either triethylamine or a triethylamine–acetic acid mixture. High temperatures also favored the formation of N-phenylmaleimide. The results of these studies are summarized in Table II.

Our results indicate that the N-phenylmaleimide formed with acetyl chloride–triethylamine mixtures at or below room temperature is derived from N-phenylmaleamic acid and not from N-phenylisomaleimide. Kinetic evidence for a direct route to N-arylmaleimides in acetic anhydride–sodium acetate dehydration systems[8,13] has also been published. Unfortunately, rearrangement of isoimides to imides is a competing reaction in the acetic anhydride–sodium acetate systems. Since this does not seem to be the case in the acetyl chloride–triethylamine system, this system can probably be used to investigate the mechanism of the direct conversion of N-arylmaleamic acids to N-arylmaleimides.

The role of amine concentration on the course taken by maleamic acid dehydrations with acetyl chloride–triethylamine mixtures can be rationalized in terms of the general mechanism for amic acid dehydrations that has evolved[7,8,14] during the last ten years. The first step in these reactions might be envisioned (Scheme I) as the

SCHEME I



formation of the mixed anhydride 1 by reaction of the maleamic acid with acetyl chloride or acetic anhydride. The subsequent cyclization step could involve either the carbonyl oxygen atom or the amide nitrogen atom. The former would be expected to be the more reactive in relatively neutral media (path I), so that isomale-

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(14) M. L. Ernst and G. L. Schmir, J. Amer. Chem. Soc., 88, 5001 (1966).

imides would be the favored products. However, in media of higher basicity, or presumably also at high temperature, the amide ion might form and this could then participate in cyclization reactions which lead either to the isoimide or the imide (path II).

The path taken by the reaction will depend on the position of the equilibrium between the neutral intermediate **1** and its ion (**2** + **3**) and also on the relative electron densities of the oxygen and nitrogen atoms in the ion (**2** + **3**). When *N*-alkylmaleamic acids are used, the equilibrium would tend to form the neutral intermediate and this would be most likely to form the isoimide. When substituents capable of stabilizing the amide ion, such as phenyl groups, are present, the ion may be present in appreciable amount, especially at high amine concentration. In this case, the imide can form in addition to the isoimide. The ion (**2** + **3**) can yield either imide or isoimide depending on whether the cyclization step involves the carbonyl oxygen or the amide nitrogen. This may depend to a certain extent on the relative electron densities of the two atoms in a particular compound. When electron-releasing substituents (*e.g.*, alkyl) are present on the nitrogen atom, a high electron density on the carbonyl oxygen might be anticipated, and this would favor the formation of isoimide (path IIb). When electron-withdrawing substituents (*e.g.*, phenyl) are present, the electron density on the oxygen atom may be reduced to such an extent that imide formation may be favored (path IIa).[15]

A complete analysis of the mechanism should give consideration to stabilities, reactivities, and rates of interconversion of the various conformers of the amide and its ion, but such consideration is inappropriate at the present time.

Experimental Section

Preparation of Maleamic Acids.—With the exception of 1,2-bis(3-carboxyacrylyl)hydrazine,[6] all N-substituted maleamic acids were prepared according to the method of Liwschitz, *et al.*[16] They were purified by dissolution in dilute $NaHCO_3$, followed by precipitation with HCl, washing with cold water, and drying. Their melting points agreed with literature values. New materials prepared were *N*-(*sec*-butyl)maleamic acid [mp 87° (*Anal.* Calcd for $C_8H_{13}NO_3$: C, 56.14; H, 7.60; N, 8.18. Found: C, 56.30; H, 7.65; N, 8.03)], and *N*-(*tert*-butyl)-maleamic acid [mp 157–158° (*Anal.* Calcd for $C_8H_{13}NO_3$: C, 56.14; H, 7.60; N, 8.18. Found: C, 56.34; H, 7.62; N, 8.11)].

General Procedure for the Preparation of Isomaleimides Using Acetyl Chloride or Acetic Anhydride.—A solution of the maleamic acid (0.1 mol) and triethylamine (0.2 mol) in methylene chloride (200 ml) was cooled to the desired temperature. Acetyl chloride or acetic anhydride (0.1 mol) was added dropwise with stirring. The temperature was kept constant during the addition and also after that for a certain time. This was followed by filtration and treatment of the filtrate with either dilute sodium bicarbonate or dilute sodium hydroxide solution. When bicarbonate was added, the solution had to stand from 0.5–2 hr. This caused loss of some *N*-alkylisomaleimides since they are sensitive to water and hydrolyze slowly. The best procedure was to simply treat the product with the stoichiometric amount of dilute sodium hydroxide. The methylene chloride layer was separated, washed, and dried. The solvent was then removed under reduced pressure and the residue was distilled under reduced pressure or recrystallized, depending on whether it was liquid or solid. This procedure worked satisfactorily for the following compounds: *N*-(*n*-propyl)isomaleimide [bp 59° (2 mm) (*Anal.* Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.47; N, 10.07. Found: C, 60.20; H, 6.18; N, 9.96)]; *N*-(*n*-butyl)isomaleimide [bp 62° (1 mm)]; *N*-(*sec*-butyl)isomaleimide [bp 60° (1 mm) (*Anal.* Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.25; H, 7.59; N, 8.91)]; *N*-(*tert*-butyl)isomaleimide [bp 45° (0.5 mm) (*Anal.* Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.45; H, 7.12; N, 9.00)]; and *N*-phenylisomaleimide[17] (mp 61°). The yields are given in Tables I and II.

N,*N*′-biisomaleimide was also prepared by the above procedure. It was insoluble in methylene chloride so the solids formed in the reaction were collected, washed successively with water, dilute $NaHCO_3$, and water, and then dried. Recrystallization from DMF yielded pure material, mp 26°.

Preparation of Isomaleimides Using Trifluoroacetic Anhydride–Triethylamine.—The procedure of Cotter, *et al.*,[3] was followed to prepare *N*-phenylisomaleimide, *N*-(*n*-propyl)isomaleimide, *N*-(*n*-butyl)isomaleimide, *N*-(*sec*-butyl)isomaleimide, and *N*-(*tert*-butyl)isomaleimide for comparison purposes. The compounds obtained were identical (ir, nmr, vpc) with the products obtained when acetyl chloride or acetic anhydride was used in the presence of triethylamine.

Analysis of Product Mixtures.—In these studies, traces of imides in the isoimides were determined by reacting the products with dilute acid. This treatment caused the isoimides to be hydrolyzed, but the imides were not affected. The imide (if present) was extracted with carbon tetrachloride and detected by infrared spectroscopy.

Product compositions were also determined by ir and nmr analyses. The carbonyl groups in the isomaleimides absorbed at 1800 cm^{-1}, and their vinylic protons were observed (CCl_4) as an AB pattern (J = 6 cps) centered at 6.8–7.1 ppm, whereas the imide carbonyls absorbed at 1680–1730 cm^{-1} and the imides showed a singlet olefinic resonance at 6.5–6.8 ppm.

Isomerization of *N*-Substituted Isomaleimides.—*N*-Phenylisomaleimide, *N*-(*n*-propyl)isomaleimide, and *N*-(*n*-butyl)isomaleimide were isomerized with sodium acetate–acetic acid[3] to obtain the corresponding imides. *N*-(*n*-Propyl)isomaleimide and *N*-(*n*-butyl)isomaleimide were also isomerized by vigorous heating. However, *N*-phenylisomaleimide, *N*-(*sec*-butyl)isomaleimide, and *N*-(*tert*-butyl)isomaleimide could not be rearranged to the corresponding imides by heat. Furthermore, *N*-(*sec*-butyl)isoimide and *N*-(*tert*-butyl)isomaleimide were unchanged after being refluxed for 1 hr with a mixture of NaOAc and benzene.

Treatment of *N*-Phenylisomaleimide with Triethylamine or a Triethylamine-Acetic Acid Mixture.—A mixture of pure *N*-phenylisomaleimide (1 g, 0.006 mol), benzene (35 ml), and triethylamine (0.1 g, 0.001 mol) was stirred at room temperature for 6 hr. A portion of the mixture ws then evaporated to dryness under reduced pressure. The melting point (61°) and infrared spectrum of the residue showed it to be essentially pure *N*-phenylisomaleimide. A similar experiment in which equimolar amounts of triethylamine and acetic acid were present also failed to cause isomerization.

Registry No.—Acetyl chloride, 75-36-5; triethylamine, 121-44-8; acetic anhydride, 108-24-7; *N*-(*sec*-butyl)maleamic acid, 27396-37-8; *N*-(*n*-propyl)isomaleimide, 27396-38-9; *N*-(*n*-butyl)isomaleimide, 27396-39-0; *N*-(*sec*-butyl)isomaleimide, 27396-40-3; *N*-(*tert*-butyl)isomaleimide, 27396-41-4; *N*-phenylisomaleimide, 19990-26-2; *N*,*N*′-biisomaleimide, 6990-21-2.

Acknowledgments. —The authors are indebted to the Mobil Chemical Co. for partial support of this study.

(15) It is interesting to report at this point that the reaction of *N*-(*o*-nitrophenyl)maleamic acid with 1:1 acetyl chloride–triethylamine in methylene chloride at −15° yielded a mixture of imide and isoimide.

(16) Y. Liwschitz, Y. E. Pfeffermann, and Y. Lapidoth, *J. Amer. Chem. Soc.*, **78**, 3069 (1956).

(17) In the preparation of *N*-phenylisomaleimide, unreacted phenylmaleamic acid precipitated when water was added to the filtrate. One crystallization of the crude product from supercooled CCl_4 gave pure *N*-phenylisomaleimide.

Alkylation of Amines. A General Exhaustive Alkylation Method for the Synthesis of Quaternary Ammonium Compounds

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A method, whereby primary and secondary amines are exhaustively alkylated to their quaternary stage in a one-step procedure, has been extended to a broad spectrum of amines. The study synthetically utilizes the fact that protonation of sterically hindered amines is affected only slightly by steric hindrance, whereas nucleophilicity as measured by the rate of alkylation is considerably decreased. A sterically hindered organic base of greater base strength than the reactant amines is employed to bind the acid that is generated in alkylation reactions. Selection of an appropriate organic base as the proton acceptor enables complete alkylation of primary and secondary aromatic amines with pK_a values as low as 2.36 and alicyclic and strong aliphatic amines with pK_a values as high as 11.1. The mild and homogeneous reaction conditions result in good yields with minimal laboratory manipulations and effort. The method is of particular importance for reactions in which the amines and the alkylating agents possess labile functions.

In a previous study[1] a new quaternization method was developed, whereby primary or secondary aromatic amines are exhaustively alkylated to their quaternary stage in a one-step procedure.

In the conventional methods[2-4] for direct alkylation of primary or secondary amines to their quaternary salts, strong inorganic bases, such as sodium hydroxide or sodium carbonate, are used to bind the acid generated as the reaction proceeds. The free amines are thus liberated from their hydrohalide salts, and the equilibria are shifted toward complete alkylation. However, the harsh reaction conditions that require prolonged heating of strongly basic and generally heterogeneous reaction mixtures give rise to undesirable side reactions and consequently low yields. These methods, therefore, are of value only in those instances where both the amines and the alkylating agents are thermally stable and are insensitive to strong inorganic bases.

In the new method, an organic base that is readily protonated, yet is a relatively poor nucleophile, serves as the proton acceptor in direct alkylation reactions of primary and secondary amines to their quaternary stage. The base should fulfill the following requirements. (1) The organic base should have solubilities similar to those of the starting amines and the alkylating agents, in order to attain homogeneous reaction conditions. (2) It must be stronger in base strength (larger pK_a) than the reacting amines, in order to combine preferentially with the acid released during the reaction. (3) It must undergo alkylation at a significantly lower rate than the amines to be quaternized. (4) The acid salt of the organic base and the quaternary ammonium product should be separable on the basis of their solubilities in common solvents.

The seemingly contradictory requirements, that the organic base has a larger pK_a yet react with the alkylating agent at a slower rate than the amines to be alkylated, led to a close examination of the relationship between basicity and nucleophilicity.[5-17] Even though a direct relationship between basicity and nucleophilicity has been shown in most studies, sterically hindered amines do not react with alkylating agents at the rates expected on the basis of their pK_a values.[7,11,13,14]

It was concluded that the interaction between a proton and a hindered amine and the interaction of the same amine with an alkylating agent must be substantially different. The proton, due to its small size and electron deficiency, appears to be able to approach the nitrogen of an amine and form a chemical bond in spite of steric hindrance. On the other hand, a sterically hindered nucleophile is hampered or even completely blocked in its attack on the alkylating agent. Whereas electron-donating groups favor the protonation of the amine, the inherent bulk of these groups retards alkylation. Severely hindered amines, therefore, exhibit an inverse relationship between basicity and nucleophilicity.

Sommer and Jackson[1] selected the complete alkylation of aniline and substituted aniline derivatives with methyl iodide in the presence of the hindered base, 2,6-lutidine, to test the validity and practical implementation of the above concepts. Primary and secondary aromatic amines with pK_a values ranging from 3.8 to 5.3 were successfully quaternized in good yields in a one-step procedure.

The present study synthetically applies the new quaternization method to a broad spectrum of amines, extending the method to include weak aromatic amines as well as alicyclic and strong aliphatic amines.

The synthetic utility of the new alkylation reaction lies in the ease by which high yields of quaternary products can be obtained directly from the generally more accessible primary amines at ambient temperature and under mildly basic reaction conditions. Quaternary compounds possessing labile functions that either cannot be prepared at all or are prepared with considerable

(1) H. Z. Sommer and L. L. Jackson, *J. Org. Chem.*, **35**, 1558 (1970).
(2) P. Karrer, "Organic Chemistry," 4th ed, Elsevier, Amsterdam, 1950, p 128.
(3) J. Goerdeler in Houben-Weyl, "Methoden Der Organishen Chemie, Stickstoffverbingdungen," Eugen Muller, Ed., Vol. XI/2, Georg Thieme Verlag, Stuttgart, Germany, 1958, pp 587-640.
(4) W. Krucker, "Synthese de Sels d'Ammonium quaternaires Derives d'Aminophenols et Etude de leur Action sur la Transmission Neuromusculaire," J. Peyronnet, Paris, 1951, pp 11-60.
(5) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).
(6) (a) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **78**, 2570 (1956); (b) *ibid.*, **79**, 5441 (1957).
(7) K. Clarke and K. Rothwell, *J. Chem. Soc.*, 1885 (1960).
(8) D. P. Evans, H. B. Watson, and R. Williams, *ibid.*, 1345 (1939).
(9) A. I. Biggs and R. A. Robinson, *ibid.*, 388 (1961).
(10) E. Folkers and O. Runquist, *J. Org. Chem.*, **29**, 830 (1964).
(11) H. C. Brown and X. R. Mihm, *J. Amer. Chem. Soc.*, **77**, 1723 (1955).
(12) H. C. Brown and R. H. Holmes, *ibid.*, **77**, 1727 (1955).
(13) H. C. Brown and A. Cahn, *ibid.*, **77**, 1715 (1955).
(14) H. C. Brown, D. Gintis, and H. Podall, *ibid.*, **78**, 5375 (1956).
(15) (a) G. W. Aska and E. Grunwald, *ibid.*, **89**, 1371 (1967); (b) *ibid.*, **89**, 1377 (1967).
(16) M. M. Fickling, A. Fischer, B. R. Mann, J. Packer, and J. Vaughan, *ibid.*, **81**, 4226 (1959).
(17) (a) A. Fischer, W. J. Galloway, and J. Vaughan, *J. Chem. Soc.*, 3591 (1964); (b) *ibid.*, 3596 (1964).

difficulties by the conventional exhaustive alkylation methods can now be synthesized in a one-step procedure without much effort from primarily amines or even directly from their acid salts.

The general procedure simply involves dissolving the amine, an appropriate sterically hindered organic base, and the alkylating agent, such as methyl iodide, in a suitable solvent and allowing the reaction mixture to stand at room temperature for a number of hours. A stoichiometric amount of the base is important. Although a sufficient amount of proton acceptor must be present to bind the acid released, an excess should be avoided to prevent formation of the methiodide of the acceptor base. Methyl iodide is normally taken in excess. The choice of the proton acceptor and the selection of the appropriate solvent are the two most important factors governing the reaction path. In principle, any organic base that is stronger in base strength and weaker in nucleophilicity than the specific amine to be alkylated can be employed to compel the reaction toward complete alkylation. Whereas only slightly greater base strength suffices, substantially lower nucleophilicities than those of the reacting amines are preferential. Additionally, the yields are greatly dependent on the differences in solubilities between the protonated base and the quaternary product in common solvents. Preferably, a combination of base and reaction solvent is selected to effect precipitation of either the desired product or the hydrohalide salt of the base. The following few guidelines facilitate the choice of the proper organic base and a convenient solvent scheme.

Quaternary ammonium compounds are generally more ionic in character than acid salts of amines and, hence, are less soluble in organic solvents. In both instances, the more aliphatic groups present in the molecule and the greater their size, the greater the solubility in organic solvents. The reactivities of the alkyl halides are in the order of iodides > bromides > chlorides. In the same order, both the quaternary and the amine salts are in most cases more soluble in organic solvent media.

The choice of the reaction solvent for alkylation reactions is dictated by the reactants used. For less reactive nucleophiles, such as amines with relatively low pK_a's, or those that are somewhat sterically hindered, solvents of higher dielectric constants are advantageous. A rough measure of relative rates for a variety of common organic solvents is provided in Table I.

If an anion other than the ion resulting from the reaction mixture is preferred the quaternary ammonium halide is easily exchanged by conventional ion exchange procedure.[18]

Several hindered organic bases were studied and are listed with their pK_a values in Table II. The first base investigated was 2,6-lutidine which has been successfully applied[1] to aromatic amines in the pK_a range from 3.86 to 5.34. In this study, trifluoromethylaniline has been quaternized in 84% yield using 2,6-lutidine as the proton acceptor.

In an attempt to extend the applicability of the method to amines with pK_a values lower than 3.86, di-*n*-propylaniline has been found to be of value. This base appears to be slightly more sterically hindered and approximately one order of magnitude weaker in base strength than 2,6-lutidine. Di-*n*-propylaniline enabled the quaternization of *m*-nitroaniline ($pK_a = 2.6$)[19] in nearly quantitative yield and *p*-aminobenzoic acid ($pK_a = 2.36$)[19] in 84% yield. However, attempts to quaternize *p*-nitroaniline ($pK_a = 1$)[20] were unsuccessful.

The scope of this exhaustive alkylation method has been extensively broadened with the introduction of strong sterically hindered organic bases. Thus, benzylamine ($pK_a = 9.3$)[19] underwent complete methylation in 85% yield, using *N*,*N*-dicyclohexyl-*N*-methylamine as the basic reagent. Tributylamine served as a good reagent for more basic amines, such as cyclohexylamine ($pK_a = 10.6$) and *n*-butylamine ($pK_a = 10.6$).[21] The quaternary products were obtained in 73 and 92% yields, respectively. The readily available tri-*n*-butylamine is advantageous in that its hydrohalide salts are soluble in less polar solvents, such as ethyl acetate, thereby affording in many instances effortless isolation of the desired products.

In the search for an "all purpose" reagent applicable to a wide spectrum of amines, 1,2,2,6,6-pentamethylpiperidine (PMP) appeared to be the base, possessing the required chemical and physical properties, by which this objective could be achieved. The five methyl groups surrounding the ring nitrogen, it was surmised, produce severe steric hindrance, whereas the inductive effects of the methyl groups increase basicity to make PMP one of the strongest organic bases known. As shown in Tables III and IV, PMP has been successfully applied over a pK_a range of 2.5 to 11, and excellent yields of quaternary products have been obtained. The apparent disadvantage that the PMP halo acid salts frequently precipitate from the reaction mixture together with the quaternary compounds can easily be overcome by simple extraction of the PMP halo acids with ace-

TABLE I

RELATIVE QUATERNIZATION RATES IN VARIOUS SOLVENTS[a]

Solvent	Approximate relative rate	Solvent	Approximate relative rate
Hexane	1	Ethanol	200
Diethyl ether	4	Methanol	285
Benzene	38	Acetone	340
1-Butanol	70	Acetonitrile	375
Chloroform	100	Nitromethane	500
Ethyl acetate	125	Dimethylformamide	900
Methyl ethyl ketone	150		

[a] F. F. Blicke and R. H. Cox, "Medicinal Chemistry," Vol. III, Wiley, New York, N. Y., 1956, p 51.

TABLE II

STERICALLY HINDERED AMINES USED AS PROTON ACCEPTORS

Base	pK_a
Di-*n*-propylaniline	5.63[a]
N,*N*-Diethylaniline	6.52[a]
2,6-Lutidine	6.77[b]
Dicyclohexylmethylamine	
Tri-*n*-butylamine	10.89[c]
1,2,2,6,6-Pentamethylpiperidine (PMP)	11.25[d]

[a] See ref 10. [b] See ref 7. [c] See ref 21. [d] See ref 22.

(18) M. M. Markowitz, *J. Org. Chem.*, **22**, 983 (1957).

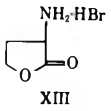
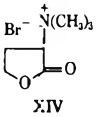
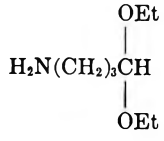
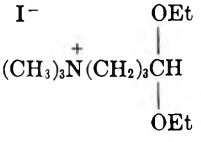
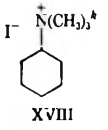
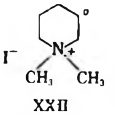
(19) Dictionary of Organic Compounds, Oxford University Press, New York, N. Y., 1965.

(20) H. H. Stroh and G. Westphal, *Ber.*, **96**, 184 (1963).

(21) H. K. Hall, Jr., *J. Phys. Chem.*, **60**, 63 (1956).

TABLE III

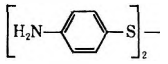
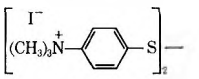
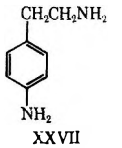
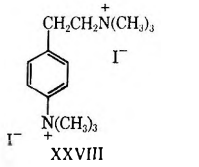
MONOAMINES QUATERNIZED WITH METHYL IODIDE IN THE PRESENCE OF VARIOUS STERICALLY HINDERED ORGANIC BASES

Amine	pK_a	Solvent	Base	Quaternary	Yield, %
p-COOHPhNH$_2$	2.36[a] (amine)	DMF[b]	PhN(*n*-Pr)$_2$	*p*-COOHPh$\overset{+}{N}$(Me)$_2$I$^-$[c]	84
I				II	
m-NO$_2$PhNH$_2$	2.6[a]	DMF	PhN(*n*-Pr)$_2$	*m*-NO$_2$Ph$\overset{+}{N}$(Me)$_3$I$^-$[e]	98
		DMF	PMP[d]		86
III		DMF	(*n*-Bu)$_3$N	IV	65
p-CF$_3$PhNH$_2$		DMF	PhN(*n*-Pr)$_2$	*p*-CF$_3$Ph$\overset{+}{N}$(Me)$_3$I$^-$	67
V				VI	
m-CF$_3$PhNH$_2$		DMF	PhN(*n*-Pr)$_2$	*m*-CF$_3$Ph$\overset{+}{N}$(Me)$_3$ I$^-$	84
		DMF	2,6-Lutidine		84
VII				VIII	
PhNH$_2$	4.65[f]	DMF	PhN(Et)$_2$	Ph$\overset{+}{N}$(Me)$_3$ I$^-$[g]	57
IX				X	
PhCH$_2$NH$_2$	9.30[a]	DMF	Dicyclohexyl-methylamine	PhCH$_2\overset{+}{N}$(Me)$_3$ I$^-$[h]	85
XI		DMF	(*n*-Bu)$_3$N	XII	64
		DMF	(*n*-Bu)$_3$N		43[i]
		CH$_3$CN	(*n*-Bu)$_3$N		43
XIII		EtOAC	(*n*-Bu)$_3$N	XIV	44
		EtOAC	PMP		90
XV				XVI	
Cyclohexylamine	10.6[j]	DMF	(*n*-Bu)$_3$N		73
XVII				XVIII	
n-BuNH$_2$	10.61[l]	DMF	(*n*-Bu)$_3$N	(*n*-Bu)$\overset{+}{N}$(CH$_3$)$_3$ I$^-$[m]	92
XIX				XX	
Piperidine	11.05[n]	DMF	PMP		78
XXI				XXII	
NH(Et)$_2$	11.11[l]	Acetone	PMP	$\overset{+}{N}$(Et)$_2$(Me)$_2$ I$^-$[o]	90
XXIII				XXIV	

[a] See ref 19. [b] DMF = *N*,*N*-dimethylformamide. [c] A. Zaku and W. Tachoc, *J. Chem. Soc.*, 562 (1941). [d] PMP = 1,2,2,6,6-pentamethylpiperidine. [e] A. Zaku, *J. Chem. Soc.*, 1078 (1930). [f] See ref 10. [g] See ref 16. [h] G. M. Coppinger, *J. Amer. Chem. Soc.*, 76, 1372 (1954). [i] The I$^-$ was exchanged to the Br$^-$ by means of ion exchange resin. [j] C. W. Bird and R. C. Cookson, *J. Chem. Soc.*, 2343 (1960). [k] Z. J. Vejdelek, M. Rajsner, and M. Protwa, *Collect. Czech. Chem. Commun.*, 25, 245 (1960); *Chem. Abstr.*, 54, 6580 (1960). [l] See ref 21. [m] V. Brann, *Justus Liebigs Ann. Chem.*, 382, 16 (1911). [n] See ref 22. [o] R. O. Clinton and S. C. Laskowski, *J. Amer. Chem. Soc.*, 74, 2226 (1952).

TABLE IV

DIAMINES QUATERNIZED WITH METHYL IODIDE IN THE PRESENCE OF STERICALLY HINDERED ORGANIC BASES

Diamine	pK_a	Solvent	Base	Bisquaternary	Yield, %
 XXV		DMF	PMP	 XXVI	93
 XXVII		DMF	PMP	 XXVIII	97
$H_2N(CH_2)_nNH_2$				$(CH_3)_3N^+(CH_2)_nN^+(CH_3)_3$ $2I^-$	
XXIX, $n = 3$	10.54[a]	DMF	$(n\text{-Bu})_3N$	XXX, $n = 3$[b]	51
		DMF	PMP		57
XXXI, $n = 4$	10.71[a]	DMF	$(n\text{-Bu})_3N$	XXXII, $n = 4$[b]	40
		DMF	PMP		80
XXXIII, $n = 10$		DMF	$(n\text{-Bu})_3N$	XXXIV, $n = 10$[c]	52
		CH_3CN	$(n\text{-Bu})_3N$		42
		DMF	PMP		82

[a] See ref 19. [b] E. J. Zaimis, *Brit. J. Pharmacol.*, **5**, 424 (1950). [c] F. Calvert and N. Fernandez, *An. Real Soc. Espan. Fis. Quim., Ser. B*, **47**, 728 (1951); *Chem. Abstr.*, **46**, 10103 (1952).

tone, in which most quaternary ammonium salts are insoluble. In those instances where the quaternary products are soluble in relatively nonpolar solvents, exemplified by the methiodide of γ-aminobutyraldehyde diethyl acetal (XV), ethyl acetate is a suitable reaction solvent from which the PMP hydriodide precipitates out, as the reaction proceeds, while the methiodide remains in solution. After removal of the precipitate, mere evaporation of the solvent produced the analytically pure desired compound in 90% yield. The reaction with *p*-nitroaniline ($pK_a = 1$) resulted in appreciable amounts of quaternized PMP solely. Hence, the lower limit of the usefulness of PMP appears to be for amines with pK_a's in the vicinity of 2. The upper limit is determined by the basicity of PMP, *i.e.*, pK_a of 11.25.

As examples for direct quaternization of amines containing labile functions, the methiodides of an acetal, γ-trimethylammoniumbutyraldehyde iodide diethyl acetal (XV), a lactone, α-dimethylamino-γ-butyrolactone methobromide (XIII), and a bisquaternary disulfide, bis(4-dimethylaminophenyl) disulfide dimethiodide (XXV), were synthesized in good yields from the corresponding primary amines.

Table IV lists the bisquaternary ammonium compounds that were prepared directly from primary diamines in a one-step procedure. Here, a reaction solvent has to be selected in which the various monoquaternary intermediates that are formed during the reaction are soluble to ensure subsequent alkylation. The monoquaternary compounds still remaining as impurities can be easily removed from the bisquaternary products utilizing solubility differences. Of the cases cited in Table IV, the monoquaternary intermediates are soluble in hot acetone, in which the bisquaternary materials are insoluble.

In conclusion, it is noteworthy to cite an example that emphatically illustrates the underlying principle upon which the new exhaustive alkylation method is based. *m*-Nitroaniline ($pK_a = 2.6$)[19] was preferentially and completely methylated in 86% yield in the presence of 1,2,2,6,6-pentamethylpiperidine ($pK_a = 11.25$)[22] which is about 10^9 times greater in base strength than *m*-nitroaniline, whereas no quaternized product of 1,2,2,6,6-pentamethylpiperidine was detected.

Experimental Section

Materials.—All solvents and reagents were the best commercial grade available and were used as received, with the exception of bis(4-aminophenyl) disulfide (XXV) which was purified by recrystallization from benzene with activated carbon treatment. The material thus purified melted at 68–68.5°. All melting points are uncorrected.

1,2,2,6,6-Pentamethylpiperidine (PMP).—A solution of 20.0 g (0.14 mol) of 2,2,6,6-tetramethylpiperidine and 40.0 g (0.28 mol) of methyl iodide in 20 ml of methyl alcohol was kept at ambient temperature overnight. The crystals that formed were removed by filtration, washed with a 1:1 acetone–ether solution and then with ether, and dried under vacuum to give 28.0 g of 1,2,2,6,6-pentamethylpiperidine hydriodide. An additional 7.0 g was obtained by the addition of ether to the mother liquid, mp 279–280° (71% yield). *Anal.* Calcd for $C_{10}H_{22}IN$: C, 42.5; H, 7.8; I, 44.8; N, 4.7. Found: C, 42.2; H, 7.6; I, 45.0; N, 4.9. The hydriodide was converted to the free amine by stirring with 175 ml of 5% sodium hydroxide solution. The amine was extracted with ether, and the ether extract was dried with sodium sulfate and evaporated to give 17.1 g (92% yield) of 1,2,2,6,6-pentamethylpiperidine (PMP) as a colorless liquid.

General Procedure.—Methyl iodide (excess) is added to a solution of the amine or amine salt and the acceptor base in stoichiometric amounts in an appropriate solvent (see Tables III and IV). The amount of excess of methyl iodide taken is not critical, and amounts from 25 to 100% excess produce satisfactory results. The reactions are normally complete in a few hours at room temperature, although for convenience the reaction mixture is allowed to stand overnight. In many cases the quaternary ammonium compound precipitates directly from the reaction mixture. Mere washing of the precipitate with solvents such as

(22) H. K. Hall, Jr., *J. Amer. Chem. Soc.*, **79**, 5444 (1957).

TABLE V
ANALYTICAL DATA OF NEW METHIODIDES

Compd	Formula	Temp, °C	Calcd, % C	H	I	N	X	Found, % C	H	I	N	X
VI	$C_{10}H_{13}INF_3$	195–196	36.2	4.0	38.4	4.2	17.2 (F)	36.2	3.9	38.5	4.0	17.2 (F)
VIII	$C_{10}H_{13}INF_3$	242–243	36.2	4.0	38.4	4.2	17.2 (F)	36.5	3.9	38.1	4.0	16.9 (F)
XVI	$C_{11}H_{26}INO_2$	71–72	40.0	7.9	38.5	4.2		39.9	7.9	38.5	4.5	
XIV	$C_7H_{14}BrNO_2$	210–211	37.2	6.7	35.6 (Br)	6.2		37.6	6.6	35.6 (Br)	6.4	
XXVIII	$C_{14}H_{26}I_2N_2$	260–261	35.3	5.5	53.3	5.9		35.0	5.8	53.0	5.7	
XXVI	$C_{18}H_{26}I_2N_2S_2$	145–146	36.7	4.4	43.2	4.8	10.9 (S)	37.0	4.6		4.7	10.6 (S)

acetone, ethyl acetate, or ether results in generally analytically pure products.

For those instances in which little or no precipitate is formed, a relatively nonpolar solvent, such as acetone, ethyl acetate, or ether, is employed to precipitate the product together with various amounts of acceptor base hydriodide. The latter is then removed by extraction with acetone or 6% *N*,*N*-dimethylformamide in acetone. The remaining quaternary salt is dried to give pure product.

When 1,2,2,6,6-pentamethylpiperidine is used as the sterically hindered base, the precipitate that forms as the reaction proceeds is treated with either acetone at reflux temperature or with 6% *N*,*N*-dimethylformamide in acetone at room or slightly elevated temperatures to dissolve coprecipitated pentamethylpiperidine hydriodide.

It should be noted that, in the exhaustive methylation reaction of the diamines, the precipitates that are obtained directly from the reaction mixture, or by the addition of a nonpolar solvent, should be heated and stirred with acetone at reflux temperature to remove any of the various monoquaternary intermediates that might be present as impurities. These are generally soluble in hot acetone, whereas the bisquaternary compounds are insoluble. Because the reactions are exothermic, slow addition of the alkylating agent is advisable.

Representative examples of the general procedure along with exceptions are described below. The known quaternary products were identified by their melting points, elemental analyses, and nmr spectra. Analytical and physical data of compounds not found in the literature are given in Table V.

N,*N*-**Dimethyl-3-(trifluoromethyl)aniline Methiodide (VIII).**—A solution of 3.0 g (18.6 mmol) of *m*-(trifluoromethyl)aniline, 6.6 g (37.2 mmol) of di-*n*-propylaniline, and 14.2 g (0.1 mol) of methyl iodide in 15 ml of *N*,*N*-dimethylformamide was kept at room temperature overnight. The precipitated product was then collected on a filter, washed with acetone and then with ether, and dried to give 5.2 g (84% yield) of VIII as colorless crystals, mp 242–243°. *Anal.* Calcd for $C_{10}H_{13}F_3IN$: C, 36.2; H, 4.0; F, 17.2; I, 38.4; N, 4.2. Found: C, 36.5; H, 3.9; F, 16.9; I, 38.1; N, 4.0.

Trimethylbutylammonium Iodide (XX).—To a solution of 0.73 g (0.01 mol) of *n*-butylamine and 3.7 g (0.02 mol) of tri-*n*-butylamine in 5 ml of *N*,*N*-dimethylformamide, 5.68 g (0.04 mol) of methyl iodide was added gradually. After standing overnight, the addition of ether precipitated white solid crystals. The precipitate was removed by filtration, recrystallized from ethanol, washed with ether, and dried to give 2.25 g (92% yield) of XX, mp 223–225°. *Anal.* Calcd for $C_7H_{18}IN$: C, 34.6; H, 7.4; N, 5.8. Found: C, 34.7; H, 7.6; N, 5.9.

N,*N*-**Dimethyl-3-nitroaniline Methiodide (IV).**—A solution of 500 mg (3.6 mmol) of *m*-nitroaniline, 1.12 g (7.2 mmol) of 1,2,2,-6,6-pentamethylpiperidine, and 3.1 g (21.6 mmol) of methyl iodide in 5.0 ml of *N*,*N*-dimethylformamide was kept overnight at room temperature. The solid that formed was removed by filtration and washed with hot acetone to give 0.95 g (86%) of IV as pale yellow crystals, mp 198–199°. *Anal.* Calcd for $C_9H_{13}IN_2O_2$: C, 35.2; H, 4.2; I, 41.1; N, 9.1; O, 10.4. Found: C, 35.4; H, 4.2; I, 41.5; N, 9.3; O, 10.2.

4-Dimethylaminobutyraldehyde Diethyl Acetal Methiodide (XVI).—A solution of 500 mg (3.1 mmol) of γ-aminobutyraldehyde diethyl acetal and 960 mg (6.2 mmol) of 1,2,2,6,6-pentamethylpiperidine in 10.0 ml of ethyl acetate was treated with 14.2 g (0.1 mol) of methyl iodide. The tenfold excess of methyl iodide aided in keeping all the quaternary product in solution. The reaction mixture was allowed to stand overnight at room temperature. The pentamethylpiperidine hydriodide that precipitated was removed by filtration, and the filtrate evaporated under reduced pressure at ambient temperature to give a white solid which was washed with ether and dried to give 940 mg (90% yield) of XVI, mp 71–72°. *Anal.* Calcd for $C_{11}H_{26}INO_2$: C, 40.0; H, 7.9; I, 38.5; N, 4.2. Found: C, 39.9; H, 7.9; I, 38.5; N, 4.5.

α-Dimethylamino-γ-butyrolactone Methobromide (XIV).—A solution of 500 mg (2.7 mmol) of α-amino-γ-butyrolactone hydrobromide and 1.5 g (8.1 mmol) of tri-*n*-butylamine in 10.0 ml of ethyl acetate was treated at ambient temperature with 2.5 g (16.2 mmol) of methyl iodide. A precipitate formed almost immediately. After 3 hr, the solid was removed by filtration and washed with ethyl acetate and then ether.

The product thus obtained was dissolved in methanol and passed through a Bio-Rad analytical anion exchange resin column (AG1-X8) saturated with bromide ions. The eluent was concentrated to 15 ml and upon addition of ether a solid precipitated. The solid material was collected on a filter and vacuum dried at ambient temperature to give 320 mg (44% yield) of XIV, mp 210–211°. *Anal.* Calcd for $C_7H_{15}BrNO_2$: C, 37.2; H, 6.7; Br, 35.6; N, 6.2. Found: C, 37.6; H, 6.6; Br, 35.6; N, 6.4.

