Loss of a Methyl Group in an Acid-catalysed Baeyer–Villiger Oxidation of 4,4-Dimethylcholestan-3-one [1]

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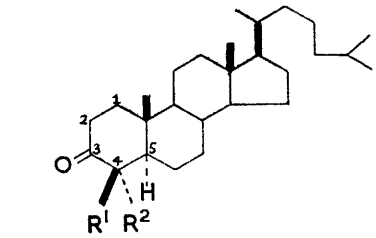
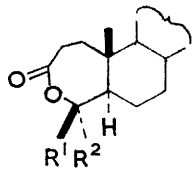
Oxidation of 4,4-dimethylcholestan-3-one with peroxy-acid in the presence of mineral acid gives the lactone 4aα-methyl-4-oxa-A-homocholestan-3-one. This reaction has been shown to proceed by way of a number of intermediates including 4a,4a-dimethyl-4-oxa-A-homocholestan-3-one, 4-methyl-4-methylene-3,4-secocholestan-3-oic acid, the corresponding epoxide, 4ξ-methyl-4ξ-formyl-3,4-secocholestan-3-oic acid, and 4α-methylcholestan-3-one. Deuteriation studies confirm the proposed sequence of intermediates and further suggest that the loss of the 4-methyl substituent, which occurs in the original reaction, is not stereospecific.

DURING an investigation into the oxidation of 4,4-dimethyl-3-oxosteroids and related compounds with peroxy-acids, we have found that treatment of 4,4-dimethylcholestan-3-one (I) with *m*-chloroperbenzoic acid or perbenzoic acid in the presence of mineral acid gives a product (65%) identical with 4aα-methyl-4-oxa-A-homocholestan-3-one (IV).[2] This apparently unique loss of a methyl group in a Baeyer–Villiger oxidation merited a careful investigation of the reaction.

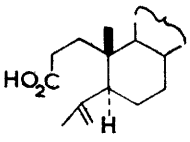
In the absence of mineral acid, oxidation of 4,4-dimethylcholestan-3-one (I) with *m*-chloroperbenzoic acid gives the expected product, 4a,4a-dimethyl-4-oxa-A-homocholestan-3-one (V).[2] Hence, at the outset it seemed likely that this might be an intermediate in the original reaction. Furthermore, treatment of the dimethyl lactone (V) with 10% sulphuric or hydrochloric acid in acetic acid, under conditions of acidity similar to those used in the original oxidation, gave in high yield 4-methyl-4-methylene-3,4-secocholestan-3-oic acid (VII),



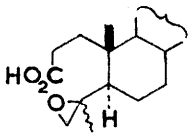
(I) $R^1 = R^2 = Me$
(II) $R^1 = H$, $R^2 = Me$
(III) R^1 or $R^2 = Me$, R^2 or $R^1 = CHO$



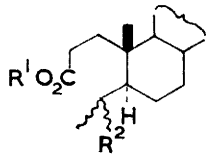
(IV) $R^1 = H$, $R^2 = Me$
(V) $R^1 = R^2 = Me$
(VI) $R^1 = Me$, $R^2 = H$



(VII)



(VIII)



(IX) $R^1 = Me$, $R^2 = CHO$
(X) $R^1 = H$, $R^2 = CHO$
(XI) $R^1 = H$, $R^2 = CO_2H$
(XII) $R^1 = H$, $R^2 = O{\cdot}CHO$

identical with the product obtained by pyrolysis of the dimethyl lactone (V).[2] Since oxidation of either the dimethyl lactone (V) or the unsaturated acid (VII), under the conditions of the original acid-catalysed oxidation of (I), gave the monomethyl lactone (IV) in similar yields to that of the original reaction, compounds (V) and (VII) are probably intermediates in the reaction sequence.

Oxidation of the unsaturated acid (VII) with *m*-chloroperbenzoic acid gave a thermally unstable product, purified by low temperature crystallisation from methanol. The mass and n.m.r. spectra of this compound establish its structure as 4ξ-methyl-4ξ-epoxymethylene-3,4-secocholestan-3-oic acid (VIII). The n.m.r. spectrum showed an AB system (τ 7·28 and 7·37, J_{AB} 4·5 c./sec.) due to the *gem*-protons of the epoxide ring, together with singlets at τ 8·72 and 9·04 due to the 4- and 10-methyl substituents respectively. Since the n.m.r. spectra of both the total crude and the recrystallised product are identical in showing only one AB system for the protons of the epoxide ring and only one singlet for the 4-methyl substituent, the epoxidation is probably stereospecific, although from the evidence available the stereochemistry of the product cannot be assigned.

