Preparation and Isomerisation of some Steroidal Hydroxy Epoxides†

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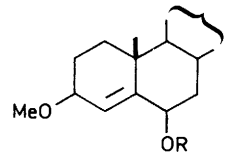
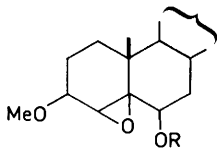
The preparation of 4β,5-epoxy-3β-methoxy-5β-cholestan-6β-ol (**3**), its 4α,5α-isomer (**5**), and their 3-epimers, (**16**) and (**21**) respectively, are described. It is shown that the vicinal hydroxy epoxide (**21**) and the isomeric compound 5,6β-epoxy-3α-methoxy-5β-cholestan-4α-ol (**22**) are interconvertible by a process of epoxide migration.

In connection with our studies of the influence of neighbouring hydroxy groups on the cleavage of acetals and epoxides[1] the isomeric epoxides (**3**), (**5**), (**16**), and (**21**) were required. We now describe the preparation of these and some other epoxides, and report the ready interconversion of compounds (**21**) and (**22**).

4β,5-Epoxy-3β-methoxy-5β-cholestan-6β-ol (**3**) and its 4α,5α-isomer (**5**) were readily obtained as a 2:1 mixture, efficiently separated by chromatography, upon treatment of 3β-methoxy-cholest-4-en-6β-ol (**1**) with *m*-chloroperbenzoic acid. The 4α,5α-epoxide (**5**) was also obtained in quantitative yield by saponification of the previously described[2] acetate (**6**).

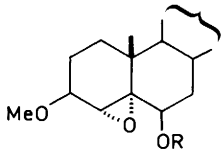


(**1**) R = H
(**2**) R = Ac



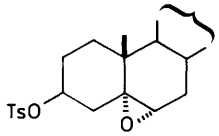
(**3**) R = H
(**4**) R = Ac

+

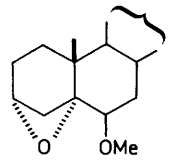


(**5**) R = H
(**6**) R = Ac

In order to prepare the isomeric epoxides (**16**) and (**21**) it was necessary to obtain 5,6α-epoxy-3α-methoxy-5α-cholestane (**11**) as an intermediate. An attempt to prepare the last-named compound by treatment of 5,6α-epoxy-5α-cholestan-3β-ol toluene-*p* sulphonate (**7**) with methanolic sodium methoxide gave instead 3α,5-epoxy-6β-methoxy-5α-cholestane (**8**) as the major product, together with a smaller amount of cholesterol α-epoxide (**9**). The structure of the oxetane (**8**) follows from its n.m.r. spectrum (see Experimental section); the chemical shifts of the protons on C-4 and their geminal coupling constant are comparable with other reported values for 3,5-epoxysteroids.[3] It appears that cleavage of the epoxide ring of compound (**7**) by nucleophilic attack of methoxide ion at C-6 occurs in preference

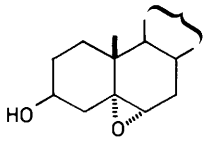


(**7**)



(**8**)

+



(**9**)

