224. *Steroids and Related Compounds. Part I. Isomeric Cholestenediols.*

By VLADIMIR A. PETROW.

The dehydration of various derivatives of cholestane-3 : 5 : 6-triol to the corresponding Δ^4-cholestene-3 : 6-diols has been carried out. The further dehydration of these compounds to $\Delta^{4:6}$-cholestadien-3-ol has been attempted, but definite products could not be isolated.

Dehalogenation of cholesteryl ester dibromides with various reagents has been examined as another possible method of preparing $\Delta^{4:6}$-cholestadien-3-ol. *cis*-Δ^5-Cholestene-3 : 4-diol was isolated in each case from the products.

"Monobromocholesteryl benzoate" has been identified as 5 : 5′-dibromo-3 : 3′-dibenzoyloxy-6 : 6′-dicholestanyl. Its dehalogenation has been examined.

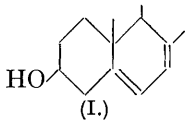
THE method at present available for the production of 7 : 8-dehydrocholesterol (I) is the dehydration of Δ^5-cholestene-3 : 7-diol (Windaus, Lettré, and Schenck, *Annalen*, **1935**, **520**, 98). As an alternative route, the dehydration of cholestane-3 : 5 : 6-triol derivatives and the dehalogenation of cholesteryl ester dibromides have been studied.

Westphalen (*Ber.*, 1915, **48**, 1064) dehydrated cholestane-3 : 5 : 6-triol diacetate (Pickard and Yates, J., 1908, **93**, 1678; Westphalen, *loc. cit.*) to 3 : 6-diacetoxy-Δ^4-cholestene (II). The removal of the C_6-hydroxyl group from this compound should furnish $\Delta^{4:6}$-cholestadien-3-ol (III), which might be expected, by analogy with the production of dehydroergosterol from ergostadientriol (I) (Windaus and Lüttringhaus, *Annalen*, 1930, **481**, 119), to isomerise readily to the desired 7 : 8-dehydrocholesterol (I).

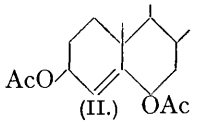
The diacetate (II) distilled unchanged on heating. The *dibenzoate* was stable up to about 290°/5 mm.; resinification then occurred.

Since cholesterilene can be obtained in good yield by the dry distillation of cholesteryl acetate under slightly reduced pressure (unpublished result; cf. Heilbron and Sexton, J., 1928, 347), it seemed probable that (III) might be obtained from 3-*benzoyloxy*-6-*acetoxy*-Δ^4-*cholestene* (IV) by distillation: this compound decomposed above 280°/5 mm., but

benzoic acid was evolved, *i.e.*, preferential removal of the C_3 hydroxyl group took place. 6-*Acetoxy*-3-*methoxy*-Δ^4-*cholestene* was stable and distilled unchanged.



(I.)



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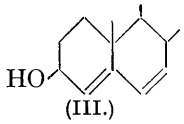

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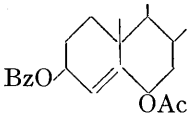

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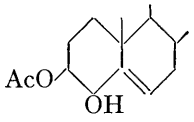

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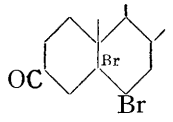

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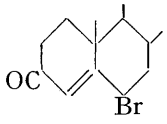

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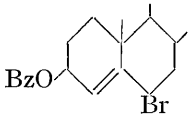
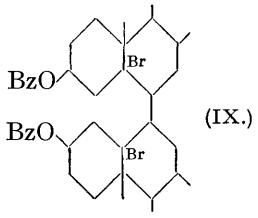


(VIII.)



(IX.)

The removal of two molecules of hydrogen bromide from cholesterol dibromide suggested another method of preparing (III). Treatment of cholesteryl acetate dibromide with potassium acetate in absolute alcohol gave cholesteryl acetate (cf. Urushibara and Ando, *Bull. Chem. Soc. Japan*, 1936, **11**, 434) together with cis-4-*hydroxy*-3-*acetoxy*-Δ^5-*cholestene* (V), m. p. 177°. The identity of the latter was established by acetylation; the *cis*-3 : 4-diacetoxy-Δ^5-cholestene obtained, m. p. 167°, was identical with the compound described by Rosenheim and Starling (this vol., p. 377) and by Butenandt and Hausmann (*Ber.*, 1937, **70**, 1154) and gave *cis*-Δ^5-cholestene-3 : 4-diol on hydrolysis. Treatment of cholesteryl acetate dibromide with sodium acetate in aqueous-alcoholic solution gave similar results.

