retrieval either after structural formulas have been fragmented into bits and pieces, which have been assigned code numbers, or after structural formulas have been converted to chemical notations would be novel to a great number of chemistry students.

WHO SHOULD TEACH THE CHEMICAL LITERATURE COURSE?

It is doubtful that there are many university personnel who are knowledgeable in all of the above mentioned topics. The people most aware of these subjects are away from the college campus and employed by government and industry as literature chemists, chemical information specialists, and chemical librarians. These people should be invited to colleges for the purpose of giving courses in chemical literature.

Another idea is the establishment of a correspondence course in chemical literature by a special committee of the Division of Chemical Literature of the American Chemical Society. The course could consist of a study guide, exercises, and questions. Tuition, credits, and administrative details could be resolved through cooperative efforts of the committee and the departments of chemistry of participating colleges and universities.

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Steroids: From Chemistry to Law

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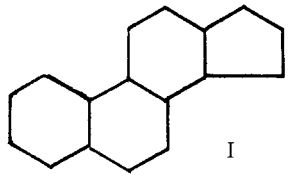
Received November 20, 1970

The growth and evolution of the literature of steroid chemistry are surveyed and the unique character of steroid patents is illustrated.

Steroids are compounds containing the perhydrocyclopentanophenanthrene nucleus (I). They include sterols, bile acids, sex hormones, adrenocortical hormones, cardiac



I

glycosides, sapogenins, and some alkaloids. The development of steriod chemistry can be divided into the following periods: prehistory, to 1900; classical, 1900–32, the period in which the structure of the nucleus was almost completely elucidated; early modern, 1932–47, which started with the "new" formulas and covers the years when the basic chemistry of nearly all the known naturally-occurring groups of steroids were settled in detail; and late modern, 1947 to date, largely dominated by the search for methods of synthesizing cortisone and related compounds.[1]

I would like to add another period, beginning with the easy handling of optical rotatory dispersion and circular dichroism that enabled chemists to have a basis for studying the stereochemistry of steroids on a scientific basis. Actually, Arago[2] discovered the phenomenon of optical activity in 1811; Biot[3] laid the foundation for spectropolarimetry in 1817, when he reported the angle of rotation becomes greater if the measurement is carried out at shorter wavelengths.

Stagnation characterized the period until 1953. Then Djerassi and coworkers brought spectropolarimetery back to life; the substances they measured are more than what had been investigated the preceding 140 years.[4]

Lowry[5] attributes the long period of stagnation to the invention of the Bunsen burner (1866), which made it extremely easy to produce monochromatic light instead of using a monochromator, which had been particularly troublesome in the previous century. One had only to hold a piece of rock salt in the flame to measure the optical rotation of a substance. Owing to the simplicity of this method, nearly all the earlier workers did not pay attention to the valuable information of a complete rotatory dispersion curve.

The period 1953 to 1960 was the octant rule period and the year 1961 was the beginning of a new period in steroid chemistry. This period began with the work of Moffitt, Woodward, Moscowitz, Klyne, and Djerassi.[6]

The evolution of the steroid literature is shown by the following statistics of publications per year:[7]

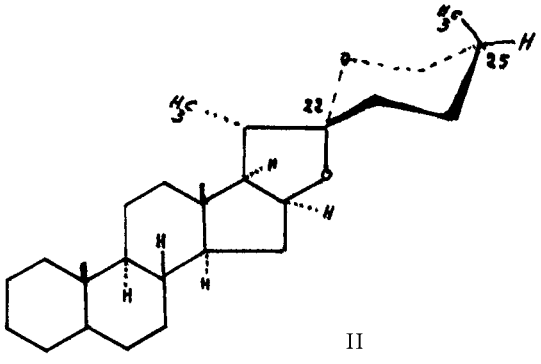
1910–25	~10
1926–32	10–40
1933–39	40–100
1940–45	80–50
1946–48	90–120
1949–53	150–130, 210, 290, 320

The number of known steroid compounds until 1953 was 8000;[8] by 1961 it was 21,000. This number is now (1970)

more than 42,000 owing to the application and proof of the octant rule. The increase during the last period not only lies in the great number of publications dealing with steriods and steroid derivatives but with new researchers working in the field. As stated by Barton[9] "the steroids have a chemistry which is not only logically predictable in many respects, but also intimately related to the general interests of organic and physical-organic chemists."

Two years after the octant rule, Djerassi[10] directed attention to the golden mine of steroids: "The appearance of a cyclopentanoperhydrophenanthrene skeleton in a journal article is often sufficient to make even the experienced organic research chemist turn the pages rapidly without a further glance at the article. This applies especially to physical-organic chemists, who thus miss a veritable gold mine of interesting problems and very convenient model substances, but the synthetic chemist is equally guilty of this bias." The ambiguity of steroid derivatives and complications in nomenclature were clarified by the sequence rule.[11]

The importance of the sequence rule appears in steroid chemistry when the substituents are on additional spiro-rings and lie approximately in the plane of the A-E ring system; such substituents cannot be designated α or β, as these letters specify that the substituent lies, respectively, in front of or behind the plane of the ring system. Compound II illustrates such a situation with respect to position 25; it can be named 25,S-5β-spirostan or 22 R,25 S-5β-spirostan. This rule also offers an alternative to αF, βF system for designation of stereochemistry in an aliphatic 17-side chain of a steroid. The relation



II

between steroids and law is centered in patents. Steroid patents are assigned by the patent office to class 260–397. The number of steroid patents is increasing rapidly. In 1945, more than 250 U.S. patents were granted on the preparation and use of steroids and their derivatives.[12] Since then thousands of patents have been granted in the different fields of steroid chemistry.