1-Dimethylamino-2-(4-dimethylaminophenyl)ethane Dimethiodide (XXVIII).—1-Amino-2-(4-aminophenyl)ethane (1.0 g, 7.3 mmol), 4.53 g (29.2 mmol) of 1,2,2,6,6-pentamethylpiperidine, and 11.5 g (88 mmol) of methyl iodide were dissolved in 10.0 ml *N*,*N*-dimethylformamide. Heat evolved immediately, and a precipitate formed. After the mixture was kept at room temperature overnight, 250 ml of a 6% *N*,*N*-dimethylformamide in acetone solution were added and stirred for 20 min under reflux conditions. The remaining solid was collected on a filter and redissolved in methanol. Addition of ethyl acetate, filtration, and drying produced 3.4 g (97% yield) of XXVIII as white crystals, mp 260–261°. *Anal.* Calcd for $C_{14}H_{26}I_2N_2$: C, 35.3; H, 5.5; I, 53.3; N, 5.9. Found: C, 35.0; H, 5.8; I, 53.0; N, 5.7.

Registry No.—II, 880-00-2; IV, 27389-55-5; VI, 27389-56-6; VIII, 27389-57-7; X, 98-04-4; XII, 4525-46-6; XIV, 27389-60-2; XVI, 1116-78-5; XVIII, 3237-34-1; XX, 7722-19-2; XXII, 3333-08-2; XXIV, 4325-24-0; XXVI, 21787-24-6; XXVIII, 27389-67-9; XXX, 27389-68-0; XXXII, 23045-52-5; XXXIV, 1420-40-2; PMP, 79-55-0.

Acknowledgments.—The authors are indebted to Mr. R. D. Deibel for his valuable assistance in the experimental work and to Mr. C. A. Rush, Mr. J. M. Corliss, Mr. S. S. Cruikshank, Mr. E. J. W. Rhodes, Mrs. M. F. Buckles, and Mrs. N. B. Scholtz, Analytical Chemistry Department, for the microanalyses.

The Formic Acid–Formaldehyde Methylation of Amines[1]

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The formic acid–formaldehyde methylation of benzylamines has been investigated relative to reaction parameters and competing reactions. The formation of tertiary amine is favored over secondary amine, even when less than stoichiometric amounts of formaldehyde are used. Excess formaldehyde gives only a small increase in the tertiary amine yield. Formation of benzaldehyde is markedly reduced by the addition of sodium formate, presumably through enhancement of the reduction step of the methylation sequence. The absence of acid or specific base catalysis of the aldehyde formation along with a substituent effect trend suggests that the carbonyl side product results from hydrolysis of a benzylideneamine formed in an oxidation–reduction sequence of primary amine and Schiff base.

Although the formic acid–formaldehyde (Eschweiler–Clarke[2,3]) methylation of amines is a method of extensive synthetic utility,[4] it has received only limited critical investigation.[4a,5] In contrast to the mixtures which are often obtained through the methylation of primary amines with methyl iodide, the formic acid–formaldehyde method generally leads to good yields of the *N*,*N*-dimethyl tertiary amines. In some cases the formation of a carbonyl product derived from the amine can markedly reduce the useful yield.[6]

In the following, we have used benzylamines as our model and have approached the reaction from three aspects: (1) in what way do the reaction parameters affect the synthetic utility of the reaction, (2) what is the origin of the carbonyl side product, and (3) can the reaction mechanism be more clearly defined through the use of proposed intermediates and the detection of minor side products?

Results and Discussion

The formation of *N*,*N*-dimethylbenzylamine (**5**) from benzylamine (**1**) using formic acid–formaldehyde is expected to follow the sequence given in Scheme I. Work

SCHEME I

$$C_6H_5CH_2NH_2 + H_2C{=}O \rightleftharpoons \underset{\mathbf{1}}{C_6H_5CH_2NHCH_2OH} \rightleftharpoons C_6H_5CH_2N{=}CH_2 + H_2O$$

$$\underset{\mathbf{2}}{C_6H_5CH_2N{=}CH_2} + HCO_2H \longrightarrow \underset{\mathbf{3}}{C_6H_5CH_2NHCH_3} + CO_2$$

$$\underset{\mathbf{3}}{C_6H_5CH_2\overset{CH_3}{\overset{|}{N}}CH_2OH} \overset{H^+}{\rightleftharpoons} C_6H_5CH_2\overset{CH_3}{\overset{|}{N^+}}{=}CH_2 + H_2O$$

$$\underset{\mathbf{4}}{C_6H_5CH_2\overset{CH_3}{\overset{|}{N^+}}{=}CH_2} + HCO_2H \longrightarrow \underset{\mathbf{5}}{C_6H_5CH_2N(CH_3)_2} + CO_2 + H^+$$

using ^{14}C-labeled formaldehyde or formic acid has confirmed that under the usual reaction conditions the methylation can be attributed to the formaldehyde and the reduction to the formic acid.[7]

When benzylamine (**1**) in 3 molar equiv of formic acid (88%) is allowed to react with 0.5–4.0 molar equiv of formaldehyde at 80°, the major basic product is *N*,*N*-dimethylbenzylamine (**5**) accompanied by small amounts of unreacted starting material **1** and *N*-methylbenzylamine (**3**). In addition, benzaldehyde (**6**), *N*-benzylformamide (**7**), *N*-benzyl-*N*-methylformamide (**8**), and *N*-methyldibenzylamine (**9**) are found. Selected reactions run at 50° provide comparable results with a considerably decreased rate of reaction.

As is illustrated in Figure 1, the yield of tertiary amine **5** increases in a nearly linear manner with increasing formaldehyde up to 1.5 molar equiv and then appears to level off somewhat below the maximum theoretical yield. Consistent with this is the corresponding decrease in primary and secondary amines, **1** and **3**, respectively, found principally as the formamides in the reaction mixture. These results demonstrate that formation of the tertiary amine **5** is the preferred reaction pathway, even when less than a stoichiometric amount of formaldehyde is utilized. The secondary to tertiary amine methylation is clearly faster than the primary to secondary amine reaction.

Formamide formation slows the methylation sequence by making the amine less available. A similar result has been observed in the related Wallach reaction.[8] When *N*-benzylformamide (**7**) is used as the starting material in an excess of formaldehyde, only about 50% of the amide is hydrolyzed and converted to further products. In this case the major reaction product is the Schiff base **2**, since insufficient formic acid is produced by the hydrolysis of **7** for complete reduction. Tertiary amine **5** and a trace of secondary amide **8** account for the formic acid released.

In order to demonstrate the importance of the Schiff base **2** in the proposed reaction scheme, a run using preformed **2** was carried out under the usual reaction conditions. As shown in Table I, the results are very similar to a run starting with benzylamine (**1**).

The formation of a carbonyl product, in this case benzaldehyde (**6**), generally is observed in the formic acid–formaldehyde methylation reaction and can reduce the synthetic utility.[6] The formation of such a carbonyl product has generally been attributed to hydrol-

(1) Acknowledgment is made to the National Science Foundation, to the donors of the Petroleum Research Fund administered by the American Chemical Society, and to the California State College, Los Angeles Foundation, for partial support of this work.

(2) W. Eschweiler, *Chem. Ber.*, **38**, 880 (1905).

(3) H. T. Clarke, H. B. Gillespie, and S. Z. Weishaus, *J. Amer. Chem. Soc.*, **55**, 4571 (1933).

(4) (a) M. L. Moore, *Org. React*, **5**, 301 (1949); (b) L. Spialter and J. A. Pappalardo, "The Acyclic Aliphatic Tertiary Amines," Mcmillan, New York, N. Y., 1965, p 45.

(5) A. F. Meiners, C. Bolze, A. L. Scherer, and F. V. Morriss, *J. Org. Chem.*, **23**, 1122 (1958).

(6) W. E. Parham, W. T. Hunter, R. Hanson, and T. Lahr, *J. Amer. Chem. Soc.*, **74**, 5646 (1952).

(7) W. Tarpey, H. Hauptmann, B. M. Tolbert, and H. Rapoport, *ibid.*, **72**, 5126 (1950).

(8) E. Staple and E. C. Wagner, *J. Org. Chem.*, **14**, 559 (1949).

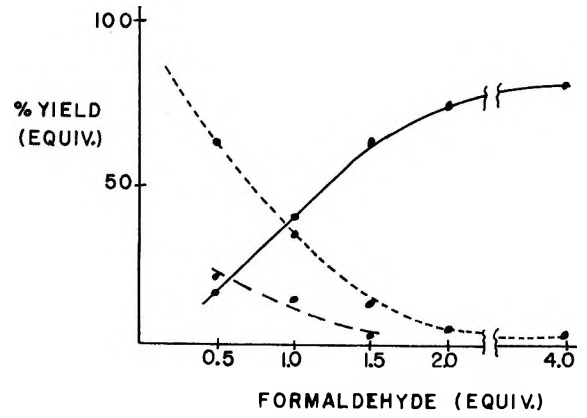


Figure 1.—Yield of primary amine + amide (------), secondary amine + amide (— —), the tertiary amine (——) as formaldehyde proportion changes.

TABLE I

COMPARISON OF PRODUCT YIELDS USING BENZYLAMINE (1) OR SCHIFF BASE 2 AS STARTING MATERIAL

Products	% yield[a] Benzylamine (1)[b]	Schiff base 2[c]
Primary amine 1	0	0
Primary amide 7	5.2	4.5
Secondary amine 3	0.1	0
Secondary amide 8	0.3	0
Tertiary amine 5	75	68
Benzaldehyde (6)	22	22
Schiff base 2		Trace

[a] Reported as equivalent per cent. [b] Reaction run for 24 hr at 80° using 1.0 equiv of 1, 2.0 equiv of formaldehyde, and 3.0 equiv of formic acid. [c] Reaction run for 24 hr at 80° using 1.0 equiv of 2, 1.8 equiv of formaldehyde, and 3.6 equiv of formic acid.

ysis of the isomerized Schiff base **10** as illustrated for our system.[3,9] Cope, *et al.*,[9] considered the stereochem-

$$\underset{\mathbf{2}}{C_6H_5CH_2N{=}CH_2} \rightleftharpoons \underset{\mathbf{10}}{C_4H_5CH{=}NCH_3} \xrightarrow{H_2O} \underset{\mathbf{6}}{C_6H_5CHO} + CH_3NH_2$$

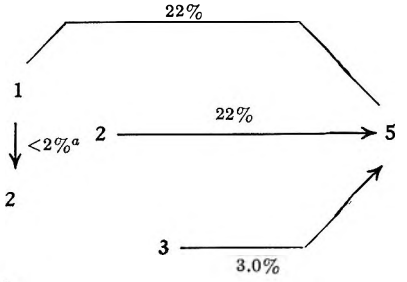
ical consequences of the isomerization by investigating the formic acid–formaldehyde methylation of optically active amines in which the asymmetric carbon atom is adjacent to the nitrogen atom. They found that the tertiary amine product showed essentially complete retention of configuration even when the appropriate carbonyl product was also formed. This suggests that the isomerized Schiff base **10** must be hydrolyzed considerably faster than it isomerizes to Schiff base **2** and that **10** is not the source of secondary amine **3**.

In order to better understand the equilibrium between Schiff base **2** and isomerized Schiff base **10** and its relationship to the carbonyl product benzaldehyde, both of these compounds were prepared and subjected to various aspects of the methylation reaction. As discussed earlier (Table I) the reaction of Schiff base **2** with formic acid–formaldehyde leads to products similar to the benzylamine reaction. On the other hand, the reaction of the isomerized Schiff base **10** with formic acid–formaldehyde leads to over 97% of benzaldehyde with less than 3% of amines observed. This indicates that the extent of isomerization of **10** to **2** must be small, consistent with the stereochemical results.[9]

In this study the benzaldehyde appears to be produced after formation of the Schiff base **2**, since very little benzaldehyde is found during the methylation of *N*-methylbenzylamine (**3**) or by the initial formation of the Schiff base.[10] The relevant data is shown in Scheme II.

SCHEME II

EQUIVALENT PER CENT OF BENZALDEHYDE FORMED IN VARIOUS STAGES OF THE METHYLATION REACTION



[a] See ref 10.

An alternate route to benzaldehyde formation might involve hydrolysis of the benzylideneamine (**11**) formed through an oxidation–reduction interaction between Schiff base **2** and primary amine **1**. This appears to be

$$\underset{\mathbf{2}}{C_6H_5CH_2N{=}CH_2} + \underset{\mathbf{1}}{C_6H_5CH_2NH_2} \rightleftharpoons \underset{\mathbf{3}}{C_6H_5CH_2NHCH_3} + \underset{\mathbf{11}}{C_6N_5CH{=}NH} \longrightarrow \underset{\mathbf{6}}{C_6H_5CHO} + NH_3$$

the mechanism for aldehyde formation in the Sommelet reaction.[11]

Actually one does not expect the isomerization, **2** → **10**, to occur readily under the reaction conditions,[12] although such an isomerization can be favored with suitable compounds.[13] In order to determine if acid or specific base catalysis might be involved in such an isomerization, the methylation reaction was run with the addition of hydrochloric acid (to provide a pH below 1). No significant difference in the tertiary amine **5** to benzaldehyde (**6**) yields was observed. In contrast, the addition of 3 equiv of sodium formate to a typical methylation (to test the possibility of a specific base-catalyzed isomerization) resulted in a marked decrease in benzaldehyde (from the usual 22 to 4%). Addition of sodium acetate shows a similar but smaller reduction of aldehyde formation, presumably through the subsequent

(9) A. C. Cope, E. Ciganek, L. J. Fleckenstein, and M. A. P. Meisinger, *J. Amer. Chem. Soc.*, **82**, 4651 (1960).

(10) The independent formation of Schiff base **2** from **1** and formaldehyde is carried out in the absence of formic acid, thus does not exactly duplicate reaction conditions. However, benzaldehyde formation in this step is unexpected.

(11) (a) S. J. Angyal, D. R. Penman, and G. P. Warwick, *J. Chem. Soc.*, 1742 (1953); (b) S. J. Angyal, *Org. React.*, **8**, 197 (1954); (c) V. Franzen, *Justus Liebigs Ann. Chem.*, **600**, 109 (1956); (d) H. R. Snyder and J. R. Demuth, *J. Amer. Chem. Soc.*, **78**, 1981 (1959).

(12) (a) J. R. Demuth, *Diss. Abstr.*, **16**, 235 (1955); (b) F. G. Baddar and Z. Iskander, *J. Chem. Soc.*, 203 (1954).

(13) E. J. Corey and K. Achiwa, *J. Amer. Chem. Soc.*, **91**, 1429 (1969).

increase in formate. It appears that formate, acting as the reducing agent, increases the relative rate of secondary (and subsequently tertiary) amine formation at the expense of the pathway to the carbonyl product. This may be a useful technique for increasing the synthetic utility of the reaction.

We have also carried out the methylation reaction with a series of substituted benzylamines. One would predict that election-withdrawing groups would favor the isomerization route to the aldehyde (**2** → **10** → **6**),[12b] while they would inhibit the transfer of hydride required for the oxidation–reduction pathway (**1** → **11** → **6**). Our results (Table II) indicate a small effect. The

TABLE II

INFLUENCE OF SUBSTITUENT ON TERTIARY AMINE *vs.* ALDEHYDE FORMATION WITH SUBSTITUTED BENZYLAMINES

Substituent[a]	% tertiary amine	% aldehyde	Ratio
p-OCH_3	75	23	3.2
p-CH_3	74	14	5.3
m-CH_3	79	19	4.2
H	76	22	3.5
m-OCH_3	85	15	5.7
p-Cl	86	9	9.5
m-Cl	85	7	12.1

[a] Arranged in increasing electron-withdrawing influence: C. D. Ritchie and W. F. Sager, *Progr. Phys. Org. Chem.*, 2, 323 (1964), and ref 14.

trend is, in general,[14] consistent with electron-withdrawing groups decreasing the relative amount of aldehyde formation as expected for the oxidation–reduction isomerization pathway.[15]

In the methylation reactions of benzylamine (**1**), a small amount of *N*-methyldibenzylamine **9** (<2%) is observed. This product presumably arises from a typical Wallach reaction[8] of the benzaldehyde (**6**) and *N*-methylbenzylamine (**3**) formed during the reaction.

$$\underset{\mathbf{6}}{C_6H_5CHO} + \underset{\mathbf{3}}{C_6H_5CH_2NHCH_3} \xrightarrow{H^+} \longrightarrow$$

$$C_6H_5CH{=}{}^{+}\overset{CH_3}{\overset{|}{N}}CH_2C_6H_5 \xrightarrow{HCO_2H} \underset{\mathbf{9}}{(C_6H_5CH_2)_2NCH_3} + CO_2 + H^+$$

Interestingly, the reaction of the isomerized Schiff base **10** with formic acid in the presence of water[16] yields a significant amount of **9** (see Table III). In this case the large amount of benzaldehyde formed readily combines with the secondary amine **3** formed by reduction.

TABLE III

REACTION OF ISOMERIZED SCHIFF BASE **10** WITH FORMIC ACID

Product	Equivalent %
6	34
9	17
3	2
10 (recovered)	23

(14) The results are based on final product analysis, thus are not expected to follow substituent values closely. It is, however, surprising that the methyl substituents are somewhat out of the expected order.

(15) Snyder and Demuth[11d] propose hydride loss from the nitrogen atom rather than the carbon atom in the Sommelet reaction. This is a surprising conclusion since one would expect a positive center at carbon to be favored. We believe that their results are not sufficiently internally consistent to strongly support this suggestion. Work with deuterium labeled benzylamines also supports hydride loss from the benzyl position.[11c]

(16) To account for the water normally present from the 36% formaldehyde.

Conclusions

It appears that the use of excess formaldehyde in the methylation reaction is synthetically wasteful since the tertiary amine yield is not significantly improved. The use of pre-formed Schiff base does not improve the desired reaction although amide formation may be reduced. The addition of sodium formate is a simple technique for favoring the methylation at the expense of the carbonyl side product. The pathway to the aldehyde side product is best explained as due to the hydrolysis of the benzylideneamine formed through an oxidation–reduction sequence of Schiff base **2** and tertiary amine **1**.

Experimental Section

Benzylamine and 36% formaldehyde were obtained from Matheson Coleman and Bell, and 88% formic acid from Mallinckrodt. The substituted benzylamines were obtained commercially with the exception of the *m*-methoxyl compound which was obtained through sodium–ethanol reduction of the corresponding oxime. Analyses were carried out using an F & M Model 720 gas chromatograph. An 11-ft 15% Carbowax 20M on Anachrome U column was used for analysis of the amines and an 8-ft 10% Ucon 50 on Chromosorb WAW column was used for the amides, benzaldehyde, and *N*-methyldibenzylamine. Peak areas were determined by a Disc integrator and independently determined, correction factors were applied to obtain the final analysis. Where appropriate, independent synthesis was used for product identification. Infrared spectra were obtained as solutions in CCl_4 or $CHCl_3$ using a Perkin-Elmer Infracord. Nucler magnetic resonance spectra were obtained using a Varian A-60 spectrometer in CCl_4 or $CDCl_3$ and are reported as downfield from internal TMS.

Typical Methylation.—To a 25-ml round-bottom flask is added 5.0 g (0.05 mol) of benzylamine. The flask is cooled in an ice bath and 7.2 g (0.15 *M*) of 88% formic acid is slowly added followed by 10.2 g (0.13 mol) of 36% formaldehyde. The flask is equipped with a magnetic stirrer and a condenser and placed in an 80° constant temperature bath for 24 hr. Bubbling begins very soon and continues to a noticeable extent for about 3 hr. The mixture is cooled and 15 ml of 6 *N* HCl is added. The mixture is extracted three times with 15 ml of ethyl ether, and the combined ether extracts are washed with 5 ml of water and then dried over magnesium sulfate. Evaporation gives 0.36 g of nonbasic material. The aqueous layer is made basic with 50% aqueous sodium hydroxide and extracted three times with 15-ml portions of ethyl ether. The ether layers are combined and washed with 5 ml of water and then dried over anhydrous magnesium sulfate. The ether is removed under vacuum giving 5.8 g of basic material.

Methylenebenzylamine (**2**).—To 10.0 g (0.09 mol) of benzylamine was added 0.2 mol of 36% formaldehyde, and the mixture was heated for 24 hr at 80°. An acid–base extraction of the product gave 0.6 g of nonbasic material and 11.1 g of basic material: bp 94° (1.1 mm) [lit.[11a] bp 100–130° (1 mm)]; nmr ($CDCl_3$) δ 3.38 (s, 2, $N{=}CH_2$),[17] 3.60 (s, 2, $C_6H_5CH_2$),[17] 7.23 (m, 5, C_6H_5).

***N*-Methyl-*N*-benzylformamide** (**8**).—To 5.0 g (0.04 mol) of *N*-methylbenzylamine was added 6.5 g (0.12 mol) of 88% formic acid, and the mixture was heated for 24 hr at 80°. The product was recovered by ether extraction to give 6.0 g (99%) of **8**: bp 133° (750 mm); ir (CCl_4) 3000 (amide CH), 1680 (C=O); nmr (CCl_4) δ 2.70 (d, 3, $=CH_3$), 4.37 (d, 2, $C_6H_5CH_2$), 7.20 (m, 5, C_6H_5), 8.10 (d, 1, HC=O).

***N*-Benzylformamide** (**7**) was prepared from 88% formic acid and benzylamine as above: mp 59–60° (lit.[18] mp 59.8–60.4°);

(17) Assignments based on the assumption that **2** is a cyclic trimer.[11a]

(18) C. A. Buehler and C. A. Mackenzie, *J. Amer. Chem. Soc.*, **59**, 421 (1937).

ir (CCl_4) 3570 (NH), 3050 (amide CH), 1700 (C=O); nmr (CCl_4) δ 4.30 (d, 2, $C_6H_5CH_2$), 7.27 (m, 6, C_6H_5 and NH), 8.12 (s, 1, HC=O).

N-**Methyldibenzylamine** (9).—To 5.0 g (0.025 mol) of dibenzylamine was added 0.037 mol of 88% formic acid and 0.025 mol of 36% formaldehyde. The mixture was allowed to react for 24 hr at 80° and worked up under typical methylation conditions (see above) to give 4.5 g (84%) of 9: bp 277° (750 mm) [lit.[19] bp 304–305° (765.5 mm)]; nmr (CCl_4) δ 2.05 (s, 3, CH_3), 3.42 (s, 4, $C_6H_5CH_2$), 7.23 (s, 10, C_6H_5).

Benzylidenemethylamine (10) was obtained commercially from Aldrich: nmr (CCl_4) δ 3.39 (d, 3, J = 1.5 Hz, NCH_3), 7.3–7.7 (m, 5, C_6H_5), 8.13 (m, 1, C_6H_5CH).

Registry No.—2, 4393-14-0; 7, 6343-54-0; 8, 17105-71-4; 9, 102-05-6; formic acid, 64-18-6; formaldehyde, 50-00-0.

(19) Dictionary of Organic Compounds, Oxford University Press, London, 1965, p 2181.

Studies in the Ganglioside Series. VI. Synthesis of the Trisaccharide Inherent in the Tay–Sachs Ganglioside[1]

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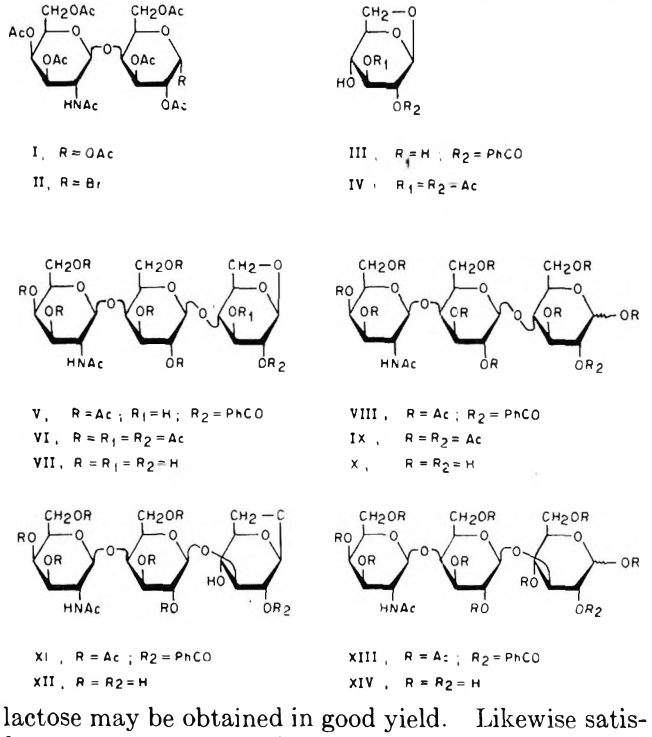
The synthesis of 2-acetamido-2-deoxy-*O*-β-D-galactopyranosyl-(1→4)-*O*-β-D-galactopyranosyl-(1→4)-D-glucopyranose (X) is reported. It involves the Koenigs–Knorr reaction of 2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-α-D-galactopyranosyl bromide (II) with 1,6-anhydro-2,3-di-*O*-acetyl-β-D-glucopyranose (IV). Opening of the anhydro ring of the resulting 1,6-anhydro-2,3-di-*O*-acetyl-4-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-β-D-galactopyranosyl]-β-D-glucopyranose (VI) followed by catalytic de-*O*-acetylation gave the trisaccharide X. The use of 1,6-anhydro-2-*O*-benzoyl-β-D-glucopyranose (III) as aglycon led, in addition, to the 1→3 isomer, 2-acetamido-2-deoxy-*O*-β-D-galactopyranosyl-(1→4)-*O*-β-D-galactopyranosyl-(1→3)-D-glucopyranose (XIV).

The linear carbohydrate chain inherent in the molecule of the abnormal ganglioside which accumulates in the brain with Tay–Sachs disease[2,3] was shown to have the structure X.[4–6] The trisaccharide has also been obtained by hydrolytic degradation of normal gangliosides and was named "ganglio-N-triose II."[7]

A prerequisite material for the chemical approach to this carbohydrate moiety is the amino disaccharide I, whose synthesis has been recently accomplished.[8] The establishment of a glycosidic linkage at C-4 of glucopyranose posed a problem on account of the well-known low reactivity of the hydroxyl group in this position. However, in the *1C* conformation of 1,6-anhydroglucopyranose the C-2 and C-4 hydroxyls react preferentially,[9–11] since the hydroxyl in position 3 is sterically hindered by the anhydro ring and by the C–C linkage at C-5.[9] The 2-benzoyl derivative III, which can be conveniently prepared by selective benzoylation of 1,6-anhydroglucose,[10] appeared to be a suitable aglycon. Surprisingly, its condensation with the bromide II gave rise to the formation of both isomers V and XI in about equal amounts. Their separation proved to be difficult and time consuming but was eventually achieved by a combination of silica gel and silica gel G columns. Even so, part of the products was eluted as a mixture. The chromatographically pure oily isomers were eventually obtained in crystalline form and showed in the nmr spectrum the correct ratio of acetyl to phenyl protons.

During the course of our studies we found that 2,3-di-*O*-acetyl-1,6-anhydroglucose (IV) is an excellent aglycon for the unambiguous synthesis of oligosaccharides involving glycosidation at C-4 of glucose.[12] Thus,



lactose may be obtained in good yield. Likewise satisfactory was the synthesis of an amino disaccharide as a model, *viz.*, 2′-deoxy-2′-acetamidocellobiose.[13] Similarly, it was now found that the Koenigs–Knorr reaction of IV with II afforded the desired 1→4 isomer VI in a 56% yield.

The continuation of the synthesis involved opening of the 1,6-anhydro ring by means of acetic anhydride

(1) This work was supported by the U. S. National Institutes of Health, PL 480, Agreement No. 425115.

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(5) A. Saifer in "Tay–Sachs Disease," B. W. Volk, Ed., Gruane & Stratton, New York, N. Y., 1964, p 68.

(6) R. Ledeen and K. Salsman, *Biochemistry*, **4**, 2225 (1965).

(7) R. Kuhn and H. Wiegandt, *Chem. Ber.*, **96**, 866 (1963).

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(10) R. W. Jeanloz, A. M. C. Rapin, and S. Hakomori, *J. Org. Chem.*, **26**, 3939 (1961).

(11) G. Zemplén, Z. Csürös, and S. Angyal, *Chem. Ber.*, **70**, 1848 (1937).

(12) D. Shapiro, Y. Rabinsohn, and A. Diver-Haber, *Biochem. Biophys. Res. Commun.*, **37**, 28 (1969).

(13) D. Shapiro, Y. Rabinsohn, A. J. Acher, and A. Diver-Haber, *J. Org. Chem.*, **35**, 1464 (1970).

and concentrated sulfuric acid, a reaction which was accompanied by acetylation of the free hydroxyl in compounds V and XI. Treatment of the resulting polyacetates with barium methoxide led to the free trisaccharides X and XIV. Both VIII and IX yielded on deacylation the trisaccharide X with specific rotations +30.3 and +30.7°, respectively. Kuhn[7] calculated by Hudson's isorotation rule +29.7°, but his natural compound had a value of +17.3°.

The structural assignment was primarily based on the periodate oxidation of compounds VII and XII. Additional support came from the fact that, apart from VIII, the polyacetate IX whose 1→4 linkage is determined by the aglycon IV also led to the trisaccharide X. Furthermore, acetylation of X obtained *via* VIII furnished a product identical with IX. Finally, the complete structure of X was confirmed by combined gas–liquid chromatography and mass spectrometry.[14,15] This analysis was kindly performed by Dr. J. Kärkkäinen of the University of Helsinki.

Experimental Section[16]

2,3,6-Tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-α-D-galactopyranosyl Bromide (II).—To a stirred solution of the fully acetylated amino disaccharide I[8] (1.0 g, 1.47 mmol) in acetic anhydride (4 ml), cooled to 0°, was added a cold 45% solution of hydrogen bromide in acetic acid (12 ml), and the mixture was kept for 24 hr in the refrigerator (+2°). The yellow solution was concentrated *in vacuo* (<1 mm), at room temperature. For complete removal of the anhydride, the oily product was coevaporated with six portions each of 8–10 ml of toluene, and the white foamy residue was dried *in vacuo* for 2 hr. The bromide showed on tlc (benzene–ether, 9:1) a single spot, R_I 1.1, and was immediately used for the glycosidation reaction.

1,6-Anhydro-2-*O*-benzoyl-β-D-glucopyranose (III) was prepared by a modified procedure of Jeanloz, *et al.*,[10] as follows. To a solution of 1,6-anhydroglucose (12 g, 0.074 mol) in anhydrous pyridine (30 ml), cooled to −15°, was added dropwise benzoyl chloride (9.4 ml, 0.081 mol). The mixture was kept at −15° overnight, and then concentrated *in vacuo* at 40°. The residue was extracted with chloroform, and the product was chromatographed on silica gel. Ethyl acetate–methylene chloride (1:9) removed the di- and tribenzoates (6.4 g), whereupon a 1:3 mixture of the same solvents eluted the monobenzoates (9.1 g). The latter fraction contained two compounds, as was shown by tlc (ethyl acetate–methylene chloride, 3:2). Crystallization from ethyl acetate afforded 4.3 g of the fairly pure 2-benzoyl derivative. A second crystallization yielded the pure compound (3.7 g, 18%) whose physical properties were identical with those reported.[10]

1,6-Anhydro-2,3-di-*O*-acetyl-β-D-glucopyranose (IV) was prepared by the procedure recently reported from this laboratory.[13]

1,6-Anhydro-2-*O*-benzoyl-4-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-β-D-galactopyranosyl]-β-D-glucopyranose (V).—The freshly prepared crude bromide II (1.47 mmol) was dissolved in dry ethylene chloride (40 ml), and the aglycon III (1.0 g, 3.76 mmol) and mercuric cyanide (0.23 g, 1.78 mmol) were added. The reaction mixture, protected from moisture and light, was stirred at 40–42° for 5 days. The solution was concentrated *in vacuo* at room temperature to constant weight, and the solid residue was fractionated on a silica gel column (150 g, 70–325 mesh, ASTM, Merck), using ethyl acetate–ether (7:18) as eluent. The first fraction containing unreacted aglycon (0.67 g) was followed by a mixture of compounds V and XI (1.05 g, 80%, based on II). The mixture was carefully rechromatographed on silica gel G (100 g) by eluting with ethyl acetate. Three fractions were collected which contained respectively 0.4 g of V, 0.35 g of XI, and about 0.2 g of a mixture of both. Crystallization of the pure oily compound V was achieved by dissolving it in methanol (4 ml) and leaving the solution in an isopropyl ether atmosphere at room temperature for 48 hr: mp 139–141°; $[\alpha]^{26}D$ −5.3°; tlc (ethyl acetate) R_I 0.98 and R_{XI} 1.35. The ir spectrum (in KBr) showed bands at 6.05, 6.5 (acetamide), 11.2 (β-glycoside), 6.2 and 13 μ (phenyl ring). The nmr spectrum showed signals corresponding to a ratio of 21 acetyl to 5 phenyl protons.

1,6-Anhydro-2-*O*-benzoyl-3-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-β-D-galactopyranosyl]-β-D-glucopyranose (XI).—The second fraction resulting from the chromatography of the preceding reaction mixture comprised the 1→3 isomer XI, which was obtained in crystalline form as described above for compound V: mp 135–137°; $[\alpha]^{24}D$ +1.5°; tlc (ethyl acetate) R_I 0.73, R_V 0.74. The ir and nmr spectra were identical with those of V.

Anal. Calcd for $C_{39}H_{49}NO_{22}$: C, 53.00; H, 5.59. Found: C, 53.03; H, 5.70.

1,6-Anhydro-2,3-di-*O*-acetyl-4-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-β-D-galactopyranosyl]-β-D-glucopyranose (VI).—The Koenigs–Knorr reaction of the bromide II (1.47 mmol) with the aglycon IV (1.2 g, 4.87 mmol) and mercuric cyanide (1.78 mol) was carried out as described above. The residue obtained after evaporation of the solvent showed on tlc (ethyl acetate–ether, 1:3) the presence of at least two new products; ethyl acetate eluted from a silica gel G column (140 g) first the aglycon (0.95 g) and then compound VI (0.71 g, 56.5%). The last fraction contained undefined by-products. Crystallization was performed by dissolving the trisaccharide in methanol (2 ml) and leaving the solution (48 hr) in an isopropyl ether atmosphere: mp 123–125°; $[\alpha]^{23}D$ −35.2°; tlc (ethyl acetate–ether, 1:3) R_I 0.6, R_{IV} 0.3.

Anal. Calcd for $C_{36}H_{49}NO_{23}$: C, 50.05; H, 5.72. Found: C, 49.87; H, 5.76.

Periodate Oxidation of VII and XII.—For catalytic deacylation, a solution of the respective compounds V and XI (0.1 g) in absolute methanol (20 ml), cooled to −5°, was treated with 1 *N* methanolic barium methoxide (0.15 ml) during 5 hr at +2°. The solution was neutralized by stirring with Dowex 50-Wx,[8] H^+ form, and the filtrate was taken to dryness. The residue was coevaporated several times with isopropyl alcohol and dried over phosphorus pentoxide for 48 hr. The resulting homogeneous compounds VII and XII were subjected to periodate oxidation by the spectrophotometric method.[17] The former consumed 2.9 mol/mol, whereas the latter reacted with 2.3 mol of the reagent.

1,3,6-Tri-*O*-acetyl-2-*O*-benzoyl-4-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-β-D-galactopyranosyl]-α-D-glucopyranose (VIII).—Opening of the anhydro ring in V was effected by treating 0.3 g with a solution of acetic anhydride (7 ml), glacial acetic acid (3 ml), and concentrated sulfuric acid (0.07 ml) at 40° for 2 hr. Anhydrous sodium acetate (0.5 g) was then added, and the suspension was taken to dryness. The residue was extracted with methylene chloride, and the extract was washed with water and evaporated *in vacuo*. The material was purified on a silica gel G column (50 g) by eluting with ethyl acetate. Crystallization from methylene chloride (3 ml) and dry ether (3 ml) at 2° gave VIII (needles, 0.25 g, 72%): mp 126–128°; $[\alpha]^{23}D$ +46.0; tlc (ethyl acetate) R_I 1.2, R_{XIII} 0.92. The nmr spectrum showed signals corresponding to a ratio of 30 acetyl to 5 phenyl protons.

1,2,3,6-Tetra-*O*-acetyl-4-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-β-D-galactopyranosyl]-α-D-glucopyranose (IX).—The conversion of the anhydro derivative VI (0.4 g) into IX was carried out as above. The homogeneous material eluted from a silica gel G column (100 g) with ethyl acetate weighed 0.35 g (78%) and was crystallized from chloroform–isopropyl ether: mp 126–128°; $[\alpha]^{24}D$ +25.3°; tlc (ethyl acetate) R_I 0.9, R_{VI} 1.5.

Anal. Calcd for $C_{40}H_{55}NO_2$: C, 49.74; H, 5.74. Found: C, 49.91; H, 6.04.

2-Acetamido-2-deoxy-*O*-β-D-galactopyranosyl-(1→4)-*O*-β-D-galactopyranosyl-(1→4)-D-glucopyranose (X). A. From VIII.—Catalytic de-O-acylation of VIII (0.1 g) was effected as described above for V and XI. The residue resulting from evaporation of the deionized filtrate was dissolved in methanol (2 ml) and the free trisaccharide was precipitated by addition of ether (1 ml) to yield 48 mg (90%) of a hygroscopic powder: mp 185–188°; tlc (benzene–methanol, 1:2) $R_{lactose}$ 0.6; $[\alpha]^{23}D$ +30.3° (c 0.8, water) (reported[7] $[\alpha]D$ calcd, +29.7°; found, +17.3°).

(14) J. Kärkkäinen, *Carbohyd. Res.*, **11**, 247 (1969).

(15) J. Kärkkäinen, *ibid.*, in press.

(16) Optical rotations were determined in 1% chloroform solutions unless stated otherwise.

(17) G. O. Aspinall and R. J. Ferrier, *Chem. Ind. (London)*, 1216 (1957).

B. By Deacetylation of IX.—The physical properties of the trisaccharide obtained follow: mp 185–186°; $R_{lactose}$ 0.6; $[\alpha]^{23}D$ +30.7° (*c* 0.8, water).

Anal. Calcd for $C_{20}H_{35}NO_{16}\cdot{}^1/_2H_2O$: C, 43.32; H, 6.54. Found: C, 43.13; H, 6.68.

A sample of X obtained *via* VIII gave on acetylation a polyacetyl derivative identical in every respect with IX.

