Preparation and Cleavage Reactions of Some Steroidal Epoxides

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The steroidal epoxides (12), (13), (28), and (34) have been prepared and their reactions investigated. Attempts to prepare the epoxides (12) and (13) by the action of dimethylsulphonium methylide or dimethylsulphoxonium methylide on the ketone (1) gave instead the rearranged product (2) and its methyl ether (3). Compound (2) has also been obtained by base-catalysed isomerisation of the spiro-epoxide (13). Lewis acid-catalysed rearrangement of the epoxides (12), (28), and (34) into the A-homo-B-norsteroids (16), (29), and (43) respectively is described.

5-Hydroxy-3β-methoxy-5α-cholestane-6(*R*)-spiro-2′-oxirane (12), its 6(*S*)-epimer (13), 5,6α-epoxy-3β-methoxy-6β-methyl-5α-cholestane (28), and 5,6β-epoxy-3β-methoxy-5β-cholestane (34) were required by us in connection with another investigation. We now describe the preparation of these epoxides and some of their reactions.

Earlier reports [1] suggested that it might be possible to prepare the 6(*S*)-spiro-oxirane (13) by the action of dimethylsulphoxonium methylide on 5-hydroxy-3β-methoxy-5α-cholestan-6-one (1), while the action of dimethylsulphonium methylide on the ketone (1) would be expected to produce a mixture of both epoxides.

In the event neither epoxide could be isolated from the reaction of either of the ylides with the ketone (1). Instead, the action of dimethylsulphonium methylide on the ketone (1) gave 5,6α-epoxy-6β-hydroxymethyl-3β-methoxy-5α-cholestane (2) and its methyl ether (3) in yields of 65 and 35% respectively. When dimethylsulphoxonium methylide was employed as nucleophile only the alcohol (2) was obtained. The relationship between compounds (2) and (3) was established when it was found that the dimethyl ether (3) could be obtained by methylation of the alcohol (2). Treatment of compound (2) with acetic anhydride and pyridine afforded the derived acetate (4); similar treatment of the diol (5), which arises by reduction of the epoxide (2) with lithium aluminium hydride, gave a monoacetate (7). The corresponding methoxy compound (6) was obtained by lithium aluminium hydride reduction of the epoxide (3).

The structures assigned to compounds (2)—(7) followed from their i.r. and n.m.r. spectra. Thus, compound (2) absorbed in the i.r. at 3 615 cm^{-1} (O–H str.), and exhibited singlets in its n.m.r. spectrum at δ 3.33 (OCH_3) and 3.62 (CH_2OH). The presence of a primary hydroxy group was confirmed by the n.m.r. spectrum recorded for the derived monoacetate (4) which differed significantly from that of compound (2) only in that the signal for the 6β-methylene group was shifted downfield (to δ 4.09).

Formation of the hydroxymethyl compound (2) is thought to arise from the initially formed exocyclic epoxide (13) by an epoxide migration [2] involving intramolecular nucleophilic attack upon the oxirane ring by the 5α-oxygen function which is antiperiplanar with respect to the 6β-oxygen atom (see Figure 1). Formation of the methyl ether (3) in the reaction of the ketol (1) with dimethylsulphonium methylide might involve either insertion of a methylene carbene into the O–H bond of the alcohol (2) or an ionic mechanism as shown in Scheme 1.

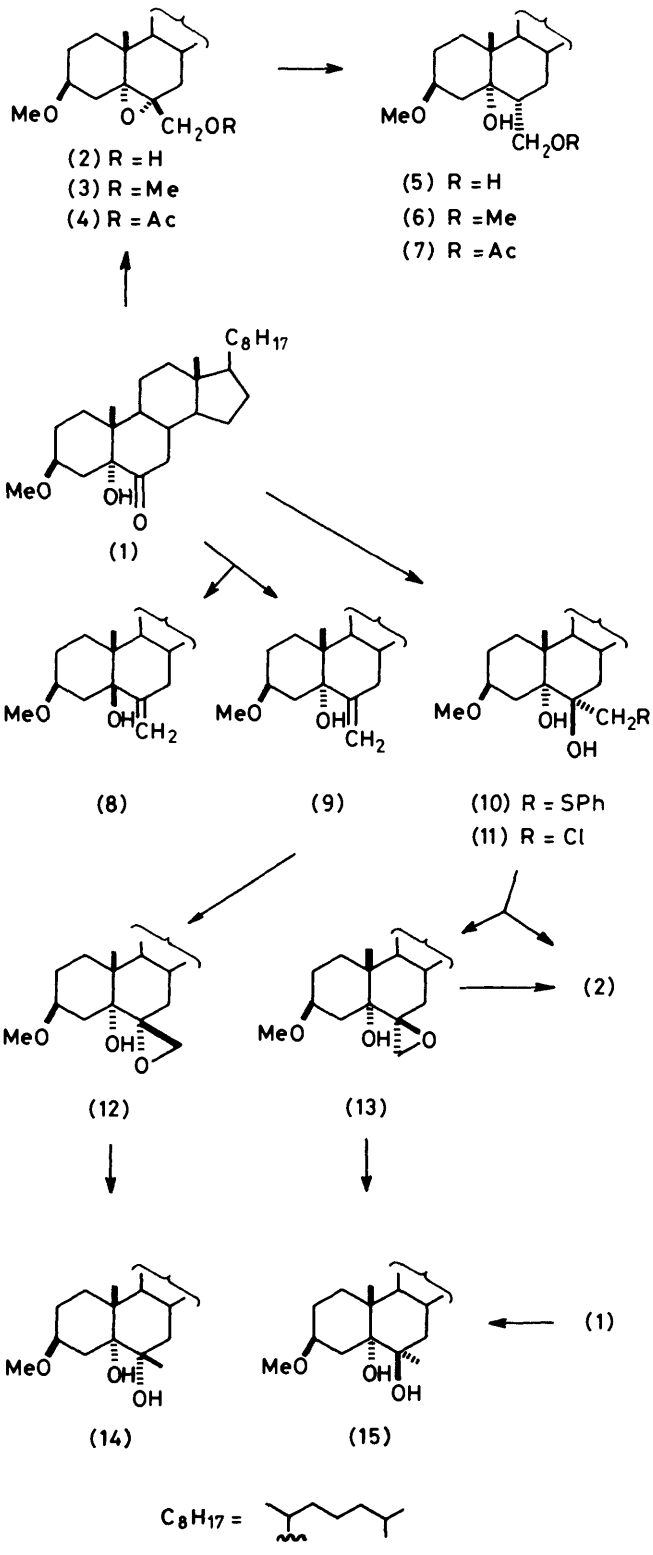
The 6(*S*)-spiro-oxirane (13) was prepared as follows (*cf.* ref. 3). Phenylthiomethyl-lithium was generated by the action of n-butyl-lithium on thioanisole in the presence of diazabicyclo[2.2.2]octane [4] and reacted with the hydroxy ketone (1) to yield the phenylthiomethyl diol (10), which was alkylated with trimethyl- or triethyl-oxonium fluoroborate to form the corresponding sulphonium salt. Subsequent base treatment (aqueous sodium hydroxide at room temperature) afforded the spiro-oxirane (13), together with a small amount of the endocyclic epoxide (2). The configuration at C-6 of compound (13) was confirmed by reduction with lithium aluminium hydride to give the diaxial diol (15), also obtained by the action of methyl-lithium or methylmagnesium iodide on the hydroxy ketone (1). Support for the epoxide migration mechanism (see Figure 1) was provided by the observation that when a solution of the exocyclic epoxide (13) in aqueous tetrahydrofuran (THF) containing potassium hydroxide was heated under reflux a 2 : 1 mixture of compounds (2) and (13) was obtained. Isomerisation of the exocyclic epoxide (13) was completed by boiling a solution of the mixture in benzene containing sodium hydride.