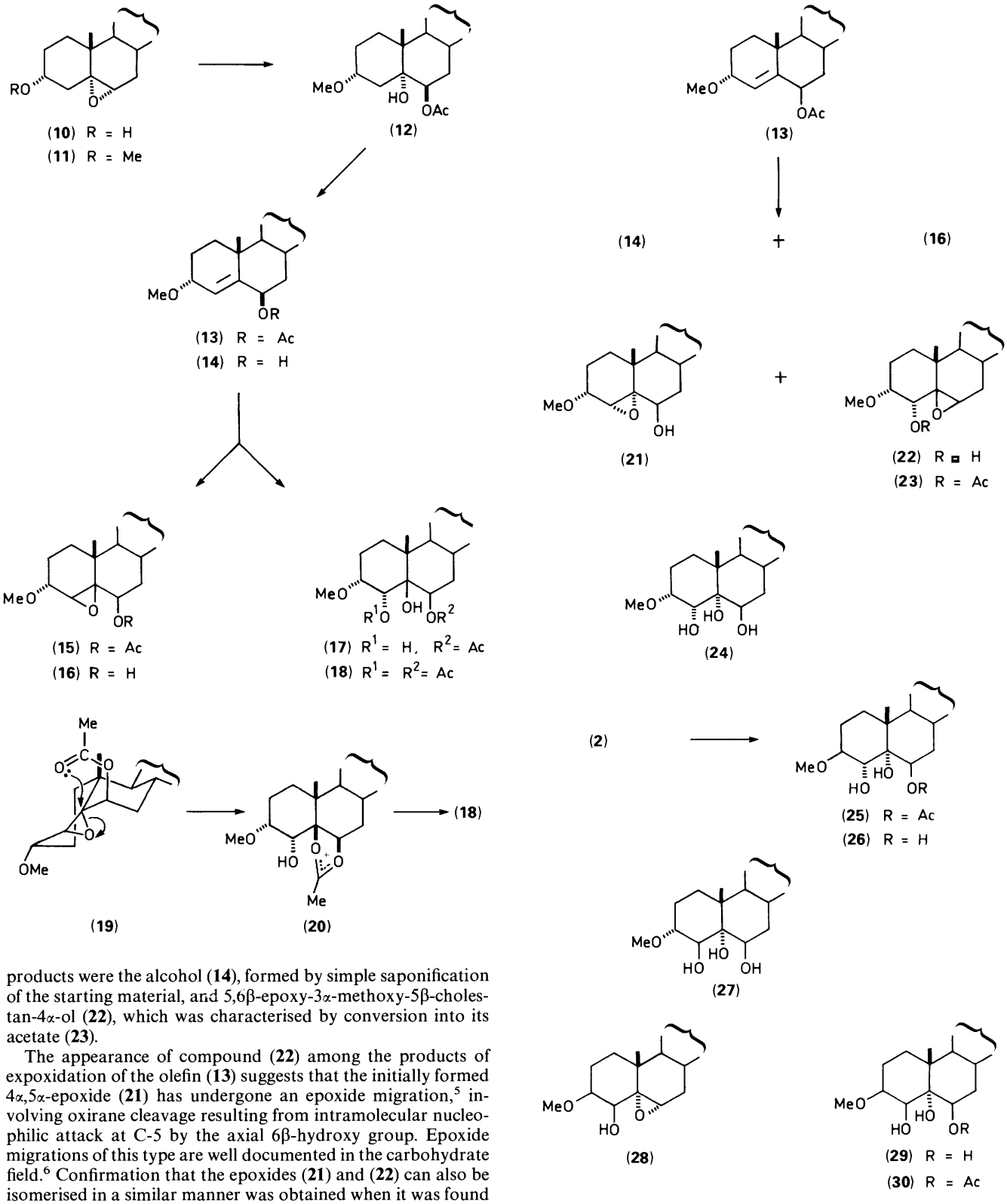
to displacement of tosylate by nucleophilic attack at C-3. The minor product (**9**), formed by hydrolysis of the 3β-tosyloxy group with retention of configuration, may arise by nucleophilic attack of methoxide ion at sulphur, resulting in S–O bond cleavage.[4]

The required intermediate (**11**) was obtained by methylation of the corresponding alcohol (**10**), itself prepared in good yield by treatment of 3-*epi*-cholesterol with *m*-chloroperoxybenzoic acid. Cleavage of the oxirane ring of compound (**11**) with acetic acid gave the hydroxy acetate (**12**) which was dehydrated with thionyl chloride and pyridine to afford 6β-acetoxy-3α-methoxy-cholest-4-ene (**13**). The desired 4β,5β-epoxide (**15**) was obtained as the major product when compound (**13**) was treated with *m*-chloroperoxybenzoic acid. Saponification of the acetate group then afforded 4β,5-epoxy-3α-methoxy-5β-cholestan-6β-ol (**16**).

Although none of the 4α,5α-epoxide (**19**) was obtained in the reaction between the olefin (**13**) and *m*-chloroperoxybenzoic acid, 6β-acetoxy-3α-methoxy-5β-cholestane-4α-5-diol (**17**) was identified as a minor product from its n.m.r. spectrum and from that of the derived diacetate (**18**). It is likely that the epoxide (**19**) is an intermediate in the formation of compound (**17**); the latter probably arises by a process involving acid-catalysed cleavage of the oxirane ring of compound (**19**) with participation of the adjacent *trans*-axial acetoxy group to give the intermediate acetoxonium ion (**20**).[2]

The desired epoxide (**21**) was finally obtained by epoxidation of the olefin (**13**) by treatment successively with acetyl hypobromite and aqueous sodium hydroxide. The structure of compound (**21**) was confirmed by reduction of its acetate (**19**) with lithium aluminium hydride to give, after re-acetylation, the hydroxy acetate (**12**). Surprisingly, the major product of the epoxidation reaction was once again the β-epoxide (**16**); other

† Preliminary account, G. A. Morrison and J. B. Wilkinson, *Tetrahedron Lett.*, 1975, 2713.



products were the alcohol (**14**), formed by simple saponification of the starting material, and 5,6β-epoxy-3α-methoxy-5β-cholestan-4α-ol (**22**), which was characterised by conversion into its acetate (**23**).

The appearance of compound (**22**) among the products of expoxidation of the olefin (**13**) suggests that the initially formed 4α,5α-epoxide (**21**) has undergone an epoxide migration,[5] involving oxirane cleavage resulting from intramolecular nucleophilic attack at C-5 by the axial 6β-hydroxy group. Epoxide migrations of this type are well documented in the carbohydrate field.[6] Confirmation that the epoxides (**21**) and (**22**) can also be isomerised in a similar manner was obtained when it was found that treatment of either with 10% methanolic potassium hydroxide under reflux gave a mixture of the two.