1,4,6-Tri-*O*-acetyl-2-*O*-benzoyl-3-*O*-[2,3,6-tri-*O*-acetyl-4-*O*-(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-galactopyranosyl)-β-D-galactopyranosyl]-α-D-glucopyranose (XIII).—The homogeneous material obtained after ring opening of XI (0.2 g) and column chromatography as described above was crystallized from ether and a few drops of hexane: yield 0.15 g (64.5%); mp 126–127°; $[\alpha]^{23}D$ +6.2°; tlc (ethyl acetate) R_I 1.3, R_{XI} 1.8, R_{VIII} 1.08. The nmr spectrum indicated a ratio of 30 acetyl to 5 phenyl protons.

Anal. Calcd for $C_{45}H_{57}NO_{26}$: C, 52.58; H, 5.59. Found: C, 52.75; H, 5.47.

2-Acetamido-2-deoxy-*O*-β-D-galactopyranosyl-(1→4)-*O*-β-D-galactopyranosyl-(1→3)-D-glucopyranose (XIV).—Catalytic deacylation of the preceding compound (0.1 g) was carried out as described for V and XI and afforded a substance which was crystallized from methanol–ether (2:1) to yield 50 mg (94%) of a white hygroscopic powder: mp 175–178°; $[\alpha]^{23}D$ +24.7° (*c* 0.9, water); tlc (benzene–methanol, 1:2) $R_{lactose}$ 0.7, R_X 1.15.

Anal. Calcd for $C_{20}H_{35}NO_{16}H_2O$: C, 42.63; H, 6.62. Found: C, 42.85; H, 6.79.

Registry No.—V, 27537-64-0; VI, 27537-65-1; VIII, 27537-66-2; IX, 27537-67-3; X, 27537-68-4; XI, 27537-69-5; XIII, 27537-70-8; XIV, 27537-71-9.

An Attempted Assignment of Absolute Configuration to the *d*-Fecht Acid and Other 2,6-Disubstituted Spiro[3.3]heptane Derivatives

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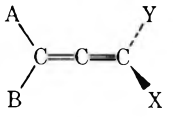
Optically active Fecht acid has been used for the preparation of a number of other optically active 2,6-disubstituted spiro[3.3]heptane derivatives. Application of Lowe's rule to the spiro[3.3]heptane system suggests the *R* configuration for the *d*-spiro[3.3]heptane-2,6-dicarboxylic acid. The optical purity of a few compounds could be determined. A discussion is given on the magnitude of the optical activity of 2,6-disubstituted spiro[3.3]heptanes, as compared to the optical activity of dissymmetrical allenes. The low optical activity of the 2,6-disubstituted spiro[3.3]heptane system gives rise to many exceptions to Lowe's rule, since other effects easily play a role in the optical activity. This is illustrated by carbonyl compounds, among which the Fecht acid (1), many of which show a sign of rotation opposite to the one expected on the basis of Lowe's rule.

In recent years several examples have been described in the literature of absolute configuration assignments to molecules of the allene and spiran type.[1-9] In most cases use was made of a chemical correlation of the configuration of the optically active allenes or spirans with centrodissymmetrical molecules of known configuration. From the results found for allenes, Lowe[10] pointed out that molecules of type a



a

are dextrorotatory at the sodium D line when A is more polarizable than B and X is more polarizable than Y. The Lowe rule is related to other models of optical activity, for example, Kirkwood's model[11] and Brewster's uniform conductor model,[12] and should be generally applicable to helical systems.[4,8] The results found in the alkylidenecycloalkane field seem to be in agreement with Lowe's rule.[4,5] Brewster and Privett, however, have pointed out that a deduction of an absolute configuration from the sign of the optical rotation in the region of the visible absorption spectrum is not without hazard when Cotton effects dominate this optical activity.[4]

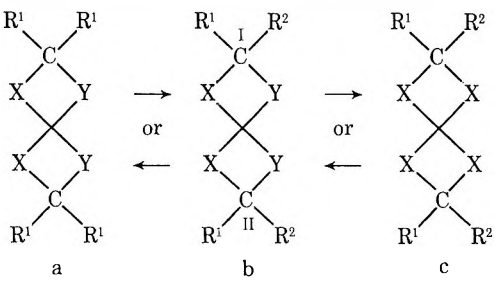
Those spirans for which the absolute configuration has been determined owe their optical activity to the nature and the relative position of the rings constituting the spiran system.[13] Two calculations[14] have been reported on the absolute configuration of spirans.[15]

(1) B. L. Crombie and P. A. Jenkins, *Chem. Commun.*, 870 (1967).
(2) R. J. D. Evans, S. R. Landor, and J. P. Regan, *ibid.*, 397 (1965).
(3) K. Shingu, S. Hagishita, and M. Nakagawa, *Tetrahedron Lett.*, 4371 (1967).
(4) J. H. Brewster and J. E. Privett, *J. Amer. Chem. Soc.*, **88**, 1419 (1966).
(5) H. Gerlach, *Helv. Chim. Acta*, **49**, 1291 (1966).
(6) G. G. Lyle and E. Tyminski Pelosi, *J. Amer. Chem. Soc.*, **88**, 5276 (1966).
(7) G. Krow and R. K. Hill, *Chem. Commun.*, 430 (1968).
(8) J. H. Brewster and R. S. Jones, *J. Org. Chem.*, **34**, 354 (1969).
(9) H. Gerlach, *Helv. Chim. Acta*, **51**, 1587 (1968).
(10) G. Lowe, *Chem. Commun.*, 411 (1965).
(11) J. G. Kirkwood, *J. Chem. Phys.*, **5**, 479 (1937); W. W. Wood, W. Fickett, and J. G. Kirkwood, *ibid.*, **20**, 561 (1952); H. Looyenga, Thesis, Leiden, 1955.
(12) J. H. Brewster in "Topics in Stereochemistry," Vol. 2, N. L. Allinger and E. L. Eliel, Ed., Interscience, New York, N. Y., 1967.

(13) An illustrative example is 2,7-diazaspiro[4.4]nonane.[7] In such a compound the spiro carbon atom will become an asymmetric carbon atom when one of the rings is made unlike the other one. 4,4′-Dimethoxy-1,1′,3,3′-tetrahydrospiro[isoindole-2,2′-isoindolium] bromide[8] belongs to the same class of compounds.

(14) Two tentative determinations of the absolute configurations of spirans whose optical activity is due only to the substitution pattern have to be mentioned. W. Kuhn and K. Bein [*Z. Phys. Chem., Abt, B*, **24**, 335 (1934)], calculated the *S* configuration for *d*-dipyruvic erythritol, and T. M. Lowry and W. C. G. Baldwin [*Proc. Roy. Soc.*, **162**, 204 (1937)], assigned the *S* configuration to *l*-spiro[3.3]heptane-2,6-diamine (**16**).

(15) A *chemical* determination of the absolute configuration of compounds in this category, for instance of the Fecht acid, is more complicated than in the case discussed in ref 13. A general route is shown in the scheme below.



Molecule a represents a chiral spiran of the category discussed in ref 13 (X ≠ Y). When the absolute configuration is known, and, in addition the absolute configuration at the carbon atoms C^I and C^{II} in molecule b ($R^1 \neq R^2$), the absolute configuration of c may be deduced.

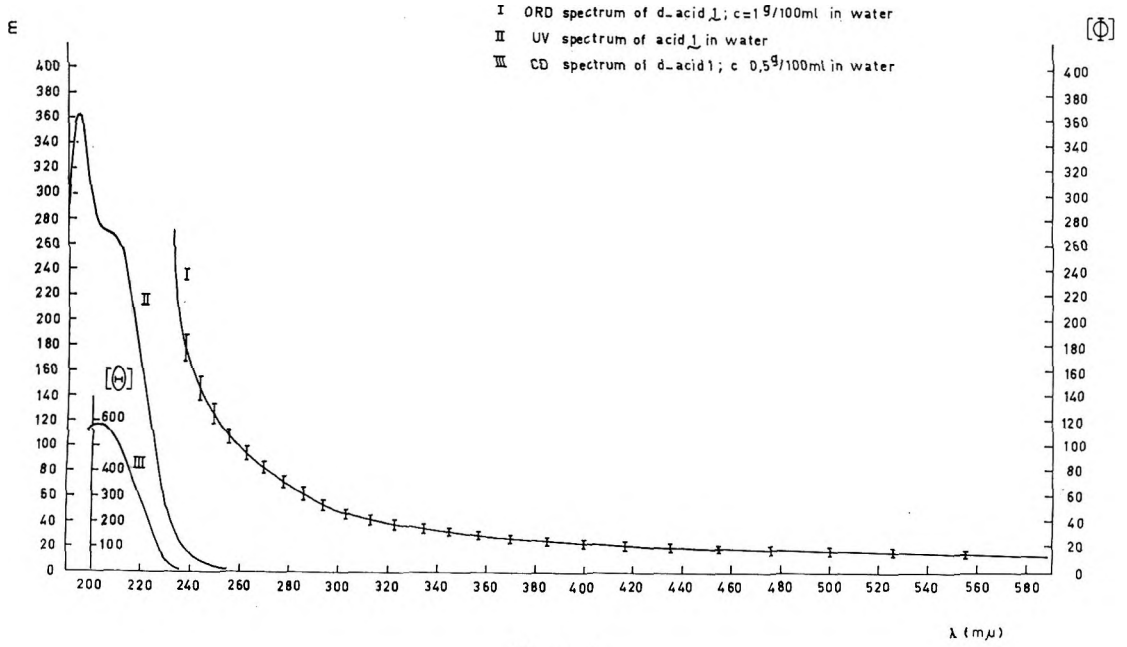
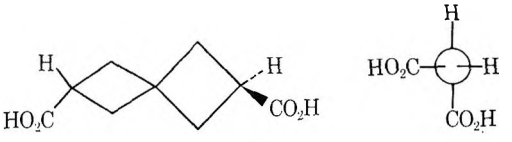


Figure 1.

Preparation of 2,6-disubstituted spiro[3.3]heptanes of known relative configuration should give information about the validity of Lowe's rule for this spiran system.

Using Backer and Schurink's method,[16] we prepared and resolved *dl*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**) (Fecht acid) and measured the ORD and the CD spectra of the *d* acid **1**, shown in Figure 1, together with the uv spectrum. The ORD spectrum shows a plain curve that could not be measured at a wavelength shorter than 230 mμ. The CD spectrum, however, shows a positive Cotton effect at 203 mμ, $[\theta]$ +570 ± 60. The sign of the Cotton effect is the same as the sign of the optical activity in the visible wavelength region; this makes an assignment of the *S* configuration, expected on basis of the Lowe rule, to the *d* acid **1** rather dubious.[17] In an attempt to clarify this assignment, the optical activities of a number of other 2,6-disubstituted spiro[3.3]heptane derivatives **3**–**17**, all prepared from optically active Fecht acid, were measured. The rotations of the compounds with the same chirality as the *d* acid **1** are summarized in Table I. The following situation makes reliable assignment of configuration difficult in general. In most compounds containing carbonyl groups, the Cotton effects dominate the optical activity even in the visible region. This means that a positive Cotton effect coupled with a positive rotation in the visible region tells us nothing about the chirality of the dissymmetric portion of the molecule. Only in those cases where (independent of solvent effects) clear sign reversal between the Cotton effect and the rotation in the visible wavelength region is observed can a configurational assignment be made on the basis of this long-wavelength rotation. For our configurational assignment, we have therefore utilized only those compounds (Table I) which show sign reversal independent of solvent effects.

Supporting this use of the sign reversal region for configurational assignment is the fact that compounds **15**, **16**, and **17** are levorotatory. These three compounds have no chromophore and these substituents (compounds **15**–**17**) cannot show conformational dissymmetry. In the compounds **13** and **14**, the substituents may occur in asymmetrical conformations, giving rise to an additional contribution to the optical activity. These compounds are levorotatory and do not show wavelength-dependent optical rotation sign reversal. Compounds **10**, **11**, and **12** possess substituents which likewise may show asymmetry due to the conformations, and further contain chromophores, which may give rise to Cotton effects. The CD spectra of **10** and **12**, however, do not show maxima or minima, and the compounds are again levorotatory; compound **11**, however, seems to constitute an exception. The behavior of compounds **10** and **12**–**17** is in accordance with Lowe's rule, suggesting for these levorotatory compounds, and by consequence for the *d*-spiro[3.3]-heptane-2,6-dicarboxylic acid (**1**), the *R* configuration.[18]



(*R*)-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**)

Agosta[19] and Gerlach[5] applied Lowe's rule to several spirans, other than Fecht's acid, successfully.

Our data indicate that the optical activity inherent

(16) H. J. Backer and H. B. J. Schurink, *Proc. Kon. Ned. Akad. Wetensch.*, **37**, 384 (1928); *Recl. Trav. Chim. Pays-Bas*, **50**, 921 (1931). The authors report the following values for the optical activity of the Fecht acid after resolution with brucine: $[\phi]_{589}$ +2.3°, $[\phi]_{546}$ +2.6°, $[\phi]_{486}$ +3.4° (*c* 6.0, water for the ammonium salt); and $[\phi]_{589}$ +1.9° (for the acid in ether solution).

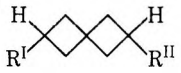
(17) An interpretation of the positive Cotton effect at 203 mμ should be possible and should give a decisive answer about the absolute configuration, according to the sector rule of Klyne for carboxylic acids [J. D. Renwick and P. M. Scopes, *J. Chem. Soc. C*, 1949 (1968)], if the conformational situation of the carboxylic groups could be clarified. This, however, is not the case.

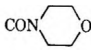
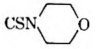
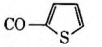
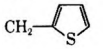
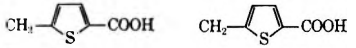
(18) Lowry and Baldwin[14] assign the opposite configurations to spiro[3.3]-heptane-2,6-diamine, based on Born's theory; *cf.* T. M. Lowry, "Optical Rotatory Power," Longmans, Green and Co., London, 1935, p 391.

(19) W. C. Agosta, *J. Amer. Chem. Soc.*, **86**, 2638 (1964).

TABLE I

OPTICAL ACTIVITIES OF COMPOUNDS OF THE TYPE



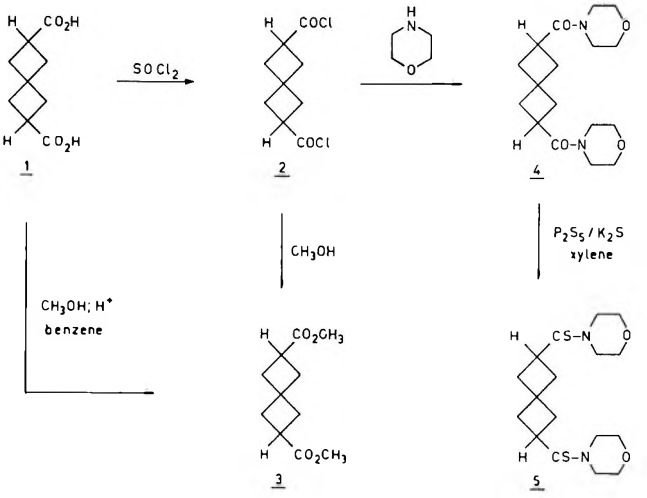
Compd	R^I	R^{II}	CD λ_{max}, mμ	CD [θ]	ORD λ_{peak}, mμ	ORD λ_{trough}, mμ	ORD Amplitude[h]	Visible region optical activity [φ]$_{5FS}$	[φ]$_{546}$	[φ]$_{436}$	[φ]$_{405}$	[φ]$_{365}$	Concn (g/100 ml)	Solvent	Remarks
1	COOH	COOH	203	+570									0.5	Water	*a*
								+8.6	+9.6	+15.4	+18.2	+23.7	5.3	Acetone	*b*
								+2.7	+3.3	+4.5	+5.1	+5.4	5.1	Ethanol, 96%	*b*
								+3.1	+3.5	+5.6	+6.3	+7.7	5.3	Ammonia, 1 *N*	*b*
3	$COOCH_3$	$COOCH_3$	209	+540									1.5	*n*-Hexane	*a*
			207	+310									1.1	Ethanol, 96%	*a*
								+3.2	+3.8	+5.7	+6.5	+7.7	5.0	Acetone	*b*
								−2.0	−2.2	−4.3	−5.5	−7.8	7.6	*n*-Hexane	*b*
								+6.7	+7.5	+12.4	+14.7	+18.6	6.2	Ethanol, 96%	*b*
4								−43.0	−49.3	−86.8	−105.9	−142.9	4.1	Ethanol, 96%	*b, d, g*
5					357	389	−4.8	−184	−192	−246 ± 10	−238 ± 15	+132	0.3	Dioxane	*c, d, f*
6								−51.5	−58.7	−103.3	−124.2		8.0	Acetone	*b, g*
7	$COCH_3$	$COCH_3$						+1.9	+2.5	+11.5	+19.1	+45.1	4.0	Acetone	*b, d, e*
								−8.6	−11.5	+2.5	+17.6	+77.4	0.6	Cyclohexane	*c, d, e*
					312	263	+27.1						0.1	Cyclohexane	*c, d, e*
8	$COC(CH_3)_3$	$COC(CH_3)_3$						−22.8	−25.5	−38.9	−40.9	−33.6	2.0	Ethanol, 96%	*b, d, f*
					317	256	+19.1	−70	−81	−138	−162	−181	0.3	Cyclohexane	*c, d, f*
9	$COC(CH_3)_3$	$CONH_2$						−16.6	−18.9	−29.8	−34.4	−37.8	2.0	Ethanol, 96%	*b, d,*
10				*i*				−10.4	−12.2	−21.9	−26.7	−36.1	4.2	Cyclohexane	*b*
													0.03	*n*-Hexane	*h*
11									+8 ± 2				4.8	Sodium hydroxide, 3 *N*	*b*
12	$(CH_2)_5COOH$	$(CH_2)_5COOH$						−7.2	−8.1	−14.0			5.0	Acetone	*b*
				i											*i*
13	CH_2OH	CH_2OH						−6.2	−6.9	−11.5	−13.7		5.2	Chloroform	*b, e*
								−3.8	−4.2	−7.6	−8.9		5.0	Ethanol, 96%	*b, e*
14	CH_2Cl	CH_2Cl						−3.8	−4.4	−7.5	−8.9		11.2	Tetrahydrofuran	*b, e*
15	CH_3	CH_3						−5.8	−6.5	−10.4	−12.3	−16.6	1.8	Cyclohexane	*c, e*
16	NH_3Cl	NH_3Cl						−15.1	−17.6	−29.9	−36.0	−48.1	2.2	Water	*b, e*
17	$N(CH_3)_3I$	$N(CH_3)_3I$						−27.0	−27.0	−42.4	−49.4	−63.8	2.6	Water	*b, d, f*

[a] Measured at room temperature in a Roussel Jouan Dichrograph II provided with a 50-W deuterium lamp. [b] Measured at room temperature in a Zeiss Lichtelektrisches Präzisionspolarimeter 005 provided with a mercury lamp. [c] Measured at room temperature with a Bendix Ericsson Polarmatic 62 spectropolarimeter provided with a 150-W xenon lamp. [d] Actually the *l* enantiomer of the acid 1 was used in the synthesis of the concerning compounds. The values in Table I are optical activities that should have been found when *d* acid 1 should have been used. [e] The starting material, the acid 1, was optically impure. The values in Table I are corrected to the optical purity of the *d* acid 1. [f] The optical activity of these compounds is not corrected for optical purity of the starting acid 1; the acid used was optically impure. [g] On further crystallization these solid compounds showed a constant optical activity, given in Table I. [h] H. Ripperger, *Z. Chem.*, 6, 161 (1966), or P. Crabbé, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," Holden-Day, San Francisco, London, Amsterdam, 1965. [i] As was expected, no measurable circular dichroism effect was found.

in the dissymmetrical 2,6-disubstituted spiro[3.3]heptane system is small[20] compared to allenes and 4-substituted alkylidenecycloalkanes,[21,22] while the influence of the Cotton effect in the visible wavelength region is much more important in the case of our spiro[3.3]-heptane-2,6-dicarboxylic acid (**1**) than it is in the case of the allene acids.

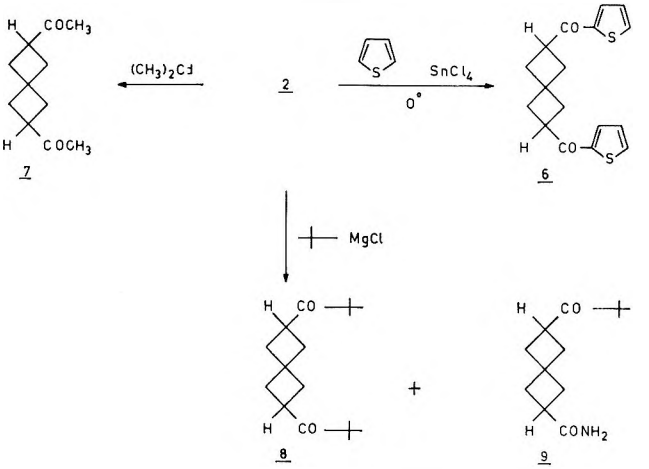
Preparation and Optical Purity.—Starting with the acid chloride **2** of optically active acid **1**, the methyl ester **3** and the morpholide **4** could be prepared in optically active form. The ester **3**, in inactive form prepared by Backer and Kemper[23,24] could also be prepared in optically active form by direct esterification of the acid **1** with methanol. The values of the optical activity of the methyl ester **3**, prepared in these two ways, were approximately the same. The thioamide **5** was prepared in moderate yield from the amide **4** by the action of phosphorus pentasulfide and potassium sulfide in xylene at 70° according to Kindler.[25] These reactions are shown in Scheme I. *l*-2,6-Bis(2′-thenoyl)spiro[3.3]heptane (**6**) was prepared from the *d* acid *via* the acid chloride **2** under mild Friedel–Crafts conditions. The 2,6-diacetyl-

Scheme I



spiro[3.3]heptane (**7**) was synthesized in low yield by reaction of **2** with dimethylcadmium. The reaction of excess **2** with *tert*-butylmagnesium chloride gave 2,6-dipivaloylspiro[3.3]heptane in low yield. During the work-up of the reaction mixture with an ammonium chloride solution, the amide **9** was formed (Scheme II). Clemmensen reduction of *l*-**6** gave a mod-

Scheme II



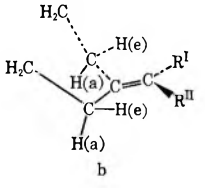
erate yield of *l*-2,6-bis(2′-thenyl)spiro[3.3]heptane (**10**) while Wolff–Kishner reduction of optically active **6** gave as expected a good yield of racemized **10**. From **10** the diacid **11** could be prepared easily by a Vilsmeier–Haack formylation,[26] followed by oxidation of the aldehyde with silver oxide in alkaline medium to the acid **11**, as shown in Scheme III. The coupling constants for the protons at the 3 and 4 positions of the thiophene rings are 3.5 cps.[27]

Desulfurization of the acid **11** was accomplished in excellent yield by addition of nickel–aluminum alloy to a boiling solution of the acid in 3 *N* sodium hydroxide solution, according to the method of Papa, Schwenk, and Ginsberg.[28] The reduction of racemic dimethyl spiro[3.3]heptane-2,6-dicarboxylate (**3**) with

(20) For the optical activity, the following expression is deduced.[12]

$$[\phi]\lambda = (144\ \pi^2 N_0/\lambda^2)(\beta + \gamma)f(n)$$

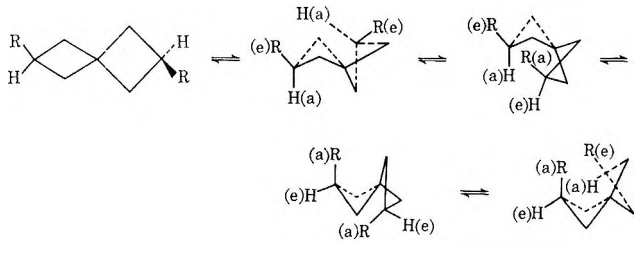
(21) The polarizability of the substituent in the 4 position is perhaps of less importance than the ability of this substituent to make one chair conformation of the cyclohexane ring more favorable than the other one. This has no influence on the sign of rotation in the reported instance,[4-6] if it is assumed that an equatorial position for the methyl group is preferred over an axial one and, secondly, that the sequence of polarizabilities between the methylene groups and axial hydrogen atoms at the 2 and 6 position in the cyclohexane ring is the same one, as the sequence of polarizabilities between methyl and hydrogen at the 4 position. The dissymmetric system is represented in structure b. This system again represents a better conductor



b

than a spiran system does, giving rise to high values of optical activity as compared to the spiran system. This is confirmed by the data of optical rotation for 4-substituted alkylidenecycloalkanes reported in the literature (ref 4 and 5, and cited references).

(22) It is clear from the C-2 symmetry of all (except one) of our spirans that conformational mobility of the spiran system itself can have no in-



fluence on the sign of the rotation but only on the magnitude. When the methyl groups in (*S*)-2,6-dimethylspiro[3.3]heptane (R = CH_3) are in the same position (both "equatorial" or both "axial"), the spiran system is in a chiral conformation giving rise to optical activity with the same sign to be expected as one should expect for the 2,6-disubstituted spiro[3.3]heptane system in which the cyclobutane rings are flat. If one substituent is in an "equatorial" and the other one in an "axial" position, the spiran system will give rise to optical activity of the opposite sign. Calculations suggest that these contributions are always smaller than the first ones and therefore are not able to dominate the optical activity.

(23) H. G. Kemper, Thesis, Groningen, 1937.

(24) (a) H. J. Backer and H. G. Kemper, *Recl. Trav. Chim. Pays-Bas*, **57**, 1249 (1938); (b) L. M. Rice and C. H. Grogan, *J. Org. Chem.*, **26**, 54 (1961).

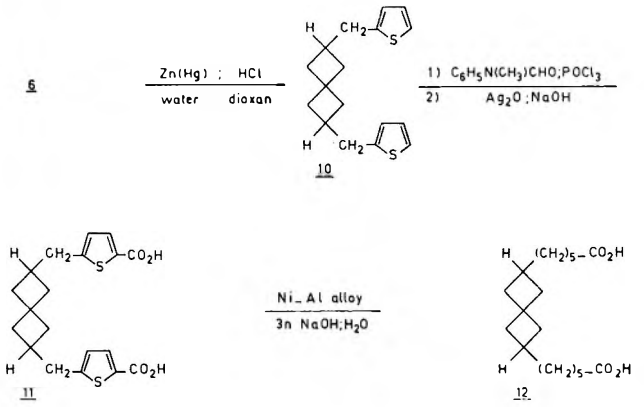
(25) K. Kindler, *Justus Liebigs Ann. Chem.*, **431**, 187 (1923); J. V. Burakevich and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 51 (1965).

(26) A. Vilsmeier and A. Haack, *Ber.*, **60B**, 119 (1927). For a general review, see G. A. Olah and S. J. Kuhn, "Friedel–Crafts and Related Reactions," Vol. III, part II, G. Olah, Ed., Interscience, New York, N. Y., 1964, p 1153.

(27) R. A. Hoffman and S. Gronowitz, *Ark. Kemi*, **16**, 563 (1960).

(28) D. Papa, E. Schwenk, and H. F. Ginsberg, *J. Org. Chem.*, **14**, 723 (1947); M. Sy, *Bull. Soc. Chim. Fr.*, 1175 (1955).

SCHEME III

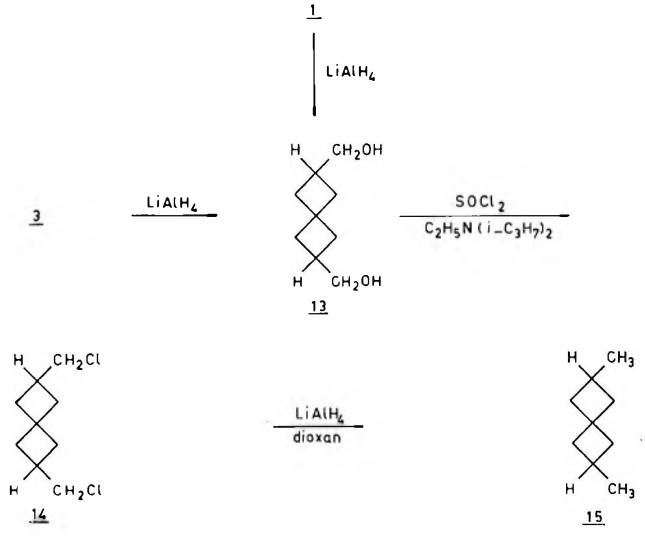


lithium aluminum hydride to yield *dl*-2,6-bis(hydroxymethyl)spiro[3.3]heptane (**13**) has been accomplished.[23,24b]

In the same way *l* diol **13** was prepared *via* the ester **3** from *d*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**). The *d* diol **13** was prepared in low yield by reduction of the *l* acid **1**.

Reaction of *l* diol **13** with thionyl chloride in ethyldiisopropylamine furnished in sufficient yield *l*-2,6-bis(chloromethyl)spiro[3.3]heptane (**14**), reduction of which with lithium aluminum hydride in boiling dioxane gave *l*-2,6-dimethylspiro[3.3]heptane (**15**) as shown in Scheme IV. Optically pure spiro[3.3]heptane-2,6-di-

SCHEME IV

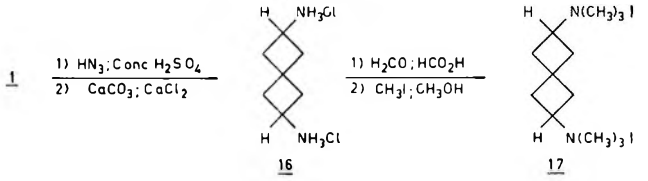


ammonium chloride (**16**) has been prepared by Janson and Pope[29] by resolution of the racemic amine with *d*- and *l*-camphorsulfonic acid.

For the *l* salt **16** these authors found $[\phi]_{578}$ −15.5°, $[\phi]_{546}$ −17.7°, and $[\phi]_{436}$ −30.5° (*c* 2.1, water). In our case *d* acid **1**, $[\phi]_{578}$ +7.8°, $[\phi]_{546}$ +8.8°, and $[\phi]_{405}$ +17.0° (*c* 5.0, acetone), was used and the amine hydrochloride **16** prepared from *d* acid **1** showed the following rotations: $[\phi]_{578}$ −13.7°, $[\phi]_{546}$ −16.0°, and $[\phi]_{436}$ −27.2° (*c* 2.2, water). This means that the optical purity of the acid **1** used is at least 90%. This value is in agreement with the maximal optical activity found by us for the Fecht acid **1**, $[\phi]_{578}$ +8.6°, $[\phi]_{546}$ +9.6°, and $[\phi]_{405}$ +18.2° (*c* 5.3 in acetone), the resolution of the Fecht acid **1** with brucine according to Backer and Schurink being as efficient as the resolution of spiro[3.3]heptane-2,6-diamine with camphorsulfonic acid according to Janson and Pope.[29,30]

The Leuckart reaction (Eschweiler–Clark procedure)[31] applied to the *d* amine hydrochloride **16**, followed by methiodation of the tertiary amine, furnished *d*-spiro[3.3]heptane-2,6-bis(dimethylamine) dimethiodide (**17**) as shown in Scheme V. There is no reason

SCHEME V



to presume racemization during the preparation of the methiodide **17**. The rotations given in Table I are therefore the values for at least 75% optically pure methiodide **17**.

The optical purity of the diol **13** was determined by oxidation of the *d* diol **13** with potassium permanganate in 1.5 *N* sulfuric acid at room temperature. The *l* acid **1** obtained in this way showed the same rotation within the error as the *l* acid **1** used for the preparation of *d* diol **13**. The *l* diol **13** prepared by reduction of the methyl ester of *d* acid **1** showed a rotation of the same magnitude as the *d* diol **13** did, proving the optical purity of the ester **3** and of the intermediate spiro[3.3]heptane-2,6-dicarbonyl chloride (**2**), used as the starting material in the preparation of compounds **3–9**.

The optical purity of 2,6-bis(chloromethyl)spiro[3.3]-heptane (**14**) or 2,6-dimethylspiro[3.3]heptane (**15**) has not been determined.

Repeated crystallization of the morpholide **4** gave a sample, the rotation of which on continued crystallization showed no further change; this indicates that the compound is probably optically pure.[32] The same argument may be applied to 2,6-bis(2′-thenoyl)spiro-[3.3]heptane (**6**). No data are available on the optical purity of the other compounds.

Experimental Section

Boiling points are uncorrected. Melting points were determined on a Mettler FP1 apparatus, at a warm-up rate of 0.2°/min unless otherwise stated.[33] Infrared spectra were recorded on a Unicam SP 200 infrared spectrophotometer. Ultraviolet spectra were obtained on a Zeiss PMQ II apparatus, Nmr spectra were recorded on a Varian A-60 instrument using tetramethylsilane as internal standard. Mass spectra were run on an AEI MS 902 mass spectrometer. Microanalyses were performed in the analytical section of our department under the supervision of Mr. W. M. Hazenberg.

Optical activity was measured on a Zeiss Lichtelektrisches Präzisionspolarimeter 005, using a 1-dm cell. Where this is mentioned, a Bendix Ericsson Polarmatic 62 is used, provided

(29) S. E. Janson and W. J. Pope, *Proc. Roy. Soc., Ser. A*, **154**, 53 (1936).

(30) It means that the *d* acid **1** used was optically pure. This is of importance since there exists some doubt about the optical purity of the Fecht acid **1** resolved *via* the brucine salt; *cf.* E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 310.

(31) M. L. Moore, *Org. React.*, **5**, 301 (1949).

(32) This method of the determination of optical purity is only relatively reliable; *cf.* M. Raban and K. Mislow, ref 12, p 199.

(33) Occasionally we record melting points (one value) instead of melting ranges. These melting points are derived when no recorder is used.

with a 150-W Xenon lamp and a 0.1-dm cell. Concentrations are given as grams/100 ml. The measurements were taken at room temperature. Ellipticity was measured with a Roussel-Jouan Dichrograph II, provided with a deuterium lamp.

***dl*-Spiro[3.3]heptane-2,6-dicarboxylic acid** (1) was prepared according to Backer and Schurink[16] starting with 200 g (0.5 mol) of 1,3-dibromo-2,2-bis(bromomethyl)propane.[34] In contrast to the procedure of these authors, the spiro[3.3]heptane-2,2,6,6-tetracarboxylic acid was not isolated by ether extraction, but, after acidification of the solution of the potassium salt in water with 400 ml of concentrated hydrochloric acid, water was evaporated and the residue pyrolyzed at 190° for 1 hr under reduced pressure (30 mm). Extraction of the reaction product in a Soxhlet apparatus with ethyl acetate, evaporation of the solvent, and crystallization of the residue from water gave *dl*-spiro[3.3]-heptane-2,6-dicarboxylic acid (1) in yields varying from 65 to 75% (lit.[16,24] 75 to 80%).

***d*-Spiro[3.3]heptane-2,6-dicarboxylic Acid** (1).—The resolution of the *dl* acid 1 was accomplished according to Backer and Schurink[16] using 171 g (0.43 mol) of brucine, 40 g (0.22 mol) of *dl*-spiro[3.3]-heptane-2,6-dicarboxylic acid, and 3 l. of distilled water. The boiling solution was filtered and placed in a haybox. After cooling to room temperature the supernatant liquid was decanted and the residue was dissolved again. After five crystallizations the brucine salt was dissolved in water and 50 ml of concentrated ammonia was added. Brucine separated and after one night it was filtrated over a Büchner funnel. The filtrate was washed with chloroform, evaporated to a volume of 50 ml, and acidified with concentrated hydrochloric acid, and the precipitated acid was recrystallized from water, yielding 8–12 g (40–60%) of the *d* acid 1: $[\phi]_{578}$ +8.7°, $[\phi]_{546}$ +9.9°, $[\phi]_{436}$ +15.9°, $[\phi]_{405}$ +18.8°, $[\phi]_{365}$ +23.9° (*c* 5.3, acetone); $[\phi]_{578}$ +2.7°, $[\phi]_{546}$ +3.3°, $[\phi]_{436}$ +4.5°, $[\phi]_{405}$ +5.1°, $[\phi]_{365}$ +5.4° (*c* 5.1, ethanol 96%); $[\phi]_{578}$ +3.1°, $[\phi]_{546}$ +3.5°, $[\phi]_{436}$ +5.6°, $[\phi]_{405}$ +6.3°, $[\phi]_{365}$ +7.7° (*c* 5.3, ammonia); $[\theta]_{203}$ +570 ± 60 in water (ref 16).

***l*-Spiro[3.3]heptane-2,6-dicarboxylic Acid** (1).—The mother liquor obtained after the first crystallization of the brucine salt of *dl*-spiro[3.3]heptane-2,6-dicarboxylic acid (1) was boiled in a beaker until the volume (originally 3 l.) was reduced to 2 l. A small amount of the salt separated on cooling. This was removed and the filtrate was concentrated again in the same way to 1 l. After separation and removal of a second crop of the salt, 40 ml of concentrated ammonia was added to the filtrate. The work-up, in the same way as described for the *d* acid 1 in the preceding section, gave 5–7 g (25–35%) of the *l* acid 1 with optical purity varying from 70 to 80% (related to the optical activity of the *d* acid 1).

Spiro[3.3]heptane-2,6-dicarbonyl Chloride (2).—A mixture of 18.5 g (0.10 mol) of spiro[3.3]heptane-2,6-dicarboxylic acid (1) and 25 ml of thionyl chloride was stirred for 90 min at 50°. Excess of thionyl chloride was removed at reduced pressure and distillation furnished 20.4 g (0.092 mol or 92%) of acid chloride, bp 103–107° (0.5 mm) [lit.[24] bp 154° (15 mm)].