Treatment of the epoxy-acid (VIII) with 10% sulphuric acid in acetic acid in the absence of oxygen gave a mixture separated into two principal components by preparative t.l.c. The material of higher R_F value was identified as 4α-methylcholestan-3-one (II) by comparison with an authentic sample.[3] The low R_F material was a carboxylic acid which could not be obtained crystalline. Conversion into the methyl ester by brief treatment with diazomethane gave a product which was acid-labile. It decomposed even in chloroform containing the usual traces of acid; accordingly the n.m.r. spectrum was determined for a solution in rigorously purified carbon tetrachloride. This spectrum showed that the product was a mixture of the two stereoisomers, methyl 4ξ-methyl-4ξ-formyl-3,4-secocholestan-3-oate (IX) present in approximately equal amounts. The aldehydic proton gave rise to two doublets at τ 0·37 (J 3 c./sec.) and 0·52 (J 0·5 c./sec.), the 4-methyl substituent to two doublets at τ 8·96 and 8·98 (J 6·5 c./sec.) and the ester methyl to two singlets at τ 6·46 and 6·48. Attempts to separate the two isomers were unsuccessful and the material was not obtained crystalline. Although the mixture did not give satisfactory elemental analyses, accurate mass measurement on the parent ion confirmed its composition. There can be little doubt as to the structures of these esters and accordingly those of the corresponding

[1] Preliminary communication, J. S. E. Holker, W. R. Jones, and P. J. Ramm, *Chem. Comm.*, 1965, 435.

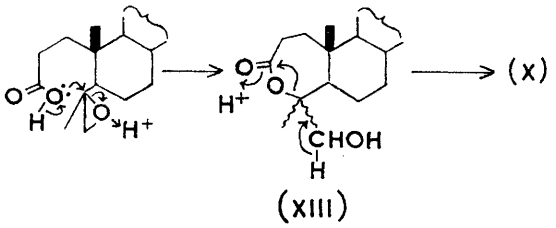
[2] D. Rosenthal, A. O. Niedermeyer, and J. Fried, *J. Org. Chem.*, 1965, **30**, 510.

[3] Y. Mazur and F. Sondheimer, *J. Amer. Chem. Soc.*, 1958, **80**, 5220.

acids (X) formed in the acid-catalysed rearrangement of the epoxide (VIII).

When the epoxy-acid (VIII) reacted with acid in the presence of air the monomethyl lactone (IV) was obtained as a major product together with reduced amounts of the 4α-methyl ketone (II) and the acid mixture (X). The lactone (IV) is likely to arise through aerial oxidation of the oxo-acid (X) to the peroxy-acid (XI), a well known type of autoxidation,[4] followed by attack of this peroxy-acid on the 4α-methyl ketone (II).

The evidence presented thus far indicates that in the original acid-catalysed Baeyer–Villiger oxidation the probable sequence of reaction intermediates is (I) ⟶ (V) ⟶ (VII) ⟶ (VIII) ⟶ (X) ⟶ (II) ⟶ (IV). Of these sequential transformations the production of intermediates (V), (VII), and (VIII) is unexceptional and requires no further comment. The isomerisation of the epoxide (VIII) to the aldehyde (X) may proceed either by the well documented mechanism involving protonation of the epoxide oxygen and hydride ion migration,[5] or by intramolecular participation of the carboxy-group (Scheme 1), in which case the hydroxy-lactone (XIII)



SCHEME 1

would be an expected intermediate.[5,6] However, no compound with this structure has been isolated. The formation of the monomethyl ketone (II) from the oxo-acid (X) presumably involves an acid-catalysed Claisen condensation to give the β-oxo-aldehyde (III) from which the loss of formic acid would be expected to occur readily under acid conditions [7,8] to give the enolic form of the monomethyl ketone (II). This would revert to the thermodynamically favoured 4α-methyl ketone. Although we have been unable to test this hypothesis on the oxo-acid (X), we did convert the corresponding ester (IX) into compound (II) under the usual conditions of acid catalysis.