Epoxide migration appears also to occur under acid conditions, as evidenced by the fact that perchloric acid catalysed hydrolysis of either of the epoxides (**21**) or (**22**) affords the same triol, to which structure (**24**), arising by diaxial cleavage of the oxirane ring of compound (**22**), may be assigned on the basis of its n.m.r. spectrum. Its 10-methyl group exhibits a signal at δ 1.14, in close agreement with that observed for the 3-epimeric triol (**26**), obtained by saponification of the acetoxy diol (**25**) which was prepared by hydroxylation of 6β-acetoxy-3β-methoxycholest-4-ene (**2**) with osmium tetraoxide. The alternative structure (**27**) which would be formed by diaxial cleavage of the α-epoxide (**21**) is excluded since the chemical shift of its 10-methyl group would be expected to be similar to that (δ1.43) exhibited by its 3-epimer (**29**). Compound (**29**) was prepared,

together with its mono-acetate (**30**) by treatment of 5,6α-epoxy-3β-methoxy-5α-cholestan-4β-ol (**28**) with acetic acid.[7]

Experimental

M.p.s were measured on a Kofler hot-stage apparatus. I.r. spectra (Nujol mulls unless stated otherwise) were recorded on a Perkin-Elmer 157G or a Pye Unicam SP1000 spectrophotometer. N.m.r. spectra were measured on a Perkin-Elmer R12, a Varian Associates A60-A, or a Bruker FX90 instrument, with deuteriochloroform as solvent. Mass spectra were measured on an A.E.I. MS902 spectrometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter for solutions in chloroform. Merck Kieselgel GF_{254} was used for t.l.c. and column chromatography. Light petroleum refers to the fraction of boiling range 60—80 °C. Ether refers to diethyl ether. Solutions in organic solvents were dried with anhydrous sodium sulphate or magnesium sulphate.

Epoxidation of 3β-*Methoxycholest*-4-*en*-6β-ol (**1**).—A solution of 3β-methoxycholest-4-en-6β-ol (**1**)[8] (744 mg) in benzene (10 ml) was treated with *m*-chloroperbenzoic acid (900 mg) at room temperature. After 3 h, ether was added and the solution was washed successively with aqueous sodium sulphite, dilute aqueous sodium hydroxide, and water, and then dried and evaporated under reduced pressure to leave a gum which was chromatographed (50 g column; chloroform as eluant). The earlier fractions afforded 4β,5-*epoxy*-3β-*methoxy*-5β-*cholestan*-6β-*ol* (**3**) (444 mg) which crystallised from acetone as needles, m.p. 124.5—126 °C, $[\alpha]_D$ −11.8° (*c* 5.15) (Found: C, 77.8; H, 10.95. $C_{28}H_{48}O_3$ requires C, 77.7; H, 11.2%); $\nu_{max.}$ 3 440 cm^{-1}; δ 1.23 (3 H, s, 10-CH_3), 3.25 (1 H, d, *J* 3 Hz, 4α-H), 3.31 (1 H, t, *J* 2.5 Hz, 6α-H), 3.46 (3 H, s, OCH_3), and 3.58 (1 H, m, $W_{\frac{1}{2}}$ 16 Hz, 3α-H); *m*/*z* 432 (M^+).

The later fractions gave 4α,5-*epoxy*-3β-*methoxy*-5α-*cholestan*-6β-*ol* (**5**) (244 mg) which crystallised from aqueous acetone as plates, m.p. 125—126 °C, $[\alpha]_D$ +21.9° (*c* 3.15) (Found: C, 78.0; H, 11.0. $C_{28}H_{48}O_3$ requires C, 77.7; H, 11.2%); $\nu_{max.}$ 3 520 cm^{-1}; δ 1.29 (3 H, s, 10-CH_3), 2.09 (1 H, m, $W_{\frac{1}{2}}$ 5 Hz, OH, exchangeable with D_2O), 2.98 (1 H, s, 4β-H), 3.21 (1 H, t, *J* 3 Hz, 6α-H), 3.30—3.70 (1 H, m, 3α-H), and 3.43 (3 H, s, OCH_3); *m*/*z* 432 (M^+).

6β-*Acetoxy*-4β,5-*epoxy*-3β-*methoxy*-5β-*cholestane* (**4**).—4β,5-Epoxy-3β-methoxy-5β-cholestan-6β-ol (**3**) (48 mg) was treated with acetic anhydride (1 ml) and pyridine (2 ml) at room temperature overnight to give the derived *acetate* (**4**) (64 mg) as a gum which crystallised from aqueous methanol as plates, m.p. 113—114 °C (Found: C, 75.7; H, 10.5. $C_{30}H_{50}O_4$ requires C, 75.9; H, 10.6%); $\nu_{max.}$ 1 745 and 1 260 cm^{-1}; δ 1.16 (3 H, s, 10-CH_3), 2.05 (3 H, s, OAc), 3.20 (1 H, d, *J* 3 Hz, 4α-H), 3.40 (3 H, s, OCH_3), 3.59 (1 H, m, $W_{\frac{1}{2}}$ 15 Hz, 3α-H), and 4.54 (1 H, t, *J* 3 Hz, 6α-H).