***d*-Dimethyl Spiro[3.3]heptane-2,6-dicarboxylate** (3) was prepared from *d*-spiro[3.3]heptane-2,6-dicarboxylic acid (1), $[\phi]_{578}$ +8.6° (*c* 5.0, acetone), *via* the acid chloride 2 and absolute methanol according to Backer and Kemper:[23,24] $n^{20}D$ 1.4626; $[\phi]_{578}$ +3.3°, $[\phi]_{546}$ +3.7°, $[\phi]_{436}$ +5.5°, $[\phi]_{405}$ +6.4° (*c* 4.8, acetone). After one distillation the optical activity remained unchanged: bp 164–167° (17 mm); $n^{20}D$ 1.4624; $[\phi]_{578}$ +3.2°, $[\phi]_{546}$ +3.8°, $[\phi]_{436}$ + 5.7°, $[\phi]_{405}$ +6.5°, $[\phi]_{365}$ +7.7° (c 5.0, acetone); $[\phi]_{578}$ −2.0°, $[\phi]_{546}$ −2.2°, $[\phi]_{436}$ −4.3°, $[\phi]_{405}$ −5.5°, $[\phi]_{365}$ −7.8° (*c* 7.6, *n*-hexane); $[\phi]_{578}$ +6.7°, $[\phi]_{546}$ +7.5°, $[\phi]_{436}$ +12.4°, $[\phi]_{405}$ +14.7°, $[\phi]_{365}$ +18.6° (*c* 6.2, ethanol 95%); $[\theta]_{209}$ +540 (*n*-hexane); $[\theta]_{207}$ +310 (ethanol 95%).

Alternative Preparation of *d*-Dimethyl Spiro[3.3]heptane-2,6-dicarboxylate (3).—A mixture of 6.2 g (0.034 mol) of *d*-spiro[3.3]-heptane-2,6-dicarboxylic acid (1) {$[\phi]_{578}$ +7.3°, $[\phi]_{546}$ +8.2°, $[\phi]_{436}$ +13.5°, $[\phi]_{405}$ +16.0° (*c* 5.2, acetone)}, 80 ml of benzene, 33 ml of methanol, and 7 ml of concentrated sulfuric acid was refluxed over a period of 5 hr. The mixture was allowed to cool, poured onto melting ice, and worked up with ether, furnishing 6.9 g (0.033 mol or 96%) of diester 3: $n^{20}D$ 1.4620; $[\phi]_{578}$ +3.2°, $[\phi]_{546}$ +3.5°, $[\phi]_{436}$ +4.9°, $[\phi]_{405}$ +5.6° (*c* 4.6, acetone).

***d*-2,6-Bis(morpholinocarbonyl)spiro[3.3]heptane** (4).—To a stirred and ice-cooled solution of 2.0 g (0.009 mol) of spiro[3.3]-heptane-2,6-dicarbonyl chloride (2), prepared from the *l* acid 1 {$[\phi]_{578}$ −6.8°, $[\phi]_{405}$ −15.6° (*c* 5.5, acetone)} in 20 ml of dioxane was added a solution of 4.0 g (0.046 mol of morpholine in 40 ml of dioxane over a period of 10 min. After a further 20 min the reaction mixture was filtered, and the solvent was removed by evaporation yielding 2.9 g of a solid residue. One crystallization from ethyl acetate gave 2.4 g of the compound, showing $[\phi]_{546}$ +37.6° (*c* 4.2, ethanol 96%). A constant optical activity of the product was observed after four crystallizations: mp 167–170°; ir (KBr) 1630 (C=O); yield 2.7 g (8.4 mol or 93%); $[\phi]_{578}$ +43.0, $[\phi]_{546}$ +49.3°, $[\phi]_{436}$ +86.3°, $[\phi]_{405}$ +105.9°, $[\phi]_{365}$ +142.9° (*c* 4.1, ethanol 96%).

Anal. Calcd for $C_{17}H_{26}N_2O_4$: C, 63.33; H, 8.13; N, 8.69; mol wt, 322.41. Found: C, 63.3, 63.3; H, 8.2, 8.0; N, 8.8, 8.7.

***d*-2,6-Bis(morpholinothiocarbonyl)spiro[3.3]heptane** (5) was prepared according to Kindler's method[25] from a homogeneous mixture of 450 mg of potassium sulfide, 500 mg of phosphorus pentasulfide, and 300 mg (0.93 mmol) of *d*-2,6-bis(morpholino-carbonyl)spiro[3.3]heptane (4), $[\phi]_{546}$ +32.2° (*c* 4.0, ethanol 96%), in 4.0 ml of dry xylene. The mixture was stirred for 1.5 hr at room temperature and 1 hr at 70°. The xylene layer was removed and the solid was extracted six times with 4-ml portions of xylene at 70°. On cooling of the combined xylene solutions, a white solid separated. Three crystallizations from ethanol (96%) furnished an analytically pure sample: mp 201.4° (warm-up rate 10°/min); mass spectrum (70 eV) *m/e* (rel intensity) 354 (100), 338 (6), 321 (18), 268 (11), 236 (24), 224 (30), 209 (23), 196 (47), 182 (26), 164 (24), 157 (44), 130 (23), 86 (95), 71 (60); ir (KBr) showed no carbonyl absorption; uv max (dioxane) 364 mμ (ε 104) and 280 (26,700); yield 160 mg (0.45 mmol or 48%) of crude product; $[\phi]_{656}$ +189 ± 3°, $[\phi]_{500}$ +216 ± 2°, $[\phi]_{456}$ +250 ± 10°, $[\phi]_{408}$ +238 ± 12°, $[\phi]_{389}$ +290 ± 26°, $[\phi]_{371}$ 0°, $[\phi]_{357}$ −185 ± 12°, $[\phi]_{342}$ −113 ± 12°, $[\phi]_{333}$ −245 ± 12°, $[\phi]_{223}$ −800 ± 60° (*c* 0.33, dioxane; Bendix Ericsson Polarmatic 62).

Anal. Calcd for $C_{17}H_{26}N_2O_2S_2$: C, 57.59; H, 7.39; N, 7.90; S, 18.09; mol wt, 354.54. Found: C, 57.6, 57.5; H, 7.4, 7.4; N, 8.1, 8.1; S, 18.0, 18.0.

***dl*-2,6-Bis(2′-thenoyl)spiro[3.3]heptane** (6).—From 20.4 g (0.092 mol) of *dl*-spiro[3.3]heptane-2,6-dicarbonyl chloride (2) the diketone was prepared under the same conditions that Schuetz and Baldwin[35] used for the preparation of 1,4-bis(2′-thenoyl)-butane. To a solution of the acid chloride 2 in 34 ml of thiophene, 140 ml of benzene, and 14 ml of carbon disulfide, stirred at 0°, was added 60 g of stannic tetrachloride at such a rate that the temperature remained below 10°. The mixture was stirred at room temperature for another hour and then poured onto 1500 g of crushed ice and 700 ml of concentrated hydrochloric acid, and the product was worked up with ether. The crude product, 26.9 g (0.085 mol or 92%), melting at 83–86°, was crystallized three times from petroleum ether (60–80°), furnishing a pure fraction melting at 81.9–82.9°: ir (KBr) 1650 cm^{-1} (C=O); uv max (96% ethanol) 261 mμ (ε 21,400) and 284 (18,300); nmr (deuteriochloroform) δ 7.66 (d, 4, J = 5.0 cps), 7.06 (quartet, 2, J = 3.6 cps and 5.0 cps), 4.07–3.48 (quintet, 2), and 2.75–2.12 (m, 8).

Anal. Calcd for $C_{17}H_{16}O_2S_2$: C, 64.52; H, 5.10; S, 20.27; mol wt, 316.43. Found: C, 64.9, 64.6; H, 5.2, 5.2; S, 20.0, 20.1.

***l*-2,6-Bis(2′-thenoyl)spiro[3.3]heptane** (6).—From 7.1 g (0.039 mol) of *d*-spiro[3.3]heptane-2,6-dicarboxylic acid (1) {$[\phi]_{578}$ +8.7°, $[\phi]_{546}$ +9.9°, $[\phi]_{405}$ +18.8° (*c* 5.2, acetone)} *via* the acid chloride 2 the diketone 6 was prepared. The crude product (10.5 g) furnished on crystallization from petroleum ether a first fraction of 4.1 g: mp 96.0–97.0°; $[\phi]_{578}$ −51.5°, $[\phi]_{546}$ −58.7°, $[\phi]_{436}$ −103.3°, $[\phi]_{405}$ −124.2° (*c* 8.0, acetone). A subsequent fraction (2.5 g) showed $[\phi]_{578}$ −45.0°, $[\phi]_{436}$ −90.4° (*c* 7.9, acetone).

***l*-2,6-Diacetylspiro[3.3]heptane** (7).—Under the conditions used by Pinson and Friess for the synthesis of methyl cyclobutyl ketone,[36] *l*-2,6-diacetylspiro[3.3]heptane (7) was prepared from 6.0 g (0.027 mol) of spiro[3.3]heptane-2,6-dicarbonyl chloride (2) {from *l* acid; $[\phi]_{578}$ −6.8°, $[\phi]_{405}$ −15.6° (*c* 5.5, acetone)}. Distillation of the crude product gave 700 mg (3.9 mmol or 14%) of diketone 7, bp 92–94° (0.6 mm). Analytically pure 7 was obtained after another distillation: $n^{20}D$ 1.4718; ir (neat)

(34) H. L. Herzog, "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, p 753.

(35) R. D. Schuetz and R. A. Baldwin, *J. Org. Chem.*, **27**, 2841 (1962).

(36) R. Pinson and S. L. Friess, *J. Amer. Chem. Soc.*, **72**, 5333 (1950).

1705 (C=O) and 1365 cm^{-1} ($COCH_3$); uv max (cyclohexane) 284 mμ (ε 64); nmr (deuteriochloroform) δ 3.38–2.84 (quintet, 2), 2.04 (s), and 2.37–2.00 (m, together 14 H); $[\phi]_{578}$ −1.5°, $[\phi]_{546}$ −2.0°, $[\phi]_{436}$ −9.2°, $[\phi]_{405}$ −15.3°, $[\phi]_{365}$ −36.0° (*c* 4.0, acetone); $[\phi]_{626}$ +9.2°, $[\phi]_{435}$ −1.6°, $[\phi]_{367}$ −78.5° (*c* 0.55, cyclohexane; Bendix Ericsson Polarmatic 62); $[\phi]_{328}$ −460°, $[\phi]_{312}$ −760°, $[\phi]_{303}$ −680°, $[\phi]_{293}$ 0°, $[\phi]_{270}$ +1320 ± 50°, $[\phi]_{263}$ +1390 ± 70°, $[\phi]_{245}$ +1300 ± 40°, $[\phi]_{239}$ +1340 ± 70°, $[\phi]_{322}$ +1490 ± 80° (*c* 0.11, cyclohexane; Bendix Ericsson Polarmatic 62).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95; mol wt, 180.25. Found: C, 73.2, 73.5; H, 9.0, 8.9.

***d*-2,6-Dipivaloylspiro[3.3]heptane (8).**—To a solution of 4.8 g (0.022 mol) of spiro[3.3]heptane-2,6-dicarbonyl chloride (2) {prepared from *l* acid; $[\phi]_{578}$ −6.8°, $[\phi]_{405}$ −15.6° (*c* 5.5, acetone)} in 50 ml of dry ether was added over a period of 30 min 40 ml of a 0.65 *N* solution of *tert*-butylmagnesium chloride in ether.

During this period and 1 hr thereafter the reaction mixture was stirred at −30°. After stirring for another 4 hr at room temperature, 100 ml of a solution of ammonium chloride in water was added and the reaction mixture was worked up in the normal way. The crude product was dissolved in cyclohexane. Concentration furnished a residue which crystallized from a mixture of equal volume of water and ethanol, to give 800 mg (0.003 mol or 14%) of **8**. After three crystallizations from ethanol with 10% water, an analytically pure sample was obtained: mp 92.8° (warm-up rate 10°/min); ir (Nujol) 1690 cm^{-1} (C=O); uv max (cyclohexane) 296 mμ (ε 67); nmr (carbon tetrachloride) δ 3.71–3.15 (quintet, 2), 2.51–1.87 (m, 8), 1.07 (s, 18); $[\phi]_{578}$ +22.8°, $[\phi]_{546}$ +25.5°, $[\phi]_{436}$ +38.9°, $[\phi]_{405}$ +40.9°, $[\phi]_{365}$ +33.6° (*c* 2.0, ethanol 96%); $[\phi]_{626}$ +86.6 ± 3.5°, $[\phi]_{400}$ +165.4 ± 3.2°, $[\phi]_{370}$ +184.0 ± 5.6°, $[\phi]_{435}$ +170.7 ± 11.1°, $[\phi]_{328}$ 0°, $[\phi]_{318}$ −175.5 ± 21.6°, $[\phi]_{307}$ 0°, $[\phi]_{286}$ +1190 ± 10°, $[\phi]_{270}$ +1620 ± 12°, $[\phi]_{250}$ +1800 ± 25°, $[\phi]_{238}$ +2120 ± 30° (*c* 0.33, cyclohexane; Bendix Ericsson Polarmatic 62).

Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67; mol wt, 264.41. Found: C, 77.4, 77.0; H, 10.7, 10.7.

***d*-6-Pivaloylspiro[3.3]heptane-2-carboxamide (9).**—As stated above the crude reaction product from **8** was dissolved in cyclohexane. White crystals separated from the mixture. The compound was isolated and recrystallized from acetone to give an analytically pure sample melting at 184.3° (warm-up rate 10°/min): ir (KBr) 3370 and 3200 (NH_2), 1655 and 1630 ($CONH_2$), 1300 cm^{-1} ($COC(CH_3)_3$); nmr (deuteriochloroform) δ 6.38–5.48 (broad s, 2), 3.81–3.25 (quintet, 1), 3.07–2.50 (quintet, 1), 2.50–1.40 (m, 8), 1.09 (s, 9); mass spectrum (70 eV) *m/e* (rel intensity) 223 (20), 166 (100), 138 (16), 121 (13), 95 (68), 93 (38), 79 (13), 77 (12), 72 (22), 67 (25), and 57 (68); $[\phi]_{578}$ +16.6°, $[\phi]_{546}$ +18.9°, $[\phi]_{436}$ +29.8°, $[\phi]_{405}$ +34.4°, $[\phi]_{365}$ +37.8° (*c* 2.0, ethanol 96%).

Anal. Calcd for $C_{13}H_{21}NO_2$: C, 69.92; H, 9.48; N, 6.27; ml wt, 223.32. Found: C, 70.2, 70.2; H, 9.6, 9.4; N, 6.2, 6.2.

***dl*-2,6-Bis(2′-thenyl)spiro[3.3]heptane (10).**—A mixture of 8.0 g (0.025 mol) of *dl*-2,6-bis(2′-thenoyl)spiro[3.3]heptane (**6**), 25 ml of 100% hydrazine hydrate, and 125 ml of diethylene glycol was kept at 150° during 4 hr and allowed to cool to room temperature. This mixture was added dropwise over a period of 45 min to a stirred solution of 20 g of potassium hydroxide in 300 ml of diethylene glycol. During the addition and for 1 hr after it the temperature was kept at 230–240° by distilling off water and excess hydrazine. The reaction mixture was cooled and then poured onto crushed ice and 100 ml of hydrochloric acid. The organic layer was taken up into ether yielding, after work-up in the normal way, removal of the solvent, and column chromatography over neutral alumina (Merck, Aktivitätsstufe 1) with cyclohexane as eluent, 5.5 g (0.019 mol or 76%), of *dl*-**10**: bp 158–160° (0.3 mm); $n^{20}D$ 1.5704; uv max (ethanol 96%) 235 mμ (ε 16,800); nmr (carbon tetrachloride) δ 7.00–6.50 (m, 6), 2.78 (d, 4), 2.66–1.42 (m, 10).

Anal. Calcd for $C_{17}H_{20}S_2$: C, 70.78; H, 6.99; S, 22.23; mol wt, 288.46. Found: C, 70.9, 70.8; H, 7.0, 7.1; S, 22.3, 22.0.

***l*-2,6-Bis(2′-thenyl)spiro[3.3]heptane (10).**—Amalgamated zinc was prepared from 200 g of zinc wool in a 2-l. three-necked round-bottomed flask. The amalgam was covered with 300 ml of 6 *N* hydrochloric acid, followed by a solution of 15.0 g (0.047 mol) of *l*-2,6-bis(2′-thenoyl)spiro[3.3]heptane {$[\phi]_{578}$ −51.5°, $[\phi]_{436}$ −103.3° (*c* 8.0, acetone)} in 350 ml of dioxane. In the boiling and stirred mixture gaseous hydrogen chloride was introduced, until after about 5 hr most of the zinc had disappeared. The reaction mixture was cooled to room temperature and then poured out into 1 l. of water and the product was taken up in ether. The ether solution was washed with bicarbonate solution and water and then dried over magnesium sulfate; ether was removed.

Column chromatography over neutral alumina (Merck Aktivitätsstufe 1) with cyclohexane as eluent yielded, after evaporation of the solvent, 6.9 g (0.024 mol or 51%) of pure 2,6-bis(2′-thenyl)spiro[3.3]heptane (**10**) as a colorless liquid, $n^{20}D$ 1.5711. The infrared spectrum is identical with that of the racemic compound: $[\phi]_{578}$ −10.4°, $[\phi]_{546}$ −12.2°, $[\phi]_{436}$ −21.9°, $[\phi]_{405}$ −26.7°, $[\phi]_{365}$ −36.1° (*c* 4.2, cyclohexane).

No maximum or minimum between 200 and 400 mμ could be detected in the circular dichroism spectrum of a solution of 7.5 mg of the *l* compound {$[\phi]_{578}$ −5.8°, $[\phi]_{436}$ −12.4° (c 5.0, cyclohexane)} in 25 ml of *n*-hexane (Merck, Uvasol).

***l*-2,6-Bis(hydroxymethyl)spiro[3.3]heptane (13).**—According to the procedure followed by Rice and Grogan,[24] 6.9 g (0.033 mol) of *d*-dimethyl spiro[3.3]heptane-2,6-dicarboxylate (**3**) {$[\phi]_{578}$ +3.2°, $[\phi]_{405}$ +5.6° (*c* 4.6, acetone)} was reduced with lithium aluminum hydride, yielding 4.1 g (26 mmol or 80%) of diol **13**, $[\phi]_{578}$ −5.4°, $[\phi]_{546}$ −6.0°, $[\phi]_{436}$ −10.0°, $[\phi]_{405}$ −12.0° (*c* 5.2: chloroform); $[\phi]_{578}$ −3.3°, $[\phi]_{546}$ −3.7°, $[\phi]_{436}$ −6.6°, $[\phi]_{405}$ −7.8° (*c* 5.0, ethanol 96%).

***d*-2,6-Bis(hydroxymethyl)spiro[3.3]heptane (13).**—*l*-Spiro[3.3]heptane-2,6-dicarboxylic acid (**1**) (2.6 g, 0.0014 mol) {$[\phi]_{578}$ −7.7°, $[\phi]_{546}$ −8.7°, $[\phi]_{436}$ −14.2°, $[\phi]_{405}$ −17.3°, $[\phi]_{365}$ −22.5° (*c* 5.0, acetone)}, was reduced with 3.5 g of lithium aluminum hydride in 100 ml of diethyl ether. During 8 hr the reaction mixture was refluxed and kept at room temperature for 3 days. The excess lithium aluminum hydride was decomposed by addition of water. Work-up furnished 300 mg (0.002 mol or 13%) of diol **13**: $[\phi]_{578}$ +3.2°, $[\phi]_{546}$ +3.8°, $[\phi]_{436}$ +6.4°, $[\phi]_{405}$ +7.5° (*c* 5.4, ethanol 96%).

Optical Purity Control of 2,6-Bis(hydroxymethyl)spiro[3.3]heptane (13).—To an emulsion of 270 mg of *d*-2,6-bis(hydroxymethyl)spiro[3.3]heptane (**13**) {$[\phi]_{578}$ +3.2°, $[\phi]_{436}$ +6.4° (*c* 5.4, ethanol 96%)} in 50 ml of 1.5 *N* sulfuric acid, stirred at room temperature, was added powdered potassium permanganate until the color disappeared slowly. The reaction mixture was filtered over a glass funnel, the residue was washed with water, and the combined filtrates were saturated with sodium sulfate and extracted with ethyl acetate. After removal of the solvent, the residue was recrystallized twice from water, furnishing 46 mg (0.25 mmol or 14%) of *l*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**), showing an infrared spectrum identical with that of the starting *l* acid **1**: $[\phi]_{578}$ −8.8°, $[\phi]_{546}$ −10.4°, $[\phi]_{436}$ −16.0°, $[\phi]_{405}$ −18.6° (*c* 4.6, acetone).

***dl*-2,6-Bis(chloromethyl)spiro[3.3]heptane (14).**—Thionyl chloride (10 ml) was added dropwise in 30 min to a mixture of 2.75 g (0.018 mol) of *dl*-2,6-bis(hydroxymethyl)spiro[3.3]heptane (**13**) and 0.3 ml of dry pyridine. The reaction mixture was cooled in an ice–salt bath in order to keep the temperature below +10°. The mixture was allowed to stand at room temperature for one night, refluxed for 3 hr on a water bath, and cooled to 0°. Water was added and the organic layer was taken up into ether and worked up in the normal way. After removal of the ether, the residue was chromatographed over neutral alumina (Merck, Aktivitätsstufe 1) with *n*-pentane as an eluent. The eluate furnished, after removal of *n*-pentane, 1.8 g (9.33 mmol or 53%) of 2,6-bis(chloromethyl)spiro[3.3]heptane (**14**), bp 130–132° (17 mm).

The compound appeared, however, to be not analytically pure. To obtain a pure sample the substance was dissolved in *n*-pentane and this solution was shaken with concentrated sulfuric acid in a separatory funnel eight times. Pentane was evaporated under reduced pressure and **14** distilled *in vacuo* at bp 122–126° (15 mm): $n^{20}D$ 1.4916; mass spectrum (70 eV) *m/e* (rel intensity) 196 (0.1), 194 (0.6), 192 (0.9), 156 (13), 1.44 (1.7), 142 (5.2), 116 (48), 108 (39), 80 (100); nmr (carbon tetrachloride) δ 3.41 (d, 4), 2.76–1.55 (m, 10).

Anal. Calcd for $C_9H_{14}Cl_2$: C, 55.97; H, 7.31; Cl, 36.72; mol wt, 193.13. Found: C, 56.1, 56.0; H, 7.4, 7.2; Cl, 36.9, 37.1.

***l*-2,6-Bis(chloromethyl)spiro[3.3]heptane (14).**—Purified thionyl chloride[37] (10 g) was added to an ice–salt bath cooled solution

(37) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 1158.

of 3.5 g (0.021 mol) of *l*-2,6-bis(hydroxymethyl)spiro[3.3]heptane (**13**) {$[\phi]_{578}$ −5.4°, $[\phi]_{436}$ −10.0° (*c* 5.2, chloroform)} in 7 ml of ethyldiisopropylamine. After the mixture was stirred for 4 hr at 90°, it was cooled and poured into cold 4 *N* hydrochloric acid. The organic layer was taken up into ether and worked up in the usual way. Removal of the solvent furnished a dark, crude product from which after distillation 3.1 g (0.016 mol or 75%) of *l*-2,6-bis(chloromethyl)spiro[3.3]heptane (**14**) was obtained: bp 116–120° (12 mm); $[\phi]_{578}$ −3.3°, $[\phi]_{546}$ −3.8°, $[\phi]_{436}$ −6.4°, $[\phi]_{405}$ −7.6° (*c* 11.0, tetrahydrofuran).

l-**2,6-Dimethylspiro[3.3]heptane** (**15**).—To a refluxing suspension of 2.5 g (0.066 mol) of lithium aluminum hydride in 20 ml of dry tetrahydrofuran was added a solution of 3.0 g (0.016 mol) of *l*-2,6-bis(chloromethyl)spiro[3.3]heptane (**14**) {$[\phi]_{578}$ −3.3°, $[\phi]_{405}$ −7.6° (*c* 11.0, tetrahydrofuran)} in 20 ml of tetrahydrofuran over a period of 20 min. After the mixture was refluxed for 16 hr, excess hydride was decomposed by adding a mixture of equal volume of water and tetrahydrofuran, and the reaction mixture was poured into cold 4 *N* hydrochloric acid. The organic material was taken up in pentane. The solution was dried over magnesium sulfate and pentane was removed by distillation at atmospheric pressure. The residue was purified by gas–liquid chromatography (F & M 775 chromatograph, 2 cm × 2 m stainless-steel column packed with 20% silicon rubber SE-30 on 60–80 mesh Chromosorb AN, oven 60°), yielding 0.9 g (7.2 mmol or 46%) of 2,6-dimethylspiro[3.3]heptane (**15**): nmr (carbon tetrachloride) δ 2.54–1.19 (m, 10), 1.01 (d, 6); mass spectrum (70 eV) *m/e* (rel intensity) 124 (1, parent peak), 109 (17), 96 (20), 95 (19), 82 (54), 81 (66), 68 (16), 67 (100), 54 (30), 41 (27), and 39 (24); $[\phi]_{578}$ −4.8° ± 0.4°, $[\phi]_{526}$ −6.1° ± 0.4°, $[\phi]_{476}$ −7.9° ± 0.3°, $[\phi]_{435}$ −9.4° ± 0.6°, $[\phi]_{400}$ −11.5° ± 0.6°, $[\phi]_{370}$ −14.1 ± 0.5°, $[\phi]_{323}$ −19.5° ± 1.1°, $[\phi]_{270}$ −29.5 ± 0.7°, $[\phi]_{250}$ −37.2° ± 0.9°, $[\phi]_{232}$ −43.9° ± 1.3° (*c* 1.8, cyclohexane; Bendix Ericsson Polarmatic 62).

Anal. Calcd for C_9H_{16}: C, 87.02; H, 12.98; mol wt, 124.23. Found: C, 86.8, 86.5; H, 12.8, 12.8.

dl-**2,6-Bis(5′-carboxy-2′-thenyl)spiro[3.3]heptane** (**11**).—*dl*-2,6-Bis(2′-thenyl)spiro[3.3]heptane (**10**) (98 g, 0.34 mol) was formylated according to Vilsmeier and Haack[26] with 142 g of *N*-methylformanilide and 128 g of phosphorus oxychloride in 500 ml of dry benzene at 35° during 2 hr. After the mixture was stirred for 1 night at room temperature, water was added and the reaction mixture was worked up in the normal way. The crude product, after solidification on standing at −20°, was washed with cold ether and recrystallized from petroleum ether (bp 40–60°), yielding 92 g (0.261 mol or 77%) of impure dialdehyde melting at 63–64°.

dl-2,6-Bis(5′-formyl-2′-thenyl)spiro[3.3]heptane (65 g, 0.189 mol) was dissolved in 1 l. of ethanol. Immediately after the addition of a solution of 60 g of sodium hydroxide in 0.5 l. of water to a stirred solution of 130 g of silver nitrate in 0.5 l. of water, the solution of the dialdehyde was added at once to the reagent. After stirring for 6 hr at 40°, solid was separated by filtration using a Büchner funnel. The residue was washed with distilled water. The filtrate was distilled at normal pressure to remove ethanol. The residue furnished, after acidification with 20 ml of concentrated hydrochloric acid and filtration, 70 g (0.186 mol or 76%, calculated on 2,6-bis(2′-thenyl)spiro[3.3]-heptane (**10**)) of *dl*-2,6-bis(5′-carboxy-2′-thenyl)spiro[3.3]heptane (**11**) melting with decomposition from 250°, after crystallization from dioxane: ir (KBr) 3700–2300 (COOH), 1670 cm^{-1} (CO); nmr (DMSO-d_6) δ 7.56 (d, 2, *J* = 3.5 cps), 6.84 (d, 2, *J* = 3.5 cps), 2.87 (d, 4, *J* = 5.5 cps), 2.45–1.43 (m, 10).

Anal. Calcd for $C_{19}H_{20}O_4S_2$: C, 60.61; H, 5.36; S, 17.03; mol wt, 376.50. Found: C, 60.7, 60.8; H, 5.4, 5.5; S, 16.9, 16.8.

d-**2,6-Bis(5′-carboxy-2′-thenyl)spiro[3.3]heptane** (**11**).—*l*-2,6-Bis(2′-thenyl)spiro[3.3]heptane (**10**) (6.5 g, 0.023 mol) {$[\phi]_{578}$ −5.8°, $[\phi]_{405}$ −12.4° (*c* 5.0, cyclohexane)} was formylated and oxidized in the way described for the racemic compound, yielding 2.9 g (0.008 mol or 30%) of the diacid **11**. The infrared spectrum (KBr) was identical with that of the racemic compound; the optical activity was $[\phi]_{546}$ +8 ± 2° (*c* 4.8, 3 *N* sodium hydroxide solution).

dl-**2,6-Bis(5′-carboxy-1′-pentyl)spiro[3.3]heptane** (**12**).—*dl*-2,6-Bis(5′-carboxy-2′-thenyl)spiro[3.3]heptane (**11**) (8.0 g, 0.021 mol) was desulfurized according to the method of Papa, Schwenk, and Ginsberg,[28] in a solution of 110 g of sodium hydroxide in 1 l. of distilled water. The refluxing solution was stirred with a Herschberg stirrer, and 100 g of Raney nickel alloy was added in small portions. Foaming of the reaction mixture was reduced by adding small amounts of amyl alcohol.

After the mixture was stirred for another 2 hr at reflux temperature, the water layer was decanted and the residue was washed with 1 l. of boiling 1 *N* sodium hydroxide solution. After cooling, the combined water layers were washed with ether and acidified with 1.5 l. of concentrated hydrochloric acid. The dicarboxylic acid **12** was dissolved in ether. The ether solution was washed with water, dried on magnesium sulfate, and evaporated, yielding 6.1 g (0.019 mol or 88%) of diacid **12**, mp 96–97° after three crystallizations from petroleum ether (bp 80–100°).

Anal. Calcd for $C_{19}H_{32}O_4$: C, 70.33; H, 9.94; mol wt, 324.47. Found: C, 70.4, 70.6; H, 9.9, 10.0.

l-**2,6-Bis(5′-carboxy-1′-pentyl)spiro[3.3]heptane** (**12**).—From 9.6 g (0.028 mol) of *l*-2,6-bis(2′-thenyl)spiro[3.3]heptane (**10**) {$[\phi]_{578}$ −11.1°, $[\phi]_{405}$ −28.2° (*c* 3.6, cyclohexane)} in the same way *l*-2,6-bis(5′-carboxy-1′-pentyl)spiro[3.3]heptane (**12**) was prepared in an overall yield of 71% (6.5 g or 0.020 mol): mp 94.9–95.4° after two crystallizations from petroleum ether (bp 80–100°); $[\phi]_{578}$ −7.2°, $[\phi]_{546}$ −8.1°, $[\phi]_{436}$ −14.0° (*c* 5.0, acetone). The CD spectrum between 200 and 400 mμ of a solution of 1.275 g in 100 ml of ethanol 95% (Merck, Uvasol) in a 0.1-cm cuvette showed no maxima or minima.

l-**2,6-Spiro[3.3]heptanediammonium Chloride** (**16**).—To a solution of 8.0 g (0.044 mol) of *d*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**) {$[\phi]_{578}$ +7.8°, $[\phi]_{546}$ +8.8°, $[\phi]_{405}$ +17.0° (*c* 5.0, acetone)} in 80 ml of concentrated sulfuric acid, stirred at a temperature of 45°, was added over a period of 15 min, a solution of hydrazoic acid,[38] prepared from 18.3 g sodium azide in 40 ml of chloroform according to Janson and Pope's procedure for the racemic compound **16**.[29] After the reaction mixture was stirred for 1 hr more, it was poured onto 500 g of crushed ice. The chloroform layer was removed and sulfuric acid in the water layer was neutralized by calcium carbonate. The suspension was filtered and the residue was washed with water, and to the combined filtrates calcium chloride was added. Calcium sulfate was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue furnished after two crystallizations from ethanol 7.6 g (0.038 mol or 87%) of *l*-2,6-spiro[3.3]-heptanediammonium chloride (**16**).

Anal. Calcd for $C_7H_{16}Cl_2N_2$: C, 42.22; H, 8.10; Cl, 35.61; mol wt, 199.14. Found: C, 42.2, 42.2; H, 8.1, 8.2; Cl, 35.4, 35.4.

dl-**Spiro[3.3]heptane-2,6-bis(dimethylamine) Dimethiodide** (**17**).—From 18.4 g (0.10 mol) of *dl*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**), *dl*-spiro[3.3]heptane-2,6-diamine (**16**) was prepared according to Janson and Pope's method.[29]

After neutralization of excess sulfuric acid with calcium carbonate, removal of excess calcium carbonate and calcium sulfate by filtration over a Büchner funnel, and washing of the residue on the filter with water, the combined filtrates were evaporated to a volume of about 25 ml. To this solution were added 15 ml of a 32% sodium hydroxide solution in water, 60 g of formic acid, and 42 g of a 35% formaldehyde solution in water.

The mixture was kept for one night at 100°, allowed to cool, poured into 25 ml of 6 *N* hydrochloric acid, and evaporated under reduced pressure. A solution of 30 g of sodium hydroxide in 90 ml of water was added. The solution was saturated with potassium carbonate and the organic layer diluted with ether. The crude tertiary amine, obtained by removal of the ether, was dissolved in 100 ml of methanol, and 100 g of methyl iodide was added. After the mixture stood for 0.5 hr, crystals appeared. After five crystallizations from methanol, colorless crystals were obtained: yield (after one crystallization) 19.4 g (0.042 mol or 42% overall); nmr spectrum (in deuterium oxide, water signal δ 5.30 used as internal reference) δ 5.20–4.61 (quintet, 1.74, *J* = 8.5 cps), 3.81 (s, 18), 3.36–3.22 (d, 8, *J* = 8.5 cps).

Anal. Calcd for $C_{13}H_{28}I_2N_2$: C, 33.49; H, 6.05; mol wt, 466.19. Found: C, 33.2, 33.3; H, 6.4, 6.4.

d-**Spiro[3.3]heptane-2,6-bis(dimethylamine) Dimethiodide** (**17**).—From 9.2 g (0.05 mol) of *l*-spiro[3.3]heptane-2,6-dicarboxylic acid (**1**), $[\phi]_{546}$ −7.5° (*c* 5.1, acetone), spiro[3.3]heptane-2,6-bis(dimethylamine) dimethiodide (**17**) was prepared in the way described, in a yield of 64% with respect to the acid **1**. The dimethiodide **17** was recrystallized three times from methanol: $[\phi]_{578}$ +27.0°, $[\phi]_{436}$ +42.4°, $[\phi]_{405}$ +49.4°, $[\phi]_{365}$ +63.8° (*c* 2.6, water).

(38) H. Wolff, *Org. React.*, **3**, 307 (1964).

Registry No.—*d*-**1**, 27259-78-5; *d*-**2**, 27259-79-6; *d*-**4**, 27317-55-1; *d*-**5**, 27317-56-2; *dl*-**6**, 27259-80-9; *l*-**6**, 27259-81-0; *l*-**7**, 27259-82-1; *d*-**8**, 27259-83-2; *d*-**9**, 27259-84-3; *dl*-**10**, 27259-85-4; *l*-**10**, 27259-86-5; *dl*-**11**, 27259-88-7; *dl*-**12**, 27259-87-6; *l*-**12**, 27259-89-8; *d*-**13**, 27259-90-1; *l*-**13**, 27259-91-2; *dl*-**14**, 27259-92-3; *l*-**14**, 27259-93-4; *l*-**15**, 27259-94-5; *l*-**16**, 27259-95-6; *dl*-**17**, 27259-96-7; *d*-**17**, 27259-97-8.

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Notes

Preparation of Guanine Pentofuranosyl Nucleosides Using a Friedel–Crafts Catalyst[1]

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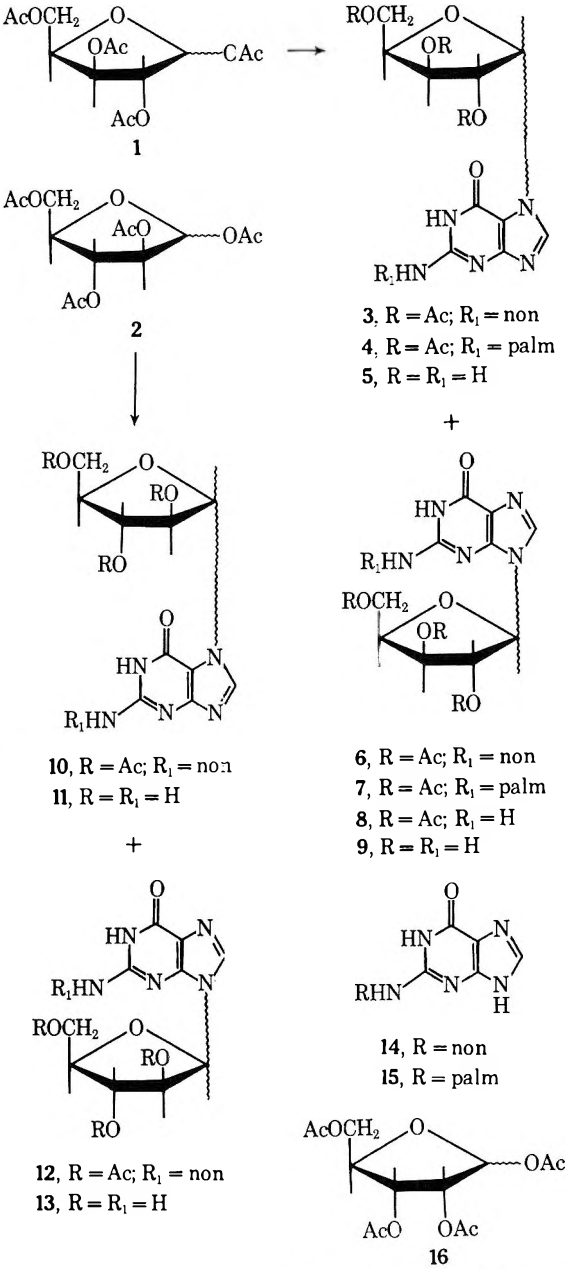
Furukawa and Honjo[2] described recently a novel and simple method of purine ribonucleoside preparation which employs Friedel–Crafts catalysts as condensing agents for the appropriate *N*-acylpurines and 2,3,5-tri-*O*-acyl-1-*O*-acetyl-D-ribofuranoses. The method gave only β-nucleosides and provided an especially useful method for the synthesis of guanosine. Because guanine nucleosides are less directly accessible by other routes[2,3] and because of our needs for considerable quantities of the guanine nucleoside (β-**9**),[4] we have applied this technique using 1,2,3,5-tetra-*O*-acetyl-D-xylofuranose (**1**) as the sugar. The results were of sufficient interest to warrant some experiments with 1,2,3,5-tetra-*O*-acetyl-D-arabinofuranose (**2**). Our findings are reported in this manuscript.