In contrast to the rearrangement of the epoxide (13) brought about by treatment with base, cleavage with hydrogen chloride in chloroform proceeded without epoxide migration to afford 6α-chloromethyl-3β-methoxy-5α-cholestane-5,6β-diol (11), the structure of which followed from its n.m.r. spectrum (see Experimental section) and its resistance to acetylation with acetic anhydride and pyridine.

The 6(*R*)-spiro-oxirane (12) was prepared in high yield by the action of *m*-chloroperbenzoic acid on the exocyclic olefin (9). Its configuration at C-6 followed from its mode of formation (normal α-attack being made particularly favourable by the allylic 5α-hydroxy group [5]), its n.m.r. spectrum (the C-19 protons give rise to a signal at δ 0.94 showing that the deshielding effect of the 6β-substituent is small), and its reduction with lithium aluminium hydride to give the diol (14), which is different from that (15) obtained by the action of methyl-lithium on the ketol (1).

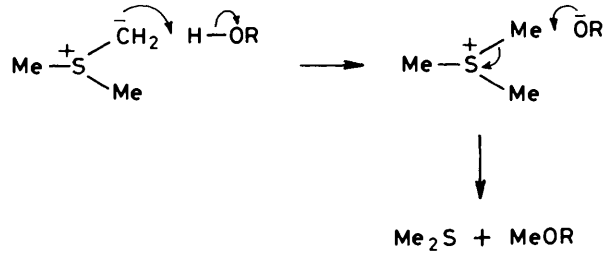
Conversion of the ketol (1) into the 6-methylene compound (9) was achieved by a Wittig reaction with methylenetriphenylphosphorane using either methyl-lithium or dimsylsodium [dimsyl = $CH_3S(O)CH_2^-$] to generate the ylide. Use of dimsylsodium as base produced varying results; at room temperature only the allylic alcohol (9) and starting material were obtained, but when the reaction was carried out at 60 °C a small amount of the epimeric allylic alcohol (8) was also obtained.

In the 6(*R*)-spiro-oxirane (12), the oxygen atom of the oxirane ring and C-10 are arranged in an antiperiplanar conformation with respect to the C-5–C-6 bond. As a consequence, brief treatment of an ethereal solution of the epoxide (12) with boron trifluoride–diethyl ether is sufficient to induce the rearrangement indicated in Figure 2 with production, in high yield, of 5-hydroxymethyl-3β-methoxy-A-homo-B-nor-5β-cholestan-4a-one (16).[6,7] In agreement with the β-hydroxy ketone structure (16), mild base treatment brought about a retroaldol elimination which afforded a C-5 epimeric mixture of 3β-methoxy-A-homo-B-norcholestan-4a-ones, from which the predominant 5β-isomer (17) was



isolated by chromatography. Support for the assignment of a *cis* A/B ring junction is provided by the chemical shift (δ 1.16) of the C-19 protons.[8]

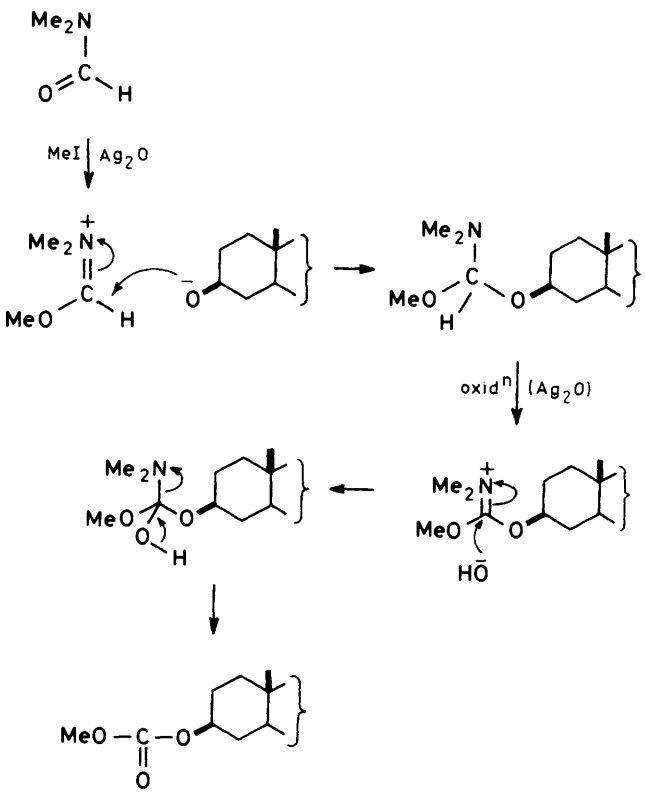
5,6α-Epoxy-3β-methoxy-6β-methyl-5α-cholestane (28) could be obtained by dehydration of 3β-methoxy-6α-methyl-5α-cholestane-5,6β-diol (15) with thionyl chloride and pyridine, a reaction which presumably involves intramolecular displacement of an intermediate 6β-chlorosulphonate by the 5α-hydroxy group. It was also prepared by epoxidation of 3β-methoxy-6-methylcholest-5-ene (26) with *m*-chloroperbenzoic acid. The olefin (26) was obtained by dehydration of the tertiary alcohol (25), which was itself prepared from 3β-methoxy-5ξ-cholestan-6-one [(23) and (24) in an equilibrium mixture of 12 : 1 *] either by treatment with methylmagnesium



Scheme 1.

* Methylation of 3β-hydroxy-5α-cholestan-6-one (21) with trimethyl orthoformate and perchloric acid (J. P. Dusza, J. P. Joseph, and S. Bernstein, *Steroids*, 1966, **8**, 495) gave initially a *ca.* 1 : 1 mixture of the 5-epimeric ketones (23) and (24); sodium ethoxide-catalysed equilibration shifted the ratio to 12 : 1 in favour of the 5α-epimer (23) [a result similar to that achieved by acid-catalysed equilibration (D. N. Jones and D. E. Kime, *J. Chem. Soc. C*, 1966, 846)], a pure sample of which was obtained by fractional crystallisation.

An attempt to methylate the ketol (21) with methyl iodide and silver oxide, using dimethylformamide (DMF) as solvent gave instead the methyl carbonate (22). A possible mechanism for this reaction is outlined in Scheme 2. Hydrolysis of the carbonate (22) with aqueous methanolic potassium hydroxide gave a mixture of the starting alcohol (21) and its 5β-epimer.



Scheme 2.

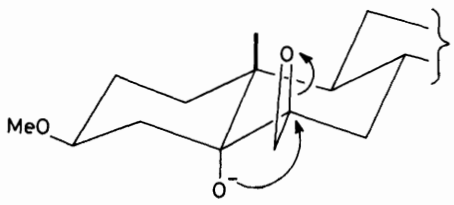


Figure 1.

