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National Historic Chemical Landmarks
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Steroid Medicines and Upjohn: A Profile of Chemical Innovation

Kalamazoo Valley Museum

American Chemical Society

"The legacy of Upjohn steroid chemistry is inexorably tied to the evolution of the entire field of organic synthesis beyond the extraordinary impact it had on human health."

— Scott E. Denmark, chemistry professor, University of Illinois, Urbana-Champaign

For many people, life would be unimaginable without medicines containing steroids. Corticosteroids, the most common steroid group, are used to treat arthritis; asthma; autoimmune diseases such as lupus, Crohn's disease, and multiple sclerosis; skin conditions; and certain types of cancer. 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 modern drug therapies would not be feasible without the practical advances developed at Upjohn for the manufacture of steroidal medicinal agents."

— Edwin Vedejs, chemistry professor, University of Wisconsin and University of Michigan

Many of these modern drug therapies would not be available today without the pioneering research and development (R&D) at The Upjohn Company between 1930 and 1990. The medicinal chemistry innovations, microbial and chemical transformation discoveries, and manufacturing processes developed by Upjohn for its steroid medicine program transformed the pharmaceutical industry and, further, the entire field of synthetic organic chemistry.

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

HUMBLE BEGINNINGS

The company was founded in 1886 in Kalamazoo, Michigan, by physician William E. Upjohn and his brother Henry as the Upjohn Pill and Granule Co. William Upjohn had patented a process for making a pill capable of crumbling under the pressure of a thumb and therefore being easily digested. The business prospered, and, in 1903, reflecting its broader portfolio, changed its name to The Upjohn Company.

A decade later, the firm hired its first research scientist, Frederick W. Heyl, a former University of Wyoming chemistry professor. He initiated the company's pioneering endocrine research program in 1933.

During the 1930s and 1940s, the company began expansions of manufacturing plants and innovations in analytical chemistry, organic chemistry, biochemistry, microbiology, and chemical engineering. Upjohn became the first to market an 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.

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. 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 C. Kendall and Harold L. Mason first identified cortisone while working at the 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, making the supply very low and the cost very high," notes Scott E. Denmark, a chemistry professor at the University of Illinois, Urbana-Champaign and former consultant for Upjohn.

The announcement of cortisone's effect on rheumatoid arthritis by Mayo's Kendall and Philip S. 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 S. Gilmore, son-in-law of William Upjohn, had launched a major five-year plant expansion project with fermentation and chemical production facilities. In 1949, he hired Richard S. Schreiber, a polymer chemist from DuPont, just three months before the cortisone announcement. Four experienced steroid chemistry teams were already in place. Knowing that other companies were already working hard on producing cortisone, Gilmore exhorted the research groups, "We want cortisone, don't spare the horses."

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 right is an absolute requirement for biological activity. There are, however, no known natural sources for starting materials that contain that 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 H. Peterson and Herbert C. 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. Upjohn had been

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

producing progesterone for years from stigmasterol, an inexpensive and abundant compound obtained from soybeans.

Peterson and Murray's microbiological conversion of progesterone into a useful hydroxylated precursor of cortisone "was not the first example of microbiological oxidation, but it was one of the first few examples of what we now call un-activated C-H functionalization and it was absolutely the first practical and spectacular example," wrote the late Edwin Vedejs in describing this work. Vedejs was a longtime consultant for Upjohn and a chemistry professor at the University of Wisconsin, Madison and the University of Michigan, Ann Arbor. "Within a decade, the Upjohn process was producing tons of useful steroid intermediates," according to Vedejs.

Also in 1952, an Upjohn group led by W. J. Haines publicly described production of another useful steroid therapy, hydrocortisone, directly by conversion of Reichstein's substance S (a hormone from the adrenal cortex) using a fungus of the Mucorales order. Unique interdisciplinary teams led by David I. Weisblat and Robert H. Levin enabled Upjohn to rapidly develop and commercialize processes for preparing both cortisone (starting in 1952) and hydrocortisone (1953) from stigmasterol. Ultimately, Upjohn so dominated steroid-active pharmaceutical ingredient manufacturing that many other pharmaceutical companies decided to purchase steroid intermediates from Upjohn for their own products. Building on this seminal research, Upjohn scientists created more than 30 steroids and analogs by 1990.