The reaction was carried out as described by Furukawa and Honjo[2] with **1** and either N^2-nonanoylguanine (**14**) or N^2-palmitoylguanine[2] (**15**) using chlorobenzene and aluminum chloride (see Table I). N^2-Nonanoylguanine (**14**) reacted faster; thus, after 2 hr at reflux, the reaction of **1** with **14** was complete, while that with **15** had progressed only to a small extent, according to tlc data. N^2-Nonanoylguanine also gave a higher ratio of 7- to 9-substituted nucleoside than **15**. Surprisingly, the α anomer was formed in large amounts with the



[non = $CH_3(CH_2)_7CO$–; palm = $CH_3(CH_2)_{14}CO$–]

α:β anomer ratio being about 1:1 for both acylguanines and for both 7 and 9 isomers. A substantial improve-

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(2) Y. Furukawa and M. Honjo, *Chem. Pharm. Bull.*, **16**, 1076 (1968). These authors noted a trace amount of 7-ribofuranosylguanine in their preparation of guanosine.

(3) G. L. Tong, K. J. Ryan, W. W. Lee, E. M. Acton, and L. Goodman, *J. Org. Chem.*, **32**, 859 (1967), and references there.

(4) (a) S. Susaki, A. Yamazaki, A. Kamimura, K. Mitsugi, and I. Kumashiro, *Chem. Pharm. Bull.*, **18**, 176 (1970); (b) A. P. Martinez, *et al.*, manuscript in preparation describing the synthesis of β-**9** *via* the mercury derivative[4c] of 2-acetamido-6-chloropurine; (c) R. H. Iwamoto, E. M. Acton, and L. Goodman, *J. Med. Chem.*, **6**, 684 (1963).

TABLE I

PREPARATION OF GUANINE NUCLEOSIDES USING ALUMINUM CHLORIDE CATALYST

Expt no.	N^2-Acylguanine, mmol	Sugar, mmol	$AlCl_3$, mmol	Reflux time, hr	Yield of product, % 9 isomer (α:β)	7 isomer (α:β)
1	**14**, 17.2	**1**, 20.8	17.2	2	58 (1:1)	10.5 (1:1)
2	**14**, 8.6	**1**, 9.4	9.0	18[a]	19 total[a]	
3	**14**, 33.4	**1**, 35.6	34.6	2[b]	51 (1:4)	13 (1:1)
4	**15**, 2.6	**1**, 3.9	4.5	18[c]	49 (1:1)	1.5 (1:1)
5	**15**, 10.0	**1**, 13.0	10.0	15	44 (1:1)	2.3 (1:1)
6	**14**, 4.1	**2**, 5.0	4.5	2	40 (4:1)	13.3 (5:1)[d]
7	**14**, 3.4	**2**, 3.7	3.4	3[b]	34 (4:1)	15.5 (5:1)[d]
8	**14**, 8.6	**16**, 10.4	11.6	2	35[e] (1:6)	11 (1:2)

[a] Considerable darkening and decomposition toward latter stages of 18-hr reaction. Because of the low yields, no effort was made to separate the isomers. [b] In expt 3 and **7**, the base **14** and $AlCl_3$ were combined first in chlorobenzene and then sugar was added. See Experimental Section. [c] This reaction was initially kept at 90° for 18 hr. There was no reaction; so the mixture was brought to reflux temperature and maintained there for 18 hr. [d] Predominant anomer assumed to be α. [e] This yield is in excellent agreement with the 35% y obtained from N^2-octanoyl guanine in ref 2.

ment in the amount of β anomer (α:β, 1:4) of the 9 isomer was realized by the slow addition of the sugar **1** to the preformed complex of N^2-nonanoylguanine (**14**) and aluminum chloride; however, the α:β ratio of the 7 isomer remained unchanged. The anomer ratios were determined from the nmr spectra in which the H-8 protons of the two anomers could be distinguished.

Column chromatography using Florisil[5] readily separated the 7 isomer from the 9 isomer, but neither the anomers of **6** nor **7** were resolved. Attempts to separate the anomers by various techniques were unsuccessful with **9** and its 3′,5′-isopropylidene derivative. However, fractional crystallization of the triacetate **8** afforded the pure α and β anomers. Deacylation of β-**8** afforded β-**9** whose properties agree with (known) literature values.[4] Likewise α-**8** and the 7 isomers, **3** and **4**, were deacylated. Thin layer chromatography was used to separate the anomers of the blocked 7 isomers, α-**3** and β-**3**. Their uv maxima occurred at identical wavelengths to each other and to the original mixture. Hence they were both 7 isomers and must be anomers.

Since the xylose **1** afforded so much α-nucleoside by the aluminum chloride process, the method was applied to 1,2,3,5-tetra-*O*-acetyl-D-arabinofuranose (**2**). Should a 1:1 mixture of nucleoside anomers be formed, this might be a useful route to β-nucleosides of arabinofuranose. Generally, such β-nucleosides have been obtained by using arabinose derivatives blocked with nonparticipating groups for the nucleoside condensations[6] or by interconversion of the corresponding xyloside.[7] Using the procedure of Furukawa and Honjo,[2] the reaction of **2** and **14** (see expt 6, Table I) afforded some of the 7-nucleoside **10**, together with the major product, the 9-nucleoside **12**; these 7 and 9 isomers were separable by Florisil chromatography. One anomer predominated for both **10** and **12**; this was shown to be the α anomer for **12** by deacylation and comparison with authentic β-**13**[8a] and α-**13**.[8b] The reaction of **2** with the preformed complex of N^2-nonanoylguanine and aluminum chloride (expt 7) did not change the anomer ratio of **12**.

The reaction of 1,2,3,5-tetra-*O*-acetyl-D-ribofuranose (**16**) with N^2-nonanoylguanine (**14**) was examined (expt 8) and found to give, after Florisil chromatography, about 11% of the 7-substituted nucleoside **17** and 35% of the 9-substituted nucleoside **18**, the corresponding ribose derivatives of **3** and **6**, respectively. The α- to β-anomer ratios were about 1:2 for **17** and 1:6 for **18**. That **17** was indeed a mixture of anomers and not a mixture of isomers was established in the same way as for **3**.

As applied to the synthesis of guanine pentofuranosides, the above results corroborate those of Furukawa and Honjo.[2] The reaction of suitable N^2-acylguanines with suitable peracylated pentofuranoses using a Friedel–Crafts catalyst like aluminum chloride is indeed a simple and direct route that affords good yields of the guanine nucleosides. With N^2-palmitoylguanine, formation of the 9-substituted nucleoside in preference to the 7 isomer is favored more than with N^2-nonanoylguanine (and perhaps N^2-octanoylguanine[2]). The anomeric nature of the 9-substituted guanine nucleoside is dependent on the pentose. One anomer of the 9-nucleoside is formed predominantly with ribose and arabinose; these are the β anomer and α anomer, respectively. This would be expected on the basis of participation by the 2-acyl group of the pentose as suggested by Furukawa and Honjo.[2] With xylose the α:β ratio of the 9-nucleoside is 1:1, but this can be altered to favor the β anomer by changing the reaction conditions. This propensity of xylose to give more of an anomeric mixture is also seen in other techniques for nucleoside condensation by the fusion method[9] and the mercury salt method.[10]

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are corrected. Optical rotations were obtained with a Perkin-Elmer Model 141 automatic polarimeter; nmr, with a Varian A-60 or HA 100; CD, with a Jasco Model ORD/UV-5, Sproule Scientific SS 107 CD modification. Evaporations were carried out *in vacuo* at or below 50° initially with a water aspirator and finishing at <0.1 mm. Anhydrous magnesium sulfate was used as drying agent. Type 3A, 1/16-in. pellets of Linde Molecular Sieves (an alkali metal aluminosilicate with 3-Å pore size) were used in the condensation reactions. Celite is a diatomaceous earth product of Johns-Manville. Tlc was run on silica gel HF (E. Merck AG Darmstadt) in these solvent system: TA, ether–

(5) Trade name for the magnesium silicate product of the Floridin Co.

(6) C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 3004 (1963).

(7) (a) W. W. Lee, A. Benitez, L. Goodman, and B. R. Baker, *J. Amer. Chem. Soc.*, **82**, 2648 (1960); (b) E. J. Reist, A. Benitez; L. Goodman, B. R. Baker, and W. W. Lee, *J. Org. Chem.*, **27**, 3274 (1962).

(8) (a) E. J. Reist and L. Goodman, *Biochem.*, **3**, 15 (1964). (b) Properties agreed with those found for α-**13** previously prepared by another route: R. W. Blackford and E. J. Reist, unpublished results.

(9) W. W. Lee, A. P. Martinez, G. L. Tong, and L. Goodman, *Chem. Ind. (London)*, 2007 (1963).

(10) O. P. Crews, Jr., and L. Goodman in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, W. W. Zorbach and R. S. Tipson, Ed., Interscience, New York, N. Y., 1968, p 139.

ethyl acetate (2:8); TB, methanol–ethyl acetate (2:8); TC, same 4:6 ratio. The spots were detected under uv light and reported as R_f in relation to solvent front.

General Method of Condensation.—To a stirred mixture of N^2-nonanoylguanine (**14**) (see expt 1, Table I, for amounts of reactants), 1,2,3,5-tetra-*O*-acetyl-D-xylofuranose (**1**), and 5 g of molecular sieves in 200 ml of chlorobenzene was added anhydrous aluminum chloride. The reaction mixture was brought to reflux in an oil bath, 20 ml of solvent was distilled off, and the reaction mixture was heated and stirred at reflux for the required length of time. The reaction mixture was evaporated to dryness and worked up as described below.

Method with Preformed Complex of N^2-Acylguanine and Aluminum Chloride.—A stirred mixture of N^2-nonanoylguanine (**14**) (see expt 3 for amounts of reactants) and molecular sieves in 300 ml of chlorobenzene was distilled to remove about 20 ml of solvent. To the hot mixture was added the aluminum chloride carefully during 2–3 min. The mixture was then heated at reflux while the sugar 1 in 90 ml of chlorobenzene was added dropwise over 3 hr. After the addition, the reaction was heated at reflux for the required length of time and evaporated to dryness. The residue was dissolved in 500 ml of ethyl acetate, diluted with 225 ml of ether, and filtered through Celite. The Celite residue was washed with 250 ml of ether–ethyl acetate (1:1). The combined filtrate and wash was evaporated to leave 19.0 g of a solid tan foam. This was thoroughly stirred in 500 ml of ether for 30 min and filtered to remove the soluble sugar and some nonanoic acid. The crude, ether-insoluble product was dissolved in 75 ml of chloroform and charged on a column (30 mm diam) of 330 g of Florisil. The initial eluents of 500 ml each of chloroform and chloroform–ethyl acetate (1:1) and the next 700 ml of methanol–ethyl acetate (1:10) were discarded. Further elution with methanol–ethyl acetate (1:10) gave a 230-ml fraction containing 2.39 g (13%, see expt 3) of the 7 isomer **3**; a 145-ml fraction contained 0.63 g (3.4%) of the 7 and 9 isomers. The next 860-ml fraction and finally 800 ml of methanol–ethyl acetate (1:4 to 2:3) afforded 9.05 g (51%) of 9 isomer **6**.

9-(2,3,5-*O*-Triacetyl-D-xylofuranosyl)-N^2-nonanoylguanine (6).—The 9 isomer **6** from the Florisil column was a solid foam: uv max (pH 1) 262 mμ (ε 17,200), 275 (sh) (14,200); uv max (pH 7) 258 (16,600), 275 (sh) (12,300); uv max (pH 13) 264 (12,800);[11] nmr ($DCCl_3$) δ 7.92 (s, H-8 of β-**6**), 7.72 (s, H-8 of α-**6**), 6.40 (d, $J_{1',2'}$ = 5.5 Hz, H-1′ of α-**6**), 5.93 (d, $J_{1',2'}$ = 2.5 Hz, H-1′ of β-**6**) with the relative areas of the peaks for α:β being 1:4; nmr (DMSO-d_6) δ 8.05 and 8.00 (both s, H-8 of β-**6**) and α-**6**, respectively), 6.35 (d, $J_{1',2'}$ = 5 Hz, H-1′ of α-**6**), 5.88 (d, $J_{1',2'}$ = 3 Hz, H-1′ of α-**6**); R_f 0.25 in TA. No satisfactory chromatographic system was found that would resolve the α and β anomers of **6**.

Anal. Calcd for $C_{25}H_{35}N_5O_9$: 54.6; H, 6.42; N, 12.7. Found: C, 54.4; H, 6.59; N, 13.0.

7-(2,3,5-*O*-Triacetyl-D-xylofuranosyl)-N^2-nonanoylguanine (3).—The 7 isomer **3** from the Florisil column was a solid foam: uv max (pH 1) 218 mμ (ε 15,700), 264 (16,100); uv max (pH 7) 223 mμ (ε 21,800), 264 (14,300); uv max (pH 13) 269 mμ (ε 10,700);[14] nmr ($CDCl_3$) δ 8.17 and 8.02 (both singlets, H-8 of anomers), 6.95 (d, $J_{1',2}$ = 3.5 Hz, H-1′) and 6.54 (d, $J_{1',2'}$ = 1.8 Hz, H-1′) with the relative areas of the peaks for the α:β anomers being about 1:1; R_f 0.50 in solvent TA. Repeated development (3–4 times) in ether resolved the anomer of **3** with approximate R_f 0.57 and 0.67.

Anal. Calcd for $C_{25}H_{35}N_5O_9$: C, 54.6; H, 6.42; N, 12.7. Found: C, 54.7; H, 6.43; N, 12.8.

For uv analysis, some **3** was separated by thin layer chromatography using multiple development (5 times) with ether–ethyl acetate (6:4) as solvent to afford the anomers with R_f 0.53 and 0.67. These spots were eluted and their uv measured. The maxima of both were found to occur at wavelengths identical with that reported above for the original mixture. Hence both are 7 isomers and must be anomers.

7-(D-Xylofuranosyl)guanine (5).—A solution of 1.00 g (1.82 mmol) of **3** and 2.0 ml of 1 *N* sodium methoxide in 50 ml of absolute methanol was heated at reflux for 3 hr, neutralized with 2 *N* hydrochloric acid, and evaporated. The residue was triturated with a mixture of 75 ml of chloroform and 75 ml of water, and then collected on a filter and washed with water and ether to afford 0.32 g (62%) of **5**. Recrystallization from water afforded 0.30 g (55%) of white crystalline **5**: mp above 290°; $[\alpha]^{20}D$ −70 (*c* 0.5, DMF); uv max (pH 1), 249 mμ (ε 10,300); uv max (pH 7) 217 mμ (ε 21,800), 240 (sh) (6200), 285 (7600); uv max (pH 13) 240 (sh) (7700), 282 (6800).[15]

Anal. Calcd for $C_{10}H_{13}N_5O_5 \cdot {}^2/_3H_2O$: C, 40.6; H, 4.89; N, 23.7. Found: C, 40.8; H, 4.58; N, 23.7.

9-(D-Xylofuranosyl)guanine (9).—Deacylation of 5.0 g of the anomeric mixture of **6** by the procedure used for **3** afforded 1.64 g (64%) of the anomeric mixture **9**, $[\alpha]^{21}D$ −28 (*c* 0.25, H_2O). This crystallized readily from water to give a 70% recovery of **9**, mp 228–230°, $[\alpha]^{20}D$ −29 (*c* 0.25 H_2O). The anomers could not be separated by column chromatography on Dowex 1 (Cl^-) nor by crystallization of the 2′,3′-*O*-isopropylidene derivative.

A mixture of 1.51 g of **9**, $[\alpha]^{21}D$ −28 (*c* 0.25, H_2O), was treated with 2.5 ml of acetic anhydride in 50 ml of pyridine for 2 hr at 65° to afford the tri-*O*-acetyl derivative **8**, R_f 0.29 (β-**8**) and 0.24 (α-**8**) in TB. Crystallization from methanol afforded 0.55 g (26%) of **9-(2,3,5-tri-*O*-acetyl-β-D-xylofuranosyl)guanine** (β-**8**):[4b] mp 236–237°; $[\alpha]^{20}D$ −16 (*c* 0.50, DMF); nmr (D_6MSO) δ 7.74 (s, H-8), 5.83 (d, $J_{1',2'}$ = 3 Hz, H-1′) with no signals for α anomer observed (probably 5% detectable); R_f 0.29 in TB; R_f 0.71 in TC. The mother liquors were evaporated and the residue was crystallized from acetone twice to give 0.25 g (12%) of **9-(2,3,5-tri-*O*-acetyl-α-D-xylofuranosyl)guanine** (α-**8**): mp 218–219°; $[\alpha]^{20}D$ +33 (*c* 0.50, DMF); uv max (pH 1) 258 mμ (ε 11,800), 280 (sh) (7900); uv max (pH 7) 253 mμ (ε 13,000), 270 (sh) (9000); uv max (pH 13), 258–266 mμ (ε 11,000); nmr (DMSO-d_6) δ 7.65 (s, H-8), 6.22 (d, $J_{1',2'}$ = 5 Hz, H-1′) with no signals of β-**8** (probably 5% detectable); R_f 0.24 in solvent TB.

Anal. Calcd for $C_{16}H_{19}N_5O_8$: C 46.9; H, 4.68; N, 17.1. Found: C, 46.9; H, 4.78; N, 16.7.

Deacylation of β-**8**, as done for **3**, afforded β-**9**, $[\alpha]^{20}D$ −55 (*c* 0.50, DMF) and $[\alpha]^{20}D$ −35 (*c* 0.25, H_2O). Two recrystallizations from water did not change the rotation: $[\alpha]^{20}D$ −36.1 ± 1.6 (*c* 0.25, H_2O); other properties agreed with known values.[4] Similarly, deacylation of α-**8** afforded 54% of α-**9**: mp 260–261°; $[\alpha]^{20}D$ −15.3 (*c* 0.5, H_2O); uv max like that of β-**9**; R_f 0.21 in TC.

Anal. Calcd for $C_{10}H_{13}N_5O_5 \cdot H_2O$: C, 39.9; H, 5.02. Found: C, 39.5; H, 4.74.

7-(2,3,5-Tri-*O*-acetyl-D-arabinofuranosyl)-N^2-nonanoylguanine (10).—The 7 isomer **10** from the Florisil column was a solid foam: uv max like that of **3**;[14] R_f 0.28–0.38 dumbbell shaped; α and β anomers?) in TA.

Anal. Calcd for $C_{25}H_{35}N_5O_9$: C, 54.6; H, 6.42; N, 12.7. Found: C, 54.1; H, 6.57; N, 12.2.

9-(2,3,5-Tri-*O*-acetyl-D-arabinofuranosyl)-N^2-nonanoylguanine (12).—The 9 isomer **12** from the Florisil column was a solid foam: uv max like that of **6**;[11] R_f 0.10 in TA; nmr ($DCCl_3$) δ 7.83 (s, H-8 of α-**12**), 7.78 (s, H-8 of β-**12**), 6.05 (d, $J_{1',2''}$ = 2.5 Hz, H-1′ of α-**12**) with the H-1′ of β-**12** not being definitely located. The relative areas of the H-8 peaks for α:β were 4.3:1.2. CD results confirm that major product is α anomer.

Anal. Calcd for $C_{25}H_{35}N_5O_9$: C, 54.6; H, 6.42; N, 12.7. found: C, 54.1; H, 6.57; N, 12.9.

A portion of **12** was deacylated to **13**, whose CD indicated it to be mainly α anomer and whose properties were like those of an authentic sample of α-**13**[8b] and not β-**13**.[8a]

7-(2,3,5-Tri-*O*-acetyl-D-ribofuranosyl)-N^2-nonanoylguanine (17).—The 7 isomer **17** from the Florisil column was a solid foam: $[\alpha]^{23}D$ +20 (*c* 0.50, $CHCl_3$); nmr (DMSO-d_6) δ 8.32 (s, H-8 of β-**17**), 8.18 (s, H-8 of α-**17**), 6.66 (d, $J_{1',2'}$ = 5 Hz, H-1′ of α-**17**), 6.18 (d, $J_{1',2'}$ = 5.5 Hz, H-1′ of β-**17**) with the respective peak areas for the α:β anomers being 1:2; uv max was like that of **3**; R_f 0.31–0.39 in TA.

Anal. Calcd for $C_{25}H_{35}N_5O_9$: C, 54.6; H, 6.42; N, 12.7. Found: C, 54.3; H, 6.38; N, 12.5.

For uv analysis, some **17** was separated by thin layer chromatography using multiple development (5 times) with ether–ethyl acetate (6:4) as solvent to afford two spots with R_f 0.33 and 0.46. These were eluted and their uv measured. The maxima of both occurred at wavelengths identical with that reported above for the original mixture. Hence both are 7 isomers and must be anomers.

(11) The uv is similar to N^2-acetyl-9-benzylguanine[12] and N^2-acyl-9-alkylguanines.[13]

(12) B. Shimizu and M. Miyaki, *Chem. Pharm. Bull.*, **15**, 1066 (1967).

(13) K. Nagasawa and Y. Kato, *ibid.*, **16**, 1674 (1968).

(14) The uv is similar to N^2-acetyl-7-benzylguanine.[12]

(15) The uv is similar to 7-benzylguanine.[12]

9-(2,3,5-Tri-*O*-acetyl-D-ribofuranosyl)-N^2-nonanoylguanine (18).—The 9 isomer **18** from the Florisil column was a solid foam: $[\alpha]^{22}D$ −43 (*c* 0.50, $CHCl_3$); nmr (DMSO-d_6) δ 8.10 (s, H-8 of β-**18**), 7.94 (s, H-8 of α-**18**), 5.95 (d, $J_{1',2'}$ = 5.5 Hz, H-1′ of β-**18**) with H-1′ of α-**18** not discernible above noise level, but perhaps at 6.3; the peak areas for H-8 of α:β are 1:6; uv max was like that of **6**; R_f 0.11 in TA.

Anal. Calcd for $C_{25}H_{35}N_5O_9$: C, 54.6; H, 6.42; N, 12.7. Found: C, 54.3; H, 6.38; N, 12.5.

Registry No.—**3** (α isomer), 27460-34-0; **3** (β isomer), 27460-35-1; **5**, 27460-36-2; **6** (α isomer), 27460-37-3; **6** (β isomer), 27460-38-4; **8** (α isomer), 27460-39-5; **8** (β isomer), 27460-40-8; **9** (α isomer), 27462-38-0; **9** (β isomer), 27462-39-1; **10**, 27462-40-4; **12** (α isomer), 27462-41-5; **12** (β isomer), 27462-42-6; **17** (α isomer), 27617-86-3; **17** (β isomer), 27462-43-7; **18** (α isomer), 27570-86-1; **18** (β isomer), 27462-43-7.

Furano Compounds. XII. Synthesis of Furano[2,3-*b*]xanthones

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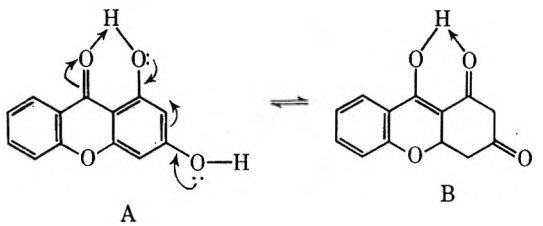
Syntheses of furano[2,3-*b*]xanthones from 3-hydroxyxanthone have been recorded earlier.[1b] Since many naturally occurring xanthones possess a phloroglucinol unit, attempts have now been made to add a furan ring to 1,3-dihydroxyxanthone.

For the addition of a [2,3-*b*]-fused furan ring, the essential step is to introduce a 2-formyl or 2-acetyl group into the 1,3-dihydroxyxanthone molecule. 1,3-Dihydroxyxanthone undergoes formylation to yield 1,3-dihydroxy-4-formylxanthone.[2] However, acetylation of 1,3-dihydroxyxanthone under normal Friedel–Crafts or Fries conditions results in a mixture of products. Using freshly fused $ZnCl_2$, HOAc, and Ac_2O, Badawi, *et al.*,[3] acetylated 2-methyl-5,7-dihydroxychromone to get 2-methyl-5,7-dihydroxy-6-acetylchromone. When 1,3-dihydroxyxanthone was submitted to acetylation under these conditions, a single crystalline product could be obtained. This was identified as 1,3-dihydroxy-2-acetylxanthone (**1**).

The reactivity of the 2 position of 1,3-dihydroxyxanthone may be attributed to the presence of its 2,4-dihydroxybenzoyl moiety A which may undergo tautomeric change to a β-diketonic structure B containing a reactive methylene group in the 2 position.



A B

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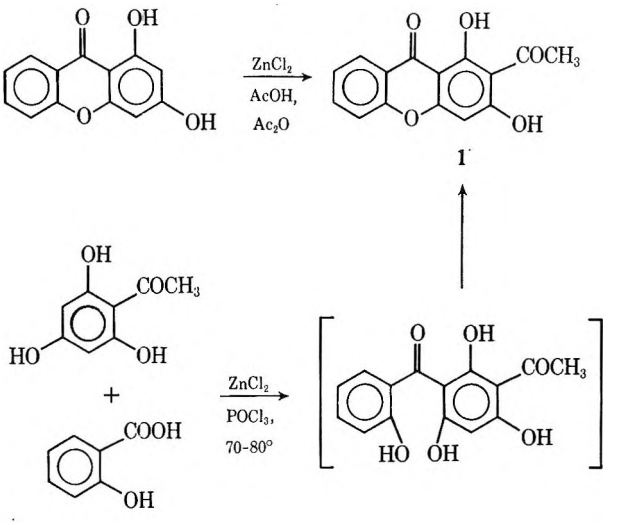
(2) G. S. Puranik, Ph.D. Thesis, Karnatak University, Dharwar, India, 1964; A. Mustafa, *Chem. Heterocycl. Compounds*, **23**, 169 (1967).

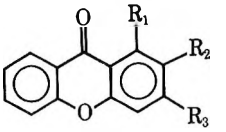
(3) M. M. Badawi and M. B. E. Fayez, *Tetrahedron*, **21**, 2965 (1965).

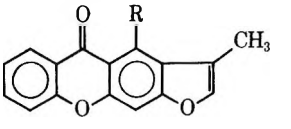
The identity of **1** has been proved by another synthesis involving condensation of phloroacetophenone with salicylic acid in the presence of freshly fused $ZnCl_2$ and $POCl_3$. This reaction probably entails the nonchelated *p*-hydroxyl group in the formation of the γ-pyrone ring.



Location of the acetyl group at the 2 position is confirmed by the fact that **1** affords a new 1,2,3-trihydroxyxanthone upon Dakin oxidation. The trimethyl ether of this is different from 1,3,4-trimethoxyxanthone.[2] On acetylation using $B(OAc)_3$ and Ac_2O, 1,2,3-diacetoxyxanthone gave 1-hydroxy-2,3-diacetoxyxanthone, since the chelated hydroxyl forms a boracetate complex while the nonchelated hydroxyls undergo normal acetylation. Acetylation using Ac_2O and a drop of pyridine yielded 1,2,3-triacetoxyxanthone. Methylation of 1-hydroxy-2,3-diacetoxyxanthone using methyl iodide and silver oxide in acetone yielded 1-methoxy-2,3-diacetoxyxanthone which on hydrolysis with alkali gave 1-methoxy-2,3-dihydroxyxanthone.

Condensation of ethyl bromoacetate with **1** using acetone/K_2CO_3 yielded exclusively ethyl 1-hydroxy-2-acetyl-9-oxo-3-xanthyloxyacetate (**2g**) since the 1-hydroxyl group is strongly chelated by both the xanthone and acetyl carbonyls. Hydrolysis of **2g** with 5% Na_2CO_3 in acetone gave 1-hydroxy-2-acetyl-9-oxo-3-xanthyloxyacetic acid (**2h**). When heated with sodium acetate/acetic anhydride, **2h** underwent cyclization with decarboxylation and acetylation yielding 1-acetoxy-3-methylfurano[4,5-*b*]xanthone (**3a**). Hydrolysis with 5% alcoholic potash smoothly converted it into the required 1-hydroxy-3-methylfurano[2,3-*b*]xanthone **3b**.





2a, R_1, R_2, R_3 = OH
b, R_1, R_2, R_3 = OCH_3
c, R_1 = OH; R_2, R_3 = $OCOCH_3$
d, R_1, R_2, R_3 = $OCOCH_3$
e, R_1 = OCH_3; R_2, R_3 = $OCOCH_3$
f, R_1 = OCH_3; R_2, R_3 = OH
g, R_1 = OH; R_2 = $COCH_3$; R_3 = $-OCH_2COOEt$
h, R_1 = OH; R_2 = $COCH_3$; R_3 = $-OCH_2COOH$

3a, R = $OCOCH_3$
b, R = OH

Experimental Section

1,3-Dihydroxy-2-acetylxanthone.[1]—Freshly fused $ZnCl_2$ (4 g) was dissolved in acetic acid (8 ml) by heating. Acetic anhydride (4 ml) and 1,3-dihydroxyxanthone (4 g) were added. The reaction mixture was heated at 145–150° for 1–5 hr, cooled, and poured into ice–water. Solid gradually separated out and was filtered and washed with water. The crude product was sublimed at 240–250° (8 mm). Crystallization from alcohol/acetic acid yielded **1** as pale yellow needles, mp 208–209° (1.4 g). It gave a blood red color with ethanolic ferric chloride.

Anal. Calcd for $C_{15}H_{10}O_5$: C, 66.67; H, 3.70. Found: C, 66.34; H, 3.98.

Its 2,4-dinitrophenylhydrazone formed tiny orange needles, mp 297° (acetic acid).

Anal. Calcd for $C_{21}H_{14}O_8N_4$: N, 12.45. Found: N, 12.24.

A mixture of salicylic acid (2 g), phloroacetophenone (3.5 g), freshly fused $ZnCl_2$ (6 g), and $POCl_3$ (20 ml) were heated at 70–80° for 2 hr. The reaction product was cooled and poured into ice–water. The yellow solid that separated was filtered and washed with 10% $NaHCO_3$ and water. The crude product was sublimed at 248–250° (8 mm). Crystallization from ethanol/acetic acid yielded **1** as pale yellow needles, mp and mmp (with the above sample) 208–209°, yield 0.8 g.

Anal. Calcd for $C_{15}H_{10}O_5$: C, 66.67; H, 3.70. Found: C, 66.43; H, 3.88.

1,2,3-Trihydroxyanthone (2a).—**1** (1.35 g) was dissolved in 10 ml of 4% NaOH, 10 ml of pyridine was added, and the mixture was cooled in an ice bath. Hydrogen peroxide (12 ml, 20 vol) was added dropwise with shaking during 5 min. The reaction mixture was left for 1 hr. Acidification yielded **2a** as a yellow solid. It crystallized from alcohol as yellow needles, mp 265°, yield 0.75 g. The ethanolic solution gave a dark green color with ferric chloride solution.

Anal. Calcd for $C_{13}H_8O_5$: C, 63.93; H, 3.28. Found: C, 64.17; H, 3.54.

1,2,3-Trimethoxyxanthone (2b).—**2a** (0.2 g) was refluxed with Me_2SO_4 (0.6 g) and anhydrous K_2CO_3 (2 g) for 10 hr. Potassium salts were filtered off and the filtrate after removal of solvent furnished **2b** as a colorless solid. It crystallized from alcohol as needles, mp 191°. It gave no color with $FeCl_3$ solution.

Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.13; H, 4.89. Found: C, 66.97; H, 4.63.

1,3,4-Trimethoxyxanthone.—1,4-Dihydroxy-3-methoxyxanthone[4] (0.2 g) in anhydrous acetone (100 ml) was treated with anhydrous potassium carbonate (2.0 g) and dimethyl sulfate (2.5 ml), and the mixture was refluxed for 54 hr. The potassium salts were filtered and the solvent was removed. The residue on crystallization from alcohol gave 1,3,4-trimethoxyxanthone as needles, mp 164°, yield 0.12 g. It gave no color reaction with ethanolic ferric chloride.

Anal. Calcd for $C_{16}H_{14}O_5$: C, 67.1; H, 4.9. Found: C, 67.4; H, 5.0.

1,2,3-Triacetoxyxanthone (2d).—**2a** (0.1 g) with acetic anhydride (5 ml) and pyridine (a drop) gave **2d** as colorless shining cubes, mp 213° (alcohol), $FeCl_3$ test negative.

Anal. Calcd for $C_{19}H_{14}O_8$: C, 61.62; H, 3.78. Found: C, 61.88; H, 3.95.

1-Hydroxy-2,3-diacetoxyxanthone (2c).—**2a** (1.0 g) was refluxed with boron triacetate (1.5 g) and acetic anhydride (8 ml) for 10 min. The yellow diacetoborate that separated on cooling was filtered and washed with anhydrous ether. Subsequently it was suspended in water (50 ml) and heated to boiling when it decomposed. **2c** thus obtained crystallized from alcohol as pale yellow needles, mp 203–204°, yield 0.8 g. It gave a dark brown ferric chloride test.

Anal. Calcd for $C_{17}H_{12}O_7$: C, 62.19; H, 3.66. Found: C, 62.55; H, 3.91.

1-Methoxy-2,3-diacetoxyanthone (2e).—**2c** (0.5 g) in acetone (100 ml) was refluxed with methyl iodide (2 ml) and active Ag_2O (1 g) for 20 hr. The reaction product was filtered and the filtrate on removal of solvent yielded **2e** which crystallized from alcohol as colorless needles, mp 111°, yield 0.45 g. It gave a negative ferric chloride test.

Anal. Calcd for $C_{18}H_{14}O_7$: C, 63.15; H, 4.09. Found: C, 63.37; H, 3.90.

1-Methoxy-2,3-dihydroxyanthone (2f).—**2e** (0.25 g) was refluxed with alcoholic potash (5%, 10 ml) for 1 hr. Subsequent acidification yielded **2f** which crystallized from alcohol as colorless pale yellow needles, mp 176°. With $FeCl_3$ it gave a green color immediately changing to reddish brown.

Anal. Calcd for $C_{14}H_{10}O_5$: C, 65.11; H, 3.88. Found: C, 65.58; H, 3.67.

Ethyl 1-Hydroxy-2-acetyl-9-oxo-3-xanthyloxyacetate (2g).—**1** (1.35 g) in acetone (300 ml) was refluxed with ethyl bromoacetate (0.85 g) and anhydrous K_2CO_3 (6 g) for 10 hr. The potassium salts were filtered off and the solvent was removed from the filtrate. As no residue was obtained, the potassium salts were suspended in water and decomposed with dilute HCl. The solid that separated was filtered and washed with water. **2g** thus obtained crystallized from alcohol/acetic acid as colorless plates, mp 210°. It gave a reddish brown color with $FeCl_3$, yield 0.9 g.

Anal. Calcd for $C_{19}H_{16}O_7$: C, 64.04; H, 4.49. Found: C, 64.22; H, 4.63.

1-Hydroxy-2-acetyl-9-oxo-3-xanthyloxyacetic Acid (2h).—**2g** (0.75 g) in acetone (300 ml) was refluxed with aqueous Na_2CO_3 (60 ml, 5%) for 3 hr. Removal of acetone and acidification yielded **2h** which crystallized from acetic acid as colorless plates, mp 253°. It gave a reddish brown color with $FeCl_3$, yield 0.6 g.

Anal. Calcd for $C_{17}H_{12}O_7$: C, 62.19; H, 3.66. Found: C, 62.51; H, 3.84.

1-Acetoxy-3-methylfurano[4,5-*b*]xanthone (3a).—**2h** (0.55 g) was refluxed with NaAc (0.6 g) and Ac_2O (6 ml) for 2 hr. Subsequent work-up gave **3a** which crystallized from aqueous alcohol as pale yellow needles, mp 173–174°, yield 0.45 g. It gave a negative $FeCl_3$ test.

Anal. Calcd for $C_{18}H_{12}O_5$: C, 70.13; H, 3.89. Found: C, 70.59; H, 4.01.

1-Hydroxy-3-methylfurano[2,3-*b*]xanthone (3b).—**3a** (0.4 g) was refluxed with alcoholic potash (5%, 15 ml) for 1 hr. Subsequent acidification gave **3b** which crystallized from alcohol as yellow needles, mp 232°, yield 0.3 g. It gave a green color with $FeCl_3$.

Anal. Calcd for $C_{16}H_{10}O_4$: C, 72.18; H, 3.76. Found: C, 72.66; H, 3.81.

Registry No.—**1**, 27460-08-8; **1** 2,4-DNP, 27460-09-9; **2a**, 27519-51-3; **2b**, 27460-10-2; **2c**, 27460-11-3; **2d**, 27460-12-4; **2e**, 27460-13-5; **2f**, 20362-26-9; **2g**, 27460-14-6; **2h**, 27460-15-7; **3a**, 27460-16-8; **3b**, 27460-17-9; 1,3,4-trimethoxyxanthone, 27460-18-0.

(4) V. V. Kane, A. B. Kulkarni, and R. C. Shah, *J. Sci. Ind. Res., Sect. B*, **18**, 75 (1959).

The Cyclization of *cis*- and *trans*-2-(2-Methoxycyclohexyl)ethanol to *cis*- and *trans*-Perhydrobenzofurans[1]

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We have reported[2] that compounds of type **1** undergo cyclization with tosyl chloride–pyridine to form perhydrobenzofurans **2**, with loss of a methoxyl group. This reaction, which we first observed in degradations of the antibiotic fumagillin,[3] involves a methoxonium ion intermediate.[4]

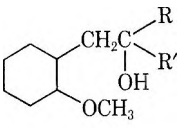
(1) Aided by Grant 2252-C from the Petroleum Research Fund of the American Chemical Society, for which we express our appreciation.