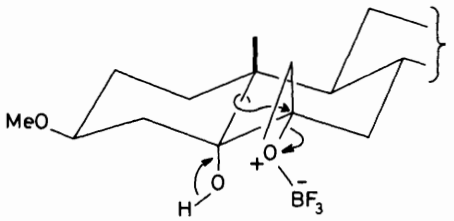
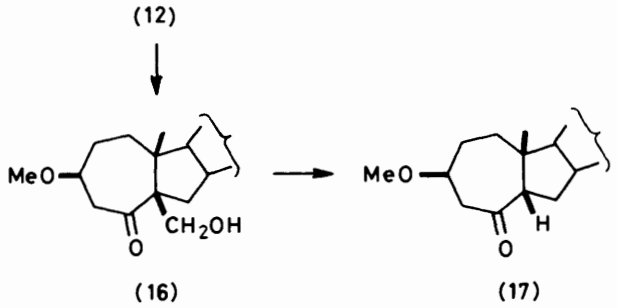
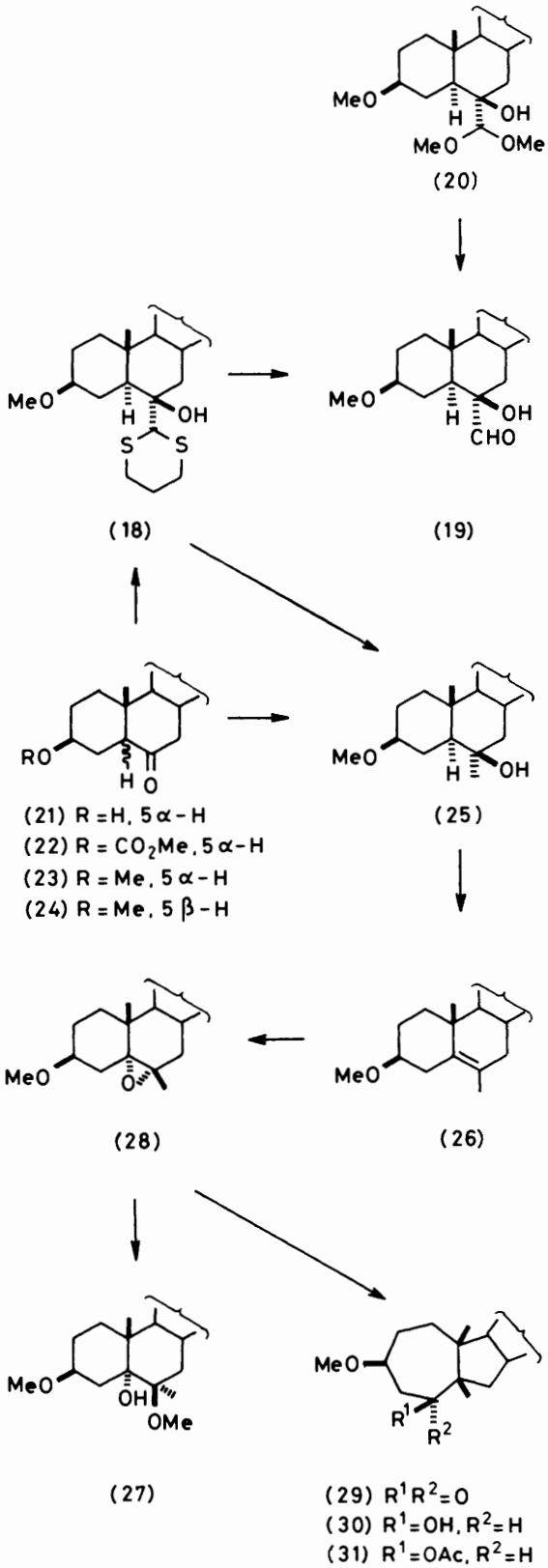


Figure 2.





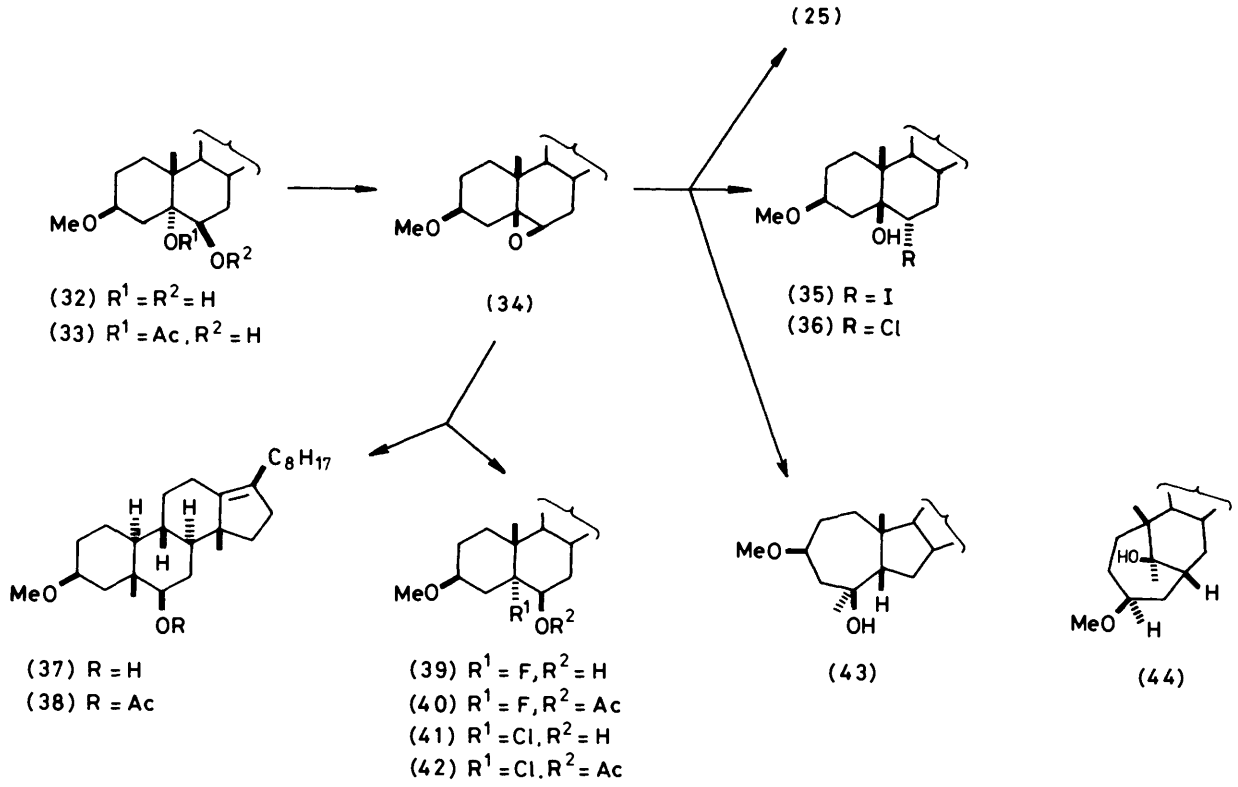
iodide or by desulphurisation, with Raney nickel, of the derived dithiane adduct (18). Hydrolysis of the dithiane adduct (18) with methyl iodide and aqueous acetone afforded the aldehyde (19) in excellent yield, whilst cleavage with mercury(II) oxide and mercury(II) chloride in aqueous methanol gave a mixture of the aldehyde (19) and its dimethyl acetal (20).

When a solution of the epoxide (28) in benzene was treated with boron trifluoride–diethyl ether it rearranged in a manner analogous to that reported [9,10] for other 6-substituted-5,6-epoxycholestanes to give the A-homo-B-norketone (29), the i.r. carbonyl frequency of which (1 689 cm^{-1}) is similar to those reported for analogous structures.[6,9,11] Further confirmation of the assigned structure was provided by its n.m.r. spectrum, and those of its lithium aluminium hydride reduction product (30) and the derived acetate (31) (see Experimental section.)

When the epoxide (28) was treated with boron trifluoride–diethyl ether in the presence of a suitable nucleophile, diaxial cleavage of the oxirane ring occurred. Thus, in methanol, 3β,6β-dimethoxy-6α-methyl-5α-cholestan-5-ol (27) was obtained.

5,6β-Epoxy-3β-methoxy-5β-cholestane (34) has previously been reported [12] only in admixture with the corresponding 5α,6α-epoxide. It has been obtained in a pure state in the present work by treatment of 5-acetoxy-3β-methoxy-5α-cholestan-6β-ol (33) under strong basic conditions. The diol monoacetate (33) was prepared from the diol (32) by successive diacetylation and half-saponification.

When the epoxide (34) was treated with methylmagnesium iodide in diethyl ether no product arising from simple nucleophilic cleavage of the oxirane ring was isolated, in contrast to the result reported [13] for the corresponding reaction involving 5,6β-epoxy-5β-cholestan-3β-ol. Instead, in addition to unchanged epoxide (34) (30%), 3β-methoxy-6α-methyl-5α-cholestan-6β-ol (25) (11%), identified by comparison with an authentic specimen, 6α-iodo-3β-methoxy-5β-cholestan-5-ol



(35) (12%), and 3β-methoxy-4aα-methyl-A-homo-B-nor-5β-cholestan-4aβ-ol (43) (15%) were obtained.