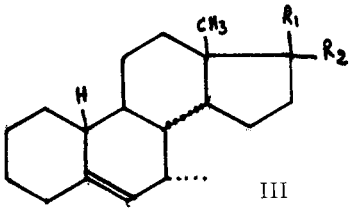
A striking feature in steroid patents is the absence of cases concerning compulsory license and infringement. In my opinion, there are many reasons for these phenomena.

INFRINGEMENT

[The monopoly given to a patent is the right to exclude others not only from making things covered by the patent but also from using or vending such things. A patent is infringed by the manufacture, use, or sale of the invention substantially as claimed by the patent.]

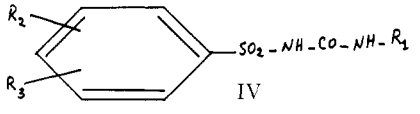
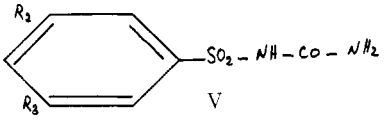
1. The method with which the steroid patent is written, in itself, is more complicated than that of other patents. For example, U.S. Patent 3,383,393, May 14, 1968, says:[8] The invention relates to novel 7-alkyl-19-norsteroids and to a process for the preparation thereof.

More particularly, the invention relates to the novel 3-unsubstituted-19-norsteroids of the general formula (III)



III

where Y = an alkyl group, R_1 = OH or O-acyl, R_2 = hydrogen or a saturated or unsaturated hydrocarbon radical with 1–4 carbon atom or R_1 and R_2 together = keto group. Comparing this steroid patent with another non-steroid patent—e.g., tolbutamide,[14] German Patent 22,868—claims 1 and 8 read:

> 1. A process for the manufacture of sulphonyl ureas of the general formula (IV)
>
> 
>
> IV
>
> in which R_1 represents an aliphatic or cycloaliphatic hydrocarbon radical containing from 2 to 8 carbon atoms, and R_2 and R_3 each represent hydrogen or an alkyl or alkoxy group containing at most 6 carbon atoms, wherein the above products are obtained according to methods which may generally be used for the manufacture of sulphonyl ureas.
>
> 8. A process as claimed in claim 1 wherein compounds of the formula V
>
> 
>
> V
>
> are reacted with primary amines of the formula R_1–NH_2 in which R_2 and R_3 have the meaning given above.

It is clear from these two patents that the second can easily be infringed: "the assessor informed me that if she were told to read claims 1 and 8 and then to make a tolbutamide, she is convinced that she could make it after some experimental work." The plaintiff also added: "Dr. Vincent Barry, who holds very high qualifications in chemistry and who has been, since 1944, the director of the Medical Research Bureau, which has done so much valuable work, said that if the problem of the toxicity of the para amino group in carbutamide had been given to his team, they would have had tolbutamide available within two months."

2. Due to the sensitivity of the steroid molecule any change in the conditions will result in either a marked decrease or increase in the yield or perhaps no yield at all. For example, in the preparation of pro-vitamin C

(Δ^7-cholesterol), Nes et al.[15] reported that "Bernstein et al. have reported a yield of 24% for pure 7-dehydrocholestryl acetate. However, in repeated experiments in this laboratory by essentially the same procedure as used by these authors we were unable to obtain a yield as high as this. The over-all yield of 7-dehydrocholestryl acetate obtained by the 3,5 dinitrobenzoate technique of Bide et al. failed to give yields comparable with those obtained with the isocaproate.

3. Production of steroids is a matter of know-how ("Gewußt wie") more than a matter of equations, and interpretations and the availability of starting materials play a main role.

4. In the German patent law, changing the conditions of production of a steroid when accompanied by a notable increase in the yield permits a new patent for these critical new conditions.[16]

COMPULSORY LICENSE

[In certain countries (other than the United States, but not in the field of atomic energy) a patentee may under certain conditions be required to grant a compulsory license to a party in that country who wishes to practice the invention for a consideration.]

1. The main conditions managing compulsory licenses as nonworking, insufficient working, interdependence of patents, concerning atomic energy are not fulfilled.

2. The fundamental object of the patent is to encourage the replacement of inferior goods and processes by the superior; as the different synthetic steroids have different biological activity; as every company has its own facilities for the production of a special steroid. Hence, compulsory licenses are of no importance in this field.

3. In general, compulsory license is in contradiction to the "laissez faire laissez passez" principle.

4. Djerassi's description of steroids as a "mine of gold" means more research, more discoveries of steroids with physiological activity, and hence no need for compulsory licenses.

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Computer-Generated Substructure Codes (Bit Screens)*

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Received January 5, 1971

Substructure searching has been a timely subject for many years now. This is quite understandable since almost all of the questions a chemist takes to his library or computer involve chemical structures. The ability to economically search large files of compounds is the goal of many research projects.

Unfortunately, serial searches of all the structures contained in a large file (>100,000 compounds) can consume considerable amounts of computer time. Efficient screens can greatly reduce computer search time.

This paper presents a set of binary screens computer-generated from Wiswesser Line Notations (WLNs), which greatly reduce computer time for substructure searching of files consisting of hundreds of thousands of compounds. These screens should, therefore, prove of value to any system which includes WLN records.

ICRS (INDEX CHEMICUS REGISTRY SYSTEM)

In 1968, the Institute for Scientific Information initiated its *Index Chemicus Registry System (ICRS)*[1] which consists of a data base containing information being reported in

* Presented in part at the Fifth Middle Atlantic Regional Meeting at the University of Delaware, Newark, Delaware, April 1-3, 1970.

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