Landmark Lesson Plan:
Steroid Medicines: A Profile of Chemical Innovation

Grades: 9-12
Subject areas: Organic Chemistry, Green Chemistry, Pharmaceuticals and History
Based on the National Historic Chemical Landmark on Steroid Medicines and Upjohn: A Profile of Chemical Innovation
Principal author: Erica K. Jacobsen

The following inquiry-based student activities are designed for use in high school lesson planning. The activities, videos and article will help students understand the timeline and innovations involved in developing steroid medicines — including cortisone — and in devising a practical, affordable way to make them.

The content is designed as a ready-to-go lesson, easily implemented by a teacher or substitute to supplement a unit of study. In organic chemistry, the activities relate to steroid structures. In green chemistry, the activities connect several principles of sustainability to past steroid research. In pharmaceuticals, the activities relate to the medical use of steroids. In history, the activities highlight the multi-decade path of steroid research.

All resources are available online at www.acs.org/LandmarkLessonPlans.

While these activities are thematically linked, each is designed to stand alone as an accompaniment for the article provided on pages three to five. Teachers may choose activities based on curricular needs and time considerations.

- Take a few minutes to introduce the lesson with a few conversation starters. "What first comes to mind when you hear the word 'steroids'?" Many will think of anabolic steroids and their abuse by some athletes. "What other steroids are part of the world around you and part of your body?"
- Show the ACS Reactions video "How to Catch Dopers" (3 min., 45 sec.), https://youtu.be/oWOwLwMc0rc. The video focuses on anabolic steroids, but also mentions other steroid compounds. It shares that there are legitimate medical uses for steroids. It then discusses how chemists work to detect those using them illegally to boost athletic performance.
- Have students read the article on **Steroid Medicines: A Profile of Chemical Innovation**.
- Distribute the **Activities** selected for the class.
- Use the **Answer Guide** for student feedback and discussion.
- For an extension related to how we can find possible medicinal compounds in nature and either use them from organisms or manufacture them in the lab, show the ACS Reactions video "Dragon's Blood Could Save Your Life" (4 min., 6 sec.), https://youtu.be/j8glywrQvbE.
- Share and discuss the September 2007 *ChemMatters* article "Percy Julian: Rising Above Racism" http://bit.ly/ACS-Julian. It traces Percy Julian's life and education, and the racism he encountered. It discusses his research, including his work on steroids.

Student Activities with Objectives

History Exercise: Chronology of Steroid Medicine Research (15–20 min.)

- Using the handout, students place major events from the research and development of steroid medicines from the 1920s to the 1990s. They consider why there was a race among companies to manufacture cortisone and also how The Upjohn Company built its research teams and its facilities to encourage progress.

Steroid Structures (15–20 min.)

- Students recognize that steroids have the same basic "skeleton" and consider why they can have dramatically different properties and effects. They also practice using bond line notation, or skeletal structures, with these compounds.

Steroids and Green Chemistry (20–25 min.)

- Students compare the paths used to produce cortisone and to upcycle the waste material from this process into hydrocortisone. They then discuss how three principles of green chemistry can relate to past steroid research.

Use of Steroid Medicines (5–10 min.)

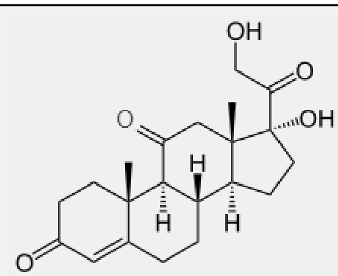
- Students look for changes to the structure of a hydrocortisone molecule and discuss why even a single change could be beneficial for use in medicine. They also imagine a world without steroids and describe the possible effect on the world

Steroid Medicines: A Profile of Chemical Innovation

For many people, life would be unimaginable without medicines containing steroids. Corticosteroids, the most common steroid group, are used to treat arthritis, asthma, skin conditions and certain types of cancer, as well as autoimmune diseases such as lupus, Crohn's disease and multiple sclerosis. Some steroids are available today as over-the-counter treatments for minor irritations such as mosquito bites; other steroids are literally life-saving prescription medicines. Many of these modern drug therapies would not be available today without the pioneering research and development (R&D) that took place at The Upjohn Company between 1930 and 1990.

The race for cortisone

Steroids are natural or synthetic compounds that function in the body as signaling molecules or as components of cell membranes. Examples include corticosteroids such as cortisone, sex hormones such as estrogen, and the anabolic steroids sometimes abused by athletes.



In cortisone, shown here, the oxygen atom shown in red is required for biological activity.

All steroids share a core molecular structure of 17 carbon atoms, bonded in four fused rings: three six-member cyclohexane rings and one five-member cyclopentane ring.