The iodo compound (35), the structure of which followed from its spectral properties (see Experimental section) probably arises by attack of magnesium iodide, known to exist in equilibrium with dimethylmagnesium and methylmagnesium iodide, on the oxirane ring. In accord with this view, none of the iodo compound was formed when the reaction was repeated using, as solvent, benzene, in which magnesium iodide is insoluble. The observed diequatorial cleavage of the oxirane is doubtless a consequence of the large size of the iodide ion; attack at C-5 to give diaxial cleavage would involve the iodide ion in severe non-bonded interactions with the axial hydrogen atoms at C-1 and C-3. In support of this view we have shown that, while the epoxide (34) reacted with hydrogen chloride in chloroform to give the diaxial chlorohydrin (41) virtually quantitatively, dilute aqueous hydrochloric acid reacted to give a mixture of the diaxial chlorohydrin (41) (64%) and the diequatorial chlorohydrin (36) (15%). Formation of the diequatorial product in the aqueous medium is ascribed to solvation of the chloride ions, resulting in a bulkier nucleophile than in chloroform, and thus making attack at C-6 more competitive.

The 6β-hydroxy compound (25) doubtless arises from the corresponding 6-oxo compound (21) formed by Lewis acid-catalysed rearrangement of the epoxide (34). However, the major rearrangement process involves migration of the C-10–C-5 bond leading to the formation of an A-homo-B-nor ketone which reacts with the Grignard reagent to produce the alcohol (43). When the reaction was repeated using benzene as solvent, the only products isolated were the tertiary alcohols (25) and (43). It should be noted that while the spectral data for the alcohol (43) are fully in accord with the structure assigned, the alternative *abeo*-structure (44) cannot be excluded. Such a structure would arise by reaction of methylmagnesium iodide with the corresponding *abeo*-ketone, which would be formed by a rearrangement of the epoxide (34) involving migration of the C-4–C-5 bond.

Treatment of the epoxide (34) with boron trifluoride–diethyl ether in diethyl ether afforded mainly the diaxial fluorohydrin (39) together with a small amount of the backbone-rearranged product (37). The structure of the fluorohydrin followed from its spectra, and from the formation of the parent epoxide (34) by hydrolysis of the fluorohydrin acetate (40) with ethanolic sodium hydroxide.

When the reaction between the epoxide (34) and boron trifluoride–diethyl ether was repeated using benzene as solvent the fluorohydrin (39) and the olefin (37) were again obtained, with the latter predominating. The products were separated by chromatography of their respective acetates (40) and (38). The structures assigned to compounds (37) and (38) were supported by their mass spectra. Both exhibited molecular ions and showed base peaks corresponding to loss of the C-17 side-chain, characteristic of $\Delta^{13(17)}$ olefins.[14] The position of the double bonds in these compounds was confirmed by n.m.r. double-resonance experiments which revealed that the C-21 protons were coupled with a single proton at δ 2.38 in the alcohol (37) and δ 2.34 in the acetate (38), from which it followed that the C-20 proton was allylic in both cases. The backbone rearrangement thus established for the methoxy epoxide (34) is analogous to that reported [14] for the corresponding hydroxy epoxide.

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 297 spectrophotometer. N.m.r. spectra were measured on a Perkin-Elmer R32A instrument, with deuteriochloroform as solvent. Mass spectra were recorded on an A.E.I. MS902 spectrometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter for solu-

tions in chloroform. Merck Kieselgel G or 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.

Reaction of 5-Hydroxy-3β-methoxy-5α-cholestan-6-one (1) *with Dimethylsulphonium Methylide*.—A solution of sodium hydride (185 mg, 94% dispersion in mineral oil) in dry dimethyl sulphoxide (DMSO) (15 ml) was stirred at 70 °C under nitrogen for 45 min, then THF (14 ml) was added and the mixture was cooled to −8 °C. Trimethylsulphonium iodide (1.58 g) and DMSO (8 ml) were added to the rapidly stirred solution, followed, after 3 min, by a solution of 5-hydroxy-3β-methoxy-5α-cholestan-6-one (1) (1.02 g) in THF (5 ml). The mixture was stirred at −5 °C for 25 min, then warmed to room temperature and stirred for a further 45 min. Water was added, and the mixture was extracted with ether. The extract was washed twice with brine, dried, and evaporated under reduced pressure. Chromatography of the residue [100 g column; chloroform–ethyl acetate (1 : 1) as eluant] afforded from the early fractions 5,6α-*epoxy*-3β-*methoxy*-6β-*methoxymethyl*-5α-*cholestane* (3) (369 mg, 35%) as a viscous gum which was distilled at a pressure of 5×10^{-3} Torr (bath temp. 185 °C), $[\alpha]_D^{21}$ −16.5° (*c* 0.46) (Found: C, 78.0; H, 11.1%; M^+, 460.3914. $C_{30}H_{52}O_3$ requires C, 78.2; H, 11.4%; *M*, 460.3916); $\nu_{max.}$ ($CHCl_3$) 1 103 cm^{-1}; δ_H 0.61 (3 H, s, 18-H_3), 1.04 (3 H, s, 19-H_3), 3.32 (3 H, s, CH_2OMe), 3.34 (3 H, s, 3β-OMe), 3.39 (2 H, s, CH_2OMe), and 3.15—3.60 (1 H, m, 3α-H).

Later fractions gave 5,6α-*epoxy*-6β-*hydroxymethyl*-3β-*methoxy*-5α-*cholestane* (2) which crystallised from methanol or light petroleum as needles (693 mg, 65%), m.p. 151—153 °C; $[\alpha]_D^{20}$ −28.8° (*c* 0.77) (Found: C, 77.95; H, 10.9%; M^+, 446.3754. $C_{29}H_{50}O_3$ requires C, 77.95; H, 11.3%; *M*, 446.3760); $\nu_{max.}$ ($CHCl_3$) 3 615 and 1 036 cm^{-1}; δ_H 0.61 (3 H, s, 18-H_3), 1.03 (3 H, s, 19-H_3), 2.21 (1 H, exchanges with D_2O, OH), 3.33 (3 H, s, OMe), 3.15—3.50 (1 H, m, 3α-H), and 3.62 (2 H, s, CH_2OH).

Reaction of 5-Hydroxy-3β-methoxy-5α-cholestan-6-one (1) *with Dimethylsulphoxonium Methylide*.—Trimethylsulphoxonium iodide[15] (2.14 g), sodium hydride (236 mg, 94% dispersion in mineral oil), and DMSO (4 ml) were stirred together at room temperature until hydrogen evolution ceased. A solution of 5-hydroxy-3β-methoxy-5α-cholestan-6-one (1 g) in THF (20 ml) was added and the mixture was stirred at room temperature for 19 h, then at 65 °C for 3 h. Water was added to the cooled solution, which was then stirred for 30 min, and extracted with ether. The extract was washed with water, dried, and evaporated under reduced pressure. Chromatography of the residue [100 g column; chloroform–ethyl acetate (1 : 1) as eluant] afforded 5,6α-epoxy-6β-hydroxymethyl-3β-methoxy-5α-cholestane (2) (754 mg, 73%), identical with the material obtained in the preceding experiment.

Methylation of 5,6α-Epoxy-6β-hydroxymethyl-3β-methoxy-5α-cholestane (2).—5,6α-Epoxy-6β-hydroxymethyl-3β-methoxy-5α-cholestane (2) (129 mg), methyl iodide (141 mg), and silver oxide (186 mg) were stirred together in DMF (1 ml) for 26 h. The suspension was filtered, the residue was washed with methylene dichloride, and the filtrate was evaporated under reduced pressure. The organic residue was taken up in ether and washed successively with water, cold dilute hydrochloric acid, and water, then dried and evaporated under reduced pressure. Chromatography (15 g column; chloroform as eluant) afforded 5,6α-epoxy-3β-methoxy-6β-methoxymethyl-5α-cholestane (3) (83 mg, 62%), identical (t.l.c., n.m.r., and m.s.) with material described in an earlier experiment.

