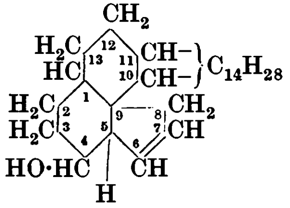
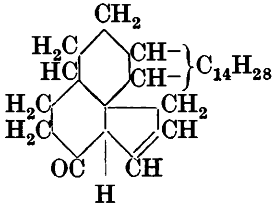
L.—*Studies in the Sterol Group. Part II. The Formation of ψ-Cholestene and Cholestenone by the Dry Distillation of Cholesterol.*

By Isidor Morris Heilbron and Wilfred Archibald Sexton.

The effect of heat on cholesterol (I) was first studied by Diels and Linn (*Ber.*, 1908, **41**, 260), who found that it was converted into a mixture of cholestenone (II) and β-cholesterol at 310°, hydrogen being evolved. Their statement that the dehydrogenation is due to the presence of minute quantities of iron or zinc in the cholesterol cannot be substantiated.

(I.)

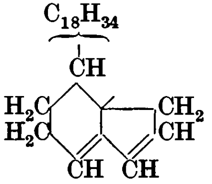


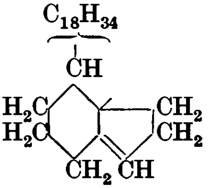


(II.)

More recently, Fantl (*Monatsh.*, 1926, **47**, 251) converted cholesterol into cholesterilene, to which the structure (III) is ascribed, by distillation with zinc dust under reduced pressure, the reaction being represented as a simple dehydration of the alcohol.

(III.)



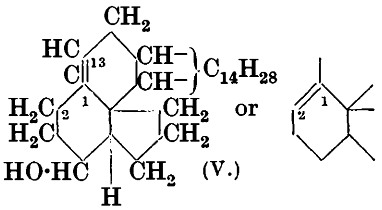


(IV.)

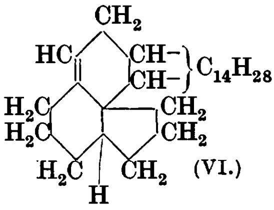
On the other hand, Windaus has shown (*Annalen*, 1927, **453**, 101) that when cholesterol is heated with nickel in absence of hydrogen the saturated ketones cholestanone and coprostanone are produced, a result which he considers may be due to the formation of *allo*-cholesterol (V) prior to the intramolecular rearrangement.

We have now found that the dry distillation of cholesterol at *atmospheric pressure* gives rise to yet another reaction whereby, together with hydrogen, water, and a complex mixture of low-boiling hydrocarbons, cholestenone and ψ-cholestene result. The former compound was isolated and recognised by means of its characteristic semicarbazone, and the identity of the ψ-cholestene was confirmed (*a*) by analysis, (*b*) by the melting point of a mixture with ψ-cholestene prepared by Mauthner's method (*Monatsh.*, 1907, **28**, 1113), (*c*) by means of its dibromide, and (*d*) through its catalytic hydrogenation to cholestane and ψ-cholestane.

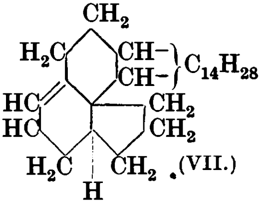
Fischer and Treibs (*Annalen*, 1926, **446**, 241) also have noted the formation of ψ-cholestene and hydrogen from boiling cholesterol at a pressure of 300 mm., but they failed to detect cholestenone. They conclude that the reaction occurs through the intermediate formation of cholesterilene (III), reduction to ψ-cholestene (IV) supposedly occurring through 1 : 4-addition. Although in agreement with these authors that the latter compound is a direct reduction product of cholesterilene, we are unable to accept their suggested mechanism for the following reasons. First, recent work by Windaus (*Nachr. Ges. Wiss. Göttingen*, Jan. 1926) points almost inevitably to the conclusion that ψ-cholestene has the structure (VI) or (VII) and not the structure (IV) originally ascribed to it (see Windaus, *Ber.*, 1919, **52**, 170), which formula indeed, as can be shown from models, could not possibly give rise to two



(V.)



(VI.)



(VII.)

isomeric saturated hydrocarbons. Secondly, there is distinct evidence that cholesterilene does not contain a conjugated linkage, as both Windaus (*Ber.*, 1906, **39**, 2261) and Fantl (*loc. cit.*) have failed to bring about its reduction by means of sodium and amyl alcohol.

We regard the formation of ψ-cholestene as the result of two distinct reactions: (*a*) dehydration of part of the cholesterol to cholesterilene, and (*b*) dehydrogenation of a further part to cholestenone, the hydrogen evolved in the latter reaction being utilised for the hydrogenation of the cholesterilene. Our experiments have led us to the conclusion that (*b*) takes place more readily than (*a*), and this interpretation is in full accord with the results obtained by other investigators. For instance, the failure of Diels and Linn (*loc. cit.*) to observe dehydration was doubtless due to their maximum temperature being considerably lower than ours. Similarly, in the reaction where Windaus employs nickel, a temperature of only 220° was reached, and this again would account for the absence of either ψ-cholestene or its reduction products. A review of the evidence indeed seems to show that the dehydrogenation of the secondary alcohol group is the fundamental reaction which takes place during the decomposition of cholesterol by heat.

