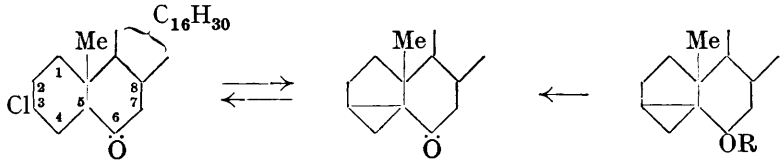
143. *Studies in the Sterol Group. Part XXXVI. The Oxidation of* i-*Cholesterol and its Derivatives.*

By I. M. HEILBRON, J. HODGES, and F. S. SPRING.

Oxidation of *i*-cholesterol, *i*-cholesteryl acetate and *i*-cholesteryl methyl ether gives " heterocholestenone " in good yield. An examination of this ketone reveals that it does not contain an ethylenic linkage and that on treatment with dilute hydrochloric acid it is converted into α-3-chloro-6-ketocholestane. These observations in conjunction with the fact that " heterocholestenone " is readily obtained from the chloro-ketone show that the former is to be represented by (II). *i*-Cholesterol is therefore (III; R = H), a structure originally suggested by Wallis, Fernholz, and Gephart. The ketone obtained indirectly from *i*-cholesterol by Ford, Chakravorty, and Wallis cannot be homogeneous or alternatively it cannot have the structure (II) ascribed to it by these authors. Reduction of " heterocholestenone " with aluminium *iso*propoxide gives an alcohol, characterised as its acetate, m. p. 60°, which may be an epimer of *i*-cholesteryl acetate; the reaction is being further investigated.

THE oxidation of *i*-cholesterol was studied by Wallis, Fernholz, and Gephart (*J. Amer. Chem. Soc.*, 1937, **59**, 137), who isolated from the neutral fraction a solid product of unsharp melting point, from which they obtained an oxime, m. p. 143—144°. Ford, Chakravorty, and Wallis (*J. Amer. Chem. Soc.*, 1938, **60**, 413) showed that on hydrolysis by means of alcoholic sulphuric acid, the oxime gave a ketone, m. p. 110—111°, which on treatment with hydrogen chloride in acetic acid yielded α-3-chloro-6-ketocholestane (I). Prior to the appearance of the memoir of Ford, Chakravorty, and Wallis we also had effected the conversion of *i*-cholesterol and its derivatives into α-3-chloro-6-ketocholestane and we now report upon our results because there are certain marked differences in the intermediates isolated by us and by the American authors.

In our hands the oxidation of either *i*-cholesterol, *i*-cholesteryl acetate or *i*-cholesteryl methyl ether with chromic acid at room temperature * gives a ketone, $C_{27}H_{44}O$, m. p. 97°, $[\alpha]_D^{18^\circ}$ + 40·9°, identical with the " heterocholestenone " prepared by Windaus and Dalmer (*Ber.*, 1919, **52**, 168) by treatment of α-3-chloro-6-ketocholestane (I) with alcoholic potassium hydroxide solution or alternatively by sublimation of the chloro-ketone (Windaus and Staden, *Ber.*, 1921, **54**, 1059). Windaus and Dalmer clearly considered the ketone to be unsaturated and this belief was substantiated by its catalytic hydrogenation to 6-ketocholestane. We find that " heterocholestenone " exhibits an absorption spectrum indicative of an isolated carbonyl group and therefore it cannot be 6-keto-Δ^4-cholestene. Moreover it fails to react with perbenzoic acid and gives no coloration with tetranitromethane in chloroform solution. Furthermore on treatment with hydrochloric acid in acetic acid " heterocholestenone " is quantitatively converted into α-3-chloro-6-ketocholestane (I), a reaction similar to that exhibited by *i*-cholesterol and its derivatives with the same reagent (Beynon, Heilbron, and Spring, J., 1936, 907; 1937, 1459). " Heterocholestenone " therefore contains a bridge ring and not an ethylenic linkage and must have the structure (II); the ketone, m. p. 110—111°, described by Ford, Chakravorty, and Wallis is either not homogeneous or it cannot have the structure (II) ascribed to it by these authors. The conversion of *i*-cholesterol and its derivatives into " heterocholestenone " has thus been effected without rupture of the bridge ring system. The



(I.) (II.) (III.)