6β-*Acetoxymethyl*-5,6α-*epoxy*-3β-*methoxy*-5α-*cholestane* (4).—A solution of 5,6α-epoxy-6β-hydroxymethyl-3β-methoxy-5α-cholestane (2) (113 mg) in acetic anhydride (1.5 ml) and pyridine (6 ml) was stirred for 1.75 h, then the mixture was poured into aqueous sodium chloride and extracted with ether. The extract was evaporated under reduced pressure, and the residue was chromatographed (10 g column; chloroform as eluant) to give 6β-*acetoxymethyl*-5,6α-*epoxy*-3β-*methoxy*-5α-*cholestane* (4) (120 mg, 97%) as an oil, which was distilled under reduced pressure (2×10^{-1} Torr; bath temp. 208 °C) (Found: C, 76.05; H, 10.55; M^+, 488.3858. $C_{31}H_{52}O_4$ requires C, 76.2; H, 10.7%; *M*, 488.3865); $\nu_{max.}$ (film) 1 741 cm^{-1}; δ_H 0.62 (3 H, s, 18-H_3), 1.04 (3 H, s, 19-H_3), 2.08 (3 H, s, OAc), 3.33 (3 H, s, OMe), 3.29—3.50 (1 H, m, 3α-H), and 4.09 (2 H, s, CH_2OAc).

6α-*Hydroxymethyl*-3β-*methoxy*-5α-*cholestan*-5-*ol* (5).—5,6α-Epoxy-6β-hydroxymethyl-3β-methoxy-5α-cholestane (2) (190 mg) and lithium aluminium hydride (245 mg) were heated together under reflux in ether (15 ml) for 1 h. Dilute hydrochloric acid was added to the cooled mixture and the organic fraction was diluted with ether, then separated and washed twice with water, and dried. Evaporation under reduced pressure left 6α-*hydroxymethyl*-3β-*methoxy*-5α-*cholestan*-5-*ol* (5) (180 mg, 95%), m.p. 180—180.5 °C (needles, from methanol); $[\alpha]_D^{22}$ +6.1° (*c* 0.61) (Found: C, 77.55; H, 11.55. $C_{29}H_{52}O_3$ requires C, 77.6; H, 11.7%); *m/z*, 430 (100%, $M^+ - H_2O$); $\nu_{max.}$ ($CHCl_3$) 3 615, 3 470, and 1 090 cm^{-1}; δ_H 0.66 (3 H, s, 18-H_3), 0.94 (3 H, s, 19-H_3), 3.0—3.4 (2 H, exchange with D_2O, 2 × OH), 3.37 (3 H, s, OMe), 3.3—3.85 (2 H, m, 3α-H and *H*CHOH), and 4.11 (1 H, d, *J* 10 Hz, HC*H*OH).

Treatment of the alcohol (5) (69 mg) with acetic anhydride (0.5 ml) and pyridine (3 ml) at room temperature for 2 h afforded the derived *acetate* (7) (61 mg, 81%) which was crystallised from methanol, m.p. 116—118 °C; the melt resolidified and finally remelted at 128—130 °C; $[\alpha]_D^{21}$ +16° (*c* 0.77) (Found: C, 75.65; H, 11.05. $C_{31}H_{54}O_4$ requires C, 75.85; H, 11.1%); $\nu_{max.}$ ($CHCl_3$) 3 585, 1 738, and 1 093 cm^{-1}; δ_H 0.66 (3 H, s, 18-H_3), 0.98 (3 H, s, 19-H_3), 1.90 (1 H, exchanges with D_2O, OH), 2.06 (3 H, s, OAc), 3.34 (3 H, s, OMe), 3.3—3.8 (1 H, m, 3α-H), 4.04 (1 H, dd, J_{gem} 11 Hz, J_{vic} 4.5 Hz, *H*CHOAc), and 4.26 (1 H, dd, J_{gem} 11 Hz, J_{vic} 4.5 Hz, HC*H*OAc). Irradiation at δ_H 1.92 caused the multiplets at δ_H 4.04 and 4.26 to collapse to a pair of doublets, each exhibiting *J* 11 Hz.

3β-*Methoxy*-6α-*methoxymethyl*-5α-*cholestan*-5-*ol* (6).—5,6α-Epoxy-3β-methoxy-6β-methoxymethyl-5α-cholestane (3) (265 mg) and lithium aluminium hydride (219 mg) were heated under reflux in ether (20 ml) for 2 h; dilute hydrochloric acid was added to the cooled mixture and the product was extracted into ether. The extract was washed twice with brine, then dried and evaporated under reduced pressure to leave an oil (255 mg). Chromatography (25 g column; chloroform as eluant) afforded 3β-*methoxy*-6α-*methoxymethyl*-5α-*cholestan*-5-*ol* (6) (234 mg, 88%), m.p. 121—121.5 °C (from methanol); $[\alpha]_D^{20}$ +14.5° (*c* 1.07) (Found: C, 78.05; H, 11.75; M^+, 462.4084. $C_{30}H_{54}O_3$ requires C, 77.85; H, 11.75%; *M*, 462.4073); $\nu_{max.}$ 3 515 and 1 108 cm^{-1}; δ_H 0.65 (3 H, s, 18-H_3), 0.91 (3 H, s, 19-H_3), 3.18 (1 H, exchanges with D_2O, OH), 3.26 (1 H, d, *J* 9 Hz, *H*CHOMe), 3.31 (3 H, s, CH_2OMe), 3.36 (3 H, s, 3β-OMe), 3.40—3.75 (1 H, m, 3α-H), and 3.79 (1 H, d, *J* 9 Hz, HC*H*OMe).

3β-*Methoxy*-6α-*phenylthiomethyl*-5α-*cholestane*-5,6β-*diol* (10).—1,4-Diazabicyclo[2.2.2]octane (2.0 g), thioanisole (2.0 g), and dry THF (30 ml) were cooled to 0 °C and stirred together under a stream of dry nitrogen. n-Butyl-lithium (14 mmol) was added during 5 min, and the red solution was then stirred for 45 min at room temperature; the solution was cooled again to 0 °C and a solution of 5-hydroxy-3β-methoxy-5α-cholestan-6-one (1) (2.018 g) in THF (20 ml) was added, causing the immediate loss of colour. After being stirred at room temperature for 11 h, the mixture was poured into water (250 ml) and extracted successively with ether and chloroform. The combined extracts were washed with brine, dried, and chromatographed (100 g column), eluting initially with chloroform–light petroleum (1 : 1) then gradually changing to chloroform, to give 3β-*methoxy*-6α-*phenylthiomethyl*-5α-*cholestane*-5,6β-*diol* (10) (1.635 g, 65%) as needles from methanol, m.p. 133—134.5 °C; $[\alpha]_D^{24}$ −1.8° (*c* 3.55) (Found: C, 75.5; H, 10.05; S, 5.6; M^+, 556.3939. $C_{35}H_{56}O_3S$ requires C, 75.5; H, 10.15; S, 5.75%; *M*, 556.3950); $\nu_{max.}$ ($CHCl_3$) 3 600—3 300, 1 585, and 1 094 cm^{-1}; δ_H 0.68 (3 H, s, 18-H_3), 1.21 (3 H, s, 19-H_3), 1.59 (1 H, exchanges with D_2O, OH), 2.41 (1 H, exchanges with D_2O, OH), 3.2—3.75 (1 H, m, 3α-H), 3.35 (5 H, s, OMe and CH_2S), and 7.15—7.50 (5 H, m, Ph).

Later fractions gave unchanged starting material (1) (739 mg, 35%).

