Conversion of Lanosterol into a Compound with the Carbon Skeleton of Fusidic Acid

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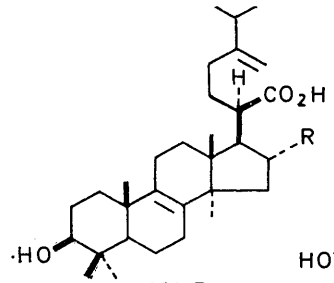
A recently established method for the monodemethylation of triterpenes at C-4 has been used to convert lanosterol into 3β-acetoxy-9,11α-epoxy-4α,14α-dimethyl-5α-cholestane. A boron trifluoride-catalysed 'backbone' rearrangement of this epoxide produced 3β-acetoxy-29-nor-8α,14β-dammara-9(11),13(17)-diene and 3β-acetoxy-4α,14α-dimethyl-5α,9β-cholestan-11-one.

WITH lanosterol derivatives as model compounds we have been exploring the possibility of converting the carbocyclic skeleton of the fungal acids, such as eburicoic acid (I) and tumulosic acid (II), into that present in the triterpenoid antibiotic, fusidic acid (III).[1-4] This transformation may be broken down into two parts, (*a*) the removal of a 4-methyl group, and (*b*) the migration of the methyl groups at positions 14 and 13 to C-8 and C-14, respectively. In recent communications[5,6] we have described two methods for monodemethylation at position 4 in lanosterol derivatives, and we now report the 'backbone' rearrangement of a 4-demethyllanostane derivative to give a 'fusidane' derivative.

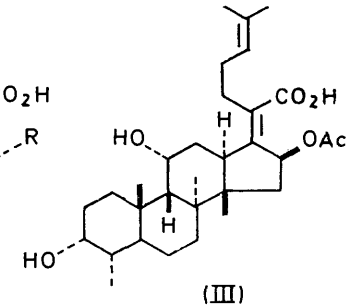
There are numerous examples of methyl group migrations in terpenes[7] and steroids;[8] invariably these are brought about by the generation of a cationic centre adjacent to the carbon atom bearing the methyl group. Rearrangement has been shown to occur in cases in which the carbonium ion is developed by (*a*) ionisation of an electronegative substituent,[8a] (*b*) protonation of an olefinic linkage,[8b] and (*c*) acid-catalysed opening of an epoxide.[8c] Since fusidic acid contains an 11α-hydroxy-group, it seemed appropriate to initiate the required 'backbone' rearrangement with a Lewis acid-catalysed cleavage of a 9α,11α-epoxide. We were hopeful that this would introduce the required group at C-11 with concomitant migration of the 9β-H and 14α-methyl and 13β-methyl groups. However, about the time this work

[1] W. O. Godtfredsen and S. Vangedal, *Tetrahedron*, 1962, **18**, 1029.
[2] W. O. Godtfredsen, W. von Daehne, S. Vangedal, A. Marquet, D. Arigoni, and A. Melera, *Tetrahedron*, 1965, **21**, 3505.
[3] W. O. Godtfredsen, C. Albrettsen, W. von Daehne, L. Tybring, and S. Vangedal, *Antimicrobial Agents and Chemotherapy*, 1965, 132.
[4] W. O. Godtfredsen, W. von Daehne, L. Tybring, and S. Vangedal, *J. Medicin. Chem.*, 1966, **9**, 15.
[5] R. Kazlauskas, J. T. Pinhey, J. J. H. Simes, and T. G. Watson, *Chem. Comm.*, 1969, 945.
[6] K. F. Cohen, R. Kazlauskas, and J. T. Pinhey, *Chem. Comm.*, 1971, 1419.
[7] J. F. King and P. de Mayo, in 'Molecular Rearrangements,' Part 2, ed. P. de Mayo, Interscience, New York, 1964, p. 813.
[8] D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, (*a*) p. 261; (*b*) p. 291; (*c*) p. 363.