Unfortunately the product sequence determined by the above stepwise procedure does not rule out variants in the original acid-catalysed Baeyer–Villiger reaction. For example, in the presence of an excess of peroxy-acid in the original reaction the oxo-acid (X) might undergo a Baeyer–Villiger reaction to give the two diastereoisomeric formate esters (XII), which on subsequent displacement of formic acid, would give a mixture of the 4aα- and 4aβ-methyl lactones (IV) and (VI) respectively. To test the feasibility of this route the mixed oxo-esters (IX) were hydrolysed to the corresponding acids (X) which were then treated with *m*-chloroperbenzoic acid under the normal Baeyer–Villiger conditions. The product from this reaction was isolated but not characterised, and then treated with mineral acid to give 4aα-methyl lactone (IV). The other expected product, the 4aβ-methyl lactone (VI), did not appear to be present.

The reason for this became clear when it was shown that an authentic sample of compound (VI) was isomerised on treatment with acid to give the 4aα-methyl lactone (IV) together with a second product which could not be obtained pure since it isomerised to the 4aα-methyl lactone on crystallisation. However, since all attempts to detect this second compound in the original acid-catalysed oxidation were unsuccessful, it seems probable that, at best, there is only minor participation of this route.

Further evidence for the proposed sequence of reaction intermediates was obtained by deuteriation studies. 2,2-Dideuterio-4,4-dimethylcholestan-3-one (XIV), prepared by treatment of compound (I) with dideuteriosulphuric acid in *O*-deuterioacetic acid, was subjected to the usual sequence of reactions [types (I) ⟶ (V) ⟶ (VII) ⟶ (VIII) ⟶ (X) + (II) + (IV)] with deuteriohydrochloric acid in *O*-deuterioacetic acid used to generate the unsaturated acid [type (VII)] and dideuteriosulphuric acid in *O*-deuterioacetic acid to convert the epoxy-acid [type (VIII)] into its transformation products types [(X), (II), and (IV)]. The pattern of deuterium incorporation for each compound was clearly indicated by mass spectrometry and n.m.r. studies (see Experimental section) and is summarised in Scheme 2. In the case of compounds (XVI)—(XX) mass spectrometry indicated additional species containing one or two fewer deuterium atoms than those shown. In the case of the 4α-methyl ketone (XIX) the deuterium distribution was confirmed by exchange with sulphuric acid in acetic acid when the three deuterium atoms at C-2 and C-4 were exchanged, whereas the deuterium atoms in the 4α-methyl substituent were retained.

These results are entirely compatible with the processes suggested earlier and provide evidence for further conclusions: (*a*) the absence of deuterium at C-5 in all the products examined indicates the non-participation of any intermediate with a 4,5-double bond, and (*b*) in the unsaturated acid (XVI) substitution of deuterium at all five positions of the isopropenyl group indicates equilibration presumably by way of the tertiary carbonium ion in which both 4-methyl substituents are stereochemically equivalent. Hence, even if the generation of the unsaturated acid involves the stereospecific loss of a proton from either the 4aα- or 4aβ-methyl substituent in compound (V), acid-catalysed equilibration

[4] T. A. Turney, 'Oxidation Mechanisms,' Butterworth, London, 1965, p. 171.