5-*Hydroxy*-3β-*methoxy*-5α-*cholestane*-6(S)-*spiro*-2′-*oxirane* (13).—3β-Methoxy-6α-phenylthiomethyl-5α-cholestane-5,6β-diol (10) (124 mg) and trimethyloxonium fluoroborate (198 mg) were stirred together in methylene dichloride (2 ml) at room temperature for 30 min, then aqueous sodium hydroxide (2M; 5 ml) was added and the mixture was stirred rapidly for 12 h, then diluted with water and extracted with methylene dichloride. The extract was washed with water, dried, and evaporated under reduced pressure to leave a colourless crystalline residue that was chromatographed [15 g column; chloroform–ethyl acetate (2 : 1) as eluant] to yield, from the early fractions, 5-*hydroxy*-3β-*methoxy*-5α-*cholestane*-6(S)-*spiro*-2′-*oxirane* (13) (69 mg, 70%), m.p. 165—167 °C (from methanol); $[\alpha]_D^{24}$ −26.3° (*c* 0.8) (Found: C, 77.8; H, 11.15; M^+, 446.3757. $C_{29}H_{50}O_3$ requires C, 78.0; H, 11.3%; *M*, 446.3760); $\nu_{max.}$ 3 540 and 1 103 cm^{-1}; δ_H 0.68 (3 H, s, 18-H_3), 1.07 (3 H, s, 19-H_3), 1.48 (1 H, exchanges with D_2O, OH), 2.24 (1 H, d, *J* 4.5 Hz, 3′-H_R), 2.85 (1 H, d, *J* 4.5 Hz, 3′-H_S), 3.31 (3 H, s, OMe), and 3.3—3.75 (1 H, m, 3α-H). This was followed by 5,6α-epoxy-6β-hydroxymethyl-3β-methoxy-5α-cholestane (2) (9 mg, 9%), identical (t.l.c., n.m.r., and m.p.) with material obtained as described in an earlier experiment.

Reaction of the diol (10) (126 mg) with triethyloxonium fluoroborate (290 mg) gave 5-hydroxy-3β-methoxy-5α-cholestane-6(*S*)-spiro-2′-oxirane (13) (59 mg, 59%) and 5,6α-epoxy-6β-hydroxymethyl-3β-methoxy-5α-cholestane (2) (37 mg, 37%).

3β-*Methoxy*-6α-*methyl*-5α-*cholestane*-5,6β-*diol* (15).—(a) A solution of 5-hydroxy-3β-methoxy-5α-cholestan-6-one (190 mg) in ether (15 ml) was heated under reflux with methylmagnesium iodide (10 mmol) for 12 h. Saturated aqueous ammonium chloride was added to the cooled mixture and the product was extracted into ether. The extract was washed with water, dried, and evaporated under reduced pressure to give 3β-*methoxy*-6α-*methyl*-5α-*cholestane*-5,6β-*diol* (15) (135 mg, 69%), m.p. 147.5—148.5 °C (from ether–light petroleum); $[\alpha]_D^{20}$ −5.5° (*c* 1.05) (Found: C, 77.6; H, 11.7. $C_{29}H_{52}O_3$ requires C, 77.6; H, 11.7%); *m/z* 448 (M^+); $\nu_{max.}$ 3 495, 3 425, 1 149, and 1 078 cm^{-1}; δ_H 0.69 (3 H, s, 18-H_3), 1.20 (6 H, s, 19-H_3 and 6α-Me), 1.40 (1 H, exchanges with D_2O, OH), 1.95 (1 H, exchanges with D_2O, OH), 3.36 (3 H, s, OMe), and 3.3—3.65 (1 H, m, 3α-H).

(b) A solution of methyl-lithium in ether (8 ml; 1.6M) was added to 5-hydroxy-3β-methoxy-5α-cholestan-6-one (184 mg) and the mixture was kept for 10 min. Water was added and the product was extracted with ether. The extract was washed successively with 2M hydrochloric acid and water, dried, and evaporated under reduced pressure to leave 3β-methoxy-6α-methyl-5α-cholestane-5,6β-diol (15) (175 mg, 92%), identical (t.l.c., and n.m.r.) with material obtained as described in (a).

(c) A mixture of 5-hydroxy-3β-methoxy-5α-cholestane-6(*S*)-spiro-2′-oxirane (13) (60 mg) and lithium aluminium hydride (271 mg) was heated under reflux in ether (8 ml) for 2.5 h. When cool, the mixture was worked up in the usual way. Chromatography [15 g column; chloroform–ethyl acetate (2 : 1) as eluant] afforded 3β-methoxy-6α-methyl-5α-cholestane-5,6β-diol (15) (53 mg, 88%), identical (t.l.c., i.r., m.p., and mixed m.p.) with material obtained as described in (a).

Isomerisation of 5-*Hydroxy*-3β-*methoxy*-5α-*cholestane*-6(S)-*spiro*-2′-*oxirane* (13).—Solutions of the epoxide (13) (50 mg) in THF (6 ml) and potassium hydroxide (100 mg) in water (1 ml) were mixed and heated under reflux for 5 h. When cool, the mixture was diluted with water and extracted with chloroform. T.l.c. of the extract showed the reaction to be incomplete. The residue left after evaporation under reduced pressure was treated with sodium hydride (300 mg, 94% dispersion in mineral oil) in boiling benzene (6 ml) for 7.5 h. The cold mixture was diluted with ether and the organic solution was washed with water, dried, and evaporated under reduced pressure. Chromatography (10 g column; chloroform as eluant) afforded 5,6α-epoxy-6β-hydroxymethyl-3β-methoxy-5α-cholestane (2) (42 mg, 84%), m.p. 151—153 °C (from methanol), identical (t.l.c. and mixed m.p.) with authentic material.

6α-*Chloromethyl*-3β-*methoxy*-5α-*cholestane*-5,6β-*diol* (11).—Dry hydrogen chloride was bubbled through a solution of 5-hydroxy-3β-methoxy-5α-cholestane-6(*S*)-spiro-2′-oxirane (13) (100 mg) in chloroform (10 ml) for 45 min. After being stirred for a further 15 min, the solution was diluted with chloroform (15 ml), washed with water, and dried. Chromatography [15 g column; chloroform–ethyl acetate (19 : 1) as eluant] afforded 6α-*chloromethyl*-3β-*methoxy*-5α-*cholestane*-5,6β-*diol* (11) (83 mg, 77%) as a non-crystallisable oil (Found: *m/z*, 464.3435. $C_{29}H_{49}{}^{35}ClO_2$ ($M^+ - H_2O$) requires *m/z*, 464.3421); *m/z*, 464 ($M^+ - H_2O$) and 446 ($M^+ - HCl$ or 2 H_2O); $\nu_{max.}$ 3 440 and 1 086 cm^{-1}; δ_H 0.69 (3 H, s, 18-H_3), 1.21 (3 H, s, 19-H_3), 1.7 and 2.08 (each 1 H, exchanges with D_2O, OH), 3.35 (3 H, s, OMe), 3.2—3.7 (1 H, m, 3α-H), 3.74 (1 H, d, *J* 11 Hz, *H*CHCl), and 3.95 (1 H, d, *J* 11 Hz, HC*H*Cl).

Reactions of Methylenetriphenylphosphorane with 5-*Hydroxy*-3β-*methoxy*-5α-*cholestan*-6-*one* (1).—(a) A mixture of methyltriphenylphosphonium bromide (9.0 g) and n-butyl-lithium (15.7 ml; 1.6M ethereal solution) in ether (50 ml) was stirred at room temperature under nitrogen for 1.5 h. A solution of 5-hydroxy-3β-methoxy-5α-cholestan-6-one (862 mg) in ether (50 ml) was added and the mixture was stirred overnight. The ether was removed by distillation and was progressively replaced with THF (80 ml). After being heated under reflux for 5.5 h, the mixture was diluted with water and cooled. The product was extracted with ether and the combined organic fractions were washed with water, dried, and evaporated under reduced pressure to leave a yellow oil which was chromatographed (80 g column), eluting initially with chloroform and gradually changing to chloro-

form–ethyl acetate (1 : 3), to yield 3β-*methoxy*-6-*methylene*-5α-*cholestan*-5-*ol* (9) (310 mg, 36%) as a non-crystallisable gum which was distilled (10^{-2} Torr; bath temp. 146 °C) (Found: C, 81.15; H, 11.25; M^+, 430.3808. $C_{29}H_{50}O_2$ requires C, 80.85; H, 11.7%; M, 430.3811); δ_H 0.62 (3 H, s, 18-H_3), 0.81 (3 H, s, 19-H_3), 1.50 (1 H, exchanges with D_2O, OH), 3.35 (3 H, s, OMe), 3.4—3.8 (1 H, m, 3α-H), and 4.70 and 4.80 (together 2 H, $w_{\frac{1}{2}}$ 3.5 Hz, 6-CH_2).

