PART III

THE NUCLEAR MAGNETIC RESONANCE SPECTRA OF SOME 11H-INDENO-

[2,1-\(a\)] PHENANTHRENE DERIVATIVES AND THE STRUCTURE

OF C\(_{26}\) HYDROCARBON FROM CHOLESTEROL
The Nuclear Magnetic Resonance Spectra of Some $11H$-Indeno-
$[2,1-a]$phenanthrene Derivatives and the Structure of $C_{26}$
Hydrocarbon from Cholesterol.

During the last few years, nuclear magnetic resonance
spectroscopy has grown up to be one of the most powerful tool in
elucidating the structure of organic molecules. Together with
mass spectrometry, this new technique has largely replaced the
classical methods of degradative chemistry which not only
requires relatively large amount of sample materials but is also
very pains-taking and time-consuming. In the early sixties,
this laboratory was involved in the structure elucidation of a
$C_{26}$ hydrocarbon obtained as a minor product during selenium
dehydrogenation of cholesterol, by total synthesis of a suggested
structure. However, the synthetic hydrocarbon proved to be
different from the natural one and the problem was left unsolved.
At that time, the application of nuclear magnetic resonance
spectroscopy was in its early stage of development and could not
be used in our laboratory.

The structural problems of the steroids have long been
satisfactorily solved and almost all the important members of the
family have since then been totally synthesised. Naturally, the
interest in the structure of the above mentioned hydrocarbon has
subsided and the problem is therefore still left unsolved. In a
recent review on the dehydrogenation of organic molecules

1. Z. Valenta, 'Elucidation of organic structures by Physical
and Chemical methods', Part II, eds, K.W. Bentley and G.W.
a fresh mention has been made of this hydrocarbon and because of our earlier involvement, we thought that the use of nuclear magnetic resonance spectroscopy could easily solve the problem. The present work has been undertaken with two major objectives in view, namely, (i) to make a systematic study of the chemical shifts and coupling constants of the aromatic protons in 11H-indeno[2,1-a]phenanthrene and its derivatives, and (ii) to establish the structure of the C_{26} hydrocarbon from cholesterol, a derivative of the above aromatic ring system, from its spectral data. The subject does not conform to the general heading of the main thesis but as will be seen in the sequel, the geometry of the molecules and the relative disposition of the substituents are the major points to be investigated in this chapter and thus the study if not distinctly related to stereochemistry at least refers to chemistry in space. A review of the earlier work is given below.

The work dates back to 1927 when Diels\(^2\) discovered the use of selenium for dehydrogenation of organic molecules which subsequently became one of the most useful chemical tool for the elucidation of the structures of natural products (for various reviews, see references 3-6). The dehydrogenation of steroid

---

molecules was first undertaken by Diels and coworkers and
subsequently by Ruzicka and others, and gave a mixture of higher
aromatic compounds of which some are identified and a few are not.
Thus dehydrogenation of cholic acid (I) at various temperatures
afforded chrysene (II), picene (III), a cyclopentenophenanthrene
(IV) (commonly known as Diels hydrocarbon), an 11H-indeno[2,1-a]
phenanthrene (V) and one or two unidentified products 2,7-10.

In view of the special susceptibility of the steroids to
undergo molecular rearrangement, it is often very difficult to
explain the formation of the different hydrocarbons during
dehydrogenation particularly those formed at high temperatures.
As to the mechanism of dehydrogenation by selenium, it has been
suggested 11 that a reasonable pathway involves a \( -\)complex of
selenium with a double bond or an aromatic ring. This then
rearranges to a hydroperoxyselenide which undergoes thermal disso-
ciation a selenol and the latter either loses hydrogen selenide
to give an olefin, or is oxidised to a diselenide, or undergoes
a homolytic C-Se bond cleavage followed by further radical
reactions. Whatever be the mechanism, selenium dehydrogenation
often follows the same course as sulphur or palladium dehydro-
genations and the rearrangements observed are not specially
attributable to the influence of selenium but rather to the high
temperatures used.

