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REACTIONS OF EPOXIDES—V*

REARRANGEMENTS OF 5,6-EPOXY-6-METHYL-CHOLESTANES WITH BORON TRIFLUORIDE

J. W. BLUNT, M. P. HARTSHORN and D. N. KIRK
University of Canterbury, Christchurch, New Zealand

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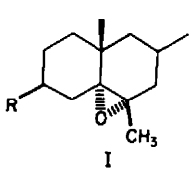
Abstract—5,6α-Epoxy-6β-methyl-5α-cholestane, like its 3β-acetoxy derivative, undergoes rearrangement with boron trifluoride to give the 5β-methyl-A-homo-B-nor-4a-ketone. The 3-deoxy-4a-ketone, however, undergoes a further rearrangement with boron trifluoride to give 5-methyl-5β-cholestan-6-one. 3β-Acetoxy-5,6β-epoxy-6α-methyl-5β-cholestane reacts rapidly with boron trifluoride to give a fluorohydrin, which suffers a slower rearrangement to give both the 5β-methyl-A-homo-B-nor-4a-ketone and 3β-acetoxy-5-methyl-5α-cholestan-6-one. In contrast, the 3-deoxy 5β,6β-epoxide gives 6-methyl-cholesta-3,5-diene, 5-acetyl-B-nor-5β-cholestane, and 5-methyl-5α-cholestan-6-one.

THE rearrangement of 3β-acetoxy-5,6α-epoxy-6β-methyl-5α-steroids (Ia) to give 5-methyl-A-homo-B-nor-5β-steroidal-4a-ketones (IIa)[1] raises two questions, when examined in the context of other epoxide-boron trifluoride reactions. The questions concern respectively the importance of the 3β-acetoxy group and of the stereochemistry of the epoxide in determining the course of the rearrangement. We therefore examined the reactions of boron trifluoride with the epimeric 5,6-epoxy-6-methylcholestanes lacking a substituent at C-3, and with 3β-acetoxy-5,6β-epoxy-6α-methyl-5β-cholestane (IIIa).

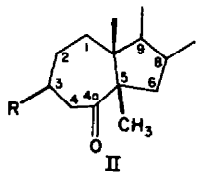
Following the procedure of Davis and Summers[2] the 3β-acetoxy-5β,6β-epoxide (IIIa) was first prepared as the minor product from the epoxidation of 6-methyl cholesteryl acetate, but when further quantities were needed an improved synthesis of the epoxide was developed. Cholesteryl acetate was treated with N-chloro-succinimide, giving the chlorohydrin (IVa) which was oxidized to give the chloro-ketone (Va) in good yield. The chloro-ketone (Va) reacted with methyl magnesium iodide to give the 6-methyl-chlorohydrin (IVb) which, without purification, was treated with alkali followed by acetic anhydride–pyridine, to give the 3β-acetoxy-5β,6β-epoxide (IIIa). The Grignard step in this synthesis proceeded well despite a report[3] that 5-halo-6-ketosteroids react with Grignard reagents to give ketonic products rather than halohydrins. We have confirmed, however, that the 5α-bromoketone is reduced by methylmagnesium iodide to give the debrominated 5α-cholestan-6-one.

* Part IV, *Tetrahedron* **20**, 2943 (1964).

[1] D. N. Kirk and V. Petrow, *J. Chem. Soc.* 4657 (1960).
[2] M. Davis and G. H. R. Summers, *J. Chem. Soc.* 4707 (1960).
[3] J. F. Bagli, P. F. Morand and R. Gaudry, *J. Org. Chem* **28**, 1207 (1963).



I
(a) R = OAc
(b) R = H



II
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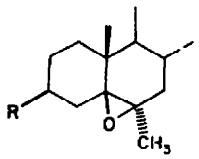
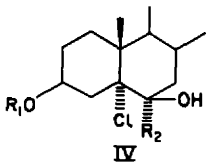
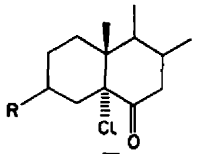
(b) R = H



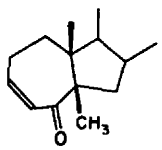
III
(a) R = OAc
(b) R = H



IV
(a) R_1 = Ac; R_2 = H
(b) R_1 = H ; R_2 = CH_3



V
(a) R = OAc
(b) R = H



VI

The 3-deoxy-5β,6β-epoxide (IIIb) was prepared in a similar manner from 5-chloro-5α-cholestan-6-one (Vb),[4] in excellent over-all yield. The deoxy-5α,6α-epoxide (Ib) was prepared from 5α-cholestan-6-one[5] by the following reaction sequence:

$$\text{6-Ketone} \xrightarrow{\text{MeMgI}} \text{6}\alpha\text{-methyl-6}\beta\text{-ol} \xrightarrow{-H_2O} \text{6-methyl-5-ene}$$

$$\xrightarrow{\text{Mono-perphthalic acid}} 5\alpha,6\alpha\text{-epoxide (Ib)}$$

The reaction between the 6β-methyl-5α,6α-epoxide (Ib) and boron trifluoride was straightforward, giving the 5β-methyl-A-homo-B-nor-4a-ketone (IIb) in high yield. The structure of this compound was indicated by its IR absorption (ν_{max} 1695·5 cm^{-1}), characteristic of a 7-membered ring ketone, and was confirmed by comparison with an authentic sample. This was prepared from the analogous 3β-acetoxy-4α-ketone (IIa) by the known route[1] comprising elimination of acetic acid on an alumina column and hydrogenation of the resulting Δ^3-4a-ketone (VI).