It follows from the foregoing that one of the ethenoid linkages in cholesterilene must occupy the same position as in ψ-cholestene, a conclusion in complete agreement with the observed simultaneous production of cholestane and ψ-cholestane by its catalytic hydrogenation (Windaus and Seng, *Z. physiol. Chem.*, 1921, **117**, 158). The formation of the latter hydrocarbons is inexplicable on the assumption that (III) represents the true position of the ethenoid linkages in cholesterilene.

EXPERIMENTAL.

Cholesterol (200 g.) obtained from cod-liver oil, crystallised from ethyl acetate until the melting point was constant at 148·5°, and dried by prolonged heating in a steam-oven, was distilled in 50 g. lots, in a slow current of carbon dioxide, from a Jena glass flask fitted with a Liebig condenser through which water was run during the preliminary stages of the distillation. A second distillation flask served as receiver, the side arm of which was connected with U-tubes, surrounded by ice and salt, for collection of the highly volatile, low-boiling products; the gaseous portion, after passing through wash-bottles containing chloroform, was collected over alkali. The cholesterol was gently heated over a free flame and soon after it had melted a copious evolution of gas commenced. When the temperature had risen somewhat, the liquid began to distil, water and light oil passing over first, followed by a yellow oil the colour and viscosity of which gradually increased until only red, syrup-like drops distilled. The distillation was stopped at this point and the reddish-yellow distillate (176 g.), which darkened rapidly on exposure to air, was taken up in ether, dried, and fractionally distilled, four fractions being collected : (*a*) 60—100°/atm. press. (3 g.), (*b*) 100—200°/atm. press. (12 g.), (*c*) 140—240°/13 mm. (21 g.), and (*d*) 240—310°/13 mm. (121 g.). The volatile liquid which had condensed in the U-tubes (4 g.) and fraction (*a*) were united and fractionally distilled, but a constant-boiling portion could be obtained neither from them nor from fractions (*b*) and (*c*). These products are probably of the same complex nature as the compounds obtained by Fantl (*loc. cit.*) and by Steinkopf on heating cholesterol with kieselguhr (*J. pr. Chem.*, 1919, **100**, 65).

ψ-Cholestene. Fraction (*d*), which constituted the main portion, was dissolved in warm acetone, and the solution left for 2 days in the ice-chest; a crystalline solid (37 g.), m. p. 60—65°, had then separated. Repeated crystallisation of this from ether–alcohol gave colourless needles, m. p. 78°, which did not depress the m. p. of ψ-cholestene prepared by Mauthner's method (*loc. cit.*) (Found : C, 87·7; H, 12·2. Calc. for $C_{27}H_{46}$: C, 87·6; H, 12·4%). The substance was further characterised by the preparation of its dibromide, needles, m. p. 116° (Mauthner, *loc. cit.*, gives 116—117°), and also by the isolation of both cholestane and ψ-cholestane following its catalytic hydrogenation. This was carried out in dry ether at room temperature in the presence of palladium-black for 50 hours, the pressure varying from 1 to 1½ atmospheres; from 3·5 g. of the initial material, 1·6 g. of pure cholestane, m. p. 80°, were obtained together with 1·0 g. of ψ-cholestane, m. p. 70—71°. These two substances gave no depression of m. p. in admixture with cholestane and ψ-cholestane prepared from cholestene and cholesterilene, respectively.

The specific rotations of ψ-cholestene obtained from three separate distillations of cholesterol were determined in chloroform solution : $[\alpha]_D = +57{\cdot}5°$ ($c = 2{\cdot}482$), $+57{\cdot}12°$ ($c = 3{\cdot}176$), and $+58{\cdot}58°$ ($c = 2{\cdot}835$). Fischer and Treibs (private communication) found $[\alpha]_D = 43{\cdot}30°$ for the ψ-cholestene obtained by them (compare Heilbron, Morton, and Sexton, this vol., p. 47).

Cholestenone. After the separation of the ψ-cholestene, the acetone filtrate was concentrated, but no further crystalline substance could be isolated. The whole of the acetone was removed and the residual oil was dissolved in alcohol and treated with excess of semicarbazide acetate. After 2 days the copious precipitate (62 g.) was filtered off, dried, and crystallised from alcohol;

the pure semicarbazone (m. p. 234°) separated in gelatinous form but gradually became crystalline. Cholestenone semicarbazone, prepared by the method of Diels and Abderhalden (*Ber.*, 1904, **37**, 3101) melted at 234° and the m. p. of a mixture of the two substances showed no depression.

After removal of the semicarbazone, the remaining solution was precipitated with water and the oil was extracted with ether and dried. The dark red oil (30 g.) was fractionally distilled in a vacuum. The fractions were yellow, rapidly darkened on exposure to air, and failed to yield either solid material or bromo-derivatives.

We desire to express our thanks to Mr. W. Doran, M.Sc., for his help in this work and also to the Advisory Council of the Department of Scientific and Industrial Research for a grant to one of us (W. A. S.).

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