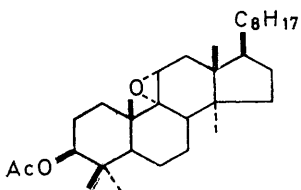
was initiated there appeared two papers [9,10] which militated against this idea. Levy and Lavie [9] found that treatment of the 9α,11α-epoxy-derivative (IV) with tin(IV) chloride resulted in ring opening with hydride migration to give 3β-acetoxy-5α,9β-lanostan-11-one (XVI), and ApSimon and Rosenfeld [10] reported the



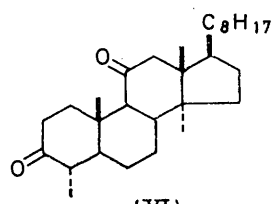
(I) R = H
(II) R = OH



(III)



(IV) R = Me
(V) R = H

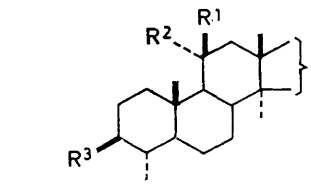


(VI)

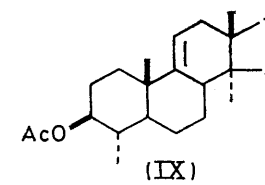
migration of the 10-methyl group in a boron trifluoride-catalysed ring opening of a steroidal 9α,11α-epoxide. Although earlier work [11] on a steroidal 9α,11α-epoxide also resulted only in formation of the 11-oxo-9β-compound, two cases had been reported [12] in which Lewis acid-catalysed rearrangement of steroidal 9α,11α-epoxides produced $\Delta^{8(14)}$-11α-hydroxy-compounds.

In our initial study we used 3β-acetoxy-9,11α-epoxy-4α,14α-dimethyl-5α-cholestane (V), which was produced most conveniently from the readily available 4α,14α-dimethyl-5α-cholestane-3,11-dione (VI).[6] Reduction of the diketone (VI) with sodium borohydride gave the expected [13] 3β,11β-diol (VII), which could be selectively acetylated [14] in acetic anhydride and pyridine to afford 3β-acetoxy-4α,14α-dimethyl-5α-cholestan-11β-ol (VIII) in high overall yield. Treatment of this compound (VIII) with phosphoryl chloride in pyridine readily effected dehydration to the 9(11)-olefin (IX), the ^{1}H n.m.r. spectrum of which showed a broad one-proton multiplet at δ 5·30 p.p.m. Finally, treatment of the olefin (IX) with *m*-chloroperbenzoic acid afforded the required 9α,11α-epoxide (V) in high yield. Assignment of the α-configuration to the epoxide (V) followed from the ^{1}H n.m.r. spectrum, in which the 11β-H signal appeared as a broad doublet (*J* 5 Hz). Examination of a Dreiding model indicated that the 11β-H would show appreciable spin–spin coupling to the 12β-H (dihedral angle 30°), whereas coupling to the 12α-H would be negligible (dihedral angle 90°).[15] For the β-epoxide model, it appeared that the dihedral angles between the 11α-H and both C-12 protons would be about 60°.

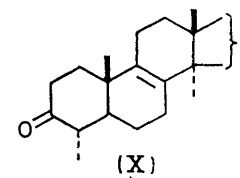
Two other routes to the olefin (IX) have been investigated, but neither proved to be as satisfactory as that just described. In the first of these, 4α,14α-dimethyl-5α-cholest-8-en-3-one (X) [5,6] was used in a sequence parallelling that employed to convert lanosterol into parkeol.[16] The 3β-alcohol (XI), obtained by sodium–t-butyl alcohol reduction of the ketone (X), was converted into the acetate (XII), which on chromic acid oxidation gave the 7,11-diketone (XIII). The saturated



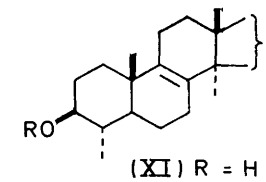
(VII) $R^1 = R^3 = OH, R^2 = H$
(VIII) $R^1 = OH, R^2 = H, R^3 = OAc$



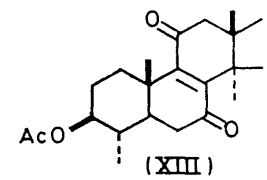
(IX)