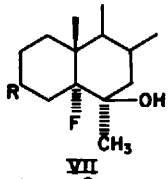
The behaviour of the 3β-acetoxy-5β,6β-epoxide (IIIa) with boron trifluoride was found to be more complicated. Brief reaction (2 min) in benzene solution gave the fluorohydrin (VIIa) in ca. 60% yield, but extension of the reaction time resulted in a rapid fall in the yield of the fluorohydrin, and the appearance of two ketonic products. The inference that the ketones were formed as a result of further transformations of the fluorohydrin (VIIa) was first confirmed by a careful study of the reaction employing thin-layer chromatography. A plate of silica gel was treated with aliquots of a typical epoxide-boron trifluoride reaction mixture at time intervals ranging from 1 to 60 min. The portion of the plate to which the spots were applied was exposed to a moist atmosphere in order to hydrolyse the boron trifluoride rapidly. The plate was developed in chloroform, and, after treatment with antimony trichloride–chloroform, revealed that the epoxide had disappeared after 3 min, giving rise to fluorohydrin (VIIa) as well as traces of other products. The decay of the fluorohydrin after 2 min was accompanied by the appearance of two ketones, the other trace

[4] C. W. Shoppee, R. H. Jenkins and G. H. R. Summers, *J. Chem. Soc.* 1657 (1958).

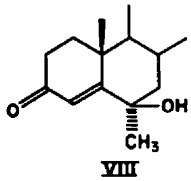
[5] Prepared from cholest-5-ene by reaction with diborane followed by chromic acid *in situ*. Cf. J. F. Bagli, P. F. Morand and R. Gaudry, *J. Org. Chem.* 27, 2938 (1962).

products also increasing gradually. A still more revealing result was obtained by employing a second thin-layer chromatogram to examine the behaviour of the fluorohydrin on treatment with boron trifluoride under the conditions employed for the epoxide reaction. The pattern of spots obtained from the fluorohydrin was indistinguishable from the original pattern using the epoxide, and showed precisely the same changes with time. Finally, the fluorohydrin was allowed to react with boron trifluoride for 45 min and the two ketones were isolated from the product.

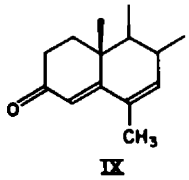
The formation of the fluorohydrin (VIIa) is exactly analogous to the behaviour of the 5β,6β-epoxide without a 6-methyl substituent.[6] A similar result was reported recently[7] for the 6-methyl-spirostane analogue, but no mention was made of subsequent changes involving the fluorohydrin. The structure (VIIa) assigned to the fluorohydrin was established by submitting it to vigorous alkaline hydrolysis followed by acetylation, when the original epoxide (IIIa) was recovered. Milder hydrolytic conditions gave the 5α-fluoro-3β,6β-diol (VIIb), which was oxidized to give the 3-ketone (VIIc). The Cotton curve ($a = +48$) was consistent with the 5α-configuration. The fluoroketone (VIIc) was converted into the 6β-hydroxy-6α-methyl-Δ^4-3-ketone (VIII) by dilute alkali, while acidic hydrolysis of either the fluoroketone (VIIc) or the Δ^4-3-ketone (VIII) gave 6-methylcholesta-4,6-dien-3-one (IX).[8]



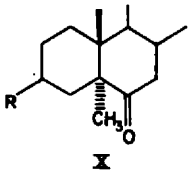
VII
(a) R = β-OAc
(b) R = β-OH
(c) R = :O
(d) R = H



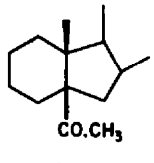
VIII



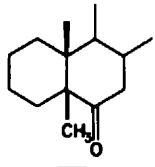
IX



X
(a) R = OAc
(b) R = H



XI

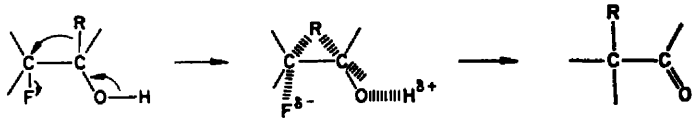


XII

The major of the two ketonic products was unexpectedly identified as 3β-acetoxy-5-methyl-A-homo-B-nor-5β-cholestan-4a-one (IIa). This ketone is the sole product of rearrangement of the 6-methyl-5α,6α-epoxide (Ia), and its formation from the 5β,6β-epoxide (IIIa) requires an inversion of configuration at the site of the methyl group. The significance of this will be discussed later. The identity of the two samples of the ketone (IIa) was confirmed by m.p. and mixed m.p., specific rotations, IR and NMR spectra, and ORD as well as by their conversion into identical samples of the Δ^3-4a-ketone (VI).