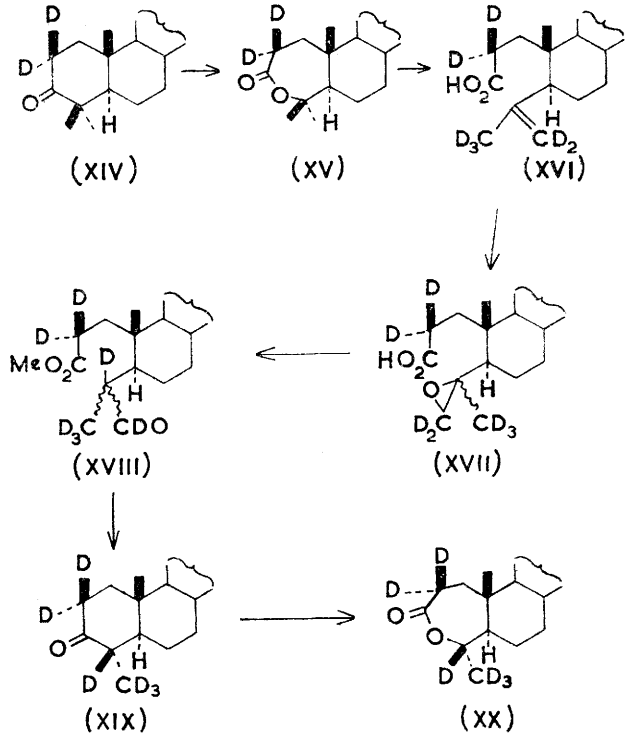
[5] A. Rosowsky, 'Heterocyclic Compounds with Three- and Four-membered Rings,' ed. A. Weissberger, Interscience, New York, 1964, p. 1.

[6] H. O. House, 'Modern Synthetic Reactions,' Benjamin, New York, 1965, p. 110.

[7] A. L. Wilds and C. Djerassi, *J. Amer. Chem. Soc.*, 1946, **68**, 1715.

[8] T. Inukai and R. Yoshizawa, *J. Org. Chem.*, 1967, **32**, 404.

then destroys any possible stereospecificity. However, if both mineral acid and peroxy-acid are present, as in the original reaction, it might still be possible to get stereospecific loss of one methyl group if the rate of epoxidation of the double bond in the unsaturated acid (VII) is greater than the rate of acid-catalysed equilibration.



SCHEME 2

In an attempt to test possible stereospecificity, the original reaction was carried out on the dimethyl ketone (I) with *m*-chloroperbenzoic acid and dideuteriosulphuric acid in *O*-deuterioacetic acid. The monomethyl lactone [type (IV)] obtained was investigated by mass spectrometry and found to contain species containing from one to six deuterium atoms. Since a completely stereospecific reaction sequence would demand no incorporation of deuterium into the 4α-methyl substituent of the lactone, and hence a maximum number of three deuterium atoms in the product, it seems likely that the reaction is hardly, if at all, stereospecific.

Further examples of this unusual reaction will be reported in future papers.

EXPERIMENTAL

Unless otherwise stated, i.r. absorption spectra were measured with a Perkin-Elmer model 125 instrument for solutions in carbon tetrachloride and ^{1}H n.m.r. spectra with either a Varian A60 or HA 100 instrument for solutions in deuteriochloroform containing tetramethylsilane as internal standard. All the compounds examined showed doublets (*J* 6 c./sec.) at τ 9·07 and 9·13 due to the 21- and 26- and the 27-methyl groups respectively and a singlet very near τ 9·33 due to the 18-methyl group. Mass spectra were measured with an A.E.I. MS9 instrument with a direct inlet system. The largest peaks in the high mass region are quoted with their relative intensities in parentheses. Optical rotations were measured for solutions in chloroform at room temperature with an ETL-NPL automatic polarimeter. Thin-layer chromatography was used to check purities and to monitor reaction. Plates (20 × 5 cm.) were coated with Merck Kieselgel G 254 in layers 0·025 cm. thick. M.p.s were determined with a hot-stage apparatus. The light petroleum used had b.p. 60—80°.

4aα-*Methyl*-4-*oxa*-A-*homocholestan*-3-*one* (IV).—Sulphuric acid (10%) in acetic acid (3 ml.) was added to a solution of 4,4-dimethylcholestan-3-one (0·5 g.) and *m*-chloroperbenzoic acid (1 g.) in dichloromethane (15 ml.). After 36 hr. at room temperature in the dark the mixture was diluted with ether (100 ml.) and the solution washed successively with water (50 ml.), 10% sodium iodide solution (50 ml.), 5% sodium disulphite solution (50 ml.), water (50 ml.), saturated sodium hydrogen carbonate solution (50 ml.), and water (3 × 50 ml.). The ether solution was dried ($MgSO_4$) and evaporated and the residue gave the lactone (IV) as fine needles (0·33 g.), m.p. 185—186·5° (from methanol). Two further crystallisations raised the m.p. to 190—191°, identical with that of a sample [2] prepared from 4α-methylcholestan-3-one [3] by oxidation with *m*-chloroperbenzoic acid. The samples had identical i.r. spectra, $\nu_{max.}$ ($CHCl_3$) 1728 cm.$^{-1}$, τ 9·07 (19-Me), 8·78 (d, *J* 7 c./sec., 4α-Me), and 5·5 (m, 4β-H), *m/e* 416 (1·00), 401 (0·15), 372 (0·44), 357 (0·24), and 315 (0·29) (Found: C, 80·9; H, 11·6. Calc. for $C_{28}H_{48}O_2$: C, 80·7; H, 11·6%).