Treatment of cholesteryl acetate dibromide with pyridine gave cholesteryl acetate in nearly quantitative yield; with silver nitrate in pyridine solution, followed by acetylation of the product, *cis*-3 : 4-diacetoxy-Δ^5-cholestene was obtained in a yield of about 20%.

Bromination of cholesteryl benzoate gives a substance that is apparently a monobromo-substitution product, together with the normal cholesteryl benzoate dibromide in small yield (Dorée and Orange, J., 1916, **109**, 53). By analogy with the spontaneous conversion of Δ^5-cholesten-3-one dibromide (VI) into 6-bromo-Δ^4-cholesten-3-one (VII) (Dane, Weg, and Schulte, *Z. physiol. Chem.*, 1936, **245**, 81) it seemed probable that the "monobromocholesteryl benzoate" was in reality 6-bromo-3-benzoyloxy-Δ^4-cholestene (VIII). The compound, however, was saturated (tetranitromethane, bromine) and had a molecular weight of the order of 1000. It must therefore be a dibromodihydrodicholesteryl derivative. Atomic-scale models show that it is best formulated as 5 : 5′-dibromo-3 : 3′-dibenzoyloxy-6 : 6′-dicholestanyl (IX) rather than the 6 : 6′-dibromo-5 : 5′-dicholestanyl compound. On dehalogenation with pyridine it gave cholesteryl benzoate in quantitative yield, and with silver nitrate in pyridine solution a product was obtained from which, after hydrolysis, both cholesterol and *cis*-Δ^5-cholestene-3 : 4-diol were isolated. Cholesteryl benzoate dibromide likewise gave the *cis*-diol on treatment either with potassium acetate in alcohol or with silver nitrate in pyridine, so the compound (IX) evidently reacts in solution as an equimolecular mixture of cholesteryl benzoate and cholesteryl benzoate dibromide.

Debromination of cholesteryl ester dibromides by the above methods thus takes the following course : (i) elimination of the bromine atom attached to C_5 takes place with the formation of a 6-bromo-3-hydroxy-Δ^4-cholestene derivative, and (ii) an intramolecular rearrangement to *cis*-4-bromo-3-hydroxy-Δ^5-cholestene occurs, followed by hydrolysis to *cis*-Δ^5-cholestene-3- : 4-diol.

Removal of two molecules of hydrogen bromide from Δ^5-cholesten-3-one dibromide

(VI) takes a normal course, yielding first the bromo-ketone (VII) and finally $\Delta^{4:6}$-cholestadien-3-one (Dane *et al.*, *loc. cit.*). The tendency of the double bond to retain an $\alpha\beta$-position with respect to the ketonic group in this compound evidently prevents the allene change taking place. The preferential formation of the *cis*-diol from cholesteryl ester dibromides, moreover, is in agreement with the observation of Butenandt (*Ber.*, 1936, **69**, 2289) that the bromine atoms in cholesterol dibromide have a *cis*-configuration with respect to the hydroxyl group and with the angular methyl group at C_{10}.

Experimental.

Microanalyses by Dr. G. Weiler are marked with an asterisk. The optical rotations were measured in chloroform solution in a 2 dm. tube.

Cholestane-3 : 5 : 6-*triol Diacetate.*—The following modified procedure gives a better yield than that of Pickard and Yates (*loc. cit.*) : Powdered cholesteryl acetate (5 g.) in glacial acetic acid (250 ml.) is treated with Merck's perhydrol (5 ml.) at room temperature for 4 days, the mixture being shaken at intervals. Water (250 ml.) is added and the precipitated solids are acetylated and purified from alcohol. Yield, 50—60%.

