Description and importance of the aromatic basic skeleton of the steroids

Nobel Lecture*

Cholesterol was discovered as long ago as 1789. Since it was found to be widely distributed in both the plant and the animal organism, and since it plays an important part in the latter (being present in blood, brain, liver, egg yolk, gall-stones, etc.), it is understandable that many chemists and physiologists should have directed their efforts, especially during the second half of the 19th century, towards determining the composition and structure of this remarkable and important substance.

Until the beginning of the 20th century, however, the results of these researches were but modest, and the hope of discovering the nature of cholesterol and of its chemical structure had not been realized.

All that had been established was its composition, C_{27}H_{46}O, and the fact that the cholesterol molecule contained one double bond and one alcoholic OH group.

This was certainly not very much! Nevertheless, on the basis of these results it had been established that cholesterol was a complex hydroaromatic system composed of four rings. Until 1900, however, all efforts to explain this system, e.g. by oxidative modification and by determination of the character of the cleavage products, had failed.

Two years later I myself succeeded in making two important observations on cholesterol. Firstly that with NaOBr it could be transformed fairly easily into a dicarboxylic acid with very good crystallizing properties and with the same number of carbon atoms as cholesterol:

\[ \text{C}_{27}\text{H}_{46}\text{O} \xrightarrow{\text{NaOBr}} \text{C}_{27}\text{H}_{46}\text{O}_2. \]

From this it was quite clear that this dicarboxylic acid was produced as a result of the splitting of one of the four rings of the cholesterol.

* Professor Diels intended to deliver his Nobel Lecture during a visit to Stockholm in May, 1951. He had completed the manuscript of this article but was prevented by illness from coming to Sweden and delivering the lecture.
Secondly, since the dicarboxylic acid no longer contained the OH group of the cholesterol, it was evident that its formation from cholesterol must involve the following process:

![Diagram of chemical reaction]

There followed from this the further important fact that the OH group was not in a side chain in the cholesterol but was linked to a ring system.

At about the same time I proved that this OH group was a secondary alcohol group, for I succeeded - which had until then been attempted in vain - in converting cholesterol by a very simple method, namely by catalytic dehydration, into the corresponding ketone: cholestenone:

\[
\text{C}_{27}\text{H}_{44}\text{O} \xrightarrow{\text{H}_2\text{O}} \text{C}_{27}\text{H}_{44}\text{O}
\]

After these successes I withdrew for the time being from cholesterol research because, owing to the ever-increasing number of collaborators, I had to familiarize myself with many other fields of organic chemistry.

During the next two decades it was primarily Windaus and Wieland who devoted themselves - and with great success - to research on cholesterol. It was a satisfaction to me that the two compounds which I had discovered - the dicarboxylic acid \(\text{C}_{27}\text{H}_{44}\text{O}_4\) and the cholestenone \(\text{C}_{27}\text{H}_{44}\text{O}\) - played an important part in these investigations and advanced the research in a not inconsiderable degree.

Thus, elucidation of the complex cholesterol molecule proceeded step by step, until already by 1919, Windaus' was able to suggest a tentative cholesterol formula (I):

![Chemical structure of cholesterol]

A few years later, however, Wieland, Schlichting, and Jacobi suggested, on the basis of the results of their research, a different structural formula:
which differs from that of Windaus by its two five-membered rings, as well as in other important respects.

It will be seen, then, that ideas on the true structure of cholesterol, and therefore on its formula, were very vague at that time.

This uncertainty prompted me, remembering my former successes in this field, to try to "get through" to the aromatic basic skeleton and determine its character by dehydration of cholesterol.

I was fully aware, of course, that many unsuccessful attempts to do this had been made with a great variety of dehydrating agents. The problem, therefore, was to discover new dehydrating methods with a specific action.

First, I tried with palladinized charcoal in boiling cholesterol, i.e. at approximately 400ºC. I had some success here in so far as I actually obtained an abundant yield of an aromatic hydrocarbon, which could be characterized satisfactorily as the familiar chrysene:

![Chrysene](image)

However, for the structural formula - and this was the problem - it was scarcely possible to draw any useful conclusion from this observation, since at the high dehydration temperature rearrangements to the chrysene, which is exceptionally stable, are quite possible. Later, however, I was able to prove that chrysene is directly related to the true basic skeleton of cholesterol.