CHART I

Cholic acid (I)  Chrysene (II)  Picene (III)

(IV)  (V)  (VI)

(1) $\rightarrow_{\text{Se}}$ (II) + (III) + (IV) + (V)

(VI) $\rightarrow$ (III)

(I) $\rightarrow$ (V)

(VII)
The different phenomena that happen with the dehydrogenation of steroids may be summed up as follows: (a) Loss of angular methyl groups and the 17-side chain; (b) elimination of the 17-side chain, cleavage of ring D, and incorporation of the 13-methyl group into a new six-membered ring as in the formation of chrysene (II); (c) a cleavage of the bond between C-13 and C-17, followed by a cyclisation to six-membered ring D, aromatisation and a further ring closer to the pentacyclic compound (VI). This explains the formation of picene (III) from cholic acid\(^\text{12}\) by further expansion (possibly by cleavage and reformation) of ring E; (d) the loss of 17-side chain with concommitant migration of 13-methyl to the vacated place which explains the formation of Diels hydrocarbon (IV); and (e) finally, cyclisation of the side chain during dehydrogenation with elimination of oxygen from a hypothetical intermediate ketone (VII) (from cholic acid as shown in chart-I) leading to 7-methyl-11H indeno[2,1-a]phenanthrene (V). (This hydrocarbon from cholic acid has been unambiguously identified by synthesis\(^\text{13}\)). Some other possible pathways have been suggested but no rigid proofs have yet been obtained in their support.

As already stated, cholesterol (VIII) or cholesteryl chloride on dehydrogenation with selenium\(^2\) (or with palladium) afforded in addition to 3-methyl-1,2-cyclopentenophenanthrene (IV), a minor hydrocarbon, m.p. 226\(^\circ\) with the molecular formula\(^{14}\) \(\text{C}_{25}\text{H}_{22}\) or

---

**Chart II**

Cholesterol (VIII)  \rightarrow  (IX)

**Scheme I**

\[
\text{MgBr} \quad \text{O} \quad \text{Me} \quad \text{Me}
\]

\[
\text{Cyclohexane} + \text{Cyclopentane} \rightarrow \text{Cyclopentane}
\]

\[
\text{CrO}_3 \quad \text{Se} \quad \text{AlCl}_3
\]

(IX)

(X)

(XI)

(XII) Ergosterol $R=\text{Me}$

(XIII) Phytosterol $R=\text{Et}$

7,8-dihydro
Based on the mechanism discussed earlier, Rosenheim and King suggested its structure as 10-isopropyl-7-methyl-11H-indeno-[2,1-a]phenanthrene (IX) presumably formed as a result of direct cyclisation of the side chain with ring D as in the case of cholic acid. Cook and coworkers synthesised the hydrocarbon (IX) by an unambiguous route (Scheme 1) by condensation of 3-5-tetralyl-ethylmagnesium chloride with 2,7-dimethyl-4-isopropylindan-1-one followed by cyclisation and dehydrogenation. The synthetic hydrocarbon m.p. 198° was found to be very similar so far ultraviolet absorption spectra and other physical properties were concerned, but was not identical with the natural one as proved by the depression of mixed melting point of the two hydrocarbons and also of the corresponding 11-keto-derivatives (X). The structure (IX) has, therefore, to be abandoned, although it became clear at this stage from the close similarity of the ultraviolet absorption spectra that the natural hydrocarbon is most probably a derivative of the 11H-indeno[2,1-a]phenanthrene (XI). The mechanism is also inadequate to explain the formation of two similar hydrocarbons but higher homologues (C27 and C28 respectively) from the dehydrogenation of ergosterol and phytosterols. Rosenheim-mechanism would predict the formation of the same hydrocarbon (IX) in all the three cases. Two other

15. O. Rosenheim and H. King, Chem. and Ind., 1933, 52, 299.
possible structures (XV) and (XVI) were suggested by Bernal and coworkers\textsuperscript{19} based on the cleavage of cholesterol molecule between C-14 and C-15 followed by formation of a six-membered ring as in (XIV) (Scheme 2). The intermediate structure (XIV) is capable of giving rise either to the pentacyclic structure (XV) or to (XVI). The mother hydrocarbon of the first structure (XV) was synthesised by Cook \textit{et al}\textsuperscript{20} who showed that its ultraviolet absorption spectra differed substantially from those of the natural hydrocarbon. The second structure (XVI) which appeared to fit in to the unit cell dimensions of the hydrocarbon as determined by X-ray crystallography\textsuperscript{19} has never been explored further.

Meanwhile, another hydrocarbon believed to have the molecular formula, C\textsubscript{21}H\textsubscript{16} was obtained from the dehydrogenation product\textsuperscript{21} of strophanthidin, a steroidal lactone (XVII)\textsuperscript{22} occurring in the seeds of 'Strophanthus kombe'. This was subsequently proved to be identical with 9-methyl-11H-indeno[2,1-a]phenanthrene (XVIII) by Bergmann\textsuperscript{23} who synthesised a specimen of it having m.p. 301\textdegree following the general procedure of Cook \textit{et al} shown in Scheme 1. Evidence presented for its identity with hydrocarbon from strophanthidin, the molecular formula of which was subsequently revised to C\textsubscript{22}H\textsubscript{16}, was, however, not conclusive since the 11-oxo-derivative could not be prepared due to scarcity of material.