4a,4a-*Dimethyl*-4-*oxa*-A-*homocholestan*-3-*one* (V).—Oxidation of 4,4-dimethylcholestan-3-one (0·5 g.) with *m*-chloroperbenzoic acid (0·62 g.) in dichloromethane (5 ml.) in the dark at room temperature (48 hr.), and isolation of the product as described above, gave the lactone (V) as microcrystals (0·17 g.), m.p. 123—125° (from methanol) (lit.,[2] 123—124°), $\nu_{max.}$ 1732 ($CHCl_3$) cm.$^{-1}$, τ 8·94 (19-Me) and 8·56 (4α- and 4β-Me), *m/e* 430 (0·11), 415 (0·05), 372 (1·00), and 357 (0·21), *m*/e* 342·7 (372 ⟶ 357) (Found: C, 81·1; H, 11·7. Calc. for $C_{29}H_{50}O_2$: C, 80·9; H, 11·7%).

4aβ-*Methyl*-4-*oxa*-A-*homocholestan*-3-*one* (VI).—Oxidation of 4β-methylcholestan-3-one [3] (83 mg.) with *m*-chloroperbenzoic acid in the usual way gave the lactone (VI) as leaflets (62 mg.), m.p. 177—179° (from ethanol) (lit.,[2] 177—179°), $\nu_{max.}$ ($CHCl_3$) 1731 cm.$^{-1}$, τ 8·98 (19-Me), 8·54 (d, *J* 7 c./sec., 4β-Me), and 5·65 (m, 4α-H), *m/e* 416 (0·05), 401 (0·04), 372 (1·00), and 357 (0·10), *m*/e* 342·7 (372 ⟶ 357).

4-*Methyl*-4-*methylene*-3,4-*secocholestan*-3-*oic Acid* (VII).—(*a*) 4a,4a-dimethyl-4-oxa-A-homocholestan-3-one (V) (0·5 g.) in dichloromethane (4 ml.) was treated with 10% sulphuric acid in acetic acid (3 ml.) at room temperature (24 hr.). After dilution with ether (50 ml.) the solution was washed with water (2 × 50 ml.), saturated sodium hydrogen carbonate solution (2 × 50 ml.), and water (3 × 50 ml.) and dried ($MgSO_4$). The ether was evaporated off and the residue gave the acid (VII) as plates (0·17 g.), m.p. 147—148° (from methanol) (lit.,[2] 117—119°), $\nu_{max.}$ 1705, 1635, and 897 cm.$^{-1}$, τ 9·10 (19-Me), 8·27 (4-Me), and 5·32 and 5·15 (AB system, *J* 10 c./sec., $CH_2{=}C\langle$), *m/e* 430 (0·11), 415 (0·05), 372 (1·00), and 357 (0·21), *m*/e* 342·7 (372 ⟶ 357) (Found: C, 81·1; H, 11·7. Calc. for $C_{29}H_{50}O_2$: C, 80·9; H, 11·7%).

(*b*) Treatment of the dimethyl lactone (V) (0·5 g.) with 20% hydrochloric acid in acetic acid (3·5 ml.) and dichloromethane (5 ml.) at room temperature (24 hr.), followed by isolation in the usual way, gave the unsaturated acid (VII)

as plates (0·48 g.), m.p. and mixed m.p. 146—147·5° (from methanol).