[6] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 4765 (1957).
[7] Chow Wei-Zan, Chu Wai-Shang and Huang-Minlon, *Acta Chim. Sinica* **29**, 364 (1963).
[8] B. Ellis, D. N. Kirk, V. Petrow, B. Waterhouse and D. M. Williamson, *J. Chem. Soc.* 2828 (1960).

The second ketone is believed to be 3β-acetoxy-5-methyl-5α-cholestan-6-one (Xa) on the basis of its IR spectrum, its negative Cotton curve ($a = -116$; cf. 3β-acetoxy-5α-cholestan-6-one, $a = -76$[9]), and its NMR spectrum, which was similar to that of 3β-acetoxy-5α-cholestan-6-one, but exhibited a peak due to the 5α-methyl group instead of the 5α-proton signal. It has been pointed out[10] that a rigid steroidal *trans*-diaxial fluorohydrin is unfavourably oriented for rearrangement leading directly to a ketone, although such rearrangements are known to occur in open-chain compounds which can assume a conformation favourable to the mechanism:



The observed formation of the 5α-methyl-6-ketone (Xa) from the fluorohydrin (VIIa) involves migration of the methyl group from a position *cis*- to the leaving F^- ion, while rearrangement leading to the 4a-ketone (IIa) requires migration of the oxygen atom from C-6. Neither process is compatible with the simple mechanism shown above, but an alternative mechanism is proposed which provides a simple pathway to both ketones. The 6β-hydroxy group in the fluorohydrin is envisaged as participating (possibly as $—O\cdot\overline{B}F_3$) in the abstraction of the fluoride ion from the 5α-position by a molecule of boron trifluoride, to give a BF_4^- ion. Both House[11] and Goldsmith[10] have demonstrated the formation of fluorohydrins from epoxides by the action of a limited amount of boron trifluoride, preferably in ether. These authors also showed that an excess of boron trifluoride in hydrocarbon solvents is required to convert the fluorohydrins into ketones. Since boron trifluoride would be expected to exert its properties as a Lewis acid more effectively in non-polar solvents than in ether, these observations are fully consistent with the mechanism postulated above. The initial product from the assisted elimination of the 5α-fluoro-substituent has a structure equivalent to the original epoxide-boron trifluoride complex. Cleavage of the epoxide bond to C-6 would then develop a carbonium ion at C-6, and subsequent migration of the 10,5 bond to 10,6 would give the 4a-ketone (IIa). The 5β-configuration of this ketone requires a non-concerted rearrangement of the epoxide, and must arise by attack upon the C-6 carbonium ion from the side originally occupied by the oxygen atom. The slow rate of this process compared with the rate of formation of the same ketone from the 5α,6α-epoxide (Ia) is compatible with the requirement of a high energy carbonium ion intermediate. The epoxide–boron trifluoride complex can also be invoked as the intermediate in the formation of the 5α-methyl-6-ketone (Xa), by migration of the 6α-methyl group, possibly concerted with rupture of the epoxide at C-5. However, this must also be a high-energy process owing to the -I effect of the 3β-acetoxy group, which opposes ionic cleavage of the epoxide at C-5.

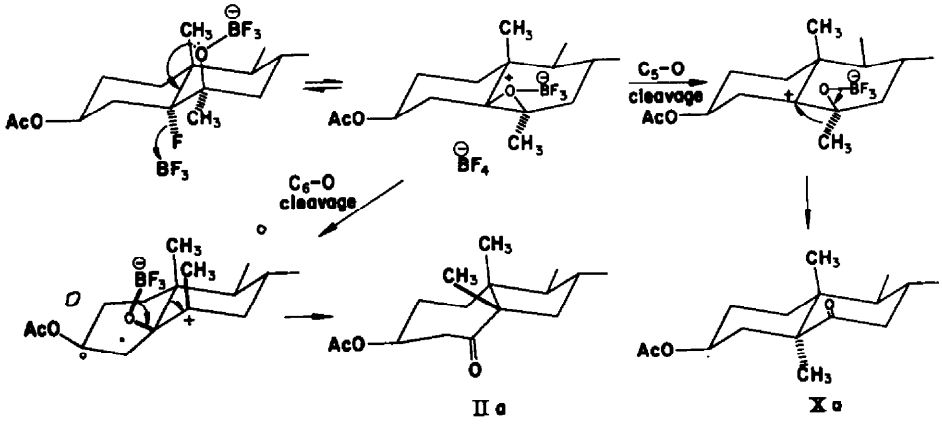
According to this interpretation the fluorohydrin (VIIa) is regarded as the product of the kinetically-preferred reaction between the 5β,6β-epoxide and boron trifluoride,

[9] W. Moffitt, R. B. Woodward, A. Moscowitz, W. Klyne and C. Djerassi, *J. Amer. Chem. Soc.* **83**, 4013 (1961).