Edward Kendall and Harold Mason first identified cortisone while working at Mayo Clinic in 1929. Twenty years later, the clinic announced the dramatic effect of injections of this steroid in alleviating symptoms in patients with rheumatoid arthritis. At the time, cortisone was still being manufactured almost entirely as an extract from animal adrenal glands, so the supply was low and the cost was high.

The announcement of cortisone's effect on rheumatoid arthritis by Mayo Clinic's Kendall and Philip Hench triggered a competitive worldwide R&D effort directed toward a single goal — the practical and affordable synthesis of cortisone and other then-rare corticosteroids.

Upjohn was poised for success because in 1945 company President Donald Gilmore had launched a major five-year plant expansion project with fermentation and chemical production facilities. He also assembled teams experienced in steroid chemistry. Knowing that other companies were already working hard on producing cortisone, Gilmore exhorted the research groups by stating, "We want cortisone, don't spare the horses."

A better synthesis

In the late 1940s, Merck & Co. was the first to produce cortisone commercially, but Upjohn soon surged ahead. Upjohn developed a process for the large-scale production of cortisone that differed from Merck's process.

The oxygen atom shown in red in the cortisone structure at left is an absolute requirement for biological activity.

There are, however, no known natural sources for starting materials that contain that

Upjohn, courtesy of www.upjohn.net

Upjohn researchers including Durey Peterson (third from left) and Herbert Murray (second from right) developed a one-step fermentation process for the production of cortisone, replacing a complex and costly series of chemical steps.

molecular feature. The only method for preparing this drug prior to 1952 was a lengthy synthesis starting from cholic acid isolated from bile.

In 1952, Upjohn biochemists Durey Peterson and Herbert Murray publicly announced they had succeeded in introducing this crucial oxygen atom by fermentation of the steroid progesterone with a common mold of the genus *Rhizopus*, thus producing a precursor of cortisone. (Progesterone itself was a handy starting material: Upjohn had been producing it for years from stigmasterol, an inexpensive and abundant compound obtained from soybeans.)

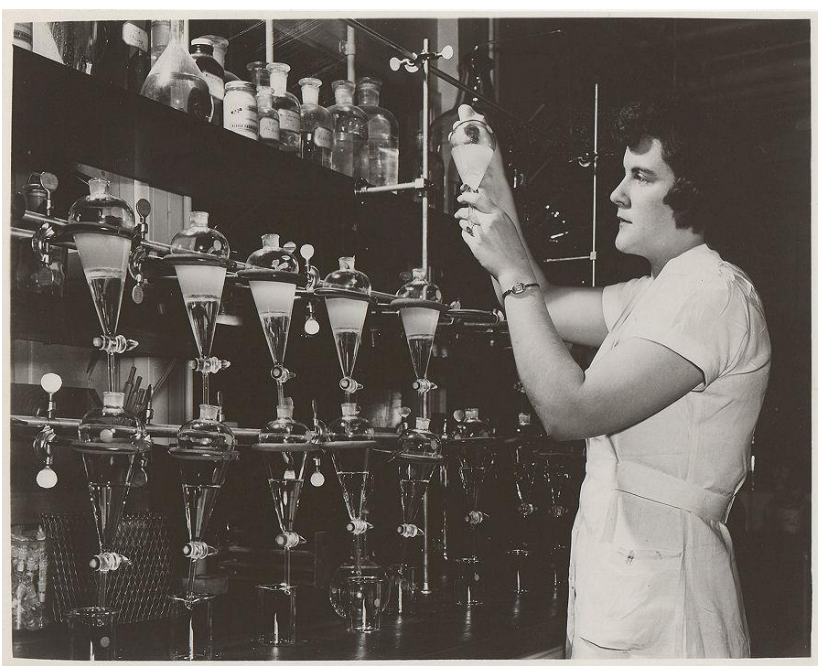
Within a decade, the Upjohn microbiological process was producing tons of useful steroid intermediates.

Also in 1952, an Upjohn group led by W. J. Haines publicly described production of another useful steroid therapy, hydrocortisone, directly by conversion of an adrenal cortex hormone using a fungus. Unique interdisciplinary teams enabled Upjohn to rapidly develop and commercialize processes for preparing both cortisone and hydrocortisone from stigmasterol. Building on this seminal research, Upjohn scientists created more than 30 steroids and analogs by 1990.

For its rich pipeline of drugs, Upjohn was acquired by Pharmacia in 1992; Pharmacia & Upjohn merged with Monsanto in 1995 to become Pharmacia, which was then acquired by Pfizer in 2002.

Organic synthesis impact

Just as important as its immediate clinical significance, Upjohn steroid research also advanced the entire field of organic synthesis. Historians of



Upjohn, courtesy of www.upjohn.net

An Upjohn chemist screens microorganisms for bioconversion of steroid intermediates in the early 1950s.