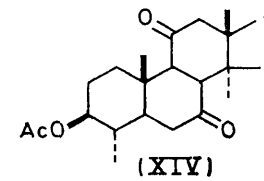
(X)



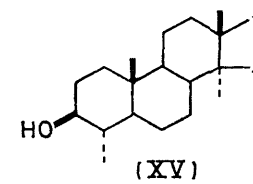
(XI) R = H
(XII) R = Ac



(XIII)



(XIV)



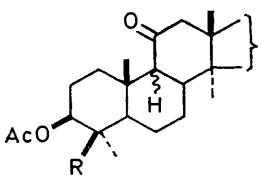
(XV)

diketone (XIV), which was readily formed by zinc–acetic acid reduction of (XIII), could not be selectively reduced to the 11-ketone by the Wolff–Kishner method. In contrast to the 4,4-dimethyl analogue,[17] even with aqueous hydrazine, reduction of both carbonyl groups

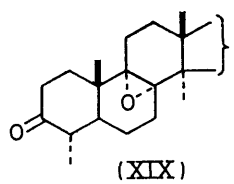
[9] E. C. Levy and D. Lavie, *Israel J. Chem.*, 1970, **8**, 677.
[10] J. W. ApSimon and J. M. Rosenfeld, *Chem. Comm.*, 1970, 1271.
[11] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 1957, 4596.
[12] J. W. ApSimon, R. R. King, and J. M. Rosenfeld, *Canad. J. Chem.*, 1969, **47**, 1989.
[13] Ref. 8, p. 133.
[14] Ref. 8, p. 26.
[15] L. M. Jackman and S. Sternhell, ' Applications of Nuclear Magnetic Resonance in Organic Chemistry,' Pergamon, London, 1969, p. 280.
[16] W. Lawrie, F. S. Spring, and H. S. Watson, *Chem. and Ind.*, 1956, 1458.
[17] G. Ourrison, P. Crabbe, and O. R. Rodig, ' Tetracyclic Triterpenes,' Hermann, Paris, 1964, p. 62.

occurred to give 4α,14α-dimethyl-5α-cholestan-3β-ol (XV). However, selective reduction was readily achieved by Raney nickel desulphurisation of the 7-ethylene thioacetal of (XIV) to yield the 11-ketone (XVII), which was converted by sodium borohydride into the 11β-alcohol (VIII) prepared before.

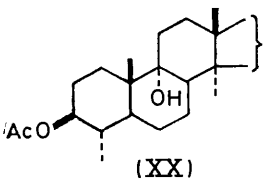
The third route to compound (IX) was based on that used by Fried [18] to introduce a 9(11)-double bond into 4,4-dimethyl analogues. Reaction of the Δ^8-3-ketone (X) with *m*-chloroperbenzoic acid led to the 8α,9α-epoxide (XIX), which was reduced with lithium and



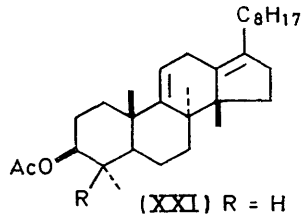
(XVI) 9β-H, R = Me
(XVII) 9α-H, R = H
(XVIII) 9β-H, R = H



(XIX)



(XX)



(XXI) R = H
(XXII) R = Me

ethylamine in the presence of t-butyl alcohol to give a mixture of two products. This mixture was best separated by alumina chromatography of the acetylated material, which afforded the olefin (XII) and the required 9α-alcohol (XX) in only moderate yield. The latter compound (XX) was cleanly dehydrated to the 9(11)-olefin (IX) with thionyl chloride in pyridine.

