The Configurations of Cholesterol Oxides, Δ^4-Cholestenediols-(3,6), and Cholestanediols-(3,6).

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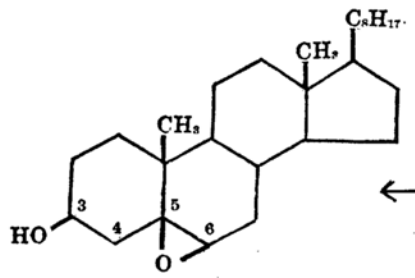
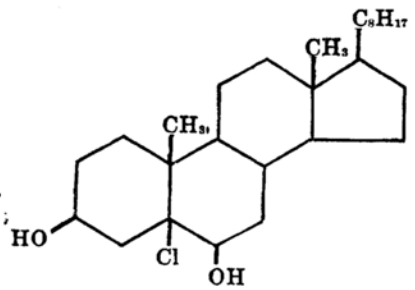
The action of perbenzoic acid on cholesterol in chloroform solution yields two isomeric cholesterol oxides.[1][2] α-Cholesterol oxide (m.p. 140–141°) is the less soluble and can be obtained in a pure state, while β-cholesterol oxide has not yet been isolated in a pure state. A similar treatment of cholesteryl acetate is reported to give mainly the acetate of β-cholesterol oxide,[2] but the homogeneity of the product thus obtained seems doubtful.[3] The α-oxide is hydrated to α-cholestanetriol-(3,5,6) when heated with water in a tube[1]; α-cholestanetriol is converted into "5-chloro-6-hydroxycholestanol" when treated with methanol-hydrochloric acid; and action of alcoholic potash on this chlorohydrin produces β-cholesterol oxide.[4][3] The β-oxide (m.p. 136°) obtained by this process is supposed to be pure.[3] Thus a complete inversion of α-oxide into β-oxide seems to occur during this transformation.

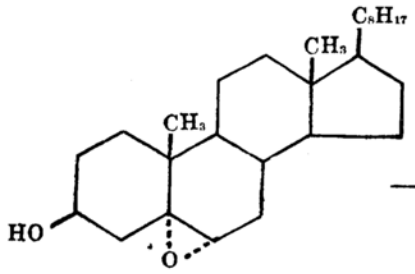
(1) T. Westphalen, *Ber.*, **48** (1915), 1064.
(2) L. Ruzicka and W. Bosshard, *Helv. Chim. Acta*, **20** (1937), 244.
(3) J. Hattori, *J. Pharm. Soc. Japan*, **60** (1940), 334.
(4) A. Windaus, *Z. physiol. Chem.*, **117** (1921), 146.



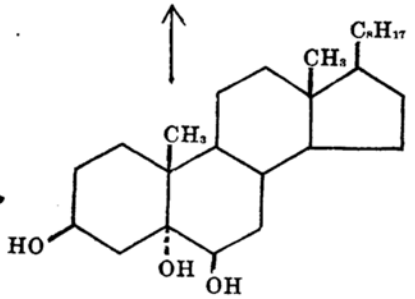
(I) β-Cholesterol oxide



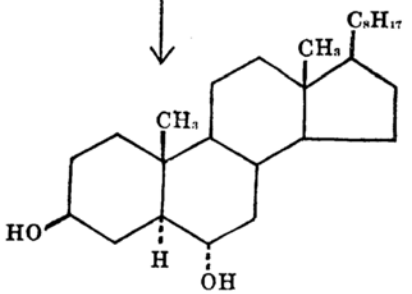
(II) 5-Chloro-6-hydroxycholestanol



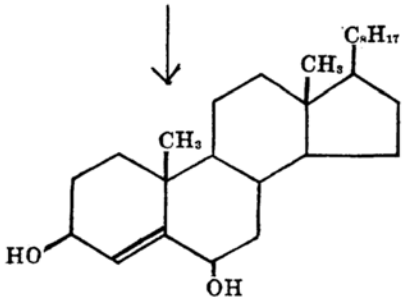
(III) α-Cholesterol oxide



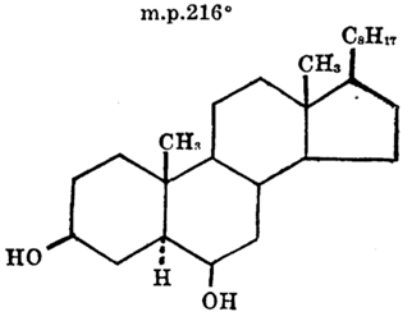
(IV) α-Cholestanetriol-(3,5,6)



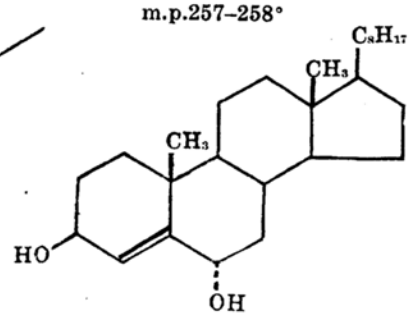
(V) Cholestanediol-(3,6)
m.p.216°



(VI) Δ^4-Cholestenediol-(3,6)
m.p.257–258°



(VII) Cholestanediol-(3,6)
m.p.194–195°



(VIII) Δ^4-Cholestenediol-(3,6)
m.p.178–179°

Formulas I and III have to be assigned to cholesterol oxides, but the configurations of the oxide rings in these stereoisomeric compounds have not yet been determined. Recently Ellis and Petrow[5] established the configurations of α- and β-cholestanetriols-(3,5,6), and showed the α-triol is cholestanetriol-(3β,5α,6β) (IV). Now, the transformation of α-cholesterol oxide into β-oxide through α-cholestanetriol and the known configuration of α-cholestanetriol enable the author to infer the configurations of cholesterol oxides.