Glossary

Adrenal glands: Located next to the kidneys, these glands produce hormones including adrenalin as well as steroids such as cortisone.

Analogs: Compounds that have similar structures.

Bile: A digestive fluid made by the liver. It contains **cholic acid**, which can be used to make cortisone.

Fermentation: This process uses a culture of microorganisms such as mold, yeast or bacteria to carry out a chemical transformation.

Organic synthesis: A branch of chemistry that involves formation of molecules containing carbon.

Steroids: Natural or synthetic compounds that function in the body as signaling molecules or as components of cell membranes. Examples include corticosteroids such as cortisone, sex hormones such as estrogen, and the anabolic steroids sometimes abused by athletes. Some steroids can have serious side-effects, so their use may need to be monitored.

Steroid intermediate: A compound that can be converted into a steroid, either through chemical reactions or with the help of microorganisms.

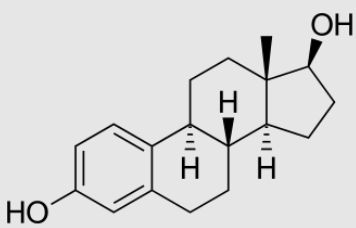
Synthesis: The reaction of chemical compounds to produce one or more different compounds.

Upcycle: This process converts waste or unwanted byproducts into higher-value products.

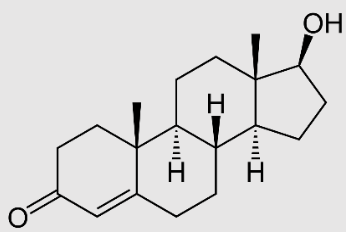
The Upjohn Company

Until the mid-20th century, steroid medicines were available only as expensive, impure, natural extracts. That changed in the early 1950s, when scientists at The Upjohn Company made several advances, bringing affordable, high-quality steroid medicines to the world.

Founded in 1886 in Kalamazoo, Michigan, Upjohn marketed the first adrenocortical hormone product in 1935. By the late 1940s, the firm had products in all four steroid classes — androgens, estrogens, progestogens, and adrenocortical hormones. These products were largely extracts from animal tissues, plasma or urine, and hormone derivatives.



Estradiol, one of the four major forms of natural estrogen



Testosterone, one of the androgen steroids

The breakthrough medical discovery that cortisone could effectively treat inflammatory disease occurred in 1949. That year was also a milestone in Upjohn's journey to synthesize and manufacture cortisone, leading to next-generation steroids. By 1990, Upjohn had become the world's leading producer of steroid intermediates and medicines.

That journey was made possible by Upjohn innovations including formation of multidisciplinary research and development teams for rapid problem-solving, utilization of sustainable materials such as soybeans as raw materials, and application of microorganisms to perform critical transformations in combination with new chemical reactions for efficient manufacturing.

Although developed for Upjohn's steroid medicine program, these innovations transformed the pharmaceutical industry as well as the entire field of synthetic organic chemistry.

science can draw a straight line between the discovery of the structure and properties of steroid molecules and the dramatic increase in research directed to the construction of fused six-membered rings that constitute three of the four rings of steroids. And the challenging five-membered ring inspired scores of creative researchers to develop synthetic methods for attaching that unit in an efficient fashion. New concepts of how to modulate chemical reactivity were introduced and refined to practical synthetic methods.

Even as Upjohn was creating new processes to produce steroids and intermediates, the company's chemistry teams were creating new tools in the field of synthetic organic chemistry. These new and more efficient ways of carrying out difficult reactions led to an increase in strategies and methods and the ability to tackle the synthesis of larger and larger molecules of greater and greater complexity.

A new life for waste

Another milestone for Upjohn was the development of a process to upcycle waste material from steroid production. Stigmasterol, the progesterone precursor, had to be separated from the related soybean sterol sitosterol. Tons of sitosterol accumulated over the years and defied repeated attempts to utilize it efficiently. Upjohn eventually developed a process to convert the sitosterol into hydrocortisone.

Today, cortisone, hydrocortisone, and later-generation steroid medicines resulting from these achievements continue to bring relief to millions of people and animals suffering from inflammatory, reproductive, and other disorders and diseases.