Treatment of the epoxide (V) with boron trifluoride–ether complex in benzene yielded the 9β,11-ketone (XVIII) and 3β-acetoxy-29-nor-8α,14β-dammara-9(11),13(17)-diene (XXI) in yields of 22 and 54%, respectively. The structure of the ketone followed from spectral data and its conversion on treatment with base and reacetylation into the more stable 9α-epimer (XVII); identification of the crystalline diene (XXI) rests mainly on the ^{1}H n.m.r. and mass spectra. Characteristic of compounds containing a 13(17)-double bond,[19] the mass spectrum of (XXI) showed an intense peak at *m/e* 341 (*M* − 113) corresponding to the ready loss of the C_8H_{17} side chain. In the ^{1}H n.m.r. spectrum of (XXI) the vinylic proton (11-H) gave rise to a narrow triplet (*J* 4 Hz) at δ 5·34 p.p.m., which collapsed to a singlet on irradiation at δ 2·70, the centre of a two-proton multiplet. The chemical shifts (2·70) of the two C-12 protons are further support for the structure (XXI), since this is within the range for bisallylic protons.[20] In addition, irradiation at δ 2·46 p.p.m., the chemical shift of the allylic proton H-20, caused the doublet at δ 0·97 due to the 21-protons to collapse to a singlet.

Since the rearrangement of the 4-demethyl epoxide (V) to the diene (XXI) proceeded so readily, we re-investigated the reaction of the 4,4-dimethyl-9,11α-epoxide (IV) under the same conditions. In contrast to the results of the earlier workers [9,10] we obtained, in addition to the 9β,11-ketone (XVI), a non-crystalline 'backbone-rearranged' diene (XXII). About the time this work was nearing completion Guest and Marples [21] reported the isolation of compound (XXII) from the same reaction, and since our results confirm their work in almost all details, we do not report these experiments.

EXPERIMENTAL

M.p.s were taken on a Kofler hot-stage apparatus. Unless otherwise stated, u.v. spectra were determined for solutions in ethanol with a Perkin-Elmer 402 spectrometer, i.r. spectra were obtained for Nujol mulls with a Perkin-Elmer 221 spectrometer, and rotations were measured for solutions in chloroform. N.m.r. spectra were recorded on either Varian A60 or Varian HA100 instruments for *ca.* 10% solutions in deuteriochloroform with tetramethylsilane as internal reference. Mass spectra were obtained with an A.E.I. MS902 instrument operated at 70 eV. Silica gel used for column chromatography was Davisons' grade 923; alumina refers to Spence type H. Light petroleum refers to the fraction of b.p. 60—80°. Organic extracts were dried over anhydrous magnesium sulphate. Analyses were performed by the Australian Microanalytical Service, Melbourne.

4α,14α-Dimethyl-5α-cholestane-3β,11β-diol (VII) *and 3β-Acetoxy-4α,14α-dimethyl-5α-cholestan-11β-ol* (VIII).—To a solution of 4α,14α-dimethyl-5α-cholestane-3,11-dione [6] (0·5 g) in methanol (20 ml) was added sodium borohydride (2 g), and the mixture was kept at room temperature overnight. Extraction with ether, after dilution with water (100 ml) and acidification with hydrochloric acid, afforded *4α,14α-dimethyl-5α-cholestane-3β,11β-diol* which formed needles (0·42 g), m.p. 164—166° (from aqueous methanol) (Found: C, 80·6; H, 12·0. $C_{29}H_{52}O_2$ requires C, 80·5; H, 12·1%); $\nu_{max.}$ 3340 and 1038 cm^{-1}; δ 4·22 (1H, m, $W_{\frac{1}{2}}$ 9 Hz, 11α-H) and 3·08 p.p.m. (1H, m, $W_{\frac{1}{2}}$ 21 Hz, 3α-H); *m/e* 432 (3%), 414 (10), 399 (15), 224 (60), and 209 (100).

The diol (VII) (0·3 g) was treated with acetic anhydride (2 ml) and pyridine (2 ml) at room temp. overnight to give *3β-acetoxy-4α,14α-dimethyl-5α-cholestan-11β-ol* (VIII), which crystallised from methanol as plates (0·26 g), m.p. 158—161°, $[\alpha]_D$ +78° (*c* 0·7) (Found: C, 78·1; H, 11·3. $C_{31}H_{54}O_3$ requires C, 78·4; H, 11·5%); $\nu_{max.}$ 3500, 1723, 1250, and 1032 cm^{-1}; δ 4·38 (1H, m, $W_{\frac{1}{2}}$ 17 Hz, 3α-H), 4·23 (1H, m, $W_{\frac{1}{2}}$ 13 Hz, 11α-H), and 2·03 p.p.m. (3H, s, OAc); *m/e* 474 (10%), 456 (16), 412 (28), 316 (44), 303 (36), and 224 (100).