(2) S. E. Cantor and D. S. Tarbell, *J. Amer. Chem. Soc.*, **86**, 2902 (1964).

(3) D. D. Chapman, S. E. Cremer, R. M. Carman, M. Kunstmann, J. G. McNally, A. Rosowsky, and D. S. Tarbell, *ibid.*, **82**, 1009 (1960); D. S. Tarbell, *et al.*, *ibid.*, **83**, 3096 (1961).

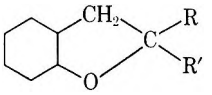
(4) S. Winstein, E. Allred, R. Heck, and G. Glick, *Tetrahdron*, **3**, 1 (1958); E. Allred and S. Winstein, *J. Amer. Chem. Soc.*, **89**, 3991, 3998, 4008, 4012 (1967); E. R. Novak and D. S. Tarbell, *ibid.*, **89**, 73 (1967); A. W. Friederang and D. S. Tarbell, *J. Org. Chem.*, **33**, 3797 (1968); J. R. Hazen and D. S. Tarbell, *Tetrahedron Lett.*, 5927 (1968); J. R. Hazen, *ibid.*, 1897 (1969); R. J. Gargiulo and D. S. Tarbell, *Proc. Nat Acad. Sci. U. S.*, **62**, 52 (1969).

Further examination of this reaction has shown that the reported[2] results require amplification and correction, for the cis and trans primary alcohols **3** and **4**.



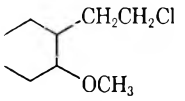
1

3, R = R′ = H, *cis*
4, R = R′ = H, *trans*

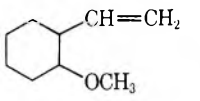


2

5, R = R′ = H, *cis*
9, R = R′ = H, *trans*



6, *cis*
7, *trans*



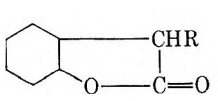
8, *trans*

The fact that the cyclization of **1** to **2** does occur with the secondary alcohol (**1**, R = CH_3; R′ = H) and the tertiary alcohol (**1**, R = R′ = CH_3), giving the corresponding 2-substituted perhydrobenzofuran **2**, is indicated by additional work,[5] as well as by the original observations.[2]

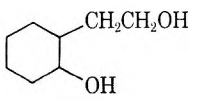
Treatment of the cis alcohol **3** with tosyl chloride–pyridine yielded 3% of *cis*-perhydrobenzofuran (**5**), identified by vpc and by its correspondence in spectral characteristics with a sample prepared by a different method.[5b] The other product, in addition to starting material, was the chloro compound **6**, identified by analysis and nmr spectrum.

The trans alcohol **4** with tosyl chloride–pyridine under several sets of conditions yielded the corresponding *trans*-chloro compound **7** and the unsaturated compound **8**. Distillation of the *trans*-chloro compound **7** or passage through a vpc column at 200° did yield a small amount of the *trans*-perhydrobenzofuran (**9**), but it is clear that no detectable amount of **9** is formed by the tosyl chloride–pyridine treatment itself. Previously,[2] the reaction product from the trans alcohol **4** was distilled at atmospheric pressure which may have formed some of the trans cyclized product **9**.

We have prepared a pure sample of **9** by treating cyclohexene oxide with malonic ester[6] which yields the *trans*-carbethoxylactone **10a**; hydrolysis and decarboxylation gives the trans lactone[6] **10b** which is converted by lithium aluminum hydride reduction to the trans diol **11**. Treatment of this diol with tosyl chloride–pyridine yielded *trans*-perhydrobenzofuran (**9**) which was characterized and shown to be different from the cis compound **5**. The synthesis of a mixture of the cis and trans compounds **5** and **9** (by cyclization of a cis–trans mixture of the diols **11**), followed by vpc separation[7] gave **9**, with properties in reasonable agreement with those of our product. A mixture of **5** and **9** was also prepared by lead tetraacetate oxidation[7] of cyclohexylethanol. Detailed ir and nmr spectral data for **5** and **9** are given in the Experimental Section.



10a, R = COOEt, *trans*
b, R = H, *trans*



11, *trans*

(5) (a) D. P. Brust and D. S. Tarbell, *J. Org. Chem.*, **31**, 1251 (1966); (b) W. E. Harvey and D. S. Tarbell, *ibid.*, **32**, 1679 (1967).

(6) S. Coffey, *Recl. Trav. Chim. Pays-Bas*, **42**, 387 (1923). The trans ring opening of an epoxide by malonate was demonstrated by W. E. Grigsby, J. Hind, J. Chanley, and F. H. Westheimer, *J. Amer. Chem. Soc.*, **64**, 2606 (1942).

Experimental Section[8]

trans-**2-Allylcyclohexanol.**[9]—Allylmagnesium bromide was prepared[10] from 195 g of magnesium turnings in 2.4 l. of ether and 400 g of allyl bromide in an equal volume of ether. To this solution, cooled in ice bath, was added dropwise 150 g of cyclohexene oxide in ether (100 ml) over a 5-hr period. The reaction complex was hydrolyzed by the slow addition of saturated ammonium chloride solution. After decanting the organic layer and thoroughly washing the salt cake with ether, the combined solution was dried, concentrated, and distilled to give 190 g (90%) of *trans*-2-allylcyclohexanol, bp 86–88° (9 mm), n^{25}D 1.4751 [reported[11] bp 94° (14 mm), n^{25}D 1.4758]. Conversion of the product to the methyl ether as below and analysis by vpc showed no trace of the cis isomer. The 3,5-dinitrobenzoate melted at 69–70° after recrystallization from methanol as reported.[11] When the cyclohexene oxide was added to the Grignard at such a rate as to cause gentle refluxing, the isolated alcohol contained 3–5% of the cis isomer.

trans-**2-Allyl-1-methoxycyclohexane** was prepared in 73% yield by methylation of the above trans alcohol with NaH and methyl iodide in DMF, bp 75–75.5° (14 mm), n^{25}D 1.4535.

trans-**2-(Methoxycyclohexyl)ethanol** (**4**) was prepared much as before[2] by oxidation with osmium tetroxide–periodate in aqueous THF, followed without isolation by sodium borohydride reduction of the aldehyde. The overall yield was 50%, and the product showed bp 114–115° (25 mm), n^{26}D 1.4640 (reported[2] n^{25}D 1.4598).

2-(2-Methoxyphenyl)ethanol was prepared in 76% yield by the above method from *o*-allylanisole.[12] Reduction of 7 g of this material with hydrogen in 30 ml of acetic acid and 3.3 g of 5% rhodium on alumina gave, after the usual work-up and distillation, the following fractions: (1) bp 50–52° (10 mm), 0.7 g; (2) bp *ca.* 117° (10 mm), 1.0 g; (3) bp 117° (10 mm), 3.5 g, n^{25}D 1.4655. Examination by vpc showed that cut 1 was mainly *cis*-perhydrobenzofuran, cut 2 was a mixture of *cis*-perhydrobenzofuran (**5**) and *cis*-2-(2-methoxycyclohexyl)ethanol (**3**), and cut 3 was pure *cis*-2-(2-methoxycyclohexyl)ethanol. The retention time of *cis*-perhydrobenzofuran was identical with that of an authentic sample.

Reaction of *cis*-2-(2-Methoxycyclohexyl)ethanol (3) with Tosyl Chloride in Pyridine.—A mixture of 3.5 g of *cis*-2-(2-methoxycyclohexyl)ethanol, pure from vpc examination, 4.7 g of tosyl chloride, and 31 ml of anhydrous pyridine was stirred for 5.5 hr at 63–65°, poured onto 50 g of cracked ice, and extracted with ether. The ether layer was washed with 10% aqueous hydrochloric acid and saturated sodium chloride solution and dried. After solvent was removed, 2 g of a crude liquid was obtained. Distillation gave these cuts: (1) bp 92–100° (15 mm), 0.15 g; (2) bp 102–103° (15 mm), n^{25}D 1.4651, 1.6 g (41%). Vpc analysis of cut 1 showed a mixture of *cis*-perhydrobenzofuran (**5**, about 3%) and the chloro compound **6** (1:1 ratio). The retention time of **5** corresponded to that of a known sample. Cut 2 showed

(7) S. Moon and B. H. Waxman, *J. Org. Chem.*, **34**, 288 (1969).

(8) Analyses were by Galbraith Laboratories; nmr spectra were taken on a Varian A-60 spectrometer in CCl_4 and $CDCl_3$, with $(CH_3)_4Si$ as an internal standard, and are reported in ppm (δ units); ir spectra were determined with a Beckman IR-10 spectrometer. Vpc analyses were done on an Aerograph Model A90, using 5 ft × 0.25 in. columns with 25% UCON Polar or 20% Carbowax 20M packing.

(9) Method of H. Felkin and G. Roussi, *Tetrahedron Lett.*, 4153 (1965), who give no experimental detail. This procedure gives a purer product stereochemically than the one used earlier.[2]

(10) O. Grummitt, E. P. Budewitz, and C. C. Chudd, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 748.

(11) J. Cologne and F. Collomb, *Bull. Soc. Chim. Fr.*, **18**, 241 (1951).

(12) R. Adams and R. E. Rindfusz, *J. Amer. Chem. Soc.*, **41**, 648 (1919).

one peak on vpc, and the nmr spectrum was identical with that of the analytical sample of the chloro compound **6** (prepared in another run).

The chloro compound **6** showed the following nmr spectrum in $CDCl_3$: 3.41 (t, J = 6 cps, CH_2Cl, 2 H), 3.3 (s, OCH_3, 3 H), 3.2–3.4 (m, OCH, 1 H), 0.8–2.3 (CH and CH_2, 11 H).

Anal. Calcd for $C_9H_{17}ClO$: C, 61.18; H, 9.63. Found: C, 61.38; H, 9.57.

cis-Perhydrobenzofuran (**5**) which was pure by vpc examination showed the following ir spectrum (cm^{-1}): 2940 (s), 2870 (s), 1445 (m), 1380 (w), 1360 (w, b), 1290 (w), 1240 (w), 1180 (w), 1155 (w), 1120 (w, b), 1080 (m), 1050 (m), 1025 (s), 1000 (w), 985 (m), 930 (w), 870 (w), 805 (w), 680 (w, b). The nmr spectrum in $CDCl_3$ showed 0.8–2.3 (b, 11 H), 3.6–4.2 (m, 3 H).

Reaction of *trans*-2-(2-Methoxycyclohexyl)ethanol (4) with Tosyl Chloride in Pyridine.—A mixture of 5 g of *trans*-2-(2-methoxycyclohexyl)ethanol, 6.3 g of tosyl chloride, and 44 ml of anhydrous pyridine was stirred for 5.5 hr at 63–65°, poured onto 70 g of cracked ice, and extracted with ether (seven 20-ml portions). The usual work-up gave 2.3 g of crude product. Distillation at 7 mm gave the following cuts: (1) bp 75–90°, 0.1 g; (2) bp 93–95°, $n^{25}D$ 1.4650, 1.7 g (30%). Vpc analysis of 1 showed a mixture of the unsaturated compound **8**, and the *trans*-chloro compound **7**. Fraction 2 showed only one peak, the chloro compound **7**; the nmr spectrum of this compound (taken in CCl_4 on a sample from a different run) showed 1.5 (m, 11 H), 2.8 (m, $CHOCH_3$), 3.22 (s, OCH_3, 3 H), and 3.45 (t, J = 6.5 cps, CH_2-CH_2Cl, 2 H).

Anal. Calcd for $C_9H_{17}ClO$: C, 61.18; H, 9.63; Cl, 20.06. Found: C, 61.31; H, 9.68; Cl, 19.76.

The structure of the unsaturated compound **8** was based on the following nmr spectrum ($CDCl_3$): 3.27 (s, OCH_3, 3 H), 3.7 (m, CHO, 1 H), 4.7–5.7 (m, vinyl H, 3 H). Ir bands appeared at 3090 and 1645 cm^{-1}.

Lactone of *trans*-(2-Hydroxycyclohexyl)acetic Acid (10b).—Coffey's procedure[7] was modified as follows. To a solution of 57 g of ethyl malonate and 9 g of sodium in 200 ml of absolute ethanol was added 33 g of cyclohexene oxide in 100 ml of absolute ethanol. The reaction mixture became semisolid after reflux for a few minutes; reflux was continued for additional 30 min. Solvent was removed under vacuum. The residual semisolid material was dissolved in 200 ml of 10% NaOH, refluxed for 3 hr, concentrated under vacuum, acidified with HCl, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried, solvent was removed, and the remaining oil was heated at 170–190° for 1 hr. Evolution of gas was observed. Distillation of resulting oil gave the lactone of cyclohexanolacetic acid, bp 97–98° (2 mm), C=O band at 1785 cm^{-1}.

***trans*-2-(2-Hydroxycyclohexyl)ethanol (11).**—To a suspension of 1.8 g of lithium aluminum hydride in 50 ml of ether was added dropwise 6.1 g of the lactone **10b**; the mixture was stirred for 30 min at 0° and then for 4 hr at room temperature. Work-up in the usual way and distillation yielded 4.1 g of the diol **11** as a viscous colorless liquid, bp 104–105° (1 mm). A sample was treated with bis(trimethylsilyl)trifluoroacetamide; vpc showed a single peak. The ir (liquid film) showed bands at 3300 (b), 1450, 1070, 1055, and 1035 cm^{-1}. The nmr in $CDCl_3$ showed 0.9–2.2 (m, CH_2 and CH, 11 H), 2.9–3.4 (m, 1 H), 3.5–3.8 (m, 2 H), 4.7 (OH, 2 H).

***trans*-Perhydrobenzofuran (9).**—The trans diol **11** (3.3 g) was heated with 6.6 g of tosyl chloride in 35 ml of dry pyridine at 95–100° for 2 hr. Distillation of the product resulting from the usual work-up gave 2.4 g of the *trans*-perhydrobenzofuran, bp 72° (25 mm), $n^{25}D$ 1.4632. This material was homogeneous when examined by vpc; addition of a pure sample of *cis*-perhydrobenzofuran (**5**) showed two peaks. Molecular weight by mass spectroscopy was 126 (calcd 126). The nmr spectrum in $CDCl_3$ showed 0.8–2.3 (11 H), 3.6–4.2 (3 H). The ir in liquid film showed the following bands, clearly different from the cis compound above: 2940 (s), 2870 (s), 1455 (m), 1390 (w), 1355 (w), 1340 (w), 1308 (w), 1290 (w), 1270 (w, b), 1190 (w), 1145 (m), 1110 (w), 1065 (s), 1055 (sh), 1020 (w), 980 (s), 930 (m), 925 (sh), 915 (sh), 857 (m), 830 (w), 660 (w, b). These properties supplant those previously reported by us.[2]

Registry No.—**3**, 27345-66-0; **4**, 27345-67-1; **5**, 10198-29-5; **6**, 27384-94-7; **7**, 27345-69-3; **9**, 27345-70-6; **10b**, 27345-71-7; **11**, 27345-72-8.

Reactivities and Electronic Aspects of Nucleic Acid Heterocycles. II. Diazomethane Methylation of Uracil and Its Methyl Derivatives[1]

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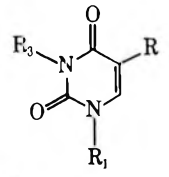
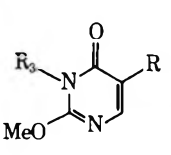
Received July 13, 1970

The methylation with diazomethane of nucleic acid constituents has been extensively studied[2] in connection with the plausible relationship[3] between the mechanism of mutagenesis and carcinogenesis. The action of diazomethane on uracil (**1**) and thymine (**1a**) was reported earlier[4] to afford only the 1,3-dimethyl derivatives, and reaction of diazomethane with uridines or the uracil residue in dinucleoside phosphates yielded exclusively the 3-N-methylation products.[5] However, in the case of diazomethane methylation of 1-β-D-arabinofuranosyl-5-fluorouracil, a minor amount of 4-O-methylation was also observed.[6]

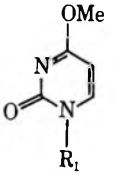
We have found that uracil (**1**), upon treatment with diazomethane, gave rise to four dimethyl compounds: 1,3-dimethyluracil (**2**), 2-methoxy-3-methyl-4-pyrimidone (**3**), 4-methoxy-1-methyl-2-pyrimidone (**4**), and 2,4-dimethoxypyrimidine (**5**). These products were isolated by preparative thin layer and gas–liquid phase



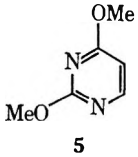
1, R = R_1 = R_3 = H
1a, R = Me; R_1 = R_3 = H
2, R = H; R_1 = R_3 = Me
6, R = R_1 = H; R_3 = Me
6a, R = R_3 = Me; R_1 = H
7, R = R_3 = H; R_1 = Me



3, R = H; R_3 = Me
3a, R = R_3 = Me
8, R = R_3 = H



4, R_1 = Me
9, R_1 = H



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chromatography. The previously unreported dimethyluracil (**3**) was identified by its nmr spectrum

(1) Support of this work by the Public Health Service Grant CA-10142 is gratefully acknowledged.

(2) (a) T. Ueda and J. J. Fox, *Advan. Carbohyd. Chem.*, **22**, 382 (1967); (b) R. L. C. Brimacombe, B. E. Griffin, J. A. Haines, W. J. Haslam, and C. B. Reese, *Biochemistry*, **4**, 2452 (1965).

(3) P. N. Magee and J. M. Barnes, *Advan. Cancer Res.*, **10**, 227 (1967).

(4) F. C. Case and A. J. Hill, *J. Amer. Chem. Soc.*, **52**, 1536 (1930).

(5) (a) J. A. Haines, C. B. Reese, and A. R. Todd, *J. Chem. Soc.*, 1406 (1964); (b) H. T. Miles, *Biochim. Biophys. Acta*, **22**, 247 (1956); (c) D. W. Visser, G. Barron, and R. Beltz, *J. Amer. Chem. Soc.*, **75**, 2017 (1953); (d) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **104**, 385 (1934); (e) A. Holy and K. H. Scheit, *Biochim. Biophys. Acta*, **123**, 430 (1966).

(6) J. J. Fox, N. C. Miller, and R. J. Cushley, *Tetrahedron Lett.*, 4927 (1966).

TABLE I

REACTION OF DIAZOMETHANE WITH URACIL AND ITS METHYL DERIVATIVES[a]

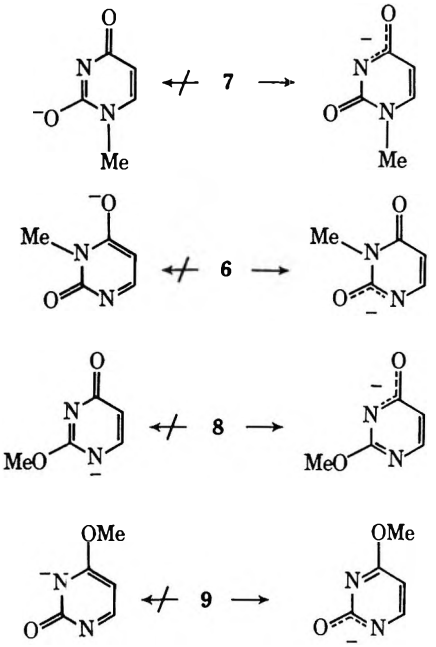
	Acidic pK_a[c]	$\nu_{C=O}^{KBr}$, cm^{-1}	Yield, %	Methylation products, % N^1,N^3	N^3,O^2	N^1,O^4	O^2,O^4	N:O ratio
Uracil (1)	9.5	1695 1630	98	73	18	4	5	3.5
Uracil (1)[b]			48	65	19	6	10	2.6
1-Methyluracil (7)	9.75	1695 1650	91	91		9		10.1
3-Methyluracil (6)	9.95	1690 1665	82	72	28			2.6
2-Methoxy-4-pyrimidone (8)	*Ca.* 8.2	1620	62		86		14	6.1
4-Methoxy-2-pyrimidone (9)	*Ca.* 10.7	1630	64			61	39	1.6
Thymine (1a)	9.9	1720 1660	99	69	20	6	5	3.1

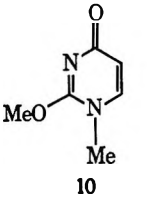
[a] The uracils (0.1 mmol) in 1 ml of methanol were stirred with 30 ml (3.5 mmol) of ethereal diazomethane at room temperature overnight. [b] Dimethylformamide replaced methanol in previous conditions. [c] D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, 9, 199 (1952); pK_a values for 8 and 9 are estimated from those reported for the corresponding ethoxy derivatives.

[($CDCl_3$) δ 3.42 (s, 3, NMe), 4.03 (s, 3, OMe), 6.17 (d, 1, J = 6 Hz, 5-H), and 7.65 (d, 1, J = 6 Hz, 6-H)] and uv absorption [$\lambda_{max}^{H_2O}$ pH 7.4 269 nm (ε 6130) and 213 (4340)], which is comparable to that of 2-ethoxy-3-methyl-4-pyrimidone.[7] Final proof of the structure was accomplished by hydrolysis of **3** in refluxing 1 *N* hydrochloric acid to give 3-methyluracil (**6**) and amination in methanolic ammonia at 100° to produce 3-methylisocytosine.[8] The percentages of the dimethyl isomers were quantitated by glpc using authentic samples as standards for calibration. The results are shown in Table I. The methylation of **1** experienced a significant solvent effect yielding greater amounts of O-methylation products in the medium of dimethylformamide–ether (1:30) than in methanol–ether (1:30). The respective N:O methylation ratios are 2.6 and 3.5 as shown in Table I. Similar solvent effect on the N:O methylation ratio has been noted for the reaction of saccharin with diazomethane.[9] Table I also reveals a methylation pattern for thymine (**1a**) resembling that of uracil (**1**). Apparently the steric and electronic effects on the course of methylation exerted by the 5-methyl group of **1a** are not significant. The unknown 3,5-dimethyl-2-methoxy-4-pyrimidone (**3a**) was identified by comparing its uv and nmr spectra with those of **3** and its hydrolysis to 3-methylthymine (**6a**).

The pathways of methylation of uracil (**1**) were studied by treating the four monomethyluracils individually with diazomethane. Thus, 1-methyluracil (**7**) gave rise to dimethyluracils **2** and **4**, 3-methyluracil (**6**) to **2** and **3**, 2-methoxy-4-pyrimidone (**8**) to **3** and **5**, and 4-methoxy-2-pyrimidone (**9**) to **4** and **5**. All glpc components of the reaction mixtures were identified, and the percentage yields of the dimethyl compounds and the N:O ratios are shown in Table I. Since methylation occurs by substitution of a methyl group in place of the active lactam hydrogen, the selectivity of the action of diazomethane on the monomethyluracils can be rationalized in terms of plausible and implausible intermediate anions as shown in Scheme I. Thus, of the six possible dimethyluracils, 2-methoxy-1-methyl-4-pyrimidone (**10**) and 4-methoxy-3-methyl-2-pyrimidone (**11**) are not formed in these diazomethane reactions. The structure of 2-ethoxy-4-pyrimidone has been determined[10] recently to be predominantly in the *o*-quinonoid form in chloroform, *e.g.* **8**, and that of 4-alkoxy-2-pyrimidone has been routinely written[11] as **9**. The results of selective methylation of **8** and **9** with ethereal diazomethane tend to confirm these fine structural assignments.

SCHEME I





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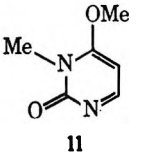

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(7) Ultraviolet spectrum of 2-*O*-ethyl-3-methyluracil [$\lambda_{max}^{H_2O}$ 216 nm (ε 3700), 271 (5900)]: M. Hirata, *Chem. Pharm. Bull.*, **16**, 430 (1968).

(8) D. J. Brown and N. W. Jacobsen, *J. Chem. Soc.*, 3172 (1962).

(9) R. Gompper, *Chem. Ber.*, **93**, 187, 198 (1960).

(10) J. Pitha, *J. Org. Chem.*, **35**, 903 (1970).

(11) (a) C. W. Noell and C. C. Cheng, *J. Heterocycl. Chem.*, **5**, 25 (1968); (b) D. Shugar and J. J. Fox, *Biochim. Biophys. Acta*, **9**, 199 (1952).

A review article[12] on the methylation of lactams with diazomethane suggests that there is an intimate relationship between the position of the amide band and the orientation of methylation. Three major regions have been cited: (1) 1620–1680 cm^{-1}, O-methylation; (2) 1680–1720, O- and N-methylation with kinetic dependence; and (3) 1730–1800, N-methylation. The factual data in Table I indicates that such a correlation for uracil and its methyl derivatives is untenable. Also as illustrated in Table I, there is no apparent relationship between the acidic pK_a of uracil and the methyl derivatives and the yields or N:O ratios of the diazomethane reactions.

Experimental Section

Instrumentation and conditions for tlc and glpc analyses have been described in details in a related paper.[13] Melting points are uncorrected and microanalyses were performed by M-H-W Laboratories, Garden City, Mich. 48135.

Reaction of Uracil and Its Methyl Derivatives with Diazomethane.—To a mixture of 0.1 mmol of each of the pyrimidines **1**, **1a**, **6**, **7**, **8**, and **9** in 1 ml of anhydrous methanol was added 30 ml (3.5 mmol) of ethereal diazomethane. The solution was allowed to stir overnight when practically all the solid material had dissolved. Longer reaction time (48 hr) was allowed for uracil (**1**) when dimethylformamide instead of methanol was used. The solution was filtered, concentrated, and diluted to 1 ml volumetrically with methanol. Quantitative analyses by glpc for the four dimethyluracils were done by comparing their peak areas with those of the authentic samples on a 6 ft × 0.125 in. column packed with 10% Carbowax 20M on Anakrom ABS 60–70 mesh at the following conditions [T_I, T_C, T_D (°C)]: **2**, 250, 170, 260; **3**, 200, 120, 260; **4**, 250, 200, 260; and **5**, 200, 100, 260, and 30 cc/min of nitrogen. A homogeneous chromatogram was observed under the highest temperatures for all the dimethyluracil standard solutions [0.5 wt % in methanol and relative retention times (min) for **2**, **3**, **4**, and **5** are 10.0, 2.5, 18.0, and 1.0, respectively], except **4** showed a 7% rearrangement to **2**, and the yield of the latter in a methylation reaction was corrected accordingly. Under the various combination temperatures cited above, the methoxypyrimidones **8** and **9** were either retained or decomposed on the column. At the high temperature end, minor peaks identifiable as *N*-methyl- and dimethyluracils were seen whose areas accounted for <1% of the methoxypyrimidone injected.[14] The glpc properties of the methylthymines resemble those of the corresponding uracils and were analyzed in a similar manner. The results of the diazomethane reactions are summarized in Table I.

2-Methoxy-3-methyl-4-pyrimidone (3).—A mixture of 0.2 g (1.6 mmol) of 2-methoxy-4-pyrimidone (**8**)[13] in 5 ml of methanol was stirred with 30 ml (3.5 mmol) of ethereal diazomethane until the evolution of nitrogen had ceased. The solution was concentrated and chromatographed on a 9-g silica gel column with 25% ethyl acetate in chloroform as eluents, yielding 0.12 g (54%) of **3**. Recrystallization from anhydrous ether and sublimation (50°, 20 mm) gave a pure sample: mp 93–95°; uv $\lambda_{max}^{H_2O}$ 269 nm (ϵ 6130), 213 (4340) at pH 7.4; ir (KBr) 1635 cm^{-1} (C=O); nmr ($CDCl_3$) δ 3.42 (s, 3), 4.03 (s, 3), 6.17 (d, 1, J = 6 Hz), and 7.65 (d, 1, J = 6 Hz).

Anal. Calcd for $C_6H_8N_2O_2$: C, 51.42; H, 5.75; N, 19.99. Found: C, 51.31; H, 5.81; N, 20.20.

3,5-Dimethyl-2-methoxy-4-pyrimidone (3a).—A mixture of 0.35 g (2.5 mmol) of 2-methoxy-5-methyl-4-pyrimidone[13] in 5 ml of methanol and 60 ml (7 mmol) of ethereal diazomethane was allowed to react, and the product was isolated as described for the preparation of **3**. Compound **3a**, 0.13 g (34%), was recrystallized from anhydrous ether and sublimed (50°, 20 mm): mp 106–108°; uv $\lambda_{max}^{H_2O}$ 272 nm (ϵ 6280), 217 (4630) at pH 7.4; ir (KBr) 1635 cm^{-1} (C=O); nmr ($CDCl_3$) δ 2.00 (d, 3, J = 1 Hz), 3.43 (s, 3), 4.00 (s, 3), 7.53 (q, 1, J = 1 Hz).

Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.54; H, 6.54; N, 18.17. Found: C, 54.54; H, 6.74; N, 18.41.

Registry No.—**1**, 66-22-8; **1a**, 65-71-4; **3**, 27460-04-4; **3a**, 27460-05-5; **6**, 608-34-4; **7**, 615-77-0; **8**, 25902-86-7; **9**, 18002-25-0; diazomethane, 334-88-3.

(12) R. Gompper, *Advan. Heterocycl. Chem.*, **2**, 245 (1962).

(13) Part I: J. L. Wong and D. S. Fuchs, *J. Org. Chem.*, **35**, 3786 (1970).

(14) Pyrolysis of 4-methoxy-2-pyrimidone (**9**), 2 mg at 210–220° for 40 min in an evacuated tube, caused complete conversion to the following products identified by glpc and tlc: **1**, **2**, **4**, **5**, **6**, and **7**. Similar treatment of the 2-methoxy analog **8** yielded all of the above products plus **3**. In both cases, uracil (**1**) and the *N*-methyluracils **6** and **7** were the major products. For a reference to thermal-induced methyl migration of monomethoxypyrimidines, see D. J. Brown and T. C. Lee, *J. Chem. Soc. C*, 214 (1970), and refer to ref 13 for thermal and catalyzed isomerization of 2,4-dialkoxypyrimidines.

Evaluation of Acyloxysilane as an Acylating Agent for Peptide Synthesis

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Received August 17, 1970

Few synthetic reactions have received more attention in recent years than that of the formation of the peptide linkage.[1] Many newer methods involving the use of ingeniously designed coupling reagents have been discovered.[2-4] Recently, in our laboratory, we found that[5] silicon tetrachloride can act as a simple and efficient coupling reagent for the formation of amide from carboxylic acid and amine according to eq 1. Because of the ready availability of silicon tetrachloride and its apparent efficacy in mediating the formation of the amide bond, we have extended our investigation to the use of silicon tetrachloride as a coupling reagent for peptide synthesis.

$$2RCO_2H + 2R'NH_2 + SiCl_4 \xrightarrow{\text{pyridine}} 2RCONHR' + (SiO_2)_n + 4HCl \quad (1)$$

Preliminary experiments indicated that the condensation between an N-protected amino acid and an amino ester with silicon tetrachloride did not yield the desired depeptide. While the N-protected amino acid could be recovered essentially quantitatively from the reaction mixture, the starting amino ester was converted into a polymeric material. Apparently, under the reaction conditions, a facile polymerization of the amino ester occurred. Similar observation was made by Birkofer[6] who found that polyglycine was obtained from the reaction of ethyl glycinate with silicon tetrachloride (reaction 2). Our task was therefore to minimize this side reaction.

$$n\text{-}NH_2CH_2CO_2C_2H_5 + (n/4)SiCl_4 \longrightarrow (\text{—}NHCH_2CO\text{—})_n + (n/4)Si(OC_2H_5)_4 \quad (2)$$

Results

Preliminary Studies.—Pertinent to the problem at hand are the following observations. Trimethylace-

(1) For a summary of reagents for peptide formation, see M. Bodanszky and M. A. Ondetti, "Peptide Synthesis," Interscience, New York, N. Y., 1966.

(2) B. Belleau and G. Malek, *J. Amer. Chem. Soc.*, **90**, 1651 (1968).

(3) T. Mukaiyama, M. Veki, R. Matsueda, and H. Maruyama, *ibid.*, **91**, 1554 (1969).

(4) G. Gawne, G. W. Kenner, and R. C. Sheppard, *ibid.*, **91**, 5669 (1969).

(5) T. H. Chan and L. T. L. Wong, *J. Org. Chem.*, **34**, 2766 (1969).

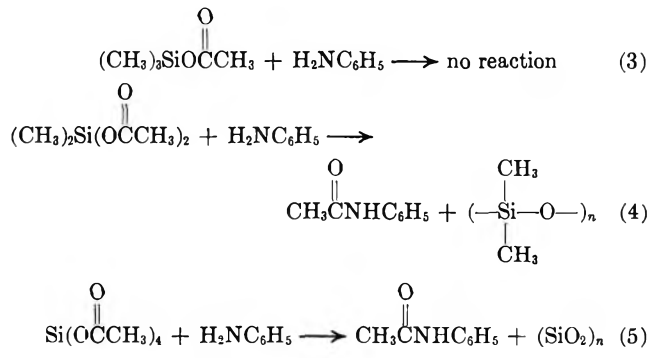
(6) L. Birkofer and A. Ritter, *Justus Liebigs Ann. Chem.*, **612**, 22 (1958).

TABLE I
PREPARATION OF DIPEPTIDES BY SILICON TETRACHLORIDE

Acid	Amine	Registry no.	Dipeptide	Conditions of tetraacyloxysilane formation	Yield, %
Phth-gly	L-leu-OMe	27462-45-9	Phth-gly-leu-OMe[a]	110°, pyridine, 30 min	48
Phth-gly	gly-OEt	2641-02-3	Phth-gly-gly-OEt	110°, pyridine, 30 min	45
Phth-DL-ala	DL-ala-OEt	27519-54-6	Phth-DL-ala-DL-ala-OEt	110°, pyridine, 2 hr	51
Bz-DL-ala	DL-ala-OEt	27462-46-0	Bz-DL-ala-DL-ala-OEt	110°, pyridine, 1 hr	58
Bz-L-leu	gly-OEt	4905-35-5	Bz-leu-gly-OEt[b]	110°, pyridine, 45 min	65
Bz-L-leu	gly-OEt		Bz-leu-gly-OEt[b]	Na salt, acetonitrile–benzene	62
Ac-DL-phe	DL-ala-OEt	27462-48-2	Ac-DL-phe-DL-ala-OEt	110°, pyridine, 1 hr	60
Ac-L-phe	L-ala-OMe	27462-49-3	Ac-phe-ala-OMe[c]	110°, pyridine, 1 hr	43
Z-gly	gly-OEt	3005-87-6	Z-gly-gly-OEt	60°, pyridine, 1.25 hr	70
Z-gly	DL-ala-OEt	4066-23-3	Z-gly-DL-ala-OEt	60°, pyridine, 1.25 hr	54
Z-DL-ala	gly-OEt	4905-31-1	Z-DL-ala-gly-OEt	60°, pyridine, 1.25 hr	15

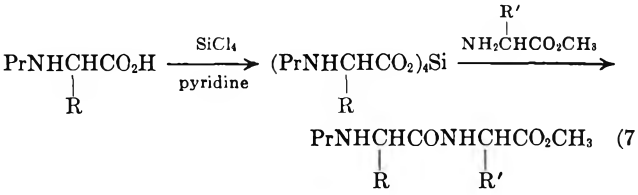
[a] $[\alpha]^{20}D$ +5.9° (c 3.6, $CHCl_3$). [b] Completely racemic product was obtained. [c] 40% DL isomer according to nmr.

toxysilane was found not to react with aniline to any significant extent, whereas dimethyldiacetoxysilane, under identical conditions (reflux benzene), reacted with aniline to give acetanilide in moderate yield (reaction 4). Tetraacetoxysilane reacted exothermically at room temperature with aniline to give acetanilide in excellent yield (reaction 5). This observation is contrary to that of Mehrotra[7] who reported that the reaction of acyloxysilane with aniline was substitution to give anilinosilane. While the origin of this difference is not clear to us, our observation does suggest that tetraacyloxysilane is a reasonable intermediate in the amide formation process (reaction 6). The first step of



this pathway, substitution of chloro group by acyloxy group at silicon, is well documented.[8] Furthermore, it may be concluded that the amines can be added subsequently to the formation of the tetraacyloxysilane, and therefore the problem of polymerization of the amino ester (reaction 2) can be circumvented in this way.

Dipeptide Synthesis.—Appropriately N-protected amino acids were converted to their tetraacyloxysilanes by either (1) heating 4 mol of the amino acid with 1 mol of silicon tetrachloride in pyridine for 30 min to 2 hr, or (2) refluxing 4 mol of the sodium salt of the amino acid with 1 mol of silicon tetrachloride in acetonitrile–benzene mixture for 2 hr. The resultant tetraacyloxysilane was not isolated and was allowed to react *in situ* immediately. To the reaction mixture, the amino ester was added and the mixture was stirred at room temperature overnight. The solvent was evaporated *in vacuo* and the residue was decomposed with water. The organic material was extracted with ethyl acetate. The ethyl acetate solution, after washing with aqueous acid and alkaline solution, was evaporated to yield the crystalline dipeptide. The yields were moderate (Table I); however, there was no effort to optimize the conditions. In this way, a number of phthaloyl- (Phth), benzoyl- (Bz), and acetyl- (Ac) amino acids were condensed with various methyl or ethyl amino esters (reaction 7). The use of benzyloxycarbonyl (Z) as N-protecting group offered considerable difficulties. While Z-gly reacted with amino esters to give the corresponding dipeptides in reasonable yields, other Z-amino acids (*e.g.*, Z-ala, Z-leu) gave only poor yield of dipeptides. Further investigations showed that in the condensation of Z-ala with silicon tetrachloride extensive cleavage of the protecting group took place. One identifiable product was found to be tetrabenzyloxysilane (60% yield based on Z-ala). While the mode of formation of this compound is far from clear, it is likely that Z-amino acids upon heating decompose to give the Leuchs' anhydride and benzyl alcohol,[9] and the latter compound is known to react with silicon tetrachloride to give tetrabenzyloxysilane.[10]



Racemization Studies.—The extent of racemization during peptide synthesis by this method has also been examined. Recently, Halpern, *et al.*, proposed[11] the use of nmr method for the detection of racemization in the coupling of Ac-L-phe with L-ala-OMe. The chemical shifts of the CMe and the OMe are different for the LL and the DL diastereomers. The relative intensities of the nmr signals therefore reflect the degree of racemization. Using this method, the Ac-phe-L-ala-OMe obtained in Table I was found to contain 40 ± 2% of the DL diastereomer. This may be compared with the 50% DL in the product by using dicyclohexylcarbodiimide as the coupling reagent to a low 6% for the Woodward's reagent K.[11]

(7) R. C. Mehrotra, *Pure Appl. Chem.*, **13**, 111 (1966).
(8) A. G. Brook, *J. Amer. Chem. Soc.*, **77**, 4827 (1955).
(9) See J. P. Greenstein and M. Winitz, "The Chemistry of the Amino Acids," Vol. 2, Wiley, New York, N. Y., 1961, p 862.
(10) I. Joffe and H. W. Post, *J. Org. Chem.*, **14**, 421 (1949).
(11) B. Halpern, L. Chew, and B. Weinstein, *J. Amer. Chem. Soc.*, **89**, 5051 (1967).