[10] D. J. Goldsmith, *J. Amer. Chem. Soc.* **84**, 3913 (1962).

[11] H. O. House, *J. Amer. Chem. Soc.* **78**, 2298 (1956).

but must also be in equilibrium with a small concentration of the epoxide–boron trifluoride complex under the reaction conditions. The alternative rearrangements of the complex to give ketones (IIa and Xa), through transition states of higher energy, are presumably favoured by greater thermodynamic stabilities of the ketones compared with the fluorohydrin.



IIa Xa

The 3-deoxy 5β,6β-epoxide (IIIb) reacted rapidly with boron trifluoride in benzene to give a mixture of products. Chromatographic separation gave a non-polar gum having UV and IR spectra which revealed the presence of ca. 60% of 6-methyl-cholesta-3,5-diene, although this could not be separated from the contaminants. This material was followed by 5-acetyl-B-nor-5β-cholestane (XI) and 5-methyl-5α-cholestan-6-one (Xb), which were imperfectly separated by the column. The 5β-acetyl-B-nor structure was assigned from a consideration of the possible ketonic structures (cf. Part IV) and the NMR spectrum, with a peak at τ7·87 providing unequivocal evidence for the presence of an acetyl group. The 5α-methyl-6-ketone was characterized by its IR spectrum and a strongly negative Cotton curve ($a = -116$). The NMR spectrum also supported the structure.

When the 3-deoxy-5β,6β-epoxide was treated with a limited amount of boron trifluoride in ether it was slowly converted into the fluorohydrin (VIId), without the appearance of ketonic products. The conversion of this fluorohydrin into ketones (Xb and XI) by boron trifluoride in benzene was demonstrated, as in the case of the 3β-acetoxy derivative, by thin-layer chromatograms. It cannot be concluded, however, that the fluorohydrin is necessarily an intermediate in the reaction of the 3-deoxy-epoxide in benzene.

The 3-deoxy-ketones (XI and Xb) are the products which would be expected from rearrangement of a C-5 carbonium ion. The 5β-acetyl-B-nor compound (XI) would be formed by migration of the 6,7-bond, and the 5α-methyl-6-ketone (Xb) by migration of the 6-methyl substituent, both with retention of the configuration of the migrating group (cf. Part IV, which describes similar reactions of a 4α-methyl-4β,5β-epoxide). The dramatic difference from the behaviour of the 3β-acetoxy 5β,6β-epoxide will be discussed in a later paper in this series.

Following our discovery that a 5β-methyl-A-nor-B-homo-6-ketone could be isomerized under the influence of boron trifluoride to give the 5β-methyl-4-ketone

(Part IV), the stability of the ketones prepared in the present work was examined. The 5β-acetyl compound (XI) and the 5α-methyl-6-ketone (Xb) were not changed significantly by contact with boron trifluoride, and the 3β-acetoxy-4a-ketone (IIa) was only slowly converted into non-polar material under similar conditions. However, the 3-deoxy-A-homo-B-nor-4a-ketone (IIb) rearranged in contact with boron trifluoride. The product was separated chromatographically to give a non-polar fraction (30%), 5-methyl-5β-cholestan-6-one (XII; 40%), and unreacted 4a-ketone (12%). The structure of the new ketone (XII) was indicated by its IR absorption (ν_{max} 1704 cm^{-1}), specific rotation ($[\alpha]_D$ −55°; cf. 5β-cholestan-6-one, $[\alpha]_D$ −42°[12]), and Cotton curve ($a = -71$; cf. 5β-cholestan-6-one, $a = -77$[9]).

An examination of Dreiding models of the 4a-ketone (IIb) and the 5β-methyl-6-ketone (XII) indicated that the total of destabilizing interactions in the latter would probably be less than the total for the 4a-ketone. However, the excess of strain energy in this A-homo-B-nor-4a-ketone was less clearly apparent than in the case of the A-nor-B-homo-6-ketone described in Part IV. We were able to establish the reversibility of the process of ketone rearrangement by treating the 5β-methyl-6-ketone (XII) with boron trifluoride. The product was again a mixture which yielded non-polar material, followed by the 5β-methyl-6-ketone (XII), and the 5β-methyl-A-homo-B-nor-4a-ketone (IIb) *in the same ratio* (ca. 3·4:1) as from the rearrangement of the 4a-ketone. This observation allows evaluation of the free energy difference between these isomers as only *ca.* 0·7 kcal mol^{-1} at 20°.

EXPERIMENTAL

Rotations were measured for $CHCl_3$ solutions at room temp. IR spectra in CCl_4 were recorded on a Perkin Elmer 421 grating spectrometer calibrated against water vapour lines in the region 1770–1670 cm^{-1}. Other IR spectra were recorded for CS_2 solutions on a Perkin Elmer 221 spectrometer. UV spectra were recorded for ethanol solutions. Alumina used for chromatography was P. Spence, Grade H. "Deactivated alumina" refers to Grade H deactivated by the addition of 5% of 10% acetic acid. Light petroleum refers to the fraction of b.p. 50–70°. ORD curves (in MeOH) were kindly determined by Professor W. Klyne.