Saponification of 6β-*Acetoxy*-4α,5-*epoxy*-3β-*methoxy*-5α-*cholestane* (**6**).—6β-Acetoxy-4α,5-epoxy-3β-methoxy-5α-cholestane (**6**) (218 mg)[2] was treated with methanolic potassium hydroxide (5%; 20 ml) at room temperature overnight. Ether was added and the solution was washed with water, dried, and evaporated under reduced pressure to give crystalline 4α,5-epoxy-3β-methoxy-5α-cholestan-6β-ol (**5**) (206 mg), identical (t.l.c., i.r., n.m.r., $[\alpha]_D$) with material obtained earlier by epoxidation of 3β-methoxycholest-4-en-6β-ol (**1**) (see above).

3α,5-*Epoxy*-6β-*methoxy*-5α-*cholestane* (**8**).—A solution of 5,6α-epoxy-5α-cholestan-3β-ol toluene-*p*-sulphonate (**7**) (162 mg)[9] in dimethylformamide (2 ml) was treated with methanolic sodium methoxide (3.5M; 2 ml) and the mixture heated at 100 °C for 4.5 h with exclusion of moisture (calcium chloride guard tube). Ether was added to the cooled reaction mixture and the solution washed with water, dried, then evaporated under reduced pressure to give a gum (152 mg). After combination with a similarly derived product, the mixture (271 mg) was chromatographed on a column of alumina (20 g, grade III; light petroleum as eluant) to give from the early fractions 3α,5-*epoxy*-6β-*methoxy*-5α-*cholestane* (**8**) (93 mg) as a gum, $[\alpha]_D$ +23.6° (*c* 3.90) (Found: C, 80.4; H, 11.7%; M^+, 416.3656; *m*/*z* 362.3194. $C_{28}H_{48}O_2$ requires C, 80.7; H, 11.6; M^+, 416.3654. $C_{24}H_{42}O_2$ requires *m*/*z* 362.3185); $\nu_{max.}$(film) 890 cm^{-1}; δ 1.04 (3 H, s, 10-CH_3), 2.04 (1 H, dd, *J* 9 and 1 Hz, 4-H), 2.59 (1 H, dd, *J* 9 and 7 Hz, collapses to a doublet, *J* 9 Hz, on irradiation at δ 4.49, 4-H), 3.31 (3 H, s, OCH_3), 3.39 (1 H, m, $W_{\frac{1}{2}}$ 6 Hz, 6α-H), and 4.49 (1 H, m, $W_{\frac{1}{2}}$ 13 Hz, the signal width is considerably reduced on irradiation at δ 2.04 and at δ 2.59, 3β-H).

The later fractions gave 5,6α-epoxy-5α-cholestan-3β-ol (**9**) (68 mg) identical (m.p., mixed m.p., t.l.c., i.r., and n.m.r.) to authentic material prepared by epoxidation of cholesterol, m.p. (ex. aqueous acetone) 139—142 °C (lit.,[9] m.p. 141—143 °C); $\nu_{max.}$ 3 350 cm^{-1}; δ 1.04 (2 H, s, 10-CH_3), 2.86 (1 H, d, *J* 4 Hz, 6β-H), and 3.55—4.10 (1 H, m, 3α-H).

5,6α-*Epoxy*-3α-*methoxy*-5α-*cholestane* (**11**).—A solution of 5,6α-epoxy-5α-cholestan-3α-ol (**10**) (218 mg) in methyl iodide (20 ml) and silver(I) oxide (600 mg) was heated under reflux for 48 h. The reaction mixture was filtered and evaporated under reduced pressure to give the crude product which was crystallised from methanol to afford 5,6α-*epoxy*-3α-*methoxy*-5α-*cholestane* (**11**) (180 mg), m.p. 119—20 °C, $[\alpha]_D$ −41.2° (*c* 12.65) (Found: C, 80.4; H, 11.65. $C_{28}H_{48}O_2$ requires C, 80.7; H, 11.6%); δ 1.04 (3 H, s, 10-CH_3), 2.73 (1 H, d, *J* 4 Hz, 6β-H), 3.30 (3 H, s, OCH_3), and 3.55 (1 H, m, $W_{\frac{1}{2}}$ 10 Hz, 3β-H); *m*/*z* 416 (M^+).