Further reading

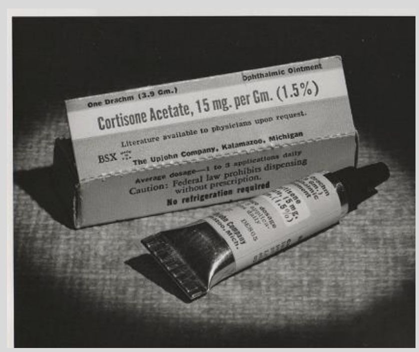
Students may wish to refer to additional information about the following topics:

Corticosteroids: These synthetic steroids are used as anti-inflammatory drugs. They closely resemble cortisol, a natural steroid and hormone (http://bit.ly/ACS-steroid)

Anti-inflammatories, contraceptives, and Mexico (http://bit.ly/ACS-hormone)

Keeping the Olympics fair by keeping them free of steroid doping (video, http://bit.ly/ACS-anabolic);

Percy Julian: Rising above racism while undertakining groundbreaking steroid research (http://bit.ly/ACS-Julian).



Upjohn, courtesy of www.upjohn.net

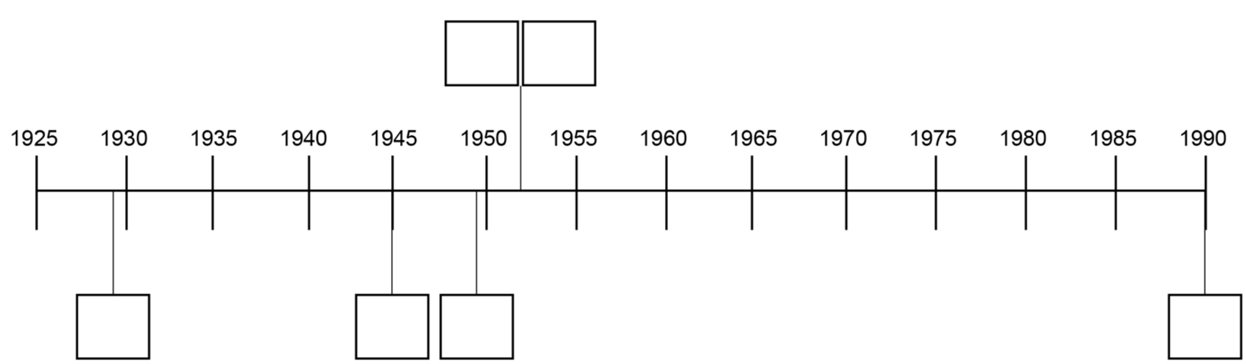
Student Name: ____________________________ Date: ____________ Period: _________

History Exercise: Chronology of Steroid Medicine Research

Steroid medicines that we can purchase off the shelf at our local drugstore have their roots in a long history of research and development. The Upjohn Company was one of the pioneers in this field, particularly from 1930 to 1990.

1. Using the handout provided, identify the year of the events related to steroid medicine research listed below and indicate their chronological order using numbers 1 through 6. Then place them in their correct location on the timeline by writing the event letter in the corresponding box.

		Year	Order
A.	The Upjohn Company produces cortisone precursor using a mold.		
B.	Upjohn produces hydrocortisone using a fungus.		
C.	Effect of cortisone on rheumatoid arthritis symptoms announced by Mayo Clinic.		
D.	Cortisone first identified at Mayo Clinic.		
E.	The Upjohn Company begins expansion project with fermentation and chemical production facilities.		
F.	Upjohn is world's leading producer of steroid medicines, with over 30 steroids and analogs.		



Student Name: ____________________________ Date: ____________ Period: _________

2. Cortisone was already available as a medicine when Mayo Clinic realized it was a useful treatment for rheumatoid arthritis. Why did the clinic’s announcement spark a competition between companies to manufacture the drug at this time?

____

____

____

____

3. The Upjohn Company achieved pioneering research and development in steroids from 1930 to 1990. Describe how the company's facilities and the grouping of its researchers contributed to this success.

____

____

____

____

Student Name: ____________________________ Date: ____________ Period: _________

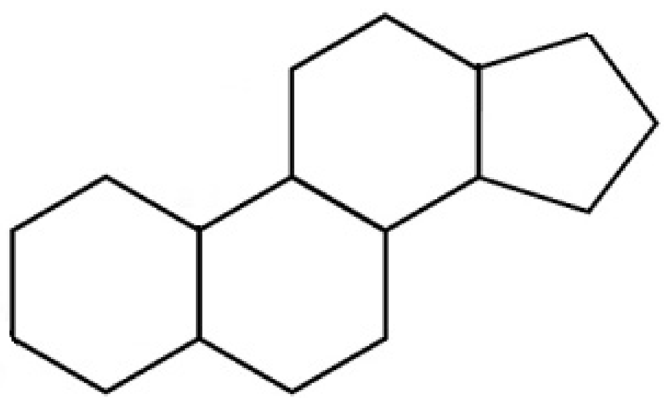
Steroid Structures

There is a wide range of steroid compounds. However, they all have the same "skeleton" to their molecular structure: 17 carbon atoms, bonded in four fused (joined) rings. Three of the rings are made up of six carbon atoms (forming a six-sided ring) and one has five carbon atoms (forming a five-sided ring).