3β-Acetoxy-4α,14α-dimethylcholest-9(11)-ene (IX).—The diol monoacetate (VIII) (56 mg) in pyridine (0·5 ml) containing phosphoryl chloride (0·3 ml) was heated on a

[18] J. Fried, J. W. Brown, and M. Applebaum, *Tetrahedron Letters*, 1965, 849.
[19] I. G. Guest and B. A. Marples, *J. Chem. Soc.* (*C*), 1970, 1626, and references therein.
[20] G. V. Baddeley, J. J. H. Simes, and T. G. Watson, *Tetrahedron*, 1970, **26**, 3799.
[21] I. G. Guest and B. A. Marples, *J. Chem. Soc.* (*C*), 1971, 1468.

steam-bath for 3 h, cooled, and then poured into water. Extraction with ether, after washing with dilute sulphuric acid and water, afforded 3β-*acetoxy*-4α,14α-*dimethyl*-5α-*cholest*-9(11)-*ene* as plates (48 mg), m.p. 115—117° (from methanol), $[\alpha]_D$ +105° (*c* 0·8) (Found: C, 81·2; H, 11·0. $C_{31}H_{52}O_2$ requires C, 81·5; H, 11·4%); $\nu_{max.}$ 1733 and 1240 cm^{-1}; δ 5·30 (1H, m, 11-H), 4·33 (1H, m, 3α-H), and 2·05 p.p.m. (3H, s, OAc); *m/e* 456 (41%), 441 (100), and 381 (35).

3β-*Acetoxy*-9,11α-*epoxy*-4α,14α-*dimethyl*-5α-*cholestane* (V).—The olefin (IX) (0·5 g) in dichloromethane (10 ml) containing *m*-chloroperbenzoic acid (0·5 g) was kept at room temp. for 3 h. The resulting solution was washed with sodium hydrogen carbonate solution and water, and dried. Crystallisation of the product from methanol gave 3β-*acetoxy*-9,11α-*epoxy*-4α,14α-*dimethyl*-5α-*cholestane* as plates, m.p. 160—163°, $[\alpha]_D$ +43° (*c* 2·0) (Found: C, 79·0; H, 11·2. $C_{31}H_{52}O_3$ requires C, 78·8; H, 11·1%); $\nu_{max.}$ 1725 and 1240 cm^{-1}; δ 4·30 (1H, m, 3α-H), 3·11br (1H, d, *J* 5 Hz, 11β-H), and 2·03 p.p.m. (3H, s, OAc); *m/e* 472 (100%), 457 (18), 443 (13), 397 (25), 331 (18), and 221 (43).

4α,14α-*Dimethyl*-5α-*cholest*-8-*en*-3β-*ol* (XI) *and* 3β-*Acetoxy*-4α,14α-*dimethyl*-5α-*cholest*-8-*ene* (XII).—4α,14α-Dimethyl-5α-cholest-8-en-3-one (X) [5,6] (3 g) was dissolved in t-butyl alcohol (50 ml) and sodium (2·5 g) was added. The mixture was heated at reflux for 3 h and methanol was then added to decompose the excess of sodium. Dilution of the mixture with water and extraction with ether afforded 4α,14α-*dimethyl*-5α-*cholest*-8-*en*-3β-*ol* (2·8 g), m.p. 132—134° (from methanol), $[\alpha]_D$ +72° (*c* 0·2) (Found: C, 83·5; H, 12·0. $C_{29}H_{50}O$ requires C, 83·9; H, 12·2%); $\nu_{max.}$ ($CHCl_3$) 3620 and 1025 cm^{-1}; δ 3·09 (1H, m, $W_{\frac{1}{2}}$ 21 Hz, 3α-H) and 1·91br p.p.m. [1H (exch.), s, OH]; *m/e* 414 (60%), 399 (100), and 381 (15).