ORGANIC SYNTHESIS IMPACT

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

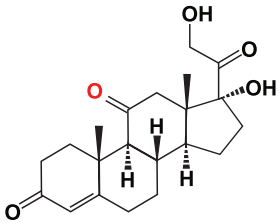
Even as Upjohn was creating new processes to produce steroids and intermediates, the company's chemistry teams were creating new tools in synthetic organic chemistry. These new and more efficient ways of carrying out difficult reactions "led to the exponential increase in strategies and methods and the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

One major contribution with widespread application was developed by Upjohn's George Slomp Jr. and James L. Johnson and described in the *Journal of the American Chemical Society* in 1958. These chemists used pyridine and ozone to break certain double bonds in a steroid intermediate while leaving untouched other double bonds next to carbonyl groups.

The other notable tool is the "Upjohn dihydroxylation," reported by Verlan Van Rheenen, Robert C. Kelly, and D. Y. Cha in *Tetrahedron Letters* in 1976. Dihydroxylation adds neighboring hydroxyl groups to alkenes. "This extremely useful transformation requires a highly toxic and expensive reagent, osmium tetroxide," according to Denmark. The Upjohn scientists found a way to reduce the amount of osmium tetroxide needed and to recover and recycle it, resulting in environmental benefits and lower costs.

Another milestone for Upjohn was the development of a process to upcycle waste material from steroid production. Stigmasterol was used as the precursor to 11-hydroxy-progesterone, but it 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 biocatalytic process to convert the sitosterol into a potential precursor for other steroids. Van Rheenen challenged Denmark to invent a way to convert that potential precursor into hydrocortisone. Denmark worked with Upjohn chemists Douglas Livingston and Bruce Pearlman to develop a process still used today for the synthesis of hydrocortisone acetate.

"The legacy of Upjohn steroid chemistry is inexorably tied to the evolution of the entire field of organic synthesis beyond the extraordinary impact it had on human health," Denmark says.



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

Steroid Medicines and Upjohn Innovation

A National Historic Chemical Landmark

The American Chemical Society (ACS) honored The Upjohn Company's innovation in steroid medicines with a National Historic Chemical Landmark (NHCL) in a ceremony at the Kalamazoo Valley Museum in Kalamazoo, Michigan, on May 17, 2019. The commemorative plaque reads:

> *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. Innovations included 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. 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.*

About the National Historic Chemical Landmarks Program

ACS established the NHCL program in 1992 to enhance public appreciation for the contributions of the chemical sciences to modern life in the U.S. and to encourage a sense of pride in their practitioners. The program recognizes seminal achievements in the chemical sciences, records their histories and provides information and resources about NHCL achievements. Prospective subjects are nominated by ACS local sections, divisions, or committees, reviewed by the ACS NHCL Subcommittee, and approved by the ACS Board Committee on Public Affairs and Public Relations.

ACS, the world's largest scientific society, is a not-for-profit organization chartered by the U.S. Congress. ACS is a global leader in providing access to chemistry-related information and research through its multiple databases, peer-reviewed journals, and scientific conferences. Its main offices are in Washington, D.C., and Columbus, Ohio.

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The Kalamazoo Section of the ACS, the Pfizer Kalamazoo Manufacturing Site, the Kalamazoo Valley Museum and the University of Illinois at Urbana-Champaign sponsored the nomination for this Landmark designation.

Cover: Upjohn's Portage site in the 1950s. Insets: Upjohn adrenal cortex extracts and cortisone ointment and (top right) a chemist screens microorganisms during cortisone research. Cover and page three photos from Upjohn, courtesy of www.upjohn.net.

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