1. Below is a simplified drawing of the steroid "skeleton." The structure uses one line for each bond. Carbon atoms are at places where two lines join and at ends of lines.

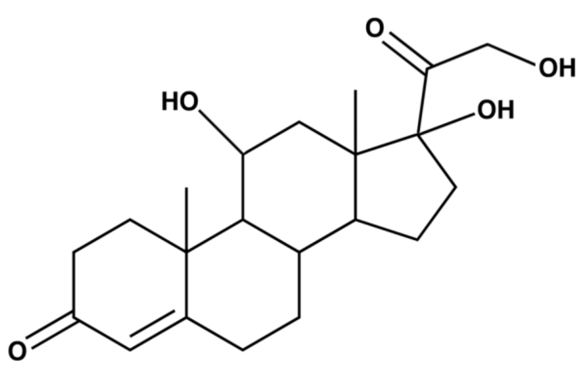
   a. Label each of these locations with a "C" to represent the carbon atoms.

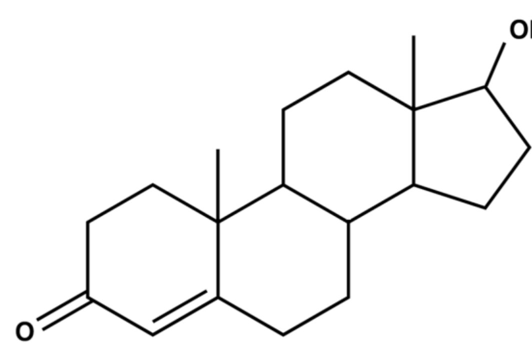
   b. How many C's did you write? _______ How many should there be? _______



2. The simplified drawing in #1 does not show hydrogen atoms or carbon–hydrogen bonds. However, they are still part of the actual compound. If shown, they would be drawn with a line for each bond, from the carbon (C) to the hydrogen (H). In the steroid "skeleton" in #1, draw the appropriate number of hydrogen atoms bonded to each carbon atom's location. *Each carbon atom should have* ***four bonds total****, whether it is to another carbon atom or to a hydrogen atom. Each hydrogen atom should have only one bond.*

3. Consider the two steroid structures below, hydrocortisone (left) and testosterone (right). Use a highlighter or colored pencil to mark the four rings that make up the "skeleton" of both steroids.





Student Name: ______________________________ Date: _____________ Period: __________

4. Look at the steroid structures in #3.

a. What do the two steroid structures have in common?

____

____

____

____

b. How do the two steroid structures differ?

____

____

____

____

c. Structure relates to function. While both of these molecules are steroids, they have different properties and effects. Explain why there are differences in properties and effects.

____

____

____

____

Student Name: ______________________________ Date: _____________ Period: __________

Steroids and Green Chemistry

The Upjohn Company's production of steroids resulted in tons of a chemical, sitosterol, that could be considered as waste. Eventually in the 1970s, the firm developed a way to upcycle this material into hydrocortisone, using bacteria as part of the process.

1. The upcycling process has several parallels to Upjohn's original path to produce cortisone. Using the article provided, complete the table below.

	Production of cortisone	**Production of hydrocortisone using waste chemical**
Name of the specific sterol used	*stigmasterol*	*sitosterol*
Original plant source of the sterol used		
Microorganism used in the process		*bacteria*
Steroid medicine produced		

Student Name: ____________________________ Date: ____________ Period: _________

2. In 1998, chemists Paul Anastas and John Warner outlined 12 principles of green chemistry. Although this was after Upjohn's several decades of major developments in steroid medicines, the principles can apply. Three are listed below. Discuss how you think each could relate to Upjohn's work.

a. "It is better to prevent waste than to treat or clean up waste after it has been created."

____

____

____

____

b. "A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable."

____

____

____

____

c. "Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment."