The alcohol (XI) (2·8 g), on treatment with pyridine (5 ml) and acetic anhydride (10 ml) at room temp. overnight, gave 3β-*acetoxy*-4α,14α-*dimethyl*-5α-*cholest*-8-*ene* (2·5 g), m.p. 101—102° (needles from methanol), $[\alpha]_D$ +96° (*c* 0·6) (Found: C, 81·2; H, 11·3. $C_{31}H_{52}O_2$ requires C, 81·2; H, 11·5%); $\nu_{max.}$ ($CHCl_3$) 1720 and 1255 cm^{-1}; δ 4·40 (1H, m, $W_{\frac{1}{2}}$ 21 Hz, 3α-H) and 2·04 p.p.m. (3H, s, OAc); *m/e* 456 (65%), 441 (100), 382 (11), and 381 (26).

3β-*Acetoxy*-4α,14α-*dimethyl*-5α-*cholest*-8-*ene*-7,11-*dione* (XIII).—To the acetate (XII) (1·0 g) in chloroform (8 ml) and acetic acid (12 ml) was added a saturated solution of chromium trioxide (2·6 g) in water, and the brown mixture was heated at reflux for 2·5 h. Dilution with water and extraction with light petroleum afforded material which crystallised from methanol to give 3β-*acetoxy*-4α,14α-*dimethyl*-5α-*cholest*-8-*ene*-7,11-*dione* as yellow needles (0·6 g), m.p. 153—155° (Found: C, 76·5; H, 10·1. $C_{31}H_{48}O_4$ requires C, 76·8; H, 10·0%); $\nu_{max.}$ ($CHCl_3$) 1725, 1670, and 1225 cm^{-1}; $\lambda_{max.}$ 272 nm (ε 8200); δ 4·38 (1H, m, 3α-H), 2·05 (3H, s, OAc), 1·32 (3H, s, 19-H_3), and 1·20 p.p.m. (3H, s, 4α-CH_3).

3β-*Acetoxy*-4α,14α-*dimethylcholestane*-7,11-*dione* (XIV).—Zinc dust (2 g) was added during 1 h to a solution of the diketone (XIII) (1 g) in acetic acid (30 ml) heated at reflux, and the heating was continued until the solution was colourless (3 h). Removal of the zinc dust, dilution with water, and extraction with light petroleum yielded 3β-*acetoxy*-4α,14α-*dimethyl*-5α-*cholestane*-7,11-*dione* (0·85 g), m.p. 181—182°, $[\alpha]_D$ +14° (*c* 0·3 in MeOH) (needles from methanol) (Found: C, 76·0; H, 10·3. $C_{31}H_{50}O_4$ requires C, 76·4; H, 10·4%); $\nu_{max.}$ ($CHCl_3$) 1728, 1705, and 1250 cm^{-1}; δ 4·38 (1H, m, 3α-H), 2·05 (3H, s, OAc), 1·27 (3H, s, 19-H_3), and 1·24 p.p.m. (3H, s, 4α-CH_3); *m/e* 486 (100%), 471 (9), 426 (14), and 277 (24).

Wolff–Kishner Reduction of the Diketone (XIV).—Hydrazine hydrate (0·5 ml) was added to a solution of the dione (XIV) (200 mg) in diethylene glycol (10 ml) and the mixture heated at 170—200° for 1 h. Potassium hydroxide (0·5 g) was then added and the mixture heated at reflux for a further 4 h. Dilution with water and extraction with ether gave material which was separated by preparative t.l.c. (silica gel; chloroform). The major fraction (74 mg) crystallised from methanol to give 4α,14α-*dimethyl*-5α-*cholestan*-3β-*ol*, m.p. 146—148° (Found: C, 83·9; H, 12·4. $C_{29}H_{52}O$ requires C, 83·6; H, 12·6%); $\nu_{max.}$ ($CHCl_3$) 3300 cm^{-1}; δ 3·00 p.p.m. (1H, m, 3α-H); *m/e* 416 (29%), 401 (6), 399 (9), 286 (46), and 261 (100).