(*c*) Prepared from the dimethyl lactone (V) (82 mg.) by pyrolysis under nitrogen according to the literature procedure,[2] the unsaturated acid (VII) formed plates (46 mg.), m.p. and mixed m.p. 149—150° (from methanol).

4ξ-Methyl-4ξ-epoxymethylene-3,4-secocholestan-3-oic Acid (VIII).—4-Methyl-4-methylene-3,4-secocholestan-3-oic acid (0·5 g.) was oxidised with *m*-chloroperbenzoic acid in the usual manner. Crystallisation of the crude product (0·44 g.) from methanol at −60° gave the *acid* (VIII) as plates (0·23 g.), m.p. 112—114·5°, $[\alpha]_D$ +20° (*c* 0·89), $\nu_{max.}$ 1710 cm.$^{-1}$, τ 9·04 (19-Me), 8·72 (4-Me), and 7·28 and 7·37 (AB quartet, *J* 4·5 c./sec., *gem* protons of epoxide ring), *m/e* 446 (0·41), 428 (0·74), 415 (0·54), 400 (0·93), 372 (1·00), 355 (0·55), and 345 (0·99) (Found: C, 77·7; H, 11·6. $C_{29}H_{50}O_3$ requires C, 78·0; H, 11·3%).

Oxidation of the dimethyl lactone (V), the unsaturated acid (VII), or the epoxide (VIII) (0·2 g. in each case) with *m*-chloroperbenzoic acid and 10% sulphuric acid in acetic acid, under the usual conditions, in each case gave the monomethyl lactone (IV) (0·12, 0·12, and 0·13 g. respectively).

Reaction of 4ξ-Methyl-4ξ-epoxymethylene-3,4-secocholestan-3-oic Acid with Mineral Acid.—Sulphuric acid (10%) in acetic acid (3 ml.) was added to the epoxide (0·5 g.) in dichloromethane (5 ml.). After 48 hr. at room temperature the solution was diluted with ether (100 ml.), washed with water (2 × 50 ml.), saturated sodium hydrogen carbonate solution (2 × 50 ml.), 5% sodium disulphite solution (50 ml.), and water (3 × 50 ml.), and dried ($MgSO_4$). After evaporation of the solvent, the residue (0·47 g.) was separated by preparative t.l.c. on Merck Kieselgel G 254 (20 × 20 × 0·1 cm.); each plate carried 0·1 g. of material. Development with benzene–ethyl acetate (4 : 1) gave (*a*) material R_F 0·8 (0·13 g.) which gave needles of 4α-methylcholestan-3-one (II), m.p. and mixed m.p. with an authentic sample[3] 121·5—122·5° (from methanol); (*b*) material R_F 0·55 (85 mg.) which gave needles of 4aα-methyl-4-oxa-A-homocholestan-3-one (IV), m.p. and mixed m.p. 189—190° (from methanol); and (*c*) an acidic material R_F 0·05—0·25 (0·16 g.) which was treated with diazomethane in ether for 2 min. The resultant ester was purified by preparative t.l.c. on Merck Kieselgel G 254 (20 × 20 × 0·1 cm.); each plate carried 80 mg. of material. Development with benzene–ethyl acetate (6 : 1) gave *methyl 4ξ-methyl-4ξ-formyl-3,4-secocholestan-3-oate* (IX) (62 mg.) as an amorphous solid, $\nu_{max.}$ 2700, 1740, and 1728 cm.$^{-1}$, τ 9·11 (19-Me), 8·98 and 8·96 (each d, *J* 6·5 c./sec., 4-Me), 6·48 and 6·46 (ester Me), and 0·52 and 0·37 (*J* < 0·5 and 3·0 c./sec. respectively, ·CHO), *m/e* 460 (0·07), 442 (0·06), 432 (0·08), 403 (0·09), 373 (0·22), 363 (0·12), 355 (0·11), 347 (0·11), 346 (0·43), and 345 (1·00) [Found: *M* (accurate mass measurement), 460·391. $C_{30}H_{52}O_3$ requires *M*, 460·392].