____

____

____

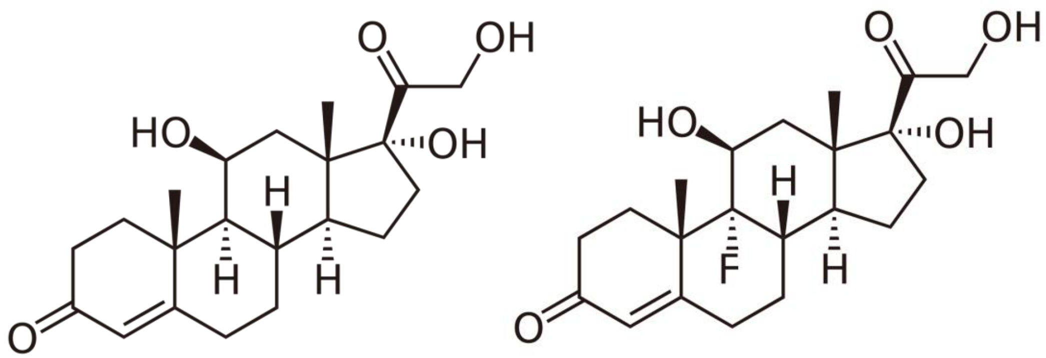
____

Student Name: ____________________________ Date: ____________ Period: _________

Use of Steroid Medicines

A major step in devising a practical synthesis of cortisone was finding a way to introduce an oxygen atom at a very specific location on the basic steroid "skeleton." Researchers also experimented with changing other substituents attached to the skeleton. Certain changes could make the medicine more potent, affect its solubility or reduce its side effects.

1. One example of a substituent change to hydrocortisone (left) is shown below. This change greatly increased the potency of the steroid. Find and circle any differences between the two structures.



2. Different substituents can affect a steroid's solubility, making it dissolve more easily in a polar solvent or more easily in a non-polar solvent. How would this difference enable a steroid to be delivered through a water-based intravenous fluid as well as an oil-based ointment?

____

____

____

3. Corticosteroids can treat a wide range of conditions, such as arthritis, skin inflammation, asthma, allergies, autoimmune diseases and more. Some can easily be purchased over the counter, such as hydrocortisone cream and steroid nasal spray. Imagine a world where these medicines could not be produced inexpensively or couldn't be produced at all. Describe the effect on someone's life if these steroids were not readily available.

____

____

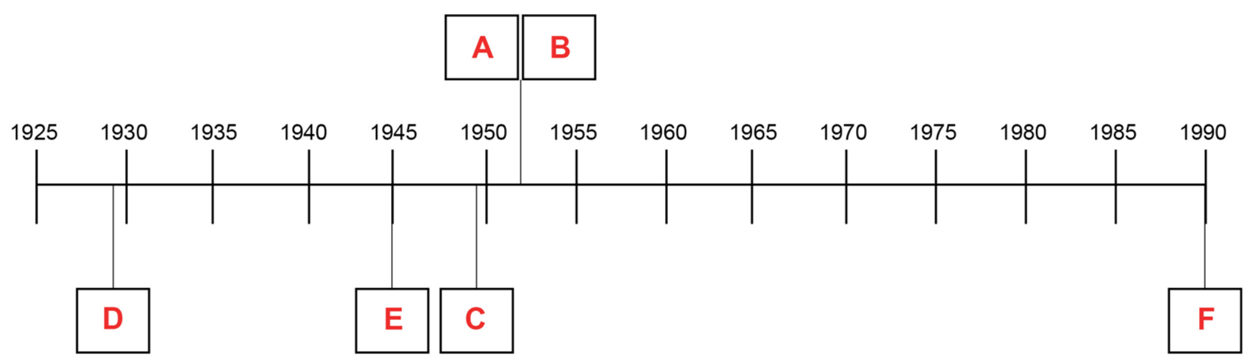
____

History Exercise: Chronology of Steroid Medicine Research

Steroid medicines that we can purchase off the shelf at our local drugstore have their roots in a long history of research and development. The Upjohn Company was one of the pioneers in this field, particularly from 1930 to 1990.

1. Using the handout provided, identify the year of the events related to steroid medicine research listed below and indicate their chronological order using numbers 1 through 6. Then place them in their correct location on the timeline by writing the event letter in the corresponding box.

		Year	Order
A.	The Upjohn Company produces cortisone precursor using a mold.	**1952**	**4 or 5**
B.	Upjohn produces hydrocortisone using a fungus.	**1952**	**4 or 5**
C.	Effect of cortisone on rheumatoid arthritis symptoms announced by Mayo Clinic.	**1949**	**3**
D.	Cortisone first identified at Mayo Clinic.	**1929**	**1**
E.	Upjohn begins expansion project with fermentation and chemical production facilities.	**1945**	**2**
F.	Upjohn is world's leading producer of steroid medicines, with over 30 steroids and analogs.	**1990**	**6**



2. Cortisone was already available as a medicine when Mayo Clinic realized it was a useful treatment for rheumatoid arthritis. Why did the clinic's announcement spark a competition between companies to manufacture the drug at this time?

At the time, cortisone was still being manufactured almost entirely as an extract from animal adrenal glands, so the supply was low and the cost was high. The goal was a practical and affordable synthesis of cortisone.

3. The Upjohn Company achieved pioneering research and development in steroids from 1930 to 1990. Describe how the company's facilities and the grouping of its researchers contributed to this success.

The company had expanded its facilities. This gave them increased capability for carrying out fermentation and chemical production. They assembled interdisciplinary teams that included researchers experienced in steroid chemistry. People from different scientific specialties could collaborate.