3β-Acetoxy-5α-chlorocholestan-6-one (Va)

Cholesteryl acetate (25 g) in acetone (600 ml) was heated under reflux with N-chlorosuccinimide (15 g), water (25 ml) and acetic acid (50 ml) for 2 hr. The hot solution was diluted with water to turbidity, and allowed to cool. The crude chlorohydrin (20·1 g) which separated as flakes was dried, dissolved in anhydrous acetone (200 ml) and treated dropwise with a slight excess of 8N-chromic acid. Addition of water gave the *6-ketone* which crystallized from acetone–MeOH as needles (12·6 g) m.p. 143–145°. A sample from EtOH had m.p. 147–149°, $[\alpha]_D$ −98·5° (*c* 1·02) ν_{max} 1735, 1232 (AcO) and 1718 cm^{-1} (C:O). (Found: C, 72·7; H, 9·9; Cl, 7·6. $C_{29}H_{47}ClO_3$ requires: C, 72·9; H, 10·2; Cl, 8·0%).

3β-Acetoxy-5,6β-epoxy-6α-methyl-5β-cholestane (IIIa)

The chloroketone (Va; 5 g) in benzene (50 ml) was added to an ethereal solution of MeMgI prepared from Mg (1·5 g) and MeI (4 ml). The mixture was left at 20° for 24 hr then poured into ice-water containing NH_4Cl. The organic layer was separated and the solvents removed at 20 mm, and the residue was treated with KOH (2 g) in MeOH (75 ml) for 3 hr at 20°. Water was then added and the steroid was isolated by use of ether. The crude 3β-hydroxy-5β,6β-epoxide was acetylated (acetic anhydride–pyridine, 1:1; 16 hr at 20°) and crystallized from MeOH–ether giving 3β-acetoxy-5,6β-epoxy-6α-methyl-5β-cholestane (2·6 g) as flakes, m.p. and m.m.p. 94–95°, $[\alpha]_D$ −1° (*c* 0·84) (lit.:[3] m.p. 95–95·5°, $[\alpha]_D$ −2°). Comparison of IR spectra confirmed the structure.

[12] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 4596 (1957).

5,6β-Epoxy-6α-methyl-5β-cholestane (IIIb)

5-Chloro-5α-cholestan-6-one (1·65 g) was treated with MeMgI, followed by methanolic KOH, as described above. The crude epoxide was adsorbed from pentane onto deactivated alumina (200 g). Elution with pentane–benzene (50:1) gave *5,6β-epoxy-6α-methyl-5β-cholestane* (1·177 g), m.p. 72–74° (hexagonal plates from acetone), $[\alpha]_D$ ±0° (*c* 0·57). (Found: C, 83·6; H, 12·0. $C_{28}H_{48}O$ requires: C, 83·9; H, 12·0%).

6α-Methyl-5α-cholestan-6β-ol

5α-Cholestan-6-one (2 g) in anhydrous ether (50 ml) was added to the Grignard reagent prepared from Mg (1 g), MeI (2·6 ml) and ether (25 ml). After 18 hr at 20° the solution was added to NH_4Cl aq and ice, and the ethereal solution was evaporated giving *6α-methyl-5α-cholestan-6β-ol* (1·58 g) m.p. 113–114° (needles from acetone), $[\alpha]_D$ +25° (*c* 0·87), ν_{max} 3597 cm^{-1} (OH). (Found: C, 83·6; H, 12·5. $C_{28}H_{50}O$ requires: C, 83·5; H, 12·5%).

6-Methylcholest-5-ene

The 6β-ol (1·39 g) in CCl_4 (14 ml) and acetic anhydride (14 ml) was treated with 60% perchloric acid (0·1 ml) for 15 min at 20°. The solution was diluted with water and $NaHCO_3$ aq, and the solvents removed at 20 mm. The product, in pentane, was passed through alumina (5 g), giving *6-methylcholest-5-ene* (1·1 g), m.p. 98–99° (needles from acetone), $[\alpha]_D$ −47° (*c* 0·97). (Found: C, 87·1; H, 12·5. $C_{28}H_{48}$ requires: C, 87·4; H, 12·6%).

5,6α-Epoxy-6β-methyl-5α-cholestane (Ib)

6-Methylcholest-5-ene (830 mg) in $CHCl_3$ (4 ml) was treated with monoperphthalic acid (610 mg) in ether (18 ml) for 18 hr at 20°. The solution was poured into 5% Na_2CO_3 aq and the product was isolated with ether, giving the *5α,6α-epoxide* (656 mg), m.p. 96·5–97·5° (needles from EtOH), $[\alpha]_D$ −21° (*c* 0·70). (Found: C, 83·9; H 12·25. $C_{28}H_{48}O$ requires: C, 83·9; H, 12·1%).

Reactions of epoxides with boron trifluoride

The general procedure was as follows: The epoxysteroid, as a 5–10% solution in anhydrous benzene, was treated with freshly-distilled BF_3–etherate (1 ml per 1 g steroid). After a suitable reaction time at 20°, the solution was poured into sat. $NaHCO_3$ aq and the product was isolated with the use of ether.