When the above experiment was repeated under oxygen-free nitrogen in a sealed tube, the epoxide (0·5 g.) gave 4α-methyl-cholestan-3-one (0·16 g.) and methyl 4ξ-methyl-4ξ-formyl-3,4-secocholestan-3-oate (83 mg.). Although a weak spot corresponding to 4aα-methyl-4-oxa-A-homocholestan-3-one was discernible on t.l.c. examination, the amount was insufficient to permit isolation.

Treatment of methyl 4ξ-methyl-4ξ-formyl-3,4-secocholestan-3-oate (20 mg.) with 10% sulphuric acid in acetic acid under the usual conditions gave 4α-methylcholestan-3-one, purified by preparative t.l.c. and crystallisation from methanol to give needles (6 mg.), m.p. and mixed m.p. 121·5—122·5°.

Conversion of Methyl 4ξ-Methyl-4ξ-formyl-3,4-secocholestan-3-oate (IX) *into 4aα-methyl-4-oxa-A-homocholestan-3-one* (IV).—The ester (IX) (20 mg.) was saponified with potassium hydroxide (5 mg.) in ethanol (1 ml.) under reflux for 1 hr. The acid (X) was isolated in ether and the total unpurified product (17 mg.) was oxidised with *m*-chloroperbenzoic acid in the usual manner. The isolated material (15 mg.) was treated with 10% sulphuric acid in acetic acid, by the usual procedure. The crude product (11·7 mg.) was purified by preparative t.l.c. and gave needles (5·8 mg.) of the lactone (IV), m.p. and mixed m.p. 184—186° (from methanol).

Isomerisation of 4aβ-Methyl-4-oxa-A-homocholestan-3-one (VI).—This lactone (0·25 g.) was treated with 10% sulphuric acid in acetic acid under the usual conditions. The crude product (0·21 g.) consisted of two major components and a small amount of polar material. Separation was effected by preparative t.l.c. on Merck Kieselgel G 254 (20 × 20 × 0·1 cm.); each plate carried 75 mg. of material. Development with benzene–ethyl acetate (6 : 1) gave (*a*) material R_F 0·5 (78 mg.) which separated from methanol in needles of 4aα-methyl-4-oxa-A-homocholestan-3-one, m.p. and mixed m.p. 189—190° and (*b*) material R_F 0·6 (82 mg.), initially homogeneous (t.l.c.), but partially isomerised on attempted recrystallisation from methanol to the 4aα-methyl lactone (IV).

Under similar conditions, treatment of the 4aα-methyl lactone with sulphuric acid gave only unchanged starting material.

Deuteriation Studies.—In the following studies the reagents used were *O*-deuterioacetic acid, isotopic purity 98 atom-% D and dideuteriosulphuric acid (96—98%), isotopic purity 99 atom-% D.

(a) *2,2-Dideuterio-4,4-dimethylcholestan-3-one* (XIV). Prepared from 4,4-dimethylcholestan-3-one by treatment with 10% dideuteriosulphuric acid in *O*-deuterioacetic acid under the usual conditions, the dideuterio-derivative formed needles from methanol, m.p. 102·5—103·5°, τ 8·95 (19-, 4α-, and 4β-methyls) [Found: *M* (mass spectrum), 416. $C_{29}D_2H_{48}O$ requires *M*, 416].

(b) *2,2-Dideuterio-4a,4a-dimethyl-4-oxa-A-homocholestan-3-one* (XV). Prepared from the dimethyl ketone (XIV) in the usual way by oxidation with *m*-chloroperbenzoic acid, the product (XV) separated from methanol in needles, m.p. 122—123°, τ 8·94 (19-Me) and 8·56 (4α- and 4β-Me) [Found: *M* (mass spectrum), 432. $C_{29}D_2H_{48}O_2$ requires *M*, 432].

(c) *2,2-Dideuterio-4-trideuteriomethyl-4-dideuteriomethylene-3,4-secocholestan-3-oic acid* (XVI). The dimethyl lactone (XV) was converted into the unsaturated acid (XVI) in the usual way with 20% deuteriohydrochloric acid in *O*-deuterioacetic acid (prepared by treating sodium chloride with dideuteriosulphuric acid and absorption of the resultant deuteriohydrochloric acid). *Compound* (XVI) separated from methanol in plates, m.p. 146·5—148°, $\nu_{max.}$ 710 cm.$^{-1}$ (replacing 897 cm.$^{-1}$ in non-deuteriated material), τ 9·09 (19-Me) [no peaks at τ 8·27, 5·32, and 5·15 due to the protons of the isopropenyl group in the parent (VII)] [Found: *m/e* 437 (1·00), 436 (0·78), and 435 (0·28). $C_{29}D_7H_{43}O_2$ requires *M*, 437].