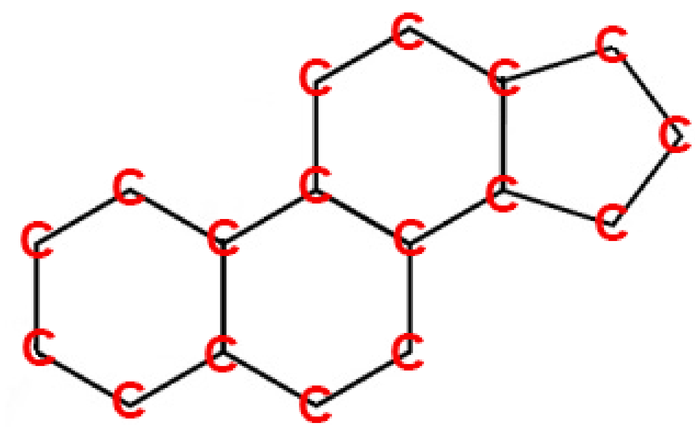
Steroid Structures

There is a wide range of steroid compounds. However, they all have the same "skeleton" to their molecular structure: 17 carbon atoms, bonded in four fused (joined) rings. Three of the rings are made up of six carbon atoms (forming a six-sided ring) and one has five carbon atoms (forming a five-sided ring).

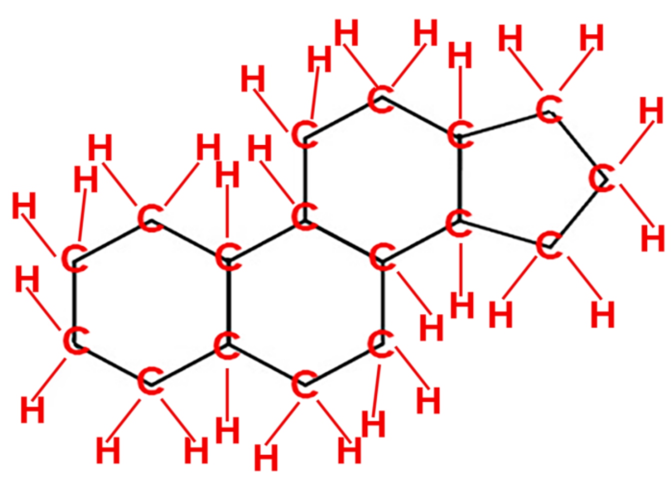
1. Below is a simplified drawing of the steroid "skeleton." The structure uses one line for each bond. Carbon atoms are at places where two lines join and at ends of lines.

   a. Label each of these locations with a "C" to represent the carbon atoms.

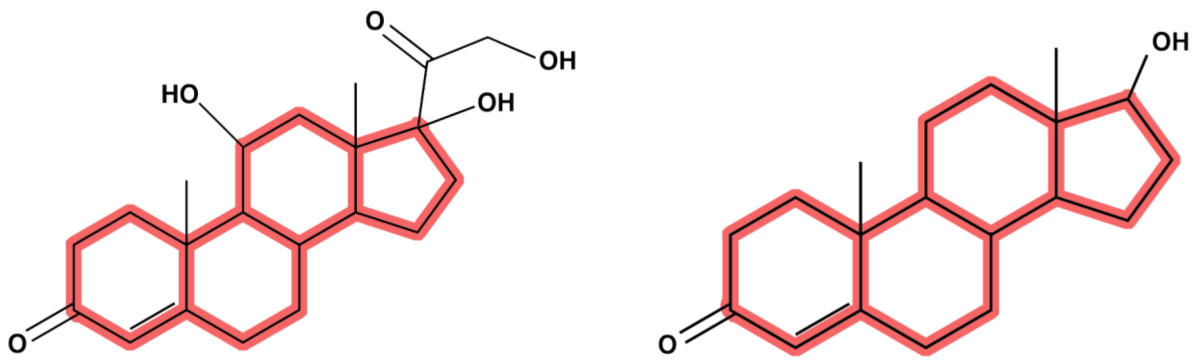
   b. How many C's did you write? **17** How many should there be? **17**



2. The simplified drawing in #1 does not show hydrogen atoms or carbon–hydrogen bonds. However, they are still part of the actual compound. If shown, they would be drawn with a line for each bond, from the carbon (C) to the hydrogen (H). In the steroid "skeleton" in #1, draw the appropriate number of hydrogen atoms bonded to each carbon atom's location. *Each carbon atom should have* <u>*four bonds total*</u>*, whether it is to another carbon atom or to a hydrogen atom. Each hydrogen atom should have only one bond.*



3. Consider the two steroid structures below, hydrocortisone (left) and testosterone (right). Use a highlighter or colored pencil to mark the four rings that make up the "skeleton" of both steroids.