Rearrangement of 3β-acetoxy-5,6α-epoxy-6β-methyl-5α-cholestane (Ia)

The reaction was allowed to proceed for 25 min, giving a deep blue solution. The product was *3β-acetoxy-5-methyl-A-homo-B-nor-5β-cholestan-4a-one* (85%) m.p. 88–90° (needles from EtOH), $[\alpha]_D$ +19° (*c* 0·65), ν_{max} (CCl_4) 1743, 1702 cm^{-1}, ORD $[\phi]_{400}$ +75°, $[\phi]_{318}$ +1210°, $[\phi]_{266}$ −2500°, $[\phi]_{252}$ −2400°, $[\phi]_{216}$ −4970°. (Found: C, 78·25; H, 11·0. $C_{30}H_{50}O_3$ requires: C, 78·55; H, 11·0%).

Rearrangement of 5,6α-epoxy-6β-methyl-5α-cholestane (Ib)

The epoxide (250 mg) was allowed to react with BF_3 for 5 min. The product was *5-methyl-A-homo-B-nor-5β-cholestan-4a-one* (188 mg), m.p. 93–93·5° (needles from EtOH), $[\alpha]_D$ −1° (*c* 0·71), ν_{max} (CCl_4) 1695·5 cm^{-1}, ORD $[\phi]_{394}$ −55°, $[\phi]_{308}$ +270°, $[\phi]_{261}$ −1580° (infl), $[\phi]_{223}$ −2850°. (Found: C, 84·1; H, 12·1. $C_{28}H_{46}O$ requires: C, 83·9; H, 12·1%).

5-Methyl-A-homo-B-nor-5β-cholest-3-en-4a-one (VI)

Compound IIa (1 g) in light petroleum was adsorbed onto alumina (40 g) for 48 hr. Elution with light petroleum–benzene (5:1) gave the Δ^3-4a-*ketone* (600 mg), m.p. 106–106·5° (needles from MeOH–pentane), $[\alpha]_D$ −70° (*c* 0·91), λ_{max} 226·5 mμ (ε 6060), ν_{max} 1673 cm^{-1}, ORD $[\phi]_{400}$ −140°, $[\phi]_{328}$ +5400°, $[\phi]_{318}$ −19,200°, $[\phi]_{276}$ −19,400°, $[\phi]_{250}$ −33,900°, $[\phi]_{242}$ −41,500°, $[\phi]_{215}$ +3450°. (Found: C, 83·9; H, 11·7. $C_{28}H_{46}O$ requires: C, 84·35; H, 11·6%).

Hydrogenation of the Δ^3-4a-*ketone* (VI)

The Δ^3-4a-ketone (400 mg) in MeOH (80 ml) was hydrogenated over 5% Pd–C. Evaporation of the solvent gave 5-methyl-A-homo-B-nor-5β-cholestan-4a-one (330 mg) m.p. and m.m.p. 93–93·5° (needles from EtOH).

Rearrangement of 3β-acetoxy-5,6β-epoxy-6α-methyl-5β-cholestane (IIIa)

(a) The epoxide (1 g) was treated with BF_3 for 2 min. The solution rapidly turned pink then purple. The extracted product was a solid which crystallized from pentane to give *3β-acetoxy-5-fluoro-6β-hydroxy-6α-methyl-5α-cholestane* (620 mg) m.p. 160–161° (needles from MeOH), $[\alpha]_D$ +5° (*c* 1·10), ν_{max} 3600, 1739 and 1236 cm^{-1}. (Found: C, 75·6; H, 10·9; F, 3·6. $C_{30}H_{51}FO_3$ requires: C, 75·25; H, 10·7; F, 4·0%).

(b) The epoxide (500 mg) was allowed to react with BF_3 for 20 min. The product was a gum which was adsorbed from light petroleum onto a column of deactivated alumina (40 g). Elution with light petroleum–benzene mixtures (100:1 to 10:1) gave non-crystalline fractions (239 mg) showing only acetoxy absorption in the IR. Elution with light petroleum–benzene (7:1 and 4:1) gave 3β-acetoxy-5-methyl-A-homo-B-nor-5β-cholestan-4a-one (97 mg), m.p. and m.m.p. 88–90° (needles from EtOH), $[\alpha]_D$ +18° (*c* 0·84), identical IR and NMR spectra.

Fractions eluted by light petroleum–benzene (3:2) afforded *3β-acetoxy-5-methyl-5α-cholestan-6-one* (50 mg), m.p. 171–172° (plates from MeOH), $[\alpha]_D$ −26° (*c* 0·27), ν_{max} 1736, 1709, 1245 and 1233 cm^{-1}, ν_{max} (CCl_4) 1735 and 1710 cm^{-1}, ORD $[\phi]_{400}$ −725°, $[\phi]_{306}$ −5950°, $[\phi]_{270}$ +5610°, $[\phi]_{234}$ +3070°. (Found: C, 78·4; H, 11·1. $C_{30}H_{50}O_3$ requires: C, 78·55; H, 11·0%).