Further elution gave unchanged ketone (1) (530 mg, 61%).

(b) A solution of dimsylsodium was prepared [16] by shaking sodium hydride (94% dispersion in mineral oil) in DMSO with the aid of an ultrasonic bath for 2 h. The solution was standardised by titration against 0.1M hydrochloric acid.

Methyl triphenylphosphonium bromide (630 mg) was stirred under nitrogen in DMSO (5 ml) and dimsylsodium (0.95 ml; 1.85M) was added. After 5 min, a solution of 5-hydroxy-3β-methoxy-5α-cholestan-6-one (1) (367 mg) in DMSO (2 ml) and ether (10 ml) was added, and the mixture was stirred vigorously at room temperature for 15.5 h and then at 50 °C for 4 h. When the mixture had cooled, water was added and the product was extracted with ether. The extract was washed successively with dilute hydrochloric acid and water, dried, and chromatographed (30 g column; chloroform as eluant) to give 3β-methoxy-6-methylene-5α-cholestan-5-ol (9) (233 mg, 64%), identical (t.l.c. and n.m.r.) with material obtained as described in (a). Further elution gave unchanged starting ketone (1) (114 mg, 31%).

(c) Sodium hydride (310 mg, 94%) and DMSO (25 ml) were warmed together at 50 °C for 2 h; methyl triphenylphosphonium bromide (4.79 g) was added, followed, after 5 min, by a solution of 5-hydroxy-3β-methoxy-5α-cholestan-6-one (1) (2.0 g) in THF (25 ml). The mixture was stirred at 60 °C for 6 h, water was added, and the product was extracted with chloroform. The extract was washed successively with dilute hydrochloric acid and water, then dried and chromatographed (200 g column; chloroform as eluant) to yield 3β-*methoxy*-6-*methylene*-5β-*cholestan*-5-*ol* (8) (136 mg, 7%) as a homogeneous gum (t.l.c. and n.m.r.) [Found: M^+, 430.3810 (100%). $C_{29}H_{50}O_2$ requires M, 430.3811]; δ_H 0.64 (3 H, s, 18-H_3), 0.80 (3 H, s, 19-H_3), 3.32 (3 H, s, OMe), 3.62 (1 H, m, $w_{\frac{1}{2}}$ 6.5 Hz, 3α-H), 4.30 (1 H, exchanges with D_2O, OH), and 4.77 and 5.17 (each 1 H, d, J 2.5 Hz, together 6-CH_2).

Further elution gave 3β-methoxy-6-methylene-5α-cholestan-5-ol (9) (871 mg, 43%) and unchanged starting ketone (1) (910 mg, 46%).

5-*Hydroxy*-3β-*methoxy*-5α-*cholestane*-6(R)-*spiro*-2′-*oxirane* (12).—A solution of 3β-methoxy-6-methylene-5α-cholestan-5-ol (9) (850 mg) in benzene (75 ml) was stirred with 3-chloroperbenzoic acid (1.2 g) for 16 h. Benzene (70 ml) was added and the solution was washed successively with aqueous sodium sulphite, aqueous sodium hydrogencarbonate, and water, dried over sodium sulphate, and evaporated under reduced pressure to give 5-*hydroxy*-3β-*methoxy*-5α-*cholestane*-6(R)-*spiro*-2′-*oxirane* (12) (811 mg, 92%) as a white powder that crystallised from acetone, m.p. 150—152 °C, resolidified, and fully melted at 168—170 °C, $[\alpha]_D^{22}$ +4.6° (*c* 1.1) (Found: C, 78.0; H, 11.0. $C_{29}H_{50}O_3$ requires C, 78.0; H, 11.3%); *m*/*z*, 428 (100%, $M^+ - H_2O$) and 416 ($M^+ - CH_2O$); $\nu_{max.}$ ($CHCl_3$) 3 585 cm^{-1}; δ_H 0.66 (3 H, s, 18-H_3), 0.94 (3 H, s, 19-H_3), 2.10 (1 H, exchanges with D_2O, OH), 2.78 (1 H, d, J 4 Hz, 3′-H_R), 2.83 (1 H, d, J 4 Hz, 3′-H_S), 3.31 (3 H, s, OMe), and 3.3—3.7 (1 H, m, 3α-H).

3β-*Methoxy*-6β-*methyl*-5α-*cholestane*-5,6α-*diol* (14).—A mixture of 5-hydroxy-3β-methoxy-5α-cholestane-6(*R*)-2′-oxirane (12) (441 mg) and lithium aluminium hydride (370 mg) was heated in ether (50 ml) under reflux for 2 h, then cooled and acidified with dilute hydrochloric acid. The mixture was extracted with ether and the extract was washed with water, dried, and evaporated under reduced pressure. Chromatography [40 g column; ethyl acetate–chloroform (1 : 2) as eluant] afforded 3β-*methoxy*-6β-*methyl*-5α-*cholestane*-5,6α-*diol* (14) (332 mg, 78%) which crystallised from methanol, m.p. 122—123 °C; $[\alpha]_D^{20}$ −2.5° (*c* 1.43) (Found: C, 78.0; H, 11.45. $C_{29}H_{52}O_3$ requires C, 77.6; H, 11.7%); $\nu_{max.}$ 3 522, 3 450, and 1 082 cm^{-1}; δ_H 0.66 (3 H, s, 18-H_3), 1.02 (3 H, s, 19-H_3), 1.27 (3 H, s, 6β-Me), 2.49 (2 H, exchange with D_2O, 2 × OH), 3.36 (3 H, s, OMe), and 3.45—3.80 (1 H, m, 3α-H).

5-*Hydroxymethyl*-3β-*methoxy*-A-*homo*-B-*nor*-5β-*cholestan*-4a-*one* (16).—A solution of 5-hydroxy-3β-methoxy-5α-cholestane-6(*R*)-2′-oxirane (12) (151 mg) in ether (5 ml) was shaken with boron trifluoride–diethyl ether (1 ml) for 5 min. Water and ether were added and the organic layer was separated, washed with water, dried, and evaporated under reduced pressure. Chromatography of the residue [15 g column; chloroform–ethyl acetate (2 : 1) as eluant] afforded 5-*hydroxymethyl*-3β-*methoxy*-A-*homo*-B-*nor*-5β-*cholestan*-4a-*one* (16) (129 mg, 86%) which crystallised from methanol as large prisms, m.p. 125—127 °C; $[\alpha]_D^{25}$ −42.0° (*c* 0.88) (Found: C, 77.85; H, 11.5; M^+, 446.3966. $C_{29}H_{50}O_3$ requires C, 78.0; H, 11.3%; M, 446.3760); *m*/*z* 416 (100%, $M^+ - CH_2O$); $\nu_{max.}$ ($CHCl_3$) 3 440 and 1 698 cm^{-1}; δ_H 0.67 (3 H, s, 18-H_3), 0.98 (3 H, s, 19-H_3), 2.10 (1 H, exchanges with D_2O, OH), 2.78 (1 H, dd, J 5 and 10 Hz, 4α-H), 2.96 (1 H, t, J 10 Hz, 4β-H), 3.37 (3 H, s, OMe), 3.15—3.50 (1 H, m, 3α-H), 3.61 (1 H, d, J 11 Hz, *H*CHOH; irradiation at δ 4.18 caused this to collapse to a singlet) and 4.18 (1 H, d, J 11 Hz, HC*H*OH; irradiation at δ 3.61 caused this to collapse to a singlet).