3 : 6-*Dibenzoyloxy*-Δ^4-*cholestene.*—25 G. of cholestanetriol diacetate in 300 ml. of acetic anhydride were treated with a few drops of concentrated sulphuric acid for 15 minutes on the water-bath. After hydrolysis the product was dissolved in 250 ml. of pyridine and heated with 25 ml. of benzoyl chloride for 1 hour on the water-bath. After extraction with 300 ml. of alcohol and purification from acetone, 3 : 6-*dibenzoyloxy*-Δ^4-*cholestene* formed silky needles, sintering at 163·5—164·5° and clearing at 182° (Found* : C, 80·5; H, 8·7. $C_{41}H_{54}O_4$ requires C, 80·7; H, 8·8%).

Δ^4-Cholestene-3 : 6-diol, obtained by hydrolysis of the dibenzoate, formed silky needles, m. p. 110·5—111·5°, from aqueous methyl alcohol (diacetate, m. p. 125°; Westphalen, *loc. cit.*). It gave a red colour with trichloroacetic acid on standing.

5-*Hydroxy*-3-*benzoyloxy*-6-*acetoxycholestane.*—2 G. of finely powdered cholesteryl benzoate in 50 ml. of glacial acetic acid were treated with 2 ml. of perhydrol for 1 hour on the water-bath. Water (50 ml.) was added, and the mixture kept overnight. The precipitated solids, after acetylation, were purified from alcohol and from light petroleum. 5-*Hydroxy*-3-*benzoyloxy*-6-*acetoxycholestane* formed flat needles, m. p. 162·5—163·5°, $[\alpha]_D$ −23·8° (c = 1·68) (Found : C, 76·3; H, 9·6. $C_{36}H_{54}O_5$ requires C, 76·5; H, 9·5%). Yield, 40—50%. On saponification it gave cholestanetriol, identified by m. p. and mixed m. p. with an authentic specimen.

3-*Benzoyloxy*-6-*acetoxy*-Δ^4-*cholestene.*—5-Hydroxy-3-benzoyloxy-6-acetoxycholestane in excess of acetic anhydride was treated with a trace of concentrated sulphuric acid for 15 minutes on the water-bath. The product was poured into water and purified from methyl alcohol–ether. 3-*Benzoyloxy*-6-*acetoxy*-Δ^4-*cholestene* separated from methyl alcohol as a flocculent mass, m. p. 138·5° (Found* : C, 78·1; H, 9·4. $C_{36}H_{52}O_4$ requires C, 78·8; H, 9·5%). On saponification it gave Δ^4-cholestene-3 : 6-diol, identified by m. p., mixed m. p., and conversion into the diacetate. It gave a yellow colour with tetranitromethane.

5 : 6-*Dihydroxy*-3-*methoxycholestane.*—25 G. of cholesteryl methyl ether, m. p. 84° (Stoll, *Z. physiol. Chem.*, 1932, **207**, 147), in 200 ml. of glacial acetic acid were treated with 25 ml. of perhydrol, with mechanical stirring, for 20 minutes on the water-bath. Water (300 ml.) was added, and the mixture kept overnight. The precipitated solids, after saponification, were dissolved in 100 ml. of light petroleum and after 12 hours the deposited crystals were removed, extracted with 50 ml. of light petroleum, and recrystallised from aqueous alcohol. 5 : 6-*Dihydroxy*-3-*methoxycholestane* formed flat plates, m. p. 154°, $[\alpha]_D$ −4·8° (c = 3·1) (Found* : C, 77·8; H, 11·5. $C_{28}H_{50}O_3$ requires C, 77·4; H, 11·5%), soluble in most organic solvents except benzene and light petroleum. Yield, 50—60%.

5-*Hydroxy*-6-*benzoyloxy*-3-*methoxycholestane.*—2 G. of 5 : 6-dihydroxy-3-methoxycholestane in 30 ml. of pyridine were treated with 2 ml. of benzoyl chloride for 24 hours at room temperature. The product was poured into water, and the precipitated solids crystallised from alcohol. 5-*Hydroxy*-6-*benzoyloxy*-3-*methoxycholestane* formed silky needles, m. p. 96·5—97·5°, $[\alpha]_D$ −33·1° (c = 2·42) (Found* : C, 77·4; H, 10·2. $C_{35}H_{54}O_4$ requires C, 78·0; H, 10·0%), moderately soluble in methyl and ethyl alcohols and readily soluble in ethyl acetate and light petroleum. Dehydration of this compound to the corresponding Δ^4-cholestene derivative with concentrated sulphuric acid in acetic anhydride solution was not successful, intractable gums being obtained.