In other fields of organic chemistry sulphur had proved to be a very useful dehydrating agent, but with cholesterol it had been a failure because its action was too vigorous, and because it entered the molecule by substitution. Thus, all in all, dehydration of cholesterol with sulphur resulted in an amorphous mixture of semi-viscous substances which could not be separated from one another.
Then, fortunately, I hit upon the happy idea of replacing sulphur by selenium, because the action of this element is much more gentle than that of sulphur, and because it does not have the tendency to enter organic molecules.

This new dehydrating agent was an unexpected success.

By heating melted cholesteryl chloride or cholesterol with selenium powder until evolution of hydrogen selenide had ceased, and by fractionating the reaction product I obtained, as main product, a large yield of a beautifully crystallized aromatic hydrocarbon with the composition \( \text{C}_{18}\text{H}_{16} \) and melting point 124-125°C. This hydrocarbon has loomed very large in the literature on organic chemistry during the past two or three decades.

Since this wholly unexpected result, obtained by a method - "selenium dehydration" - which I had recently discovered, aroused much interest everywhere, it was only natural that, like a great many chemists throughout the world, I should have attempted to explain the structure of this hydrocarbon \( \text{C}_{18}\text{H}_{16} \), which was obviously the aromatic basic skeleton of cholesterol. Strangely enough, however, the task was by no means easy, despite the fact that this was an aromatic system.

And so it was that just before my own investigation had been brought to a successful and decisive conclusion, Harper, Kon, and Ruzicka forestalled me by establishing the identity of the \( \gamma \)-methylcyclopentenophenanthrene, which they had produced by synthesis, with the hydrocarbon \( \text{C}_{18}\text{H}_{16} \), which I had obtained by dehydrating cholesterol with selenium.

Shortly after this I myself again proved the identity of the two products by converting them into the same tribromide.

Subsequently the composition and correctness of the formulation of the important hydrocarbon \( \text{C}_{18}\text{H}_{16} \) was checked and confirmed in many different quarters, and consequently the following structure has been definitely assigned to it:

![Structure of cholesterol](image_url)

The first tangible result of this discovery was the certainty that a structural formula agreeing with all experimental observations could now be drawn up for cholesterol:
Much more important for science, however, was the fact, which was gradually emerging, that an intimate connection exists between cholesterol and a large number of substances of very great importance in the medical, physiological, and biological fields. Of these we will mention in particular ergosterol and the other steroids, bile acids, sex hormones, the "heart genins" (digitoxigenin, gitoxigenin, strophanthinidin, peristogenin, uzarigenin, etc.) and the neutral sapogenins.

The hormones corticosterone and desoxy-corticosterone:

which have very recently been isolated from suprarenal cortex by Kendall and Reichstein likewise contain the characteristic ring skeleton of $\gamma$-methylcyclopentenophenanthrene, as well as all the other above-mentioned natural substances in hydrated form.

All these compounds and many others can be transformed into the hydrocarbon $C_{18}H_{26}$ with its reliably determined structure of $\gamma$-methylcyclopentenophenanthrene by the method which I discovered for dehydrating cholesterol and which I introduced into science as "selenium dehydration".

Even the remarkable observation which I described a little earlier on, namely the formation of chrysene during severe dehydration of cholesterol with palladinized charcoal, is now explainable, for it is understandable that $\gamma$-methylcyclopentenophenanthrene (I), which is probably the first substance to be produced by dehydration:
should be transformed into chrysene (II) - which is extremely stable - under
the much more vigorous conditions of dehydration with palladinized charcoal at raised temperature, and that the process should be accompanied by
ring extension and splitting-off of hydrogen.

It will rightly be asked: What is the synthetic principle on which this
obviously highly important product of \( \gamma \)-methylcyclopentenophenanthrene
is built up in nature, and why is it that this particular type which, as founda-
tion of many substances indispensable to life and of extreme physiological
and biological importance, plays such a vital role in the vegetable and animal
kingdoms? However, the time has not yet come when we can give an
answer to questions so fundamental and so important to an understanding
of the workings of Nature. But I am firmly convinced that this problem -
like all others - will eventually be solved.