4. Look at the steroid structures in #3.

a. What do the two steroid structures have in common?

They have the same four-ring skeleton. There is a double bond between two of the carbons in the first six-carbon ring. They both have oxygen double-bonded to a carbon in the first six-carbon ring. They both have two CH_3 groups.

b. How do the two steroid structures differ?

They have different atoms and/or groups attached to the skeleton.

c. Structure relates to function. While both of these molecules are steroids, they have different properties and effects. Explain why there are differences in properties and effects.

The different groups attached to each skeleton would account for this. Hydrocortisone has an OH group attached to the third six-carbon ring and a COOH group attached to the five-carbon ring, while these functional groups are not present in testosterone.

Steroids and Green Chemistry

The Upjohn Company's production of steroids resulted in tons of a chemical, sitosterol, that could be considered as waste. Eventually in the 1970s, the firm developed a way to upcycle this material into hydrocortisone, using bacteria as part of the process.

1. The upcycling process has several parallels to Upjohn's original path to produce cortisone. Using the article provided, complete the table below.

	Production of cortisone	**Production of hydrocortisone using waste chemical**
Name of the specific sterol used	*stigmasterol*	*sitosterol*
Original plant source of the sterol used	**soybeans**	**soybeans**
Microorganism used in the process	**mold**	*bacteria*
Steroid medicine produced	**cortisone**	**hydrocortisone**

2. In 1998, chemists Paul Anastas and John Warner outlined 12 principles of green chemistry. Although this was after Upjohn's several decades of major developments in steroid medicines, the principles can apply. Three are listed below. Discuss how you think each could relate to Upjohn's work.

a. "It is better to prevent waste than to treat or clean up waste after it has been created."

The article does not mention researchers actively trying to prevent waste while producing cortisone, but they did make repeated attempts to upcycle the waste. Eventually, they succeeded.

b. "A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable."

Upjohn used compounds the firm obtained from soybeans, which can easily be grown.

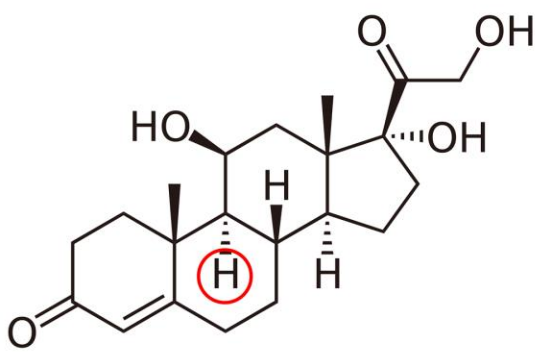
c. "Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to human health and the environment."

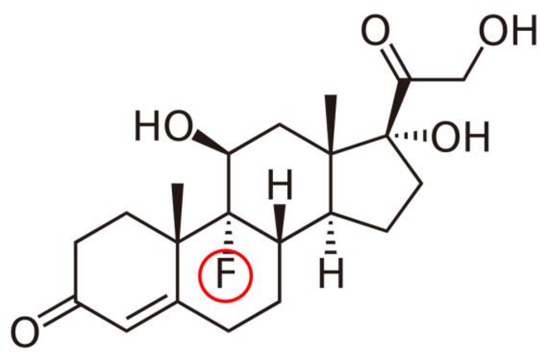
The Upjohn Company used mold and soybeans in the fermentation process for producing steroids for medicinal use.

Use of Steroid Medicines

A major step in devising a practical synthesis of cortisone was finding a way to introduce an oxygen atom at a very specific location on the basic steroid "skeleton." Researchers also experimented with changing other substituents attached to the skeleton. Certain changes could make the medicine more potent, affect its solubility or reduce its side effects.

1. One example of a substituent change to hydrocortisone (left) is shown below. This change greatly increased the potency of the steroid. Find and circle any differences between the two structures.





2. Different substituents can affect a steroid's solubility, making it dissolve more easily in a polar solvent or more easily in a non-polar solvent. How would this difference enable a steroid to be delivered through a water-based intravenous fluid as well as an oil-based ointment?

One form of the steroid would need to be able to dissolve in water, a polar solvent, while another form with different substituents could dissolve in oil, a non-polar solvent.

3. Corticosteroids can treat a wide range of conditions, such as arthritis, skin inflammation, asthma, allergies, autoimmune diseases and more. Some can easily be purchased over the counter, such as hydrocortisone cream and steroid nasal spray. Imagine a world where these medicines could not be produced inexpensively or couldn't be produced at all. Describe the effect on someone's life if these steroids were not readily available.

A world with little to no access to corticosteroids would lead to a much lower quality of life for many and, in extreme cases, no life at all.