5-*Hydroxy*-6-*acetoxy*-3-*methoxycholestane.*—2 G. of 5 : 6-dihydroxy-3-methoxycholestane in 8 ml. of acetic anhydride were heated for 1 hour on the water-bath. The product, on crystallisa-

tion from alcohol, gave white plates of 5-*hydroxy*-6-*acetoxy*-3-*methoxycholestane*, m. p. 118·5—119·5°, $[\alpha]_D$ −30·1° (*c* = 2·57) (Found* : C, 75·4; H, 10·2. $C_{30}H_{52}O_4$ requires C, 75·6; H, 10·9%).

6-*Acetoxy*-3-*methoxy*-Δ^4-*cholestene*.—0·2 G. of 5-hydroxy-6-acetoxy-3-methoxycholestane was heated for 15 minutes with 20 ml. of acetic anhydride containing a trace of concentrated sulphuric acid. The product was isolated in the usual way and dissolved in a little ether, and hot methyl alcohol added until a faint turbidity appeared. After standing overnight, the crystalline deposit was filtered off and purified from ether–methyl alcohol. 6-*Acetoxy*-3-*methoxy*-Δ^4-*cholestene* formed flat needles, m. p. 121·5—122·5°, $[\alpha]_D$ +166·6° (*c* = 0·15) (Found*: C, 78·3; H, 10·9. $C_{30}H_{50}O_3$ requires C, 78·6; H, 10·9%), moderately soluble in the usual organic solvents. The compound gave a yellow colour with tetranitromethane. In admixture with 5-hydroxy-6-acetoxy-3-methoxycholestane a m. p. depression of 20° was obtained. The compound distilled unchanged in a vacuum.

Dehalogenation of Cholesteryl Acetate Dibromide.—(a) *With potassium acetate in absolute alcohol*. 10 G. of cholesteryl acetate dibromide (m. p. 118°), 20 g. of anhydrous potassium acetate, and 400 ml. of absolute alcohol were refluxed for 48 hours. The product was evaporated to dryness under reduced pressure, and the residue extracted with light petroleum. On concentration, crystals of cis-4-*hydroxy*-3-*acetoxy*-Δ^5-*cholestene* were deposited which, after purification from light petroleum, had m. p. 176—177°, $[\alpha]$ −84·4° (*c* = 2·08) (Found* : C, 78·6; H, 10·8. $C_{29}H_{48}O_3$ requires C, 78·4; H, 10·8%). Yield, 10—15%. The product gave no colour with tetranitromethane, a deep blue trichloroacetic acid test (Rosenheim), and a purple antimony trichloride reaction. Acetylation, followed by crystallisation from acetic acid, gave needles of *cis*-3 : 4-diacetoxy-Δ^5-cholestene, m. p. 168—169°, $[\alpha]_D$ −93·6° (*c* = 3·0) (Found* : C, 76·4; H, 10·6. Calc. for $C_{31}H_{50}O_4$: C, 76·5; H, 10·4%), alone or in admixture with an authentic specimen kindly supplied by Dr. O. Rosenheim. Its identity was further confirmed by hydrolysis, *cis*-Δ^5-cholestene-3 : 4-diol being obtained, m. p. 176° (Found* : C, 80·3; H, 11·6. Calc. for $C_{27}H_{46}O_2$: C, 80·5; H, 11·5%); this was dehydrated by alcoholic hydrochloric acid to coprostenone (semicarbazone, m. p. 236—237°; 2 : 4-dinitrophenylhydrazone, m. p. 236—237°).

The light petroleum mother-liquors from the above gave, on further concentration, a microcrystalline deposit of cholesteryl acetate.

(b) *With sodium acetate in aqueous alcohol*. 6 G. of cholesteryl acetate dibromide were refluxed for 3 hours with a solution of 20 g. of sodium acetate in 200 ml. of 90% aqueous alcohol. The product was extracted with ether and formed a pale yellow gum. It was acetylated with 25 ml. of acetic anhydride for 30 minutes on the water-bath. The solution on cooling deposited a small quantity of gummy crystals, which were purified from alcohol and from glacial acetic acid and identified as the diacetate of the *cis*-diol by m. p. and mixed m. p.