Later fractions eluted by the same solvent gave the fluorohydrin (VIIa; 90 mg) m.p. 160–161°.

(c) A reaction mixture as in (b) was left for 1 hr, and gave non-polar material (270 mg), the 4a-ketone (116 mg), and the 6-ketone (58 mg). Only a trace (ca. 10 mg) of the fluorohydrin was obtained.

Hydrolysis of 3β-acetoxy-5-fluoro-6α-methyl-5α-cholestan-6β-ol (VIIa)

(a) The fluorohydrin (100 mg) and KOH (100 mg) in 90% MeOH (10 ml) were heated under reflux for 5 hr. The product, isolated by use of ether, was treated with acetic anhydride (0·5 ml) and pyridine (2 ml) at 20° for 18 hr. Water was added to precipitate the product, which was dried, dissolved in light petroleum, and adsorbed onto deactivated alumina (2 g). Elution with light petroleum–benzene (25:1) gave 3β-acetoxy-5,6β-epoxy-6α-methyl-5β-cholestane, m.p. and m.m.p. 94–95°, IR spectrum identical with an authentic specimen.

(b) The fluorohydrin (100 mg) and KOH (100 mg) in 95% MeOH (20 ml) were left at 20° for 18 hr, then the solution was diluted to turbidity, giving *5-fluoro-6α-methyl-5α-cholestane-3β,6β-diol* (67 mg), m.p. 197·5–198·5° (needles from acetone–hexane), $[\alpha]_D$ +15·5° (*c* 0·90), ν_{max} 3625 cm^{-1}. (Found: C, 77·1; H, 11·5; F, 4·1. $C_{28}H_{49}FO_2$ requires: C, 77·0; H, 11·3; F, 4·35%).

5-Fluoro-6β-hydroxy-6α-methyl-5α-cholestan-3-one (VIIc)

The 3β,6β-diol (32 mg) in acetone (8 ml) was treated with a slight excess of 8N-chromic acid, then diluted to turbidity with 1% $Na_2S_2O_5$ aq, giving the *3-ketone* (25 mg), m.p. 186–187° (needles from acetone–hexane), $[\alpha]_D$ +23° (*c* 0·70), ν_{max} 3610 (OH) and 1724 cm^{-1} (C:O), ORD $[\phi]_{400}$ +215; $[\phi]_{303}$ +1320°, $[\phi]_{288}$ −3480°; $[\phi]_{286}$ −2520°. (Found: C, 77·4; H, 10·9; F, 4·0. $C_{28}H_{47}FO_2$ requires: C, 77·4; H, 10·9; F, 4·4%).

6β-Hydroxy-6α-methylcholest-4-en-3-one (VIII)

The 5α-fluoroketone (VIIc; 30 mg) in MeOH (5 ml) was treated with KOH (30 mg) in water (0·3 ml) for 6 hr at 20°. The *4-en-3-one*, isolated by use of ether formed needles, m.p. 202–204° (from MeOH), $[\alpha]_D$ +33° (*c* 0·67), λ_{max} 236 mμ (ε = 12,030), ν_{max} 3546, 3430, 1684 and 877 cm^{-1}. (Found: C, 79·4; H, 11·1. $C_{28}H_{46}O_2 \cdot \frac{1}{2}CH_3OH$ requires: C, 79·45; H, 11·2%).

6-Methylcholesta-4,6-dien-3-one (IX)

Compound VIIc (25 mg) in MeOH (5 ml) containing conc. HCl (0·2 ml) was heated at 70° for 10 min, cooled, and diluted to turbidity. The dienone crystallized from MeOH as needles, m.p. 91–93°, λ_{max} 290·5 mμ (ε 22,750). [lit:[8] m.p. 91–92°, λ_{max} 290 mμ (ε 23,440)].

Rearrangement of 5,6β-epoxy-6α-methyl-5β-cholestane (IIIb)

(a) *In benzene.* The epoxide (700 mg) in benzene (10 ml) was treated with BF_3 etherate (0·7 ml) for 2·5 min, giving a pale yellow solution. The isolated product was adsorbed onto alumina (100 g). Elution with light petroleum gave a gum (418 mg) $[\alpha]_D$ −29°, λ_{max} 236 mμ (ε 11,600), 242 mμ (ε 13,000), and 250 mμ (ε 9,500), IR spectrum almost identical with 6-methylcholesta-3,5-diene (see