Using the supersensitive Young's test,[12] the present method of peptide synthesis gave essentially racemic Bz-leu-gly-OEt, $[\alpha]^{20}D < 1°$. This, in comparison with other coupling methods (Table II) places the present

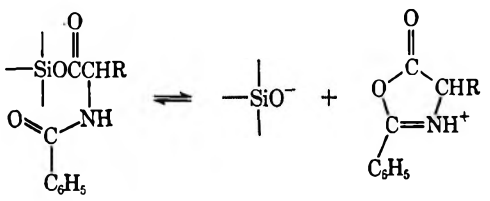
TABLE II
RACEMIZATION STUDIES BY YOUNG'S TEST

Bz-L-leu + gly-OEt ⟶ Bz-leu-gly-OEt

Method	$[\alpha]D$	L isomer, %, in excess of D isomer
Dicyclohexylcarbodiimide (NEt_3)	−5.5	16
N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline	−33.5	99[a]
Phenylisoxazolium (NEt_3), MeCN	−32.8	96
Silicon tetrachloride	<−0.4	1
Phosphorus trichloride	−0.6	2

[a] Reference 2, a result also confirmed by us.

method in an untenable position. The extensive racemization cannot be due to the presence of pyridine because, using the sodium salt of Bz-L-leu for the preparation of tetraacyloxysilane in acetonitrile–benzene, a racemic compound was also obtained. The mode of racemization is most likely due to the intervention of azalactone as an intermediate. We were indeed able to isolate 4-isobutyl-2-phenyloxazolone from the reaction mixture prior to the addition of gly-OEt. The oxazolone was found to be optically inactive. The following equilibrium may serve as the racemization mechanism.



Conclusion

The data presented in this work allows us to conclude that, while the present method can be used for peptide synthesis, the fact that the Z-protecting group shows instability under the reaction conditions and also the extensive degree of racemization during peptide synthesis renders this method not a valuable one. It may offer some advantages in the coupling of phthaloylamino acids in that silicon tetrachloride is relatively inexpensive and the reaction is generally clean and free of contamination with side products.

Experimental Section[13]

Reaction of Aniline with Acetoxysilanes. A. Trimethylacetoxysilane.—To 5 g of trimethylacetoxysilane in 20 ml of benzene was added 7.2 g of aniline. The solvent was refluxed for 3 hr and then fractionated to give back 4.5 g of acetoxysilane, 6.6 g of aniline, and a residue containing <0.5 g of acetanilide (5% based on aniline used), mp 110–112°.

B. Dimethyldiacetoxysilane.—To 3.4 g of dimethyldiacetoxysilane in 20 ml of benzene was added 3.6 g of aniline. The solution was refluxed for 2 hr. The solvent was evaporated and the residue was hydrolyzed with water and extracted with ethyl acetate. The extract, after washing with diluted acid and base, gave on evaporation 1.4 g (54%) of acetanilide.

C. Tetraacetoxysilane.—To a solution of 2.0 g of tetraacetoxysilane[14] in 20 ml of dry pyridine, 1.4 g of aniline was added slowly. The solution was left stirring overnight at room temperature. It was poured into ice–water and the aqueous filtrate was evaporated to give, on recrystallization, 1.7 g (84%) of acetanilide.

Examples of Dipeptide Synthesis. Phthaloylglycylglycine Ethyl Ester.—To a solution of 2.43 g of phthaloylglycine in 20 ml of pyridine, a solution of 0.5 g of silicon tetrachloride in 5 ml of benzene was added slowly with stirring. The mixture was heated at 110° for 30 min. To the cooled mixture, 0.61 g of ethyl glycinate was added and the mixture was stirred overnight at room temperature. The mixture was then evaporated under vacuum at 50° and the residue was hydrolyzed with water and extracted with ethyl acetate. The organic phase was washed with dilute hydrochloric acid, water, dilute sodium bicarbonate solution, and then water, The organic solution was dried and evaporated to give 0.76 g (45%) of product which on recrystallization from ethyl acetate–*n*-hexane gave a colorless solid, mp 193–195° (lit. mp 194–195°).

Acetyl-DL-phenylalanyl-DL-alanine Ethyl Ester.—To a solution of 2.5 g of acetyl-DL-phenylalanine in 20 ml of pyridine was added 0.5 g of silicon tetrachloride in 5 ml of benzene. The mixture was heated at 110° for 1 hr and cooled to room temperature. DL-Alanine ethyl ester (0.70 g) was added and the mixture was left stirring overnight. On working up, the mixture gave 1.1 g (60%) of acetyl-DL-phenylalanyl-DL-alanine ethyl ester, mp 186–188°.

Benzyloxycarbonylglycyl-DL-alanine Ethyl Ester.—To a solution of 2.5 g of benzyloxycarbonylglycine in 20 ml of pyridine heated at 60° was added 0.5 g of silicon tetrachloride in 10 ml of benzene over 40 min. The mixture was kept at about 60° for 0.5 hr and then cooled to room temperature. DL-Alanine ethyl ester (0.70 g) was added and the mixture was stirred overnight. On working up, the mixture gave 1.0 g of product, mp 52–54° (lit. mp 53–55°).

Isolation of Tetrabenzyloxysilane from the Reaction of Benzyloxycarbonylalanine with Silicon Tetrachloride.—To a solution of 1.32 g of benzyloxycarbonyl-DL-alanine in 10 ml of pyridine was added 0.25 g of silicon tetrachloride and the mixture heated at 110° for 2 hr. After cooling, the pyridine was distilled and the residue was chromatographed on column (silica gel) with benzene. The first product collected was identified by comparison with authentic sample to be tetrabenzyloxysilane (0.41 g, 60%).

Racemization Studies. A. Nmr Method, Acetylphenylalanylalanine Methyl Ester.—To a solution of 2.5 g of acetyl-L-phenylalanine in 20 ml of pyridine was added 0.5 g of silicon tetrachloride in 10 ml of benzene. The mixture was heated at 110° for 1 hr and cooled to room temperature. L-Alanine methyl ester hydrochloride (0.83 g) was added to the mixture and this was followed by 0.60 g of triethylamine. The mixture was left overnight. After the pyridine was removed *in vacuo*, the residue was hydrolyzed with a little water and extracted with ethyl acetate. The organic phase, after washing with dilute acid and base, was dried and evaporated to give 0.75 g of solid residue. Its nmr spectrum ($CDCl_3$) showed the methyl resonance as two overlapping doublets at 81 and 73 Hz downfield from TMS and relative intensities of 60:40.

B. Young's test. Benzoylleucylglycine Ethyl Ester.—To a solution of benzoyl-L-leucine (2.61 g) in 20 ml of pyridine, was added 0.47 g of silicon tetrachloride in 5 ml of ether. The mixture was heated at 100° for 45 min and cooled to room temperature. A solution of 0.575 g of ethyl glycinate in 1 ml of ether was added and the solution was stirred overnight. The mixture on working up gave 1.16 g of white solid, mp 137–145°, $[\alpha]^{17}D$ −0.5° (c 3.01, ethanol).

C. Isolation of 4-Isobutyl-2-phenyloxazolone.—To a solution of 2.78 g of benzoyl-L-leucine in 30 ml of acetonitrile was added 0.58 g of sodium hydride (53.7% in paraffin). The mixture was stirred for 1 hr. To the mixture was added 20 ml of acetonitrile and 15 ml of benzene and then 0.5 g of silicon tetrachloride in 5 ml of benzene. The mixture was heated at reflux for 2 hr and cooled to room temperature. The solvent was evaporated *in vacuo* to give a residue which was triturated with *n*-hexane. The hexane solution on evaporation gave a crystalline solid, mp 40–45°. It weighed 0.29 g (11%) and showed in ir (Nujol) ν_{max} at 1830

(12) M. Williams and G. Young, *J. Chem. Soc.*, 881 (1963).
(13) Melting points are not corrected.
(14) S. Dandegaonker, *J. Karnatak Univ.*, **7**, 95 (1964).

and 1665 cm^{-1}. It showed no optical activity, $[\alpha]^{18}D$ 0° (*c* 2.0, ethanol).

Registry No.—Silicon tetrachloride, 10026-04-7; trimethylacetoxysilane, 2754-27-0; dimethyldiacetoxysilane, 2182-66-3; tetraacetoxysilane, 562-90-3; 4-isobutyl-2-phenyloxazolone, 27460-46-4.

Some Observations on the Mechanism of a Modified Knorr Pyrrole Condensation[1a]

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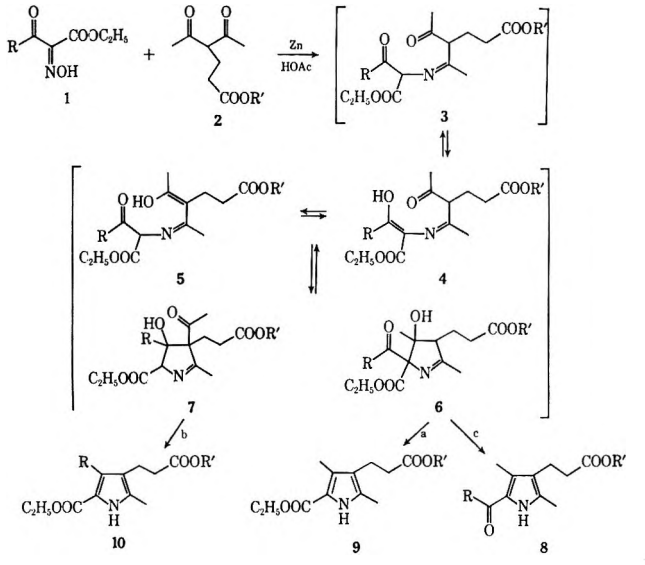
In preparing some pyrrolic intermediates for porphyrin synthesis *via* a modified Knorr condensation, contamination of the pyrrole by initially unidentified side products led us to a study of the effect of the structure of the β-keto ester on the mechanism of this reaction. It seemed conceivable that, in light of Scheme I, three

SCHEME I



pyrrolic products (**8**, **9**, and **10**) could be obtained. The postition of equilibrium between enols **4** and **5** and the relative rates of nucleophilic attack on the acyl groups of **6** and **7** are the factors which must be considered in deciding which pyrrole will predominate.

An earlier investigation of this condensation[2] showed that, when ethyl 4-acetyl-5-oxohexanoate (**2**, R′ = C_2H_5) was condensed with the oximino derivative of diethyl 3-oxoglutarate (**1**, R = CH_2COOEt), pyrrole **9** (R′ = C_2H_5) was isolated in 16.5% yield. Also, 3-methyl-2,4-pentanedione condensed with diethyl 2-oximino-3-oxoadipate (**1**, R = CH_2CH_2COOEt) to give 40% of the analogous structure, 2-carbethoxy-3,4,5-trimethylpyrrole. Since such a large percentage of starting materials remained unaccounted for, participation of path b was still a very real possibility, hence our investigation of the problem.

All of our condensations were carried out under standardized conditions (not optimized for maximum yields), and used the same β-diketone, namely, methyl 4-acetyl-5-oxohexanoate (**2**, R′ = CH_3); only the β-keto ester was varied. Ethyl acetoacetate-3-^{14}C, our first choice, afforded several advantages. First, there are no steric or electronic differences between the acyl groups that must be lost from **6** and **7**. Second, both **9** and **10** become structurally identical, eliminating any separation problem. Third, the fact that **10** is radioactively labeled permits a quantitative determination of the two potential pathways.

Labeled acetoacetic esters were converted to their oximino derivatives and condensed with an equimolar amount of **2** (R′ = CH_3). The pyrroles were isolated and purified, and their specific activities were compared to those of the starting β-keto esters. The results obtained in two experiments with the ethyl ester and one with the benzyl ester indicate that a is the major pathway for pyrrole formation (Table I).

TABLE I
CONDENSATION OF METHYL 4-ACETYL-5-OXOHEXANOATE (2) AND LABELED 2-OXIMINO-β-KETO ESTERS

β-Keto ester	Specific activity, dpm/mm: β-Keto ester	Specific activity, dpm/mm: Pyrrole	% path b	% yield of pyrrole (9 + 10)
Ethyl 2-oximinoacetoacetate-3-^{14}C, expt 1	39,960	470	1.2	45
Ethyl 2-oximinoacetoacetate-3-^{14}C, expt 2	27,890	440	1.6	37
Benzyl 2-oximinoacetoacetate-3-^{14}C	51,370	640	1.2	34

The mother liquors from the condensation with benzyl acetoacetate were then inspected for evidence of the presence of pyrrole **8** (R, R′ = CH_3) resulting from path c. Preparative tlc afforded a small amount of material identified as **8** by its uv absorption ($\lambda_{max}^{CH_3OH}$ 305 nm) and mass spectrum [*m/e* 223 (M^+, 56), 180 (5), 150 (100), 43 (48)], identical with an authentic sample prepared from 3,5-dimethyl-4-(β-carbomethoxyethyl)-2-carbethoxypyrrole by hydrolysis, decarboxylation, acetylation, and reesterification. However, its contribution was estimated to be much less than 1% of the total pyrrolic product.

The small contribution of path c in the reaction is understandable, since nucleophilic attack on **6** would prefer the more polar acetyl carbonyl. The difference between paths a and b is more complicated. In the enolic mechanism we have invoked, enol **4**, having the extended conjugation of the ester carbonyl, could be expected to predominate. In addition, molecular models show the acetyl group of **6** to present slightly less hindrance to attack. Both of these considerations favor path a, and this prediction is borne out experimentally.

Our next objective was to investigate the results of changing the steric and electronic situation by varying R in the starting β-keto ester. In this case, since two chemically different pyrroles were to be produced, evi-

(1) (a) Supported in part by Grant AI-04888 from the National Institutes of Health, U. S. Public Health Service; (b) National Institutes of Health Predoctoral Fellow.

(2) E. Bullock, A. W. Johnson, E. Markham, and K. B. Shaw, *J. Chem. Soc.*, 1430 (1958). In this paper it is recognized for the first time that use of a 3-alkyl-2,4-pentanedione, rather than acetylacetone itself, with the oximino-3-keto ester **1** causes the condensation to take a completely different course. The former gives a 2,4-dimethylpyrrole analogous to **9**, while the latter gives the normal Knorr product, 4-acetyl-2-carbethoxy-3,5-dimethylpyrrole.

dence for the presence of **10** was sought by direct mass spectral analysis of the crude pyrrolic product.

The investigation to test steric factors used the oximino derivative of ethyl pivaloylacetate [**1**, R = $C(CH_3)_3$] and β-diketone **2** (R′ = CH_3). Since the crude pyrrole, obtained in 46% yield, did not give peaks at *m/e* 295 (M^+), 280 ($M^+ - CH_3$), 222 ($M^+ - CH_2COOCH_3$), or 237 ($M^+ - CH_3 - CH_2COOCH_3$) even at high sensitivity, we concluded that path b (to form **10**) plays no role in this condensation.

If R should be an electron-donating moiety, it is possible that nucleophilic attack on the acyl group in **6** might be disfavored to a degree that appreciable reaction would proceed *via* path b, and **10** could be formed. To test this hypothesis, β-diketone **2** (R′ = CH_3) was condensed with the oximino derivative of ethyl anisoylacetate (**1**, R = *p*-$CH_3OC_6H_4$), giving a 40% yield of pyrrole. Through differential volatility, a mass spectrum of **10** (R = *p*-$CH_3OC_6H_4$, R′ = CH_3) was obtained: *m/e* 346 (7), 345 (M^+, 18), 300 (3), 299 (3), 276 (6), 226 (76), 198 (27), 135 (100). Preparative tlc afforded one band that contained pyrroles **9** (R′ = CH_3) and **10** (R = *p*-$CH_3OC_6H_4$, R′ = CH_3), based on mass spectral evidence; however, gas chromatography indicated that **10** was present in this fraction only in very minute amounts.

Apparently path b plays an increasing (although very small) part in the reaction as one varies R from $C(CH_3)_3$ through *p*-$CH_3OC_6H_4$ to CH_3. Molecular models show little steric difference between **4** and **5**, but there is slightly less steric hindrance to nucleophilic attack on the acyl group of **6** than on that of **7**. The increase in overall crowding with the bulkier R groups is reflected in lower yields of pyrrole and may accentuate differences between **6** and **7**, so that path b plays a smaller part than when R = CH_3. The electron-releasing properties of the anisyl group may hinder its irreversible loss as anisate from **6** enough so that path b is able to drain off some product as pyrrole **10**.

It appears that the major factor in determining which path will predominate is the enol distribution of the uncyclized intermediates **4** and **5**; the added stabilization that would accrue to **4** from the carbethoxy group should ensure its great predominance over **5** and hence would favor path a.

There has been a recent report[3] that modified Knorr condensation of **1** (R = CH_3) with 3-formyl-2-butanone gives two products: the expected (path a) 2,3-dimethyl-5-carbethoxypyrrole and also 2,3,4-trimethyl-5-carbethoxypyrrole resulting from path b. The 1,3-dicarbonyl system is certainly different from ours, but nonetheless it points to the reality of path b and indicates that proper choice of reactants could make it synthetically useful.

Experimental Section[4]

Methyl 4-Acetyl-5-oxohexanoate (**2**, R′ = CH_3).—Condensation of acetylacetone with methyl acrylate (2:1) using 1 mol of sodium ethoxide gave a 55–62% yield, but the product was contaminated with a small amount of the ethyl ester. Two procedures by Connor and McClellan[5] were tested: equimolar amounts of the above substrates were treated with 0.2 equiv of piperidine in one case, and 0.2 equiv of methoxide in the other. The latter gave 49% of the desired product, distilled through a 3-ft spinning-band column: bp 117–121° (5 mm) [lit.[6] bp 136.5° (11 mm)]; nmr (CCl_4) δ 2.12 (s), 3.61 (s), 2.4 (m).

Ethyl Pivaloylacetate.—This material was prepared according to the generalized procedure of Swamer and Hauser:[7] bp 83–85° (15 mm) [lit.[7] bp 96–100° (15 mm)]; nmr (CCl_4) δ 1.14 (s), 1.25 (t), 3.39 (s), 4.11 (q), 4.94 (s), 12.35 (s).

Ethyl Anisoylacetate.—The procedure used was similar to that of Wahl and Silberzweig.[8] Ethyl anisate (90.6 g, 0.50 mol) was heated at 140° while 15 g (0.65 g-atom, 30% excess) of sodium wire and 65.7 g (0.75 mol, 50% excess) of ethyl acetate (distilled from P_2O_5) were added in bits and drips, respectively, fresh sodium not being added until the previous had almost completely reacted. Addition was complete in 12 hr and the thick reddish-brown mixture was stirred at 115° for 2 days and then poured into 54 ml of concentrated HCl diluted with ice and water. The product was extracted into ether and washed with aqueous bicarbonate and water, the ether extracts were dried, and the ether was evaporated. *In vacuo* with the bath temperature below 130°, ethyl acetoacetate and ethyl anisate were distilled. The 100-ml residue was dissolved in ether, and the ether was washed with sodium carbonate solution and water and then dried. The residue obtained after evaporating the ether was vigorously shaken with saturated aqueous cupric acetate, adding aqueous potassium carbonate dropwise to neutralize the acetic acid produced. When the aqueous phase remained blue, it was removed from the dark green oil, and the green copper chelate was precipitated from the aqueous solution by adding ethanol, filtering, and washing with ethanol. Vacuum evaporation of the mother liquor and treatment again with cupric acetate gave a second crop of chelate, total yield 23.7 g (19%).

The β-keto ester was liberated by dissolving 9.5 g of the copper salt in 30 ml of glacial acetic acid, partitioning between ether and water, and washing the ether layer with saturated $NaHCO_3$ solution and water. After drying and removing the ether, the residue was distilled on a molecular still (0.06 mm, bath temperature 95°) to give the desired β-keto ester in 13% yield based on ethyl anisate added: nmr (CCl_4) δ 1.17 (t), 3.74 (s), 3.82 (s), 4.10 (q), 5.51 (s), 6.81 (d), 7.79 (d), 12.71 (s).

General Condensation Procedure.[9]—Into a 100-ml three-necked flask fitted with a dropping funnel and reflux condenser with nitrogen bubbler was introduced 75 mmol of the β-keto ester in 30 ml of glacial acetic acid. The contents were stirred and cooled in an ice bath as a solution of 5.90 g (86 mmol) of sodium nitrite in 20 ml of H_2O was added over 35 min. The mixture was stirred and cooled another 2 hr and then allowed to stand overnight.

To a 250-ml three-necked flask equipped as above was added 14.00 g (75 mmol) of methyl 4-acetyl-5-oxohexanoate in 35 ml of glacial acetic acid. The internal temperature was maintained at 65–80° while the previously prepared oxime solution was added over 1 hr 20 min, along with 12 g each of zinc dust and anhydrous sodium acetate in small portions. The mixture was stirred an additional 10 min and poured onto 400 g of ice. The precipitate was collected and dissolved in benzene, unreacted zinc was removed, and the benzene solution was evaporated to dryness.

The labeled pyrroles were recrystallized from methanol, benzene–hexane, and carbon tetrachloride, and then the specific activities were determined. The other pyrroles were dissolved in ether and washed with aqueous sodium carbonate, and the residue after evaporation was analyzed directly by mass spectroscopy.

2,4-Dimethyl-3-(β-carbomethoxyethyl)-5-carbethoxypyrrole: mp 103–104° (lit.[10] mp 104°); nmr ($CHCl_3$) δ 1.34 (t), 2.22 (s), 2.28 (s), 2.57 (m), 3.67 (s), 4.29 (q); $\nu_{max}^{CHCl_3}$ 1685, 1710, 1745 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 281 nm.

(3) M. W. Roomi and S. F. MacDonald, *Can. J. Chem.*, **48**, 1689 (1970).

(4) Specific activities were determined on a Nuclear Chicago Mark I scintillation counter; all samples were counted for at least 200 min. Mass spectra were determined by direct inlet on a Varian M-66 and on a Consolidated Electrodynamics Corp. Type 21, 103-C, instrument. Nmr spectra were measured on Varian A-60 and T-60 spectrometers. Gas chromatography was accomplished with an Aerograph A-700 instrument using a 2-ft 10% QF-1 on Chromosorb W column at 183°. Preparative tlc was done on a 1000-μ layer of Kieselgel D-5.

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(8) A. Wahl and C. Silberzweig, *Bull. Soc. Chim. Fr.*, **12**, 25 (1912).

(9) A. H. Jackson, G. W. Kenner, and G. S. Sach, *J. Chem. Soc. C*, 2045 (1967).

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2,4-Dimethyl-3-(β-carbomethoxyethyl)-5-carbobenzoxypyrrole: mp 99–100° (lit.[11] mp 99–100°); nmr (CCl_4) δ 2.15 (s), 2.25 (s), 2.48 (m), 3.56 (s), 5.23 (s), 7.27 (s); $\nu_{max}^{CHCl_3}$ 1680, 1730 cm^{-1}; $\lambda_{max}^{CH_3CH}$ 283 nm.

Registry No.—1 (R = CH_3), 5408-04-8; 1 (R = $C(CH_3)_3$), 27332-07-6; 1 (R = p-$CH_3OC_6H_4$), 27331-97-1; 2 (R′ = CH_3), 13984-53-7; benzyl 2-oximinoacetoacetate, 27331-98-2.

(11) A. Hayes, G. W. Kenner, and N. R. Williams, *J. Chem. Soc.*, 3779 (1958).

Synthesis of *endo*-4-Bromo-6-thiabicyclo[3.2.1]octane and 6-Thiabicyclo[3.2.1]oct-3-ene[1]

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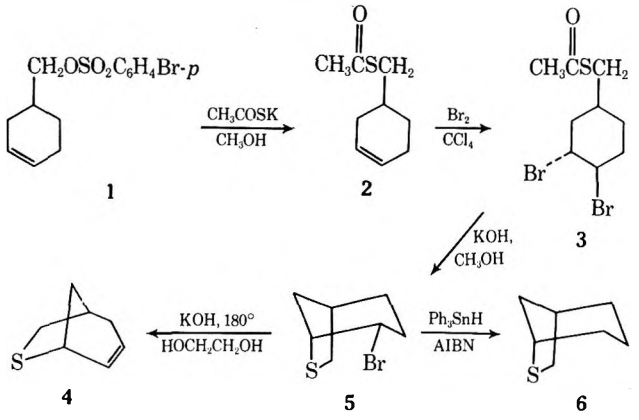
As part of a continuing program of investigation of stereochemical aspects of cyclic and bicyclic sulfur compounds, we have developed syntheses of *endo*-4-bromo-6-thiabicyclo[3.2.1]octane (**5**) and 6-thiabicyclo[3.2.1]-oct-3-ene (**4**). The synthetic sequences beginning with 3-cyclohexenylmethyl *p*-bromobenzenesulfonate (**1**) are summarized in Scheme I. Compound **1** was prepared by the sodium borohydride reduction of 3-cyclohexenecarboxaldehyde, followed by reaction of the alcohol with *p*-bromobenzenesulfonyl chloride in pyridine.

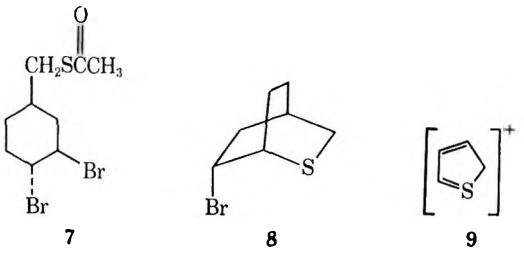
SCHEME I



The critical step in Scheme I was the bromination of the thioacetate **2**. Trans-diaxial bromination[2] could give dibromide **3** and/or **7** depending on relative conformer populations and rates of bromination. Release of the nucleophilic thiolate by treatment of the dibromothioacetate with potassium hydroxide in methanol gave bicyclic bromide **5** in 62% yield. No material which could be identified as bromide **8** was found in the reaction product; either the bromination of **2** gave exclusively **3** or dibromothioacetate **7** failed to cyclize under the reaction conditions.

(1) Part XXVII in the series, "Chemistry of Sulfoxides and Related Compounds." We gratefully acknowledge support by the National Science Foundation (GP 8648).

(2) K. Kozima, K. Sakashita, and S. Maeda, *J. Amer. Chem. Soc.*, **76**, 1965 (1954).



7 8 9

The structure of **5** was established by chemical and physical methods. Treatment of **5** with triphenyltin hydride[3] and azobisisobutyronitrile gave 6-thiabicyclo-[3.2.1]octane (**6**), identical by infrared spectroscopy[4] with that prepared by Birch and coworkers.[5] It was significant to note that the infrared spectrum of **5** was very similar to that of **6** in the 1050–650 cm^{-1} region suggesting that rearrangement did not occur during the reduction step.

The base peak in the mass spectrum of **5** was found at *m/e* 85. We suggest that this peak is indicative of the presence of a five-membered ring[6] and corresponds to ion **9**. The nmr spectrum of **5** revealed an eight-line pattern centered at δ 4.22 with coupling constants of 12, 6, and 2 Hz. This multiplet is assigned to the axial hydrogen at C-4 with the 12-Hz coupling constant due to trans-diaxial coupling.

The dipole moment of **5** in benzene solution was found to be 3.51 D. From models and model compounds the predicted dipole moment of **5** is 3.7 D (chair conformation) or 3.8 D (boat conformation). The isomeric *exo*-4-bromo-6-thiabicyclo[3.2.1]octane would be expected to have a dipole moment of 1.0 D (chair conformation) or 2.8 D (boat conformation).

The bicyclic bromide **5** was significantly unreactive. The common methods for achieving elimination, displacement, and solvolytic reactions on secondary bromides were unsuccessful. The sodium iodide in acetone test was negative after 23 hr at reflux.[7] The bromide **5** was recovered after 2 days in refluxing acetic acid, after 4 days in refluxing *tert*-butyl alcohol containing 10 equiv of potassium *tert*-butoxide, and after attempts to make lithium and Grignard reagents. The lack of success in these and similar reactions can probably be attributed to the close proximity of the sulfur to the departing bromide. SN1, SN2, and elimination reactions all involve a planar or developing planar transition state at C-4. Models of such a transition state reveal severe steric crowding between the departing bromine and the sulfur.

Two reactions of bromide **5** were successful. The first of these, triphenyltin hydride reduction, has been mentioned above. Dehydrobromination to yield 40% of 6-thiabicyclo[3.2.1]oct-3-ene (**4**) was achieved using potassium hydroxide in ethylene glycol at 180° for 18 hr. The nmr of **4** revealed two vinyl hydrogens. One was a broadened doublet centered near δ 5.4. The second was a broadened triplet pattern centered near δ 6.1. The pattern exhibited by these vinyl hydrogens was remarkedly similar to that observed in the vinyl region of

(3) E. J. Kupchik and R. E. Connolly, *J. Org. Chem.*, **26**, 4747 (1961).

(4) API Research Project 44 Catalog, in No. 1861.

(5) S. F. Birch, R. A. Dean, N. J. Hunter, and E. V. Whitehead, *J. Org. Chem.*, **22**, 1590 (1957).

(6) The mass spectra of a number of bicyclic sulfides will be discussed in detail in a future paper.

(7) For another example of a bicyclic sulfur compound which failed to respond to this test see E. D. Weil, K. J. Smith, and R. J. Gniber, *J. Org. Chem.*, **31**, 1669 (1966).

bicyclo[3.2.1]oct-3-en-6-one and numerous other bicyclo[3.2.1]oct-2-ene derivatives. On the other hand, the pattern found in the vinyl region of related bicyclo[2.2.2]octene derivatives was consistently much sharper and more symmetrical.[8]

Experimental Section

3-Cyclohexenylmethyl *p*-Bromobenzenesulfonate (1).—Sodium borohydride reduction of 3-cyclohexenecarboxaldehyde in absolute ethanol gave 3-cyclohexenylcarbinol, bp 64–65° (4.8 mm), n^{25}D 1.4827, in 87% yield. To a solution of 3-cyclohexene-1-carbinol (70 g, 0.625 mol) in 360 ml of anhydrous pyridine at −10° was slowly added 190 g (0.745 mol) of *p*-bromobenzenesulfonyl chloride over a period of 30 min. The reaction mixture was constantly stirred in a methanol–ice bath during addition. The reaction was stirred for 2 hr at −10° after addition was complete, allowed to stand in a refrigerator for 24 hr, and poured directly into a 1-l. ice solution containing 180 ml of concentrated hydrochloric acid. Vigorous stirring produced a white slushy solid. Filtration of the solid, drying over anhydrous magnesium sulfate in methylene chloride, removal of methylene chloride by vacuum distillation, and recrystallization from absolute ethanol at −40 and −78° gave 157 g (0.469 mol, 75%) of 3-cyclohexenylmethyl *p*-bromobenzenesulfonate (1), mp 33–35° (lit.[9] 34.5–35°).

3-Cyclohexenylmethyl Thioacetate (2).—To 400 ml of anhydrous methanol containing 3-cyclohexenylmethyl *p*-bromobenzenesulfonate (80 g, 0.242 mol) was added, with constant stirring at room temperature, 100 ml of anhydrous methanol containing 18.5 ml (0.262 mol) of thioacetic acid and 14.5 g (0.258 mol) of potassium hydroxide. Preparation of the potassium thioacetate solution required a methanolic solution of potassium hydroxide to be added to a cooled methanolic solution of thioacetic acid.

After 24 hr of stirring at room temperature, the reaction was filtered to remove precipitated potassium *p*-bromobenzenesulfonate. Methanol was removed from the filtrate under reduced pressure. To the remaining yellow oil was added 100 ml of water and 200 ml of methylene chloride. The methylene chloride layer was then washed with 100 ml of saturated sodium hydrogen carbonate and finally two 100-ml portions of water. The methylene chloride was then dried over anhydrous magnesium sulfate and evaporated at reduced pressure to give 38.5 g (0.266 mol, 94%) of a clear yellow liquid, bp 62–63° (0.8 mm), n^{25}D 1.5118.

Anal. Calcd for $C_9H_{14}OS$: C, 63.58; H, 8.30. Found: C, 63.57; H, 8.36.

3,4-Dibromocyclohexeneylmethyl Thioacetate (3).—To 40 g (0.235 mol) of 3-cyclohexenylmethyl thioacetate and 200 ml of carbon tetrachloride cooled in an ice bath, in subdued light, was added 38.5 g (0.240 mol) of bromine in small increments, with stirring, over a period of 0.5 hr. After addition, the reaction was kept at 0° for 1 hr. The reaction was then washed with 50 ml of saturated sodium hydrogen sulfite. The carbon tetrachloride solution was dried over anhydrous magnesium sulfate and concentrated at reduced pressure. A 75-g (90%) yield of crude product was obtained, bp 150–155° (0.07 mm), n^{25}D 1.5693. A sample for analysis was obtained by molecular distillation at reduced pressure.

Anal. Calcd for $C_9H_{14}Br_2OS$: C, 32.75; H, 4.28. Found: C, 33.08; H, 4.34.

***endo*-4-Bromo-6-thiabicyclo[3.2.1]octane (5).**—Thirty-five g (0.106 mol) of 3,4-dibromocyclohexylmethyl thioacetate was added to a refluxing solution of 600 ml of methanol containing 15 g (0.268 mol) of potassium hydroxide in a 2-l. flask under nitrogen. After refluxing for 24 hr, an additional 37 g (0.112 mol) of 3,4-dibromocyclohexylmethyl thioacetate in 200 ml of methanol and 100 ml of methylene chloride solution and 17.5 g (0.312 mol) of potassium hydroxide in 100 ml of methanol were added to the refluxing solution. After refluxing for another 24 hr, an additional 15 g (0.265 mol) of potassium hydroxide was added. Twenty hr after the final addition of potassium hydroxide (total reaction time 68 hr), the solvent was removed under reduced pressure. To the crude product was then added 400 ml of methylene chloride. The methylene chloride solution was extracted with two 150-ml portions of water, dried over anhydrous magnesium sulfate, and evaporated under reduced pressure to give a yellow oil. Passing this yellow oil through a column containing 500 g of Woelm's Neutral Alumina with 1% benzene–99% hexane solution gave 2 g of an unknown unsaturated compound. Continued elution with a 10% benzene–90% hexane solution gave 29 g (0.140 mol, 62%) of 5 as a clear liquid, bp 82° (0.09 mm), n^{25}D 1.5762.

Anal. Calcd for $C_7H_{11}BrS$: C, 40.65; H, 5.35. Found: C, 41.02; H, 5.56.

6-Thiabicyclo[3.2.1]octane (6).—*endo*-4-Bromo-6-thiabicyclo[3.2.1]octane (5) (1 mmol, 0.207 g), 0.510 g (1.5 mmol) of triphenyltin hydride, and 5 mg of azobisisobutronitrile were added to a small sublimation apparatus fitted with a drying tube. The reaction mixture was heated at 80° for 24 hr. The cold finger was removed from the sublimator and yielded 20 mg of crystalline compound. The ir[4] of this compound proved to be identical with that of 6-thiabicyclo[3.2.1]octane prepared by Birch and colleagues.[5]

6-Thiabicyclo[3.2.1]oct-3-ene (4).—To 50 ml of ethylene glycol were added 4.14 g (20 mmol) of *endo*-4-bromo-6-thiabicyclo[3.2.1]-octane and 8.95 g (160 mmol) of potassium hydroxide. This solution was heated to 180° and kept between 180 and 190° for 18 hr. After 18 hr the reaction was cooled and 400 ml of water was added. The aqueous solution was extracted with three 100-ml portions of pentane. The pentane extracts were combined and solvent was removed at reduced pressure. About 40 ml of water was added to the residual oil and the aqueous mixture was extracted with 40 ml of pentane. The pentane extract was dried over anhydrous magnesium sulfate. Removal of solvent at reduced pressure gave 1.6 g of a clear yellow oil containing 6-thiabicyclo[3.2.1]oct-3-ene. The material was purified by preparative gas phase chromatography on an SE-30 column. Pure 4 had bp 197–200°, n^{20}D 1.5601.

Anal. Calcd for $C_7H_{10}S$: C, 66.62; H, 7.99. Found: C, 66.67; H, 8.05.

Dipole Moment of *endo*-4-Bromo-6-thiacyclo[3.2.1]octane.—The Dipolemeter DM 01 manufactured by Wissenschaftlich-Technische Werkstatten was used for the measurements. The dipole moments were measured in benzene solution at 25 ± 0.01°. The moments were calculated essentially by the method of Halverstadt and Kumler[10] utilizing an IBM 707 computer programmed as described by Allinger.[11] The dipole moment data are $\alpha = 17.491$, $\beta = 0.986$, $e_1 = 2.2724$, $P_2 = 297.7$, $d = 0.87329$, and $M_D = 45.9360$ giving a dipole moment of 3.510 ± 0.019 D.

The model compounds used for calculation of the predicted dipole moments were cyclohexyl bromide (2.24 D),[12] thiane (1.71 D),[13] thiolane (1.90 D),[13] and cyclohexylmethyl sulfide (1.66 D).[14]

Registry No.—2, 27345-73-9; 3, 27345-75-1; 4, 27345-74-0; 5, 27345-76-2.

(8) We thank Professor N. A. LeBel for providing nmr spectra of these model compounds.