(c) *With silver nitrate in pyridine solution*. To a solution of 10 g. of silver nitrate in 200 ml. of pyridine were added, in small portions with shaking, 10 g. of cholesteryl acetate dibromide. The mixture was warmed gently until solution was complete and left overnight at room temperature. The product was extracted with ether and acetylated (50 ml. of acetic anhydride for 1 hour on the water-bath). On cooling, crystals were deposited which, after purification from glacial acetic acid, formed needles, m. p. 166·5°, $[\alpha]_D$ −87·5° (*c* = 0·4) (Found : C, 75·9; H, 9·9. Calc. for $C_{31}H_{50}O_4$: C, 76·5; H, 10·4%), identified with *cis*-3 : 4-diacetoxy-Δ^5-cholestene by mixed m. p., by saponification to the diol, m. p. 174—175° (Found* : C, 80·6; H, 11·5. Calc. for $C_{27}H_{46}O_2$: C, 80·5; H, 11·5%), and by dehydration to coprostenone. Yield, 2·3 g.

5 : 5′-*Dibromo*-3 : 3′-*dibenzoyloxy*-6 : 6′-*dicholestanyl*.—The following procedure was adopted (cf. Dorée and Orange, *loc. cit.*) : 84 Ml. of a 27% solution of bromine in carbon disulphide were added dropwise to a solution of 63 g. of cholesteryl benzoate in 400 ml. of carbon disulphide at 0°, the mixture being mechanically stirred. The solvent was then removed under reduced pressure, the yellow gummy residue taken up in 100 ml. of chloroform, absolute alcohol added until a faint turbidity appeared, and the mixture left overnight to crystallise. The product, purified from acetone, formed prisms, m. p. 140°. Molecular weight 1060 (0·5 g. in 53 ml. of benzene raised the b. p. by 0·029°). From the acetone mother-liquor a small quantity of cholesteryl benzoate dibromide was isolated, m. p. 167°.

Dehalogenation of the Dibromodicholestanyl Compound.—5 G. of the compound were added to a 6% solution of silver nitrate in pyridine. After standing overnight at room temperature, the liquid was poured into water and extracted with ether. The product was evaporated to dryness and dissolved in a little pyridine, and alcohol added. The crystalline deposit, after crystallisation from acetone–methyl alcohol, was extracted with a large bulk of boiling alcohol

and filtered hot. The insoluble residue consisted of cholesteryl benzoate. The filtrate, on cooling, deposited flat needles, m. p. 133—134° (Found* : C, 81·7; H, 10·0%), from which, by saponification and crystallisation from light petroleum, the *cis*-diol was obtained, m. p. 176° (Found : C, 80·3; H, 11·5. Calc. for $C_{27}H_{46}O_2$: C, 80·5; H, 11·5%), identified by mixed m. p. and by conversion into the diacetate, m. p. 167°.

Dehalogenation of Cholesteryl Benzoate Dibromide.—(a) *With potassium acetate in alcohol.* 1·0 G. of cholesteryl benzoate dibromide in 40 ml. of acetone was added to a suspension of excess of anhydrous potassium acetate in 40 ml. of absolute alcohol, and the mixture refluxed for 3 hours. The product was evaporated to dryness under reduced pressure, and the residue extracted with ether. On addition of alcohol, crystals of cholesteryl benzoate were obtained. The mother-liquor deposited a further crop of material. This was hydrolysed, and the product extracted once with a small quantity of light petroleum and refluxed for 1 hour with 2 ml. of acetic anhydride. Crystals were deposited on cooling, which, after purification from alcohol, gave *cis*-3 : 4-diacetoxy-Δ^5-cholestene, m. p. 168° (Found : C, 76·2; H, 10·6. Calc. for $C_{31}H_{50}O_4$: C, 76·5; H, 10·4%), identified by mixed m. p.

(b) *Dehalogenation with silver nitrate in pyridine.* 0·5 G. of the dibromide was added to a solution of 0·5 g. of silver nitrate in 10 ml. of pyridine, and the mixture heated on a water-bath for 15 minutes. The liquid was poured into water and extracted with ether. The resulting oil was hydrolysed, and the product acetylated by heating for 1 hour on the water-bath with 2 ml. of acetic anhydride; crystals were deposited on cooling, identified as before with *cis*-3 : 4-diacetoxy-Δ^5-cholestene.

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