below). Fractions eluted by light petroleum–benzene (20:1) gave *5-acetyl-B-nor-5β-cholestane* (XI; 91 mg) m.p. 100–100·5° (flakes from MeOH–pentane), $[\alpha]_D$ +58° (*c* 0·90), ν_{max} (CCl_4) 1697 cm^{-1} ORD $[\phi]_{400}$ +520°, $[\phi]_{312}$ +1480°, $[\phi]_{279}$ +140°, $[\phi]_{222}$ +2320°. (Found: C, 83·8; H, 12·1. $C_{28}H_{48}O$ requires: C, 83·9; H, 12·1%). Fractions eluted by light petroleum–benzene (15:1) were mixtures of ketones (140 mg). Light petroleum–benzene (10:1) afforded *5-methyl-5α-cholestan-6-one* (46 mg), m.p. 105–107° (needles from MeOH), $[\alpha]_D$ −30° (*c* 0·48), ν_{max} (CCl_4) 1705·5 cm^{-1}, ORD $[\phi]_{400}$ −500°, $[\phi]_{307}$ −5480°, $[\phi]_{270}$ +6160°, $[\phi]_{234}$ +4080°, $[\phi]_{217}$ +4440°. (Found: C, 83·7; H, 12·0. $C_{28}H_{48}O$ requires: C, 83·9; H, 12·1%).

Rechromatography of intermediate fractions gave additional 5β-acetyl compound (20 mg) and 6-ketone (21 mg).

(b) *In ether.* The epoxide (400 mg) in dry ether (10 ml) was treated with BF_3–etherate (0·2 ml) for 1·5 hr. The product, isolated in the usual manner, was adsorbed onto deactivated alumina (12 g). Elution with light petroleum gave unreacted epoxide (103 mg). Light petroleum–benzene (50:1 and 20:1) gave *5-fluoro-6α-methyl-5α-cholestan-6β-ol* (VIId; 264 mg), m.p. 80–82° (needles from MeOH), $[\alpha]_D$ ±0° (*c* 1·03), ν_{max} 3600 (OH), 954, 938 and 880 cm^{-1}. (Found: C, 80·2; H, 11·9; F, 4·1. $C_{28}H_{49}FO$ requires: C, 80·0; H, 11·7; F, 4·5%).

Hydrolysis of this fluorohydrin (90 mg) in 5% ethanolic KOH under reflux for 2 hr gave the 5β,6β-epoxide (IIIb; 61 mg), m.p. and m.m.p. 72–74° (from acetone).

6-Methylcholesta-3,5-diene

6β-Methylcholest-4-en-3-one (100 mg), $NaBH_4$ (40 mg) and NaOH (40 mg) were heated under reflux in MeOH (20 ml) for 2 hr. The solution was then made strongly acidic by the addition of conc. HCl, and heating was continued for a further 30 min. The product, isolated by use of ether, was filtered in pentane through alumina (10 g). Evaporation of the solvent gave *6-methylcholesta-3,5-diene*, m.p. 86–88° (prisms from acetone), $[\alpha]_D$ −126° (*c* 0·46), λ_{max} 236 (ε 20,350), 242·5 (ε 21,000), and 251 mμ (ε 15,680), ν_{max} 3030, 1645, 935, 882, 798, 756, and 739 cm^{-1}. (Found: C, 87·7; H, 12·1. $C_{28}H_{46}$ requires: C, 87·9; H, 12·1%).

Isomerization of 5-methyl-A-homo-B-nor-5β-cholestan-4a-one-(IIb) with boron trifluoride

A solution of the 4a-ketone (320 mg) in anhydrous benzene (5 ml) was treated with BF_3–etherate (0·32 ml). After 24 hr at 20° the dark blue solution was poured into ether and $NaHCO_3$ aq. The ether was washed and evaporated, and the residual gum was adsorbed from light petroleum onto alumina (36 g). Elution with light petroleum gave a gum (95 mg) having no significant IR spectroscopic features.

Light petroleum–benzene (100:1) gave *5-methyl-5β-cholestan-6-one* (126 mg), m.p. 83·5–84° (plates from MeOH–pentane), $[\alpha]_D$ −55° (*c* 0·91), ν_{max} 1704 cm^{-1}, ORD $[\phi]_{400}$ −530°, $[\phi]_{318}$ −4000°, $[\phi]_{276}$ +3060°, $[\phi]_{230}$ +675°. (Found: C, 83·6; H, 12·2. $C_{28}H_{48}O$ requires: C, 83·9; H, 12·1%).

Fractions (32 mg) eluted by light petroleum–benzene (50:1) crystallized poorly from MeOH to give a ketone (4·5 mg) m.p. 62–63°, $[\alpha]_D$ +54 ± 5° (*c* 0·40), ν_{max} ca. 1704 cm^{-1}. The structure of this material is unknown. The mother liquors from this crystallization, and fractions (49 mg) eluted by light petroleum–benzene (25:1) gave unchanged 4a-ketone (39 mg), m.p. and m.m.p. 93–93·5°, identical IR spectrum.

Reversal of the ketone isomerization

A solution of 5-methyl-5β-cholestan-6-one (48 mg) in benzene (1 ml) was treated with BF_3–etherate (0·05 ml) for 24 hr, and the product was isolated as above. Chromatography on alumina (5 g), as above, gave a non-polar gum (24 mg), unchanged 5β-methyl-6-ketone (12 mg) m.p. 83–84°, and the 5β-methyl-A-homo-B-nor-4a-ketone (3·5 mg), m.p. and m.m.p. 90–92° identical IR spectrum.

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