---

* Oxidation of *i*-cholesteryl methyl ether in acetic acid at 97° gives 7-ketocholesteryl acetate as the sole neutral product.

formation of " heterocholestenone " from *i*-cholesterol clearly indicates that the latter is hydroxylated at C_6 and that it is to be represented by (III, R = H), a structure originally suggested by Wallis, Fernholz, and Gephart (*loc. cit.*). With the object of confirming this structure, the reduction of " heterocholestenone " with aluminium *iso*propoxide has been investigated. The product, however, was an oily alcohol, characterised by its *acetate*, $C_{29}H_{48}O_2$, m. p. 60°, which is not identical with *i*-cholesteryl acetate. The acetate, m. p. 60°, and its parent alcohol, like *i*-cholesteryl acetate and *i*-cholesterol, readily react with dilute hydrochloric acid to give cholesteryl chloride. It is possible that the acetate, m. p. 60°, is an epimer of *i*-cholesteryl acetate and with this in mind the reduction of " heterocholestenone " is being further investigated.

EXPERIMENTAL.

Oxidation of i-*Cholesterol : " Heterocholestenone."*—*i*-Cholesterol was oxidised with chromic acid at room temperature under the conditions used by Wallis, Fernholz, and Gephart (*loc. cit.*). The neutral fraction readily solidified on trituration with methyl alcohol and after repeated crystallisation from acetone, or more readily by sublimation in a vacuum, followed by crystallisation from acetone, gave " heterocholestenone " as needles, m. p. 97°, $[\alpha]_D^{18°} + 40{\cdot}9°$ ($l = 1, c = 2{\cdot}3$ in chloroform), showing no depression on admixture with an authentic specimen (Found : C, 84·1; H, 11·35. Calc. for $C_{27}H_{44}O$: C, 84·3; H, 11·5%). The *oxime* separated from methyl alcohol in colourless prisms, m. p. 123°, identical with that prepared from an authentic specimen of " heterocholestenone " (Found : C, 81·3; H, 11·2. $C_{27}H_{45}ON$ requires C, 81·1; H, 11·4%). " Heterocholestenone " was likewise obtained by the oxidation of *i*-cholesteryl acetate under exactly the same conditions, whereas the oxidation of *i*-cholesteryl methyl ether proceeded more slowly (48 hours).

α-3-*Chloro*-6-*ketocholestane from " Heterocholestenone."*—" Heterocholestenone " (0·1 g.) in glacial acetic acid (20 c.c.) and concentrated hydrochloric acid (1 c.c.) was kept overnight at room temperature. The reaction mixture was diluted with water and extracted with ether, and the extract washed with water and dried (sodium sulphate). The residue obtained on removal of the solvent was crystallised from methyl alcohol, giving α-3-chloro-6-ketocholestane in fine white needles, m. p. 131°, unchanged on admixture with an authentic specimen (Found : C, 76·7; H, 10·6. Calc. for $C_{27}H_{45}OCl$: C, 77·0; H, 10·8%).

Reduction of " Heterocholestenone."—The ketone (1·5 g.) was heated under reflux with aluminium *iso*propoxide (5 g.) in dry *iso*propyl alcohol (30 c.c.) for 48 hours. The alcohol was removed by distillation under reduced pressure, the residue treated with aqueous sodium hydroxide (10%), and the mixture extracted with ether. Removal of the solvent yielded an oil which would not crystallise. The oil was heated under reflux with an excess of acetic anhydride for 2 hours, the acetic anhydride removed under reduced pressure, and the residue taken up in alcohol. After standing at 0°, the *acetate* crystallised and after several recrystallisations from alcohol yielded hard white rosettes of needles, m. p. 60°, $[\alpha]_D^{18°} + 82{\cdot}4°$ ($l = 1$; $c = 1{\cdot}5$ in chloroform) (Found : C, 81·4; H, 11·3. $C_{29}H_{48}O_2$ requires C, 81·2; H, 11·3%).

Cholesteryl Chloride from the Acetate, m. p. 60°, and its Parent Alcohol.—The acetate or the oily alcohol (0·1 g.) in a mixture of glacial acetic acid (10 c.c.) and hydrochloric acid (0·5 c.c.) was set aside overnight. The crystalline mass was collected and recrystallised from alcohol, giving cholesteryl chloride in plates, m. p. 96°, unchanged on admixture with an authentic specimen.

7-*Ketocholesteryl Acetate from* i-*Cholesteryl Methyl Ether.*—*i*-Cholesteryl methyl ether (7 g.) in glacial acetic acid (300 c.c.) was treated with chromic acid (15·4 g.) in 80% acetic acid solution (60 c.c.), added during 40 minutes with vigorous agitation, the temperature being maintained at 97° throughout. The mixture was cooled, largely diluted with water, and extracted with ether. The extract was washed repeatedly with aqueous sodium carbonate solution and dried (sodium sulphate). The oily product remaining after removal of the ether was triturated with methyl alcohol, and the solid (1·5 g.) crystallised from methyl alcohol, from which 7-ketocholesteryl acetate separated in needles, m. p. 157°, unchanged on admixture with an authentic specimen.

Our thanks are due to the Rockefeller Foundation for a grant.

THE UNIVERSITY, MANCHESTER. [*Received, April 5th,* 1938.]