6β-*Acetoxy*-3α-*methoxy*-5α-*cholestan*-5-*ol* (**12**).—A solution of 5,6α-epoxy-3α-methoxy-5α-cholestane (**11**) (154 mg) in acetic acid (5 ml) was heated at 100 °C for 1 h. Ether was added to the cooled solution and the solution washed successively with dilute aqueous sodium hydroxide, and water, and then dried. Evaporation under reduced pressure gave a gum (162 mg) which was chromatographed (11 g column; 3% ether, 97% benzene as eluant) to afford 6β-*acetoxy*-3α-*methoxy*-5α-*cholestan*-5-*ol* (**12**) (140 mg), m.p. (ex. methanol) 66—67 °C, $[\alpha]_D$ −28.6° (*c* 8.15) (Found: C, 75.85; H, 11.2. $C_{30}H_{52}O_4$ requires C, 75.6; H, 11.0%); $\nu_{max.}$ 3 470, 1 740, and 1 245 cm^{-1}; δ 1.10 (3 H, s, 10-CH_3), 2.06 (3 H, s, OAc), 3.35 (3 H, s, OCH_3), 3.68 (1 H, m, $W_{\frac{1}{2}}$ 9 Hz, 3β-H), and 4.81 (2 H, m, $W_{\frac{1}{2}}$ 6 Hz, 6α-H, OH; the latter is exchangeable with D_2O); *m*/*z* 476 (M^+).

6β-*Acetoxy*-3α-*methoxycholest*-4-*ene* (**13**).—A solution of 6β-acetoxy-3α-methoxy-5α-cholestan-5-ol (**12**) (115 mg) in pyridine (3 ml) at 0 °C was treated with thionyl chloride (0.3 ml). After 2 h the mixture was poured into ice–water and extracted with ether. The extract was washed succssively with dilute hydrochloric acid, aqueous sodium hydrogen carbonate and water, and then dried. The solvents were removed under reduced pressure to give 6β-*acetoxy*-3α-*methoxycholest*-4-*ene* (**13**) (110 mg), homogeneous by t.l.c. and n.m.r., m.p. (ex. methanol) 81—83 °C, $[\alpha]_D$ +82.3° (*c* 5.55) (Found: C, 78.3; H, 11.0. $C_{30}H_{50}O_3$ requires C, 78.55; H, 11.0%) $\nu_{max.}$ 1 720 and 1 242 cm^{-1}; δ 1.06 (3 H, s, 10-CH_3), 1.99 (3 H, s, OAc), 3.34 (3 H, s, OCH_3), 3.65 (1 H, m, $W_{\frac{1}{2}}$ 10 Hz, 3β-H), 5.34 (1 H, t, *J* 4 Hz, 6α-H), and 5.90 (1 H, d, *J* 5 Hz, 4-H).

Epoxidation of 6β-*Acetoxy*-3α-*methoxycholest*-4-*ene* (**13**).—A solution of 6β-acetoxy-3α-methoxycholest-4-ene (**13**) (89 mg) in benzene (1 ml) at room temperature was treated with *m*-chloroperbenzoic acid (50 mg). After 48 h the product (104 mg)

was isolated and chromatographed (10 g column; 5% ether–95% benzene as eluant). The early fractions gave recovered starting material (**13**) (13 mg), identified by t.l.c.

The intermediate fractions gave 6β-*acetoxy*-5,6β-*epoxy*-3α-*methoxy*-5β-*cholestane* (**15**) (49 mg), m.p. (ex. aqueous acetone) 91.5—92.5°, $[\alpha]_D$ −10.1° (*c* 3.20) (Found: C, 76.0; H, 10.7. $C_{30}H_{50}O_4$ requires C, 75.9; H, 10.6%); $\nu_{max.}$ 1 735 and 1 250 cm^{-1}; δ 1.10 (3 H, s, 10-CH_3), 2.04 (2 H, s, OAc), 2.95 (1 H, s, 4α-H), 3.40 (3 H, s, OCH_3), 3.20—3.60 (1 H, m, 3β-H), and 4.55 1 H, t, *J* 3 Hz, 6α-H); *m/z* 474 (M^+).

The final fractions gave 6β-*acetoxy*-3α-*methoxy*-5β-*cholestane*-4α,5-*diol* (**17**) (21 mg); δ 0.98 (3 H, s, 10-CH_3), 2.10 (3 H, s, OAc), 2.49 (1 H, m, $W_{\frac{1}{2}}$ 3 Hz, OH), 2.38 (3 H, s, OCH_3), 3.35—3.70 (1 H, m, 3β-H), 3.38 (1 H, d, *J* 3 Hz, 4β-H), and 5.06 (1 H, t, *J* 4 Hz, 6α-H).

4α,6β-*Diacetoxy*-3α-*methoxy*-5β-*cholestan*-5-*ol* (**18**).—A solution of the triol monoacetate (**17**) (37 mg) in acetic anhydride (3 ml) and pyridine (3 ml) was left for 15 h at room temperature and then heated at 100 °C for 1.5 h to afford, after work-up, the 4α,6β-diacetate (**18**); δ 2.06 (3 H, s, OAc), 2.09 (3 H, s, OAc), 2.40 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, OH, exchangeable with D_2O), 3.29 (3 H, s, OCH_3), 4.85 (1 H, m, $W_{\frac{1}{2}}$ 7 Hz, 6α-H), and 5.24 (1 H, d, *J* 3.5 Hz, 4β-H).