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Condensation–Cyclization Reactions of Electron Deficient Aromatics. II. Stable Bicyclic Immonium Zwitterions from Enamines and *sym*-Trinitrobenzene[1]

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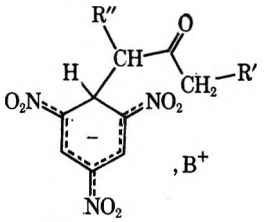
It has been known for quite some time that Meisenheimer complexes[2] like **1** are formed from *sym*-trinitro-

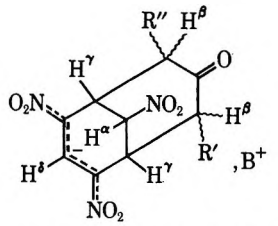
(1) Previous paper: M. J. Strauss, T. C. Jensen, H. Schran, and K. O'Conner, *J. Org. Chem.*, **35**, 383 (1970).

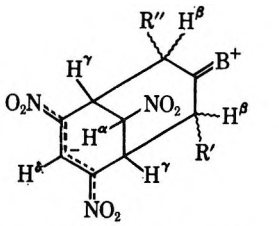
(2) J. Meisenheimer, *Justus Liebigs Ann. Chem.*, **323**, 205 (1902).

benzene (TNB), tertiary amines, and ketones when R′ and R″ are hydrogen or electron donating (*i.e.*, **1a–d**).[3–6] When R′ and/or R″ are electron withdrawing, only propenide complexes like **2** are formed (*i.e.*, **2d–f**)

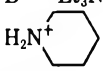


1a, R′ = R″ = H; B⁺ = Et_3NH^+
b, R′ = R″ = CH_3; B⁺ = Et_3NH^+
c, R′ = CH_3; R″ = H; B⁺ = Et_3NH^+
d, R′ = H; R″ = CH_3; B⁺ = Et_3NH^+

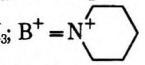




2a, R′ = R″ = CH_3; B⁺ = $Et_2NH_2^+$
b, R′ = R″ = CH_3; B⁺ = H_2N^+
c, R′ = R″ = H; B⁺ = $Et_2NH_2^+$
d, R′ = H; R″ = $COCH_3$; B⁺ = Et_3NH^+, $Et_2NH_2^+$, or

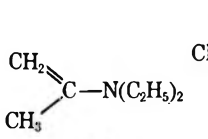


e, R′ = H; R″ = CO_2Et; B⁺ = Et_3NH^+
f, R′ = R″ = CO_2CH_3; B⁺ = Et_3NH^+

3a, R′ = R″ = CH_3; B⁺ = Et_2N^+
b, R′ = R″ = CH_3; B⁺ = 
c, R′ = R″ = H; B⁺ = Et_2N^+

when the amine is secondary or tertiary.[1,7,8] With secondary amines, **2** is also formed when R′ and/or R″ are electron donating, **2a**, **2b**,[9] or hydrogen, **2c**.[1,8,10] We have previously proposed carbanion and immonium intermediates to explain these experimental observations.[1] As a confirmation of our proposal, we report here the addition of enamines to TNB under anhydrous conditions and the isolation of the immonium intermediate **3**.

The enamine **4** was too unstable to be isolated and **3c** could not be prepared. Both **5** and **6** were isolable,



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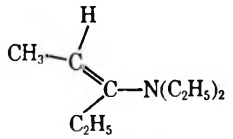

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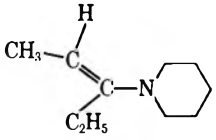
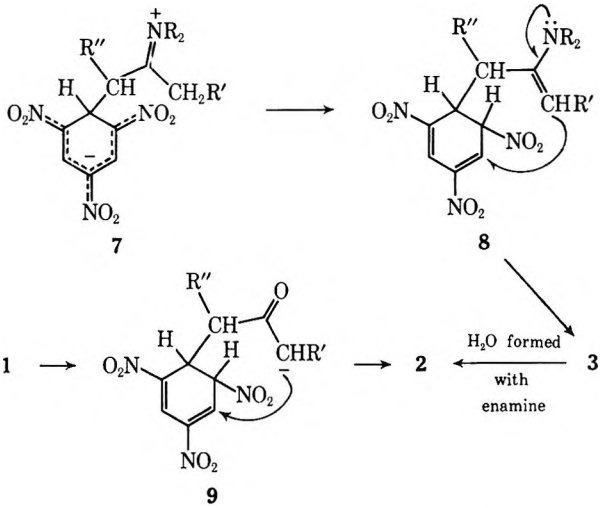


6

however, and addition of either of these to an anhydrous ether solution of TNB yields a red-brown solution. An oily brown precipitate results after several hours, and after work-up and recrystallization of this crude oil (see Experimental Section) bright red crystals of **3a** and **3b** were obtained. The structurally analogous bicyclic anions **2a** and **2b** were obtained from the reaction of diethylamine and piperidine, respectively, with TNB and diethyl ketone. Pertinent comparative spectral data are summarized in the Experimental Section. Each of the structures, **2a**, **2b**, **3a**, and **3b**, could be mixtures of isomers resulting from asymmetry at the carbon α to the keto or immonium functions and at the $CHNO_2$ bridge. Simplicity of the pmr spectra and sharp melting points lead us to conclude that only a single isomer is formed in each case. The stereochemistry of these adducts will be discussed elsewhere.

The visible spectrum of a solution of enamine and TNB in anhydrous acetonitrile exhibits a double maximum characteristic of the trinitrocyclohexadienate function in **1**.[5,6] This spectrum slowly changes to one with a maximum at ~500 nm, characteristic of the dinitropropenide function in **2** and **3**.[1,8] These spectral changes are consistent with the intermediacy of zwitterionic Meisenheimer complexes like **7**. Solutions of TNB in ethyl acetoacetate or acetylacetone have been studied using pmr and visible spectroscopy. The formation of **2d** and **2e** has been observed to occur through structures analogous to **1** when triethylamine or diethylamine is used as the base.[1,11] There is no question of intermediates like **7** or **8** with triethylamine, and the reaction probably occurs through **1** and **9**. The expected low nucleophilicity of enamines obtained from acidic ketones such as acetylacetone and ethyl acetoacetate make intermediates like **1** and **9** more likely, even with secondary amines. Immonium intermediate precursors to **2** arising from secondary amines, TNB, and relatively *nonacidic* ketones would explain the formation



7 **8** **9**

of **2a–c**, however, since with tertiary amines only **1a** and **1b** are isolated. The acidity of the protons α to R′ in **1** or **7** must be great enough so that conversion to the corresponding dienes **9** or **8** is a favorable process. If R′ is electron withdrawing, cyclization may occur through **9** to **2d–f**. If R′ is alkyl or hydrogen and tertiary amines are used, only **1a–d** can be isolated. If secondary amines are used, the formation of **7**, with a formal positive charge on nitrogen, would greatly enhance the acidity of protons α to R′ and facilitate formation of **8**. This latter intermediate could cyclize to **3** which can hydrolyze to **2**. These possibilities are strongly supported by the observation that enamines form rapidly

(3) R. Foster and C. A. Fyfe, *J. Chem. Soc. B*, 53 (1966).
(4) M. I. Foreman, R. Foster, and M. J. Strauss, *ibid.*, 147 (1970).
(5) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966).
(6) M. R. Crampton, *Advan. Phys. Org. Chem.*, **7**, 211 (1969).
(7) R. Foster, M. I. Foreman, and M. J. Strauss, *Tetrahedron Lett.*, **48**, 4949 (1968).
(8) M. I. Foreman, R. Foster, and M. J. Strauss, *J. Chem. Soc. C*, 2112 (1969).
(9) Present work.
(10) M. J. Strauss and H. Schran, *J. Amer. Chem. Soc.*, **91**, 3974 (1969).
(11) M. J. Strauss and H. Schran, unpublished results.

and reversibly in ketonic solutions of secondary amines[12] and readily react with nitro olefins.[13] In addition, careful hydrolysis of isolated **3a** yields **2a**.

Experimental Section

Pmr spectra were determined on a Varian A-60 instrument. Chemical shifts are relative to internal TMS. Visible and infrared spectra were measured on Cary-14 and Perkin-Elmer 21 spectrophotometers, respectively. Elemental analyses were performed by G. I. Robertson, Jr., Florham Park, N. J. 07932. All melting points are uncorrected.

Enamine of Diethylamine and Diethyl Ketone (**5**).—This enamine was prepared by the method of White and Weingarten[14] and was purified by distillation on a spinning-band column at reduced pressure: bp 64° (10 mm); ir 1636 cm^{-1} (NC=C); pmr ($CDCl_3$) δ 4.20 (q, 1, J = 7 Hz, NC=CH, cis). The pmr spectrum of the crude oil prior to distillation showed an additional quartet at δ 5.06 (J = 7 Hz) assigned to NC=CH, trans.

Anal. Calcd for $C_9H_{19}N$: C, 76.53; H, 13.56; N, 9.92. Found: C, 76.80; H, 13.50; N, 10.20.

Enamine of Piperidine and Diethyl Ketone (**6**).—The enamine was prepared by the method of Stork and coworkers[12] and was purified as described for **8**: bp 80° (10 mm); ir 1640 cm^{-1} (NC=C); pmr ($CDCl_3$) δ 4.39 (q, 1, J = 7 Hz, NC=CH, cis). The pmr spectrum of the crude oil prior to distillation showed an additional quartet at δ 4.70 (J = 7 Hz) assigned to NC=CH, trans.

Anal. Calcd for $C_{10}H_{19}N$: C, 78.36; H, 12.50; N, 9.14. Found: C, 78.51; H, 12.60; N, 9.16.

Diethylammonium and Piperidinium Anions (**2a and 2b**).—TNB (5.45 g), diethylamine (5.56 g), and diethyl ketone (6.55 g) were dissolved in dry DMSO (5 ml). The resulting dark oil was stirred for 24 hr at room temperature. Dry ether (500 ml) was then added and the mixture was stirred for 2 hr. The brown precipitate which formed was filtered and washed with copious amounts of dry ether. Recrystallization of this crude product from an 80:20 mixture of ether–methanol yielded red crystals of pure **2a** (0.5 g): mp 175°; vis max (CH_3OH) 508 nm (ϵ 29,500); ir (KBr) 1715 cm^{-1} (C=O); pmr (DMSO-d_6) δ 8.5 (s, H^{δ}), 5.7 (t, J = 3 Hz, H^{α}), 4.6 (broad, 2 H^{γ}), 3.0 (q, 4, J = 7 Hz, $(CH_3CH_2)_2NH_2^+$), ~2.9 (2 H^{β}, under $Et_2NH_2^+$), 1.2 (t, 6, J = 7 Hz, $(CH_3CH_2)_2NH_2^+$), 0.9 (d, 6, J = 7 Hz, R′ = R″ = CH_3).

Anal. Calcd for $C_{15}H_{24}N_4O_7$: C, 48.38; H, 6.50; N, 15.05. Found: C, 48.10; H, 6.49; N, 14.88.

Red crystals of **2b** (0.6 g) were prepared with piperidine in a similar manner: mp 161–163°; vis max (CH_3OH) 508 nm (ϵ 26,200); ir (KBr) 1710 cm^{-1} (C=O); pmr (DMSO-d_6) δ 8.4 (s, H^{δ}), 5.8 (t, J = 3 Hz, H^{α}), 4.5 (broad, 2 H^{γ}), 1.6–3.0 (m, 10, $(CH_2)_5NH^+$), ~2.8 (2 H^{β}, under $(CH_2)_5NH^+$), 0.9 (d, 6, J = 7 Hz, R′ = R″ = CH_3).

Anal. Caled for $C_{16}H_{24}N_4O_7$: C, 49.99; H, 6.29; N, 14.58. Found: C, 49.37; H, 6.38; N, 13.86.

Diethylimmonium and Piperidinium Zwitterions (**3a and 3b**).—The enamine (**5** or **6**) was added to a solution of TNB (1.0 g) in anhydrous ether (50 ml) under a dry nitrogen atmosphere. An immediate red coloration was observed which intensified with time. After 24 hr at 35°, a dark red oil separated from the solution. This was transferred to 100 ml of an 80:20 ether–methanol solution. The mixture was stirred for 1 hr during which time the oil was transformed into a finely divided red solid. Recrystallization of this material from ether–methanol solution yielded red needles of **3**.

For **3a** (0.3 g): mp 195° dec; vis max (CH_3OH) 505 nm (ϵ 26,700); ir (KBr) 1637 cm^{-1} ($C=N^+$); pmr (DMSO-d_6) δ 8.3 (s, H^{δ}), 6.1 (t, J = 3 Hz, H^{α}), 4.2 (broad, 2 H^{γ}), 3.9 (q, 4, J = 7 Hz, $(CH_3CH_2)\overset{+}{N}_2{=}C$), ~2.6 (2 H^{β}, under DMSO-d_5), 1.6 (d, 6, R′ = R″ = CH_3), 1.2 (t, 6, J = 7 Hz, $(CH_3CH_2)_2\overset{+}{N}{=}C$).

Anal. Caled for $C_{15}H_{22}N_4O_6$: C, 50.84; H, 6.26; N, 15.81. Found: C, 50.86; H, 6.27; N, 15.62.

For **3b** (0.5 g): mp 210° dec; vis max (CH_3OH) 505 nm (ϵ 23,800); ir (KBr) 1623 cm^{-1} ($C=N^+$); pmr (DMSO-d_5) δ 8.3 (s, H^{δ}), 6.0 (t, J = 3 Hz, H^{α}), 4.1 (broad, 2 H^{γ}), 1.7–3.2 (m, 10, $(CH_2)_5\overset{+}{N}{=}C$), ~2.6 (2 H^{β}, under DMSO-d_5), 1.3 (d, 6, R′ = R″ = CH_3).

Anal. Calcd for $C_{16}H_{22}N_4O_6$: C, 52.45; H, 6.05; N, 15.29. Found: C, 52.70; H, 6.26; N, 15.01.

Hydrolysis of 3a.—A solution of **3a** (0.1 g), H_2O (~0.25 ml), and DMSO (5 ml) was stirred at room temperature. Aliquots (1 ml) were taken at intervals of several hours and quenched in 5 ml of ether. Quenching yielded an orange powder which was filtered and dried to remove traces of moisture and diethyl ketone. Infrared spectra of these samples showed them to be a mixture of **2a** and **3a**, the amount of the former increasing as the hydrolysis time increased. After 12 hr at 45°, conversion to **2a** was complete.

Registry No.—**2a**, 27331-99-3; **2b**, 27332-00-9; **3a**, 27332-01-0; **3b**, 27332-02-1; *cis*-**5**, 27332-03-2; *trans*-**5**, 27332-04-3; *cis*-**6**, 27332-05-4; *trans*-**6**, 27384-95-8.

Acknowledgments.—This research was supported by the Army Research Office at Durham, Grant No. DAHCO4 69 C 0064, and the Research Corporation.

(12) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrill, *J. Amer. Chem. Soc.*, **85**, 207 (1963).
(13) M. E. Kuehne and L. Foley, *J. Org. Chem.*, **30**, 4280 (1965).
(14) W. A. White and H. Weingarten, *ibid.*, **32**, 213 (1967).

Carbamoyl Chloride Formation from Chloramine and Carbon Monoxide

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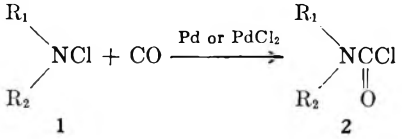
The formation of acid halide from alkyl halide and carbon monoxide in the presence of a group VIII metal compound is well known.[1] The product is described as being derived by the insertion of carbon monoxide into the carbon–halogen bond. As to the insertion of carbon monoxide into the heteroatom–halogen bond, the reaction of sulfenyl chloride with carbon monoxide has been reported recently[2] in which the carbonyl group is inserted into the sulfur–chlorine bond in the absence of any added catalyst. The present report is concerned with the insertion of carbon monoxide into the nitrogen–chlorine bond.

The reaction of chloramine (**1**) with carbon monoxide is effectively catalyzed by palladium metal or palladium chloride to produce carbamoyl chloride (**2**). The reaction proceeds fairly smoothly under milder reaction conditions. Table I summarizes the results of the carbonylation of *N*-chlorodimethylamine. The yield of **2a** (R_1 = R_2 = CH_3) depends on the reaction temperature, the nature of solvent, the amount of catalyst, and the carbon monoxide pressure. Here a trace amount of tetramethylurea was detected as the sole by-product. When the reaction temperature was higher than 50°, the yield of dimethylcarbamoyl chloride decreased and



1 2

(1) C. W. Bird, "Transition Metal Intermediates in Organic Synthesis," Logos Press and Academic Press, New York, N. Y., 1967, p 149.
(2) W. A. Thaler, *Chem. Commun.*, 527 (1968).

TABLE I

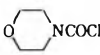
CARBONYLATION OF *N*-CHLORODIMETHYLAMINE[a]

$(CH_3)_2NCl$, mmol	Catalyst, g-atom	Solvent, ml	CO, kg/cm²	$(CH_3)_2NCOCl$, %[b]
10	Pd, 1.0	$CH_3OCH_2CH_2OCH_3$, 5	70[c]	85
10	Pd, 0.1	$CH_3OCH_2CH_2OCH_3$, 5	65[c]	36
10	Pd, 0.1	$CH_3OCH_2CH_2OCH_3$, 5	70	99
5	Pd, 0.5	$CH_3OCH_2CH_2OCH_3$, 2.5	5	8
10	Pd, 0.1	C_6H_6, 5	60	71
10	Pd, 0.1	CH_3CN, 5	60	44
10	Pd, 0.1	*n*-C_6H_{14}, 5	60	19
10	$PdCl_2$, 1.0	$CH_3OCH_2CH_2OCH_3$, 5	70[c]	42

[a] The reaction was carried out in a stainless steel pressure tube at 50° for 20 hr without stirring and shaking. [b] The yield of *N*,*N*-dimethylcarbamoyl chloride was based on the chloramine added. [c] The reaction was carried out at room temperature.

TABLE II

CARBONYLATION OF OTHER DIALKYLCHLORAMINES[a]

R_2NCl, 10 mmol	Catalyst, mmol	Solvent, ml	R_2NCOCl, %[b]
$(C_2H_5)_2NCl$	$PdCl_2$, 1.0	$CH_3OCH_2CH_2OCH_3$, 5	$(C_2H_5)_2NCOCl$, 66
$(C_2H_5)_2NCl$	$RhCl_3$, 1.0	$CH_3OCH_2CH_2OCH_3$, 5	$(C_2H_5)_2NCOCl$, 21
	$PdCl_2$, 1.0	$CH_3OCH_2CH_2OCH_3$, 5	 53
	$PdCl_2$, 0.5	C_6H_6, 4	 80
	$PdCl_2$, 1.0	$CH_3OCH_2CH_2OCH_3$, 5	 45
$C_6H_5CH_2N(CH_3)Cl$	$PdCl_2$, 1.0	$CH_3OCH_2CH_2OCH_3$, 5	$C_6H_5CH_2N(CH_3)COCl$, 15
$C_6H_5CH_2N(CH_3)Cl$[c]	$PdCl_2$, 0.5	$CH_3C_6H_5$, 7	$C_6H_5CH_2N(CH_3)COCl$, 35

[a] The reactions except where noted were carried out for 20 hr at room temperature under the carbon monoxide pressure of 50 kg/cm². [b] The yield of carbamoyl chloride is based on the chloramine added. [c] The reaction was carried out in a glass tube which was put in a stainless steel tube.

the yield of the tetramethylurea by-product increased to several per cents. Using 1,2-dimethoxyethane as solvent at 150°, product 2a reacted with the solvent to yield β-methoxyethyl-*N*,*N*-dimethylcarbamate. When pyridine was used as a solvent instead of 1,2-dimethoxyethane, the reaction did not take place and *N*-chloramine was recovered nearly quantitatively.

The carbonylation of other dialkylchloramines also proceeded using palladium chloride or rhodium trichloride as catalysts (Table II). The yields of the carbonylation products of *N*-chloropiperidine, *N*-chloromorphine, and *N*-chloro-*N*-methylbenzylamine were estimated from the amount of the corresponding urethanes derived from the carbamoyl chloride products by treatment with ethanol in the presence of triethylamine. In all cases of Table II, the ir spectra of the reaction mixtures displayed an absorption at 1735 cm^{-1} characteristic of a carbonyl group, indicating that carbonylation took place. The occurrance of carbonylation was thus indicated. The carbamoyl chloride resulting from the carbonylation of *N*-chloropiperidine could be isolated by distillation. When the reaction was carried out in a glass tube surrounded by a stainless steel tube (as indicated by footnote *c* in Table II), the yields of the carbamoyl chlorides were improved. Otherwise, the stainless steel wall of the reaction tube may catalyze the decomposition of the chloramine or the carbamoyl chloride product.

The carbonylation reaction can also be applied to monoalkylchloramine. Since *N*-methylcarbamoyl chloride and *N*-ethylcarbamoyl chloride which are formed in the reaction are unstable when subjected to glpc analysis (*e.g.*, *N*-methylcarbamoyl chloride decomposes to methyl isocyanate and hydrogen chloride at 90°), the carbonylated products were converted to methyl *N*-methylcarbamate and methyl *N*-ethylcarbamate, respectively, by treatment of the reaction mixture with methanol (Table III).

TABLE III

CARBONYLATION OF MONOALKYLCHLORAMINES

RNHCl, mmol	Catalyst, mmol	Solvent	Carbonylated product, % yield[a]
CH_3NHCl,[b] 5	Pd, 0.05	$(n\text{-}C_4H_9)_2O$	30
C_2H_5NHCl,[c] 10	$PdCl_2$, 1.0	$(C_2H_5)_2O$	22

[a] The yield of product was based on the chloramine added. [b] The reaction proceeded at 50° for 20 hr under the carbon monoxide pressure of 60 kg/cm². [c] The reaction proceeded at room temperature for 20 hr under the carbon monoxide pressure of 50 kg/cm².

The carbamoyl chloride formation from chloramine and carbon monoxide does not proceed in the absence of palladium metal, palladium chloride, or rhodium trichloride catalyst. Metallic copper, silver, and nickel as well as potassium chloroplatinate were not effective at least under reaction conditions of the present study.

Experimental Section

Materials.—Unless otherwise indicated, the reagents and authentic samples were obtained commercially. 1,2-Dimethoxyethane, benzene, *n*-hexane, di-*n*-butyl ether, and diethyl ether were dried by refluxing over sodium wire and distilled. Pyridine was dried over calcium hydride and distilled. Acetonitrile was dried over phosphorus pentoxide and distilled. The carbon monoxide cylinder was a commercial one.

Preparation of *N*-Haloalkylamines.—*N*-Chloramines were prepared according to the procedures given by Coleman.[3] *N*-Chlorodimethylamine (bp 46°), *N*-chlorodiethylamine [bp 41°

(3) G. H. Coleman and C. R. Hauser, *J. Amer. Chem. Soc.*, **50**, 1193 (1928); G. H. Coleman *ibid.*, **55**, 3001 (1933).

(95 mm)], *N*-chloropiperidine [bp 54.5–55° (35 mm)], and *N*-chloromorphorine [bp 47° (17 mm)] were isolated by fractional distillation. *N*-Chloro-*N*-methylbenzylamine was prepared from *N*-methylbenzylamine–HCl and sodium hypochlorite in an aqueous medium. The oily layer which was separated from the reaction mixture was dried over calcium chloride and subjected to the carbonylation reaction without purification by distillation. *N*-Chloromonoalkylamines were prepared from the monoalkylamine–HCl and sodium hypochlorite in the presence of ether. The ether layer was dried over calcium chloride and was subjected directly to the carbonylation reaction.

Carbonylations of Dialkylchloramines (Tables I and II).—A typical procedure is as follows. In a 50-ml stainless steel tube, palladium metal (commercial palladium metal was used directly), 0.0106 g (0.1 g-atom), *N*-chlorodimethylamine (10 mmol), and solvent (1,2-dimethoxyethane was usually employed) (5 ml) were placed and then carbon monoxide was compressed. The tube was closed and was heated at a desired temperature for about 20 hr. Then carbon monoxide was purged off and the reaction mixture was subjected to glpc analysis (a column packed with silicon on Celite was used). The products were identified by comparison of the glpc retention time and ir spectrum with the authentic *N*,*N*-dimethylcarbamoyl chloride. In the cases of *N*-chloropiperidine, *N*-chloromorphorine, and *N*-chloro-*N*-methylbenzylamine, the yields of the products were determined by the glpc analysis of the corresponding urethanes which were formed by treatment of the reaction mixture with excess ethanol in the presence of triethylamine.

Carbonylations of Monoalkylchloramines (Table III).—The following example illustrates the procedure used in the carbonylations of monoalkylchloramines. In a 50-ml stainless steel tube, palladium metal, 0.0053 g (0.05 g-atom), and *N*-chloromethylamine ether solution (5 mmol) were placed, and then carbon monoxide was compressed up to 60 kg/cm² at −78°. The tube was closed and was heated at 50° for 20 hr. The carbon monoxide was purged off, and excess methanol and triethylamine were added to the reaction mixture. The product was identified and its yield was estimated by the form of methyl *N*-methylcarbamate by glpc.

Registry No.—1 ($R_1 = R_2 = H$), 10599-90-3; 1 ($R_1 = R_2 = CH_3$), 1585-74-6; 2 ($R_1 = R_2 = H$), 463-72-9; carbon monoxide, 630-08-0.

A Convenient Synthesis of Pteroic Acid[1]

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Previous syntheses of pteroic acid[2-10] result in preparations that are contaminated with simple pteridines, presenting a formidable problem of purification. The reductive condensation of 2-acetylamino-4-hydroxy-6-formylpteridine with *p*-aminobenzoic acid or with ethyl *p*-aminobenzoate by formic acid or aryl thiols[11] was found to be unsatisfactory, giving variable yields of pteroic acid containing large amounts of pteridine impurities. The present note describes an improved version of the latter synthesis in which pteroic acid is obtained free of contaminating pteridines, thus avoiding the problem of purification.

Ethyl *p*-aminobenzoate and 2-acetylamino-4-hydroxy-6-formylpteridine in glacial acetic acid afforded the corresponding Schiff's base, which without isolation was reduced to ethyl N^2-acetylpteroate by dimethylamine borane, a procedure introduced by Billman and McDowell[12] for the reduction of aromatic Schiff's bases. Saponification of the ethyl ester of N^2-acetylpteroic acid so obtained gave pure pteroic acid which traveled as a single spot on paper chromatography and was free of all fluorescent pteridines. Conversion of this pteroic acid to dihydrofolic and tetrahydrofolic acids gave compounds that showed full enzymatic activity with dihydrofolate reductase of the L 1210 murine leukemia and with thymidylate synthetase of *E Coli*.

Dimethylamine borane appears to be the reagent of choice for the reduction of this Schiff's base. The complete reduction of the 9,10 double bond before reaction at the 5,6 or 7,8 positions is noteworthy. Continued reduction with more amine borane gives dihydro- and tetrahydropteroates. Under these conditions, the acetylpteridine aldehyde alone is reduced in the pyrazine ring before reaction at the carbonyl group takes place.

Experimental Section[13]

Glacial acetic acid (5 ml) was added to a mixture of 330 mg (2 mmol) of ethyl *p*-aminobenzoate and 307 mg (1 mmol) of 2-acetylamino-4-hydroxy-6-formylpteridine dimethylformamide monosolvate.[14] The mixture was stirred briefly. Then a solution of 100 mg of dimethylamine borane in 1.5 ml of glacial acetic acid was added. The suspension turned bright yellow. Stirring was continued at ambient temperature for 20 min. The suspension was warmed to 60° for 10 min and cooled to 25°. The solid was filtered and washed with 5 ml of glacial acetic acid, then with 10 ml of anhydrous ether. The solid was dried at ambient temperature in the dark to give 384 mg (100%) of pale yellow ethyl N^2-acetylpteroate. The solid was dissolved in 5 ml of hot (100°) dimethylformamide and cooled to 30°. Then 2 ml of anhydrous ether was added with stirring to give a homogeneous solution. After standing at ambient temperature, ethyl N^2-acetylpteroate began to crystallize. The flask was stored in a freezer (−35°) overnight. The solid was filtered, washed with anhydrous ether, and dried. This procedure gave 322 mg (84%) of the ethyl ester. The nmr spectrum in deuterated trifluoroacetic acid showed a triplet at δ 0.97 (3 H, J = 7 cps, ester CH_3), singlet at 2.0 (3 H, acetyl CH_3), quartet at 4.07 (2 H, J = 7 cps, ester CH_2), singlet at 4.84 (2 H, bridge CH_2), doublet at 7.35 (2 H, J = 9 cps, benzene CH), doublet at 7.88 (2 H, J = 9 cps, benzene CH), and a singlet at 8.67 (1 H, pteridine CH).

Anal. Calcd for $C_{18}H_{18}N_6O_4$: C, 56.53; H, 4.74; N, 21.98. Found: C, 56.5; H, 5.0; N, 21.8.

The solid ester was saponified with 50 ml of 0.10 *N* sodium hydroxide solution at 100° (under N_2) for 0.5 hr while protected

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from light. The solution was cooled to 20°. Upon adjusting to pH 3 with concentrated hydrochloric acid, pteroic acid separated as a bright yellow solid. This was centrifuged at 3000 rpm and washed thoroughly by suspension and centrifugation with three to five 10-ml portions of water. The moist solid was freeze-dried to give 263 mg of pteroic acid (84%). The nmr spectrum in deuterated trifluoroacetic acid showed a singlet at δ 4.90 (2 H, bridge CH_2), doublet at 7.49 (2 H, J = 9 cps, benzene CH), doublet at 7.85 (2 H, J = 9 cps, benzene CH), and a singlet at 8.54 (1 H, pteridine CH).

Anal. Calcd for $C_{14}H_{12}N_6O_3$: C, 53.85; H, 3.88; N, 26.92. Found: C, 53.7; H, 4.2; N, 26.8.

Paper chromatography (0.10 *N* ammonium bicarbonate) showed R_f 0.17 (quench), pteroic acid, free of all fluorescent compounds.

The sample of pteroic acid was acylated with trifluoroacetic anhydride and converted to folic acid by the mixed anhydride method as previously described.[15] Upon reduction to the dihydro form with sodium dithionite, the sample showed full activity with the two enzymes listed above.

Registry No.—Pteroic acid, 119-24-4; N^2-acetylpteroic acid ethyl ester, 27345-61-5.

Acknowledgment.—I wish to thank Miss E. J. Crawford for the enzyme assays.

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Effects of 4-Alkyl Substitution on the Photoreduction of Benzophenone

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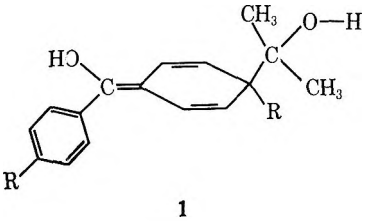
We recently investigated the photoreduction of benzophenone[2] (B) and its di-*p*-*tert*-butyl derivative[3] (TBB) in isopropyl alcohol. Both the photoreduction of TBB and the reactions of its long-lived intermediates with coreactants were surprisingly more complex than those of B. Therefore, it was of interest to examine the analogous reactions of symmetrical benzophenones with gradually increasing size of the alkyl substituent. Here we report on a similar spectroscopic investigation of the photolysis of di-*p*-methylbenzophenone (MB), di-*p*-ethylbenzophenone (EB), and di-*p*-isopropylbenzophenone (IPB) in degassed isopropyl alcohol.[4] The experimental methods, the designation of intermediates, and methods of calculation of extinction coefficients, stoichiometry, and rate constants were described previously.[2,3]

Successive short irradiations of degassed ketone solutions indicated formation of an intermediate species In_1 with λ_{max} between 330 and 350 nm. That this transformation was free of side reaction was shown by the isosbestic points at 237 and 298 nm (MB), 238 and 299 nm (EB), and 237 and 302 nm (IPB). The dark reaction of MB paralleled that of B; namely, the absorption band characteristic of In_1 decreased gradually to complete disappearance (for initial photoconversion less than 50%) or to an unchanging concentration (for conversion in excess of 50%). The spectral changes in the dark indicated that In_1 reacted bimolecularly with the residual benzophenone until one or the other was consumed. The plot of the second-order rate expression gave an excellent fit with the rate constant given in Table I. Product analysis identified only acetone and the tetramethyl-substituted benzopinacol. As for B, In_1 was oxygen sensitive and reverted to MB on exposure to air, as shown by both the uv absorption and reappearance of the characteristic ketone phosphorescence in the emission spectrum of refrozen samples at 77°K.

The dark reactions of the In_1 intermediates of EB and IPB paralleled those of B and MB only when the initial photoconversion was less than 50% but resembled that of TBB for higher conversions. The rate constants for the former reaction, derived again from excellent second-order fits, are listed in Table I. For high initial photoconversions, another slower dark reaction, competing with the In_1 + ketone reaction, was detected which converted the In_1 intermediates to yellow species designated In_2. The $In_1 \rightarrow In_2$ dark reaction of EB and IPB proved to be first order (see Table I). The yellow In_2 species were stable indefinitely (months) in the absence of oxygen but reacted rapidly on admission of air. Multicomponent absorption spectroscopy allowed calculation of the extinction coefficients of In_1 as a symmetrical broad band with λ_{max} at 333 (MB), 338 (EB), and 348 nm (IPB) and of In_2 again as an unstructured band with λ_{max} 382 nm for both EB and IPB.

Elementary molecular orbital calculations of expected electronic absorption,[5] ionic-like reaction with $(CH_3)_2$-CHONa (see below) accompanied by corresponding bathochromic shift in uv absorption, oxygen sensitivity, absence of paramagnetism,[6-11] and analogy with other unsymmetrical coupling reactions of radicals[12] suggest enol structure **1** for In_1 intermediates. Such a configuration has been proposed by several independent investi-



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gators.[2,13,14] An attempt was made to obtain direct confirmation of the nature of In_1 by recording nmr spectra of photolyzed solutions of TBB in degassed perdeu-

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TABLE I
RATE CONSTANTS FOR DARK PROCESSES

Dark reaction	Ketone B	MB	EB	IPB	TBB
In_1 + ketone, *l./(mol sec)*	2.75×10^{-3}	1.75×10^{-3}	1.12×10^{-3}	1.22×10^{-3}	2.50×10^{-3}
$In_1 \rightarrow In_2$, sec^{-1}			2.35×10^{-7}	2.63×10^{-7}	1.5×10^{-7}

terated isopropyl alcohol. The sharp singlet at δ 1.4 ppm, corresponding to methyl protons, decreased upon irradiation with concomitant increase of a new signal at 1.2 ppm, indicating changes in the chemical environment of the *tert*-butyl groups in In_1. Although the aromatic signal at 7.6 ppm decreased with photolysis, the expected vinyl proton absorption around 6.0 ppm could not be observed because of masking signals from solvent impurities. Within its sensitivity limitations, this experiment seems to confirm proposed structure **1**.

From the data in Table I, one can see that the rate constant for the dark reaction of In_1 with residual ketone changes gradually with increasing size of the alkyl substituent, with maxima for B and TBB and minimum for EB. Although the variation is relatively small, it seems to suggest coexistence of two opposing effects or a change in mechanism reminiscent of SN2–SN1 alkyl-dependent solvolysis reactions. Although the significance of this minor variation is not well understood, the absence of a pronounced substituent effect on the In_1 + ketone reaction suggests that the substituent R probably does not interfere with the alcoholic OH, the presumed reaction site.[2]

Upon mixing with isopropoxide, irradiated solutions of the ketones generated yellow metastable species, presumably enolates of **1**. The rate constants for the subsequent complex dark transformation[3] could be estimated only for EB and IPB and were comparable to those of TBB.

We found that the characteristic uv absorption of In_1 continued to increase slightly in the dark for periods up to 10 min following the initial irradiation of IPB, EB, and much less for MB. Low-temperature emission spectra of samples frozen immediately after irradiation failed to reveal the presence of a transient precursor to In_1. This behavior contrasts with that of TBB where a fluorescent precursor was detected and also with that of B where no increase in In_1 absorption was observed once photolysis ended. Despite this precursor's lack of absorption in the 275–340 nm region, the reactive short-lived intermediate is not a ketyl or other radical[6-11] with increased stability from the substituent, since such species have subsecond lifetime in liquid solution.[15] Except for TBB, its concentration never builds high enough for spectroscopic detection in any substituted ketone investigated.

Registry No.—MB, 611-97-2; EB, 21192-56-3; IPB, 21192-57-4.

Acknowledgment.—We thank the Optical Systems Branch of Goddard Space Flight Center, NASA, for support on Grant NGL-09-010-008.

(15) Esr measurements confirmed the absence of paramagnetic species.

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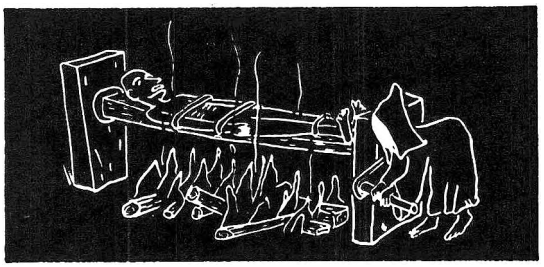

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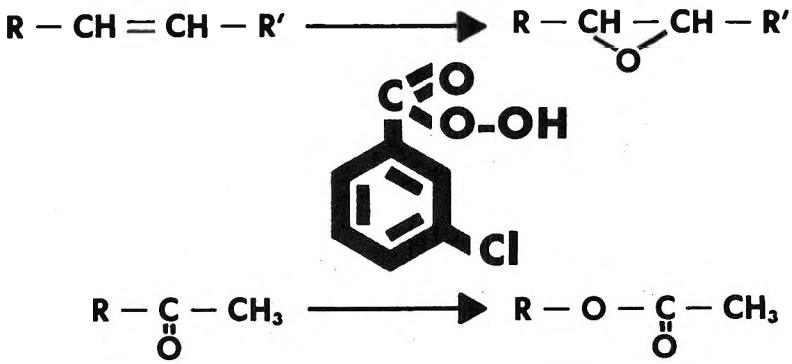

Also of great interest in the preparations of N-oxides[4] and nitrosteroids[5].

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