7,7-*Ethylenedithio*-4α,14α-*dimethyl*-5α-*cholestan*-11-*one*.—The diketone (XIV) (1·2 g) in a mixture of ethanedithiol (5 ml) and boron trifluoride–ether (5 ml) under dry nitrogen was kept overnight at room temp. Water was then added and the mixture extracted with light petroleum. The organic layer was washed with sodium hydroxide solution and water, dried, and evaporated to give the *thioacetal* (0·8 g), m.p. 151—153° (needles from methanol) (Found: C, 70·0; H, 9·9; S, 11·5. $C_{33}H_{54}O_3S_2$ requires C, 70·4; H, 9·7; S, 11·4%); $\nu_{max.}$ 1730, 1690, and 1240 cm^{-1}; δ 4·44 (1H, m, 3α-H), 3·28 (4H, s, S·CH_2·CH_2·S), 2·05 (3H, s, OAc), and 1·37 p.p.m. (3H, s, 19-H_3).

3β-*Acetoxy*-4α,14α-*dimethyl*-5α-*cholestan*-11-*one* (XVII).—A solution of the foregoing thioacetal (0·8 g) in methanol (50 ml) containing Raney nickel (10 g) was heated at reflux for 24 h and then filtered. Dilution with water and extraction with ether yielded 3β-*acetoxy*-4α,14α-*dimethyl*-5α-*cholestan*-11-*one*, m.p. 130—133° (plates from methanol); o.r.d. (ethanol) $[\phi]_{589}$ +89°, $[\phi]_{370}$ +268°, $[\phi]_{307}$ +528°, and $[\phi]_{280}$ +425° (Found: C, 78·5; H, 11·1. $C_{31}H_{52}O_3$ requires C, 78·7; H, 11·1%); $\nu_{max.}$ 1730, 1700, and 1250 cm^{-1}; δ 4·35 (1H, m, 3α-H) and 2·02 p.p.m. (3H, s, OAc); *m/e* 472 (9%), 412 (8), 303 (26), 290 (9), 250 (15), and 249 (100).

Sodium Borohydride Reduction of the Ketone (XVII).—Sodium borohydride (2 g) was added to the ketone (XVII) (0·5 g) in methanol (20 ml) and the mixture kept at room temp. overnight. After addition of water (100 ml) and acidification with hydrochloric acid, the mixture was extracted with ether to afford 3β-acetoxy-4α,14α-dimethyl-5α-cholestan-11β-ol (0·4 g), m.p. and mixed m.p. with material obtained earlier 158—161° (i.r. spectrum identical).

8,9α-*Epoxy*-4α,14α-*dimethyl*-5α-*cholestan*-3-*one* (XIX).—4α,14α-Dimethyl-5α-cholest-8-en-3-one (X) (1 g) was added to a solution of *m*-chloroperbenzoic acid (1 g) in dichloromethane (100 ml) and the mixture kept at room temp. for 3 h. Work-up as in the preparation of (V) gave 8,9α-*epoxy*-4α,14α-*dimethyl*-5α-*cholestan*-3-*one* (0·6 g), m.p. 161—163° (from methanol), $[\alpha]_D$ +6° (*c* 0·7) (Found: C, 82·0; H, 11·4. $C_{29}H_{48}O_2$ requires C, 81·8; H, 11·6%); $\nu_{max.}$ 1696 cm^{-1}; *m/e* 428 (16%), 412 (59), 410 (100), and 395 (9).

3β-*Acetoxy*-4α,14α-*dimethyl*-5α-*cholestan*-9α-*ol* (XX).—The epoxy-ketone (XIX) (1·1 g) was dissolved in ethylamine (50 ml) containing t-butyl alcohol (2 ml) and lithium (0·8 g) was added. After 1·5 h the ethylamine was allowed to evaporate and the residue was dissolved by adding ether and dilute sulphuric acid. The ether layer was washed with water, dried, and evaporated and the residue was treated overnight at room temp. with pyridine (5 ml) and acetic anhydride (5 ml). The material obtained after the