Reaction of 6β-*Acetoxy*-3α-*methoxycholest*-4-*ene* (**13**) *with Acetyl Hypobromite, followed by Sodium Hydroxide Treatment of the Products formed.*—A stirred solution of 6β-acetoxy-3α-methoxycholest-4-ene (**13**) (1.36 g) in carbon tetrachloride (6 ml) at 0 °C was treated with 0.1M acetyl hypobromite in carbon tetrachloride (30 ml), according to the general method described by Levine and Wall.[10] After 15 min ether was added and the reaction mixture washed successively with aqueous sodium sulphite and water, and then dried. The solvents were removed under reduced pressure and the product heated under reflux with methanolic potassium hydroxide (10%; 60 ml) for 20 min. Water was added and the reaction mixture extracted with ether. The extract was washed with water, dried, and evaporated under reduced pressure to give a gum (1.11 g) which was chromatographed (80 g column; 30% ether −70% benzene as eluant). The early fractions gave 4β,5-*epoxy*-3α-*methoxy*-5β-*cholestan*-6β-*ol* (**16**) (339 mg) as a gum, $[\alpha]_D$ +14.1° (*c* 4.2) (Found: C, 76.45; H, 11.1%; M^+, 432.3603. $C_{28}H_{48}O_3$ requires C, 77.7; H, 11.2; *M*, 432.3599); $\nu_{max.}$(film) 3 450 cm^{-1}; δ 1.15 (3 H, s, 10-CH_3), 2.93 (1 H, s, 4α-H), 3.42 (3 H, s, OCH_3), and 3.21—3.57 (2 H, m, 3β-H, 6α-H).

The second fraction gave 3α-*methoxycholest*-4-*en*-6β-*ol* (**14**) (301 mg), m.p. (ex. methanol) 143—144°, $[\alpha]_D$ +79° (*c* 4.50) (Found: C, 81.0; H, 11.65. $C_{28}H_{48}O_2$ requires C, 80.7; H, 11.6%); $\nu_{max.}$ 3 460 cm^{-1}; δ 1.14 (3 H, s, 10-CH_3), 3.31 (3 H, s, OCH_3), 3.60 (1 H, m, $W_{\frac{1}{2}}$ 10 Hz, 3β-H), 4.21 (1 H, *t*, *J* 3 Hz, 6α-H), and 5.71 (1 H, d, *J* 5 Hz, 4-H); *m/z* 416 (M^+).

The third fraction gave 5,6β-*epoxy*-3α-*methoxy*-5β-*cholestan*-4α-*ol* (**22**) (142 mg), m.p. (ex. aqueous methanol) 126—128 °C, $[\alpha]_D$ −12.7° (*c* 6.50) (Found: C, 77.55; H, 11.1. $C_{28}H_{48}O_3$ requires C, 77.70; H, 11.20%); $\nu_{max.}$ 3 450 cm^{-1}; δ 0.96 (3 H, s, 10-CH_3), 3.33 (3 H, s, OCH_3), 3.50—4.10 [4 H, m, 3β-H, 4β-H, 6α-H, OH; simplifies on addition of D_2O to give at δ 3.55 (1 H, d, *J* 3 Hz, 6α-H), 3.72 (1 H, m $W_{\frac{1}{2}}$ 8 Hz, 3β-H), and δ 3.88 (1 H, d, *J* 4 Hz, 4β-H)]; *m/z* 432 (M^+). Treatment with acetic anhydride–pyridine at room temperature for 10 days gave the derived *acetate* (**23**), m.p. 110—112 °C (ex. aqueous methanol), $[\alpha]_D$ −13.9° (*c* 10.25) (Found: C, 76.15; H, 10.55. $C_{30}H_{50}O_4$ requires C, 75.9; H, 10.6%); $\nu_{max.}$ 1 742 and 1 250 cm^{-1}; δ 1.01 (5 H, s, 10-CH_3), 2.01 (3 H, s, OAc), 3.30 (3 H, s, OCH_3), 3.46 (1 H, d, *J* 3 Hz, 6α-H), 3.71 (1 H, m, $W_{\frac{1}{2}}$ 9 Hz, 3β-H), and 5.18 (1 H, d, *J* 3 Hz, 4β-H); *m/z* 474 (M^+) and 414 (M^+ − AcOH).

The final fraction gave 4α,5-*epoxy*-3α-*methoxy*-5α-*cholestan*-6β-*ol* (**21**) (187 mg) as a gum, $[\alpha]_D$ +49.3° (*c* 6.15) (Found: M^+, 432.3603. $C_{28}H_{48}O_3$ requires *M*, 432.3595); $\nu_{max.}$(film) 3 430 cm^{-1}; δ 1.18 (3 H, s, 10-CH_3), 3.23 (1 H, d, *J* 4 Hz, 4β-H), 3.23 (1 H, m, $W_{\frac{1}{2}}$ 10 Hz, OH), 3.42 (3 H, s, OCH_3), and 3.72 (2 H, m, $W_{\frac{1}{2}}$ 13 Hz 3β-H, 6α-H).