The elimination of hydrogen chloride from the "5-chloro-6-hydroxycholestanol" by the above-mentioned process yields neither a Δ^4-cholestenediol nor 6-ketocholestanol through Δ^5-cholestenediol,[6] but gives a cholesterol oxide. Hence, it must be assumed that the chlorine atom at carbon atom 5 forms hydrogen chloride with the hydrogen atom attached to the hydroxyl group at carbon atom 6. Such an elimination may be easy if the chlorine atom is situated at a cis position to the hydroxyl group. If so, the substitution of a chlorine atom for the hydroxyl group at carbon atom 5 in α-cholestanetriol is accompanied by a Walden inversion, and the "5-chloro-6-hydroxycholestanol" is 5(β)-chloro-6β-hydroxycoprostanol-(3β) (II). An alternative is that a Walden inversion occurs at carbon atom 5, not when the chlorohydrin is formed from the triol, but when hydrogen chloride is eliminated from the chlorohydrin. In any case, β-cholesterol oxide should be 5,6-epoxy-coprostanol-(3β) (I), and consequently α-cholesterol oxide should be 5,6-epoxy-cholestanol-(3β) (III). It is fortunate that cholesterol oxides have been correctly designated as α and β, but the Greek letters may be more appropriately prefixed to the word "oxide," thus cholesterol α-oxide and cholesterol β-oxide.

Further, the configurations of Δ^4-cholestenediols-(3,6) and cholestanediols-(3,6) can be inferred from that of α-cholestanetriol. A Δ^4-cholestenediol-(3,6) melting at 257–258° is formed by the action of sodium acetate on cholesterol dibromide[7] or by the action of selenium dioxide on cholesteryl acetate or benzoate.[8][9] As this cholestenediol is also obtained by a Darzens dehydration of α-cholestanetriol diacetate followed by saponification,[10] it should be Δ^4-cholestenediol-(3β,6β) (VI). Another Δ^4-cholestenediol-(3,6) melting at 178–179° is obtained from 6-ketocholestanol through 5-bromo-6-ketocholestanol (acetate) and 6-keto-Δ^4-cholestenol-(3).[11] The latter cholestenediol differs from the cholestenediol melting at 257–258° only in the configuration of the hydroxyl group at carbon atom 6, because both are prepared from cholesterol as the starting substance and no change liable to cause an inversion of the hydroxyl group at carbon atom 3 is involved. Thus it is shown that the cholestenediol melting at 178–179° is Δ^4-cholestenediol-(3β,6α) (VIII).

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(5) B. Ellis and V. A. Petrow, *J. Chem. Soc.*, **1939**, 1078.

(6) H. Lettré and M. Müller, *Ber.*, **70** (1937), 1947, obtained a cholestenediol dibenzoate by eliminating hydrogen chloride from the dibenzoate of the same chlorohydrin but the product from hydrolysis of the cholestenediol dibenzoate proved to be 6-ketocholestanol.[10]

(7) J. Lifschütz, *Z. physiol. Chem.*, **106** (1919), 271; also compare foot-notes (8) and (9).

(8) O. Rosenheim, W. W. Starling, *J. Chem. Soc.*, **1937**, 377.

(9) A. Butenandt and E. Hausmann, *Ber.*, **70** (1937), 1154.

(10) V. A. Petrow, O. Rosenheim, W. W. Starling, *J. Chem. Soc.*, **1938**, 677.

(11) I. M. Heilbron, E. R. H. Jones, and F. S. Spring, *J. Chem. Soc.*, **1937**, 801.

The higher melting Δ^4-cholestenediol-(3,6) gives a saturated diol melting at 194–195° by a catalytic reduction with platinum oxide in acetic acid.[8] That the reduction product belongs to the cholestane series has not been proved but is highly probable because it is formed along with cholestane and cholestanol.[12] Then the constitution of the saturated diol should be cholestanediol-(3β,6β) (VII). Another cholestanediol-(3,6) melting at 216° is obtained by reducing 6-ketocholestanol with sodium and alcohol.[13] This diol is derived from cholestane because it was transformed into cholestane through dichlorocholestane,[13] and differs from the cholestanediol melting at 194–195° only in the configuration of the hydroxyl group at carbon atom 6. Thus the cholestanediol melting at 216° is cholestanediol-(3β,6α) (V).

Now, the experimental linking of α-cholesterol oxide to cholestanediol-(3β,6α) has been accomplished in this laboratory: Reduction of α-cholesterol oxide with sodium and amyl alcohol yields the same cholestanediol-(3,6) as obtained by the similar reduction of 6-ketocholestanol.[14] The establishment of this relationship affords a strong support to the configurations inferred from other evidences.

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(12) R. E. Marker and J. Krueger, *J. Am. Chem. Soc.*, **62** (1940), 79, obtained a cholestanediol-(3,6) melting at 190° by reducing 6-ketocholestanol with platinum oxide in alcohol. It is probably identical with the cholestanediol melting at 194–196° prepared by Rosenheim and Starling.[8] If so, this is surely a cholestane derivative.

(13) A. Windaus, *Ber.*, **50** (1917), 133.

(14) Experimental details will be reported by Dr. M. Chuman.