\textsuperscript{21} W.A. Jacobs and R.E. Elderfield, \textit{J. Biol. Chem.}, 1934, 107, 143.
\textsuperscript{23} E. Bergmann, \textit{J. Amer. Chem. Soc.}, 1938, 60, 2306.
In view of the non-depression of mixed melting points in this series of compounds, the conclusion regarding the identity of the hydrocarbons which was drawn exclusively from the mixed melting point determination, is extremely unreliable. Bergmann put forward a mechanism (Scheme 3) for its formation in which there is an initial cleavage of the bond between C-13 and C-17. A new cyclopentane ring is then formed with the inclusion of 13-methyl group followed by a further cyclisation of the side chain to form ring E. The mechanism is completely novel and without any precedence in the dehydrogenation of sterols. It is also unusual that a cyclopentane ring be formed before the new aromatic ring is built up from the acyclic chain. According to this mechanism, the cholesterol and for that matter, ergosterol and phytosterols are capable of giving rise to the intermediates (XIX), (XX) and (XXI) respectively which would lead to the formation of the hydrocarbons (XXII), (XXIII), and (XXIV). This was the state of things24 when the work from our laboratory started in 1961.

A new synthesis of 11H-indeno[2,1-α]phenanthrene was developed by Nasipuri and Roy25 based on Robinson-Mannich base ring extension procedure applied to methyl 3'-oxo-1,2-cyclopentenophenanthrene-4'-carboxylate (XXV) as shown schematically (Scheme 4). The method was found to be particularly suitable for synthesis of indenophenanthrene derivatives with substituents in ring E. Later Nasipuri26 used the reaction sequence for a

---

CHART IV

(XIX) R = H
(XX) R = Me
(XXI) R = Et

(XXII)

(XXIII)

(XXIV)

Scheme 4

\[
\text{Br} + \text{CH}_2\text{CO}_2\text{Et} \rightarrow \text{CO}_2\text{Et} \rightarrow \text{CO}_2\text{Et} \rightarrow \text{H}_2\text{SO}_4
\]

1. Esterification
2. S, Δ

(XXV) (Sodiosalt)

1. \text{CH}_3\text{COCH}_2\text{CH}_2\text{N}^+\text{Me}_3\text{I}^-
2. KOEt

Reduction

Pd/C
synthesis of 7-isobutyl-9-methyl-11H-indeno[2,1-a]phenanthrene (XXII), the proposed structure for cholesterol hydrocarbon. For the purpose, the required Mannich base was prepared from the ketoester (XXVI) which in turn was obtained from isohexanoyl chloride (a) by condensation with ethyl sodioacetoacetate followed by methylation of the resultant dioxoester, or (b) by condensation with ethyl α-methylacetoacetate and ammonolysis of the product (Scheme 4a). The ketoester was next converted into the Mannich base (XXVII) according to Mannich and Curtaz\textsuperscript{27}; the structure of the latter was proved by its conversion into the keto-acid (XXVIII) through standard procedure. The methiodide of the Mannich base was next condensed with the sodio salt of the β-oxo-ester (XXV) and the pentacyclic ketone (XXIX) thus obtained was reduced and dehydrogenated to 7-isobutyl-9-methyl-11H-indeno[2,1-a]phenanthrene (XXII), m.p. 212°. This compound was, however, found to be different from that obtained from cholesterol, a sample of which was also prepared in this laboratory. They not only had different melting points but also gave different 11-oxo-derivatives and 2,4,7-trinitrofluorenone complexes.\textsuperscript{28}

The corresponding higher homologue (XXIII) was also likewise synthesised from the ketone (XXX) by Nasipuri, Roy and Bannerjee\textsuperscript{29} and was found to be different from that derived from ergosterol. Clearly Bergmann's mechanism is not working in the case of dehydrogenation of the sterols, a revision of structures for all the three natural hydrocarbons was necessary.

\textsuperscript{27} C. Mannich and K. Curtaz, \textit{Arch. Pharm.}, 1926, \textit{264}, 741.
Scheme - 4a

\[
\text{CHCl} + \text{CH}_3\text{COCH}_2\text{CO}_2\text{Et} \rightarrow \text{CH}_3\text{COCH}_2\text{CO}_2\text{Et} \quad \text{CH}_3\text{I, NaOEt}
\]

\[
\text{EtO}_2\text{C} \xrightarrow{\text{NH}_3} \text{CO}_2\text{Et} \quad (\text{XXVI}) \quad \text{KOH, HCHO, P, piperidine, HCl}
\]

\[
\text{CO}_2\text{H} \quad (\text{XXVIII})
\]

\[
(\text{XXVII})
\]

\[
(\text{XXIX})
\]

\[
(\text{XXX})
\]