Saponification of 6β-*Acetoxy*-4β,5-*epoxy*-3α-*methoxy*-5β-*cholestane* (**15**).—A solution of 6β-acetoxy-4β,5-epoxy-3α-methoxy-5β-cholestane (**15**) (41 mg) in methanolic potassium hydroxide (5%; 20 ml) was left for 48 h at room temperature and then worked up to afford 4β,5-epoxy-3α-methoxy-5β-cholestan-6β-ol (**16**) (40 mg) identified (t.l.c. and n.m.r.) by comparison with an authentic sample prepared as described above.

Base-catalysed Isomerisation of the Epoxides (**21**) *and* (**22**).—A solution of 4α,5-epoxy-3α-methoxy-5α-cholestan-6β-ol (**21**) (123 mg) in methanolic potassium hydroxide (10%; 10 ml) was heated under reflux for 2 h. Water was added and the mixture was extracted with ether. The extract was washed with water, dried, and evaporated under reduced pressure to give a product (121 mg) which was chromatographed (8 g column; 40% ether–60% benzene as eluant) to give 5,6β-epoxy-3α-methoxy-5β-cholestan-4α-ol (**22**) (48 mg) and unchanged starting material (50 mg).

Similar treatment of 5,6β-epoxy-3α-methoxy-5β-cholestan-4α-ol (**22**) (48 mg) gave, after a similar work-up procedure, unchanged starting material (29 mg) and 4α,5-epoxy-3α-methoxy-5α-cholestan-6β-ol (**21**) (12 mg).

3α-*Methoxy*-5α-*cholestane*-4α,5,6β-*triol* (**24**).—(a) A solution of 5,6β-epoxy-3α-methoxy-5β-cholestan-4α-ol (**22**) (69 mg) in acetone (5 ml) at room temperature was treated with aqueous perchloric acid (7%; 0.5 ml). After 3 days, water was added and the reaction mixture extracted with ether. The extract was washed successively with aqueous sodium hydrogen carbonate, and water and then dried and evaporated under reduced pressure to give a gum (56 mg) which was chromatographed (6 g column; ether as eluant) to afford 3α-*methoxy*-5α-*cholestane*-4α,5,6β-*triol* (**24**) (38 mg), m.p. (ex. methanol) 149—152 °C, $[\alpha]_D$ −14.1° (*c* 1.80) (Found: C, 74.7; H, 11.2. $C_{28}H_{50}O_4$ requires C, 74.6; H, 11.2%); $\nu_{max.}$ 3 450 cm^{-1}; δ 1.14 (3 H, s, 10-CH_3), 2.50 (1 H, m, $W_{\frac{1}{2}}$ 20 Hz, OH, exchangeable with D_2O), 3.39 (3 H, s, OCH_3), 3.75 (1 H, m, $W_{\frac{1}{2}}$ 10 hz, 3β-H), and 4.05 (3 H, m, $W_{\frac{1}{2}}$ 10 Hz, 4β-H, 6α-H, OH; the last exchangeable with D_2O to leave 2 H, m, $W_{\frac{1}{2}}$ 8 Hz); *m/z* 450 (M^+).

(b) A solution of 4α,5-epoxy-3α-methoxy-5α-cholestan-6β-ol (**21**) (105 mg) in acetone (5 ml) and aqueous perchloric acid (7%; 0.5 ml) was heated under reflux for 1.5 h. Water was then added and the reaction mixture was extracted with chloroform. The extract was washed successively with aqueous sodium hydrogen carbonate, and water, and then dried and evaporated under reduced pressure to give a gum (115 mg) which was chromatographed (10 g column; 25% ether–75% benzene as eluant) to give 3α-methoxy-5α-cholestane-4α,5,6β-triol (**24**) (57 mg) identical (t.l.c., i.r., m.p., mixed m.p., and n.m.r.) with the material obtained in (a) above.

6β-*Acetoxy*-3β-*methoxy*-5α-*cholestane*-4α,5-*diol* (**25**).—A solution of 6β-acetoxy-3β-methoxycholest-4-ene (**2**) (166 mg) in pyridine (1.5 ml) at room temperature was treated with osmium tetraoxide (100 mg). After 1 week, the reaction mixture was stirred with a solution of sodium bisulphite 1.8 g), water (30 ml), and pyridine (20 ml) for 30 min. The reaction mixture was then extracted with chloroform and the extract washed successively with water, dilute hydrochloric acid, and aqueous sodium hydrogen carbonate, and then dried. The product obtained by evaporation of the chloroform under reduced pressure was chromatographed (9 g column; 25% ether–75% benzene as eluant) to give from the later fractions 6β-*acetoxy*-3β-*methoxy*-