usual work-up was chromatographed on a column of alumina (50 g). Elution with benzene gave 3β-acetoxy-4α,14α-dimethyl-5α-cholest-8-ene (XII) (0·2 g); elution with benzene–ether (9 : 1) afforded 3β-*acetoxy*-4α,14α-*dimethyl*-5α-*cholestan*-9α-*ol* (0·43 g), m.p. 163—165° (methanol), $[\alpha]_D$ +35° (*c* 0·4) (Found: C, 78·5; H, 11·8. $C_{31}H_{54}O_3$ requires C, 78·5; H, 11·5%); $\nu_{max.}$ 3580, 1720, and 1270 cm^{-1}; δ 4·32 (1H, m, 3α-H) and 2·03 p.p.m. (3H, s, OAc); *m/e* 474 (5%), 400 (33), and 399 (100).

Dehydration of the Alcohol (XX).—3β-Acetoxy-4α,14α-dimethyl-5α-cholestan-9α-ol (XX) (100 mg) was dissolved in pyridine (1·2 ml) and thionyl chloride (0·2 ml) added. After 5 min at room temp. the mixture was diluted with water and extracted with ether to give 3β-acetoxy-4α,14α-dimethyl-5α-cholest-9(11)-ene (IX) (85 mg) (identified by mixed m.p. and i.r. spectrum).

Reaction of the 9α,11α-*Epoxide* (V) *with Boron Trifluoride–Ether Complex*.—The epoxide (V) (248 mg) was dissolved in benzene (4 ml), boron trifluoride–ether complex (0·2 ml) was added, and the solution was kept at room temp. After 20 min the mixture was washed with sodium hydrogen carbonate solution and water, dried, and evaporated. The residue was separated by preparative t.l.c. [silica gel; light petroleum–ether (9 : 1)] to yield two compounds.

The more polar compound crystallised from methanol to give 3β-*acetoxy*-4α,14α-*dimethyl*-5α,9β-*cholestan*-11-*one* (XVIII) (50 mg), m.p. 172—174°, $[\alpha]_D$ +133° (*c* 1·3) (Found: C, 79·1; H, 11·4. $C_{31}H_{52}O_3$ requires C, 78·8; H, 11·1%); $\nu_{max.}$ 1735, 1710, and 1237 cm^{-1}; δ 4·52 (1H, m, 3α-H), 2·04 (3H, s, OAc), and 1·30 p.p.m. (3H, s, 19-H_3); *m/e* 472 (17%), 412 (20), 303 (50), 290 (73), and 249 (100).

The less polar compound crystallised from methanol to yield 3β-*acetoxy*-29-*nor*-8α,14β-*dammara*-9(11),13(17)-*diene* (XXI) (128 mg), m.p. 98—100°, $[\alpha]_D$ −28° (*c* 1·9) [Found: C, 81·6; H, 11·3%; *M* (mass spectrum), 454·3813; *M* − C_8H_{17}, 341·2447. $C_{31}H_{50}O_2$ requires C, 81·9; H, 11·1%; *M*, 454·3811; *M* − C_8H_{17}, 341·2480]; $\nu_{max.}$ ($CHCl_3$) 1730 and 1260 cm^{-1}; δ 5·34 (1H, t, *J* 4 Hz, 11-H), 4·36 (1H, m, 3α-H), 2·70br (2H, m, 12α-H and 12β-H), 2·46 (1H, m, 20-H), 2·06 (3H, s, OAc), and 0·97 p.p.m. (3H, d, *J* 7 Hz, 21-H_3); *m/e* 454 (93%), 439 (51), 379 (13), 369 (42), 341 (100), and 205 (55), *M** 425, 301, 256, and 231.

Treatment of the 9β-11-*Ketone* (XVIII) *with Base*.—The ketone (XVIII) (30 mg) was added to methanol (100 ml) in which sodium (0·2 g) had been dissolved; the mixture was heated at reflux overnight, diluted with water, and extracted with ether. The residue obtained on removing the solvent was acetylated with pyridine and acetic anhydride. The product was crystallised from methanol to afford 3β-acetoxy-4α,14α-dimethyl-5α-cholestan-11-one (26 mg) (identified by mixed m.p. and i.r. spectrum).

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