(d) *2,2-Dideuterio-4ξ-trideuteriomethyl-4ξ-dideuterioepoxymethylene-3,4-secocholestan-3-oic acid* (XVII). Prepared from compound (XVI) by oxidation with peroxy-acid

in the usual way, *compound* (XVII) was amorphous but homogeneous; τ 9·04 (19-Me) [no peaks at τ 8·72, 7·37, and 7·28 due to the epoxyisopropylidene group in the parent (VIII)] [Found: *m/e* 453 (0·46), 452 (0·44), and 451 (0·24), relative to 349 (1·00). $C_{29}D_7H_{43}O_2$ requires *M*, 453].

(e) *Treatment of compound* (XVII) *with acid*. With acid under the usual conditions in the presence of air compound (XVII) gave 2,2,4β-*trideuterio*-4α-*trideuteriomethylcholestan*-3-*one* (XIX) as needles from methanol, m.p. 117—119°, τ 8·96 (19-Me) [no doublet at τ 9·05 due to the 4α-methyl substituent in the parent (II)] [Found: *m/e* 406 (1·00), 405 (1·00), and 404 (0·52). $C_{28}D_6H_{42}O$ requires *M*, 406]; 2,2,4aβ-*trideuterio*-4aα-*trideuteriomethyl*-4-*oxa*-A-*homocholestan*-3-*one* (XX) as needles from methanol, m.p. 183—185°, τ 9·07 (19-Me) [no doublet at 8·78 due to the 4α-methyl substituent in the parent (IV)] [Found: *m/e* 422 (1·00), 421 (0·72), and 420 (0·31). $C_{28}D_6H_{42}O_2$ requires *M*, 422]; and *methyl* 2,2,4-*trideuterio*-4-*trideuteriomethyl*-4-*deuterioformyl*-3,4-*secocholestan*-3-*oate* (XVIII) as a gum, $\nu_{max.}$ 1740 and 1717 cm.$^{-1}$, τ 9·11 (19-Me) and 6·48 and 6·46 (OMe) [no doublets at τ 8·98, 8·96, 0·52, and 0·37 due to the 4-methyl and aldehyde substituents in the parent (IX)] [Found: *m/e* 467·436 (0·15), 466·429 (0·17), and 465 (0·09), all relative to 350 (1·00). $C_{30}H_{45}D_7O_3$ requires *M*, 467·436; $C_{30}H_{46}D_6O_3$ requires *M*, 466·429].

Treatment of compound (XIX) with 10% sulphuric acid in acetic acid under the usual conditions gave 4α-*trideuteriomethylcholestan*-3-*one* as needles from methanol, m.p. 120·5—121° [Found: *m/e* 403 (1·00) and 402 (0·34). $C_{28}D_3H_{45}O$ requires *M*, 403].

(f) *Oxidation of compound* (XIX). Treatment of this compound with peroxy-acid under the usual conditions gave 2,2,4aβ-trideuterio-4aα-trideuteriomethyl-4-oxa-A-homocholestan-3-one (XX) as needles from methanol, m.p. 187—188°, τ 9·07 (19-Me) [Found: *m/e* 422 (1·00), 421 (1·00), and 420 (0·45)].

(g) *Peroxy-acid oxidation of* 4,4-*dimethylcholestan*-3-*one in the presence of* 10% *dideuteriosulphuric acid in deuterioacetic acid*. By the usual procedure the experiment gave several deuteriated species of 4aα-methyl-4-oxa-A-homocholestan-3-one as needles from methanol, m.p. 187·5—189°, τ 9·07 (19-Me) with apparent absence of the doublet at τ 8·78 due to the 4α-methyl substituent in the non-deuteriated parent [Found: *m/e* 422 (0·79), 421 (1·00), 420 (0·90), 419 (0·67), 418 (0·39), and 417 (0·18)].

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