5α-*cholestane*-4α,5-*diol* (**25**) (60 mg), m.p. (ex. methanol) 157—159 °C, $[\alpha]_D$ +8.1° (*c* 2.70) (Found: C, 73.4; H, 10.65. $C_{30}H_{52}O_5$ requires C, 73.1; H, 10.65%); $\nu_{max.}$ 3 480, 1 705, and 1 275 cm^{-1}; δ 1.05 (3 H, s, 10-CH_3), 2.07 (3 H, s, OAc), 2.44 (1 H, m, $W_{\frac{1}{2}}$ 8 Hz, OH, exchangeable with D_2O), 3.10—3.60 (1 H, m, 3α-H), 3.43 (3 H, s, OCH_3), 3.59 (1 H, d, *J* 8 Hz, 4β-H), and 4.94 (1 H, m, $W_{\frac{1}{2}}$ 5 Hz, 6α-H).

The early fractions afforded unchanged starting material (**2**) (57 mg).

3β-*Methoxy*-5α-*cholestane*,4α,5,6β-*triol* (**26**).—A solution of 6β-acetoxy-3β-methoxy-5α-cholestane-4α,5-diol (**25**) (117 mg) in methanolic potassium hydroxide (10%; 20 ml) was heated under reflux for 10 min after which water was added and the reaction mixture extracted with ether. The extract was washed with water, dried, and evaporated under reduced pressure. The residue was crystallised from methanol to give 3β-*methoxy*-5α-*cholestane*-4α,5,6β-*triol* (**26**), m.p. 206—207 °C, $[\alpha]_D$ +21.6° (*c* 3.91) (Found: C, 74.6; H, 11.25. $C_{28}H_{50}O_6$ requires C, 74.6; H, 11.2%); $\nu_{max.}$ 3 480 cm^{-1}; δ 1.14 (3 H, s, 10-CH_3), 3.41 (3 H, s, OCH_3), 2.50—3.00 (2 H, m, 2 × OH, exchangeable with D_2O), 3.17—3.66 (1 H, m, 3α-H), 3.97 (1 H, m, $W_{\frac{1}{2}}$ 5 Hz, 6α-H), and 4.02 (1 H, d, *J* 9 Hz, 4β-H).

Reaction of 5,6α-*Epoxy*-3β-*methoxy*-5α-*cholestan*-4β-*ol* (**28**) *with Acetic Acid*.—A solution of 5,6α-epoxy-3β-methoxy-5α-cholestan-4β-ol (**28**) (128 mg) in acetic acid (10 ml) was heated at 100 °C for 12 h. Ether was added to the cooled solution and the mixture was washed successively with aqueous sodium hydroxide and water and then dried and evaporated under reduced pressure. The residue was chromatographed (8 g column; 30% ether–70% benzene as eluant). The early fractions afforded 6β-*acetoxy*-3β-*methoxy*-5α-*cholestane*-4β,5-*diol* (**30**) (69 mg) which crystallised from methanol as needles, m.p. 166—167 °C, $[\alpha]_D$ −25.4° (*c*, 1.02) (Found: C, 72.95; H, 10.45. $C_{30}H_{52}O_4$ requires C, 73.1; H, 10.65%); $\nu_{max.}$ 3 480, 3 430, 1 720, and 1 280 cm^{-1}; δ 1.35 (3 H, s, 10-CH_3), 2.01 (3 H, s, OAc), 2.30 (1 H, m, $W_{\frac{1}{2}}$ 4 Hz, OH, exchangeable with D_2O), 3.32 (3 H, s, OCH_3), 3.40—3.82 (1 H, m, 3α-H), 3.79 (1 H, d, *J* 3 Hz, 4α-H), and 5.08 (1 H, m, $W_{\frac{1}{2}}$ 5 Hz, 6α-H).

The later fractions gave 3β-*methoxy*-5α-*cholestane*-4β,5,6β-*triol* (**29**) (36 mg) which crystallised from light petroleum as needles, m.p. 184—187 °C, $[\alpha]_D$ +9.4° (*c* 0.66) (Found: C, 74.4: H, 11.1. $C_{28}H_{50}O_4$ requires C, 74.6; H, 11.2%); $\nu_{max.}$ 3 460 cm^{-1}; δ 1.43 (3 H, s, 10-CH_3), 2.97 (1 H, m, $W_{\frac{1}{2}}$ 6 Hz, OH, exchangeable with D_2O), 3.41 (3 H, s, OCH_3), 3.40—3.75 (1 H, m, 3α-H), 3.80 (1 H, t, *J* 2.5 Hz, 6α-H), 3.93 (1 H, d, *J* 4 Hz, 4α-H), and 4.16 (1 H, m, $W_{\frac{1}{2}}$ 6 Hz, OH, exchangeable with D_2O).

Treatment of the acetate (**30**) (45 mg) with methanolic potassium hydroxide (5%; 10 ml) at room temperature for 15 h gave, after work-up, the triol (**29**) (39 mg), identical (m.p., mixed m.p., t.l.c., and i.r.) with the material obtained as described above.

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