Dehydroxymethylation of 5-*Hydroxymethyl*-3β-*methoxy*-A-*homo*-B-*nor*-5β-*cholestan*-4a-*one* (16).—A mixture of 5-hydroxymethyl-3β-methoxy-A-homo-B-nor-5β-cholestan-4a-one (16) (125 mg), sodium hydroxide (180 mg), methanol (10 ml), and ether (2 ml) was stirred at room temperature for 24 h; water was added, the mixture was acidified with 2M hydrochloric acid, and the product was extracted with methylene dichloride. The extract was washed with brine, dried, and evaporated under reduced pressure to leave an oil that crystallised when shaken with methanol. Chromatography (20 g column; chloroform as eluant) yielded 3β-*methoxy*-A-*homo*-B-*nor*-5β-*cholestan*-4a-*one* (17) (69 mg, 59%), 97—99 °C (plates, from methanol); $[\alpha]_D^{17}$ +19.8° (*c* 0.67) [Found: C, 80.8; H, 11.65%; M^+, 416.3652 (100%). $C_{28}H_{48}O_2$ requires C, 80.7; H, 11.6%; M, 416.3654]; $\nu_{max.}$ 1 709, 1 106, and 1 100 cm^{-1}; δ_H 0.67 (3 H, s, 18-H_3), 1.16 (3 H, s, 19-H_3), 2.61 (1 H, t, J 10.5 Hz, 4β-H), 2.85 (2 H, dd, J 3 and 10 Hz, 4α- and 5β-H), 3.00—3.55 (1 H, m, 3α-H), and 3.37 (3 H, s, OMe).

Further elution afforded a mixed fraction (41 mg), followed by a homogeneous fraction which yielded 3β-*methoxy*-A-*homo*-B-*nor*-5α-*cholestan*-4a-*one* (4 mg, 3%) [Found: M^+, 416.3644 (100%). $C_{28}H_{48}O_2$ requires M, 416.3654]. The n.m.r. spectrum of the mixed fraction indicated a 2 : 1 mixture of the 5α and 5β epimers.

Methylation of 3β-*Hydroxy*-5α-*cholestan*-6-*one* (21).—(a) *With trimethyl orthoformate*. 3β-Hydroxy-5α-cholestan-6-one (21) (395 mg) was stirred for 10 min with a solution of perchloric acid (0.5 ml; 71%) in trimethyl orthoformate (10 ml). Water was then added, followed by aqueous sodium hydrogencarbonate. Isolation of the organic material by extraction with ether afforded an oil, the n.m.r. and i.r. spectra of which indicated it to be a 1 : 1 mixture of 3β-methoxy-5α-cholestan-6-one (23) and its 5β-epimer (24). This

epimeric mixture was heated under reflux for 2 h with ethanolic sodium ethoxide [prepared from sodium (800 mg) and ethanol (20 ml)] to give, after work-up (chloroform extraction) and chromatography [30 g column; chloroform–carbon tetrachloride (1 : 1) as eluant], a mixture (266 mg) estimated from its n.m.r. spectrum to be a mixture of the 5α- and 5β-epimers of 3β-methoxycholestan-6-one in the ratio 12 : 1. A sample of the pure 5α-epimer (23) was obtained by crystallisation from methanol, m.p. 90—92 °C (lit.,[17] 92 °C).

(b) *With sodium hydride and methyl iodide.* 3β-Hydroxy-5α-cholestan-6-one (21) (800 mg), sodium hydride (55 mg; 94% dispersion in mineral oil), and benzene (30 ml) were heated under reflux, under nitrogen, for 2.75 h; methyl iodide (10.4 g) was added and the mixture was heated for a further 16 h. Water was added, the organic layer was separated, and the aqueous fraction was extracted with ether. The combined organic solutions were washed successively with dilute hydrochloric acid and water, then dried, and evaporated under reduced pressure to leave a gum (550 mg, 60%) that was identified (t.l.c. and n.m.r.) as an equilibrium mixture of the 5-epimeric 3β-methoxycholestan-6-ones.

Methyl 6-Oxo-5α-cholestan-3β-yl Carbonate (22).—3β-Hydroxy-5α-cholestan-6-one (21) (227 mg), methyl iodide (5 g), silver oxide (393 mg), and DMF (3 ml) were stirred together at room temperature for 25 h, then filtered and the residue was extracted with ether. The extract was washed successively with dilute hydrochloric acid and brine, then dried, evaporated under reduced pressure, and the residue was chromatographed (15 g column; chloroform as eluant) to afford *methyl 6-oxo-5α-cholestan-3β-yl carbonate* (22) (47 mg, 18%) as an oil (Found: M^+ 460.3542. $C_{29}H_{48}O_4$ requires M, 460.3552); $\nu_{max.}$ ($CHCl_3$) 1 748, 1 712, and 1 280 cm^{-1}; δ_H 0.66 (3 H, s, 18-H_3), 0.75 (3 H, s, 19-H_3), 3.74 (3 H, s, $MeOCO_2$) and 4.3—4.7 (1 H, m, 3α-H).

Later fractions gave unchanged starting material (132 mg, 58%).

6α-(1,3-*Dithian*-2-*yl*)-3β-*methoxy*-5α-*cholestan*-6β-*ol* (18).—n-Butyl-lithium (20.8 mmol) was stirred under nitrogen for 30 min with an ice-cold solution of 1,3-dithiane (2.76 g) in THF (60 ml). A solution of 3β-methoxycholestan-6-one (964 mg; 5α : 5β = 12 : 1) in THF (12 ml) was added and the mixture was stirred for 84 h while it slowly warmed to room temperature. Water was added and the mixture was acidified with dilute hydrochloric acid, then extracted successively with ether and chloroform. The combined organic extracts were washed with brine, dried, and evaporated under reduced pressure. Chromatography (120 g column; chloroform as eluant) gave 6-(1,3-*dithian*-2-*yl*)-3β-*methoxy*-5α-*cholestan*-6β-*ol* (18) (967 mg, 78%) as needles, m.p. 129—130 °C (from methanol); $[\alpha]_D^{22}$ +0.19° (*c* 2.74) (Found: C, 71.5; H, 10.3; S, 11.9. $C_{32}H_{56}O_2S_2$ requires C, 71.55; H, 10.5; S, 11.95%); $\nu_{max.}$ ($CHCl_3$) 3 600—3 300 and 1 093 cm^{-1}; δ_H 0.68 (3 H, s, 18-H_3), 1.01 (3 H, s, 19-H_3), 2.01 (1 H, exchanges with D_2O, OH), 2.88 (4 H, m, $w_{\frac{1}{2}}$ 15 Hz, $SCH_2CH_2CH_2S$), 3.0—3.3 (1 H, m, 3α-H), 3.36 (3 H, s, OMe), and 4.29 (1 H, s, SCHS).

6β-*Hydroxy*-3β-*methoxy*-5α-*cholestane*-6α-*carbaldehyde* (19).—(a) A mixture of 6α-(1,3-dithian-2-yl)-3β-methoxy-5α-cholestan-6β-ol (18) (253 mg), acetone (7.5 ml), water (0.5 ml), methyl iodide (5 ml), and powdered cadmium carbonate (82 mg) was heated under reflux for 3 h. After the mixture had cooled, ether was added, and the mixture was then washed successively with 2M hydrochloric acid and water, dried, and evaporated under reduced pressure to leave a yellow oil which was purified by chromatography (5 g column; chloroform as eluant) to give 6β-*hydroxy*-3β-*methoxy*-5α-*cholestane*-6α-*carbaldehyde* (19) (183 mg, 87%), m.p. 102—104 °C (from ether) [Found: *m/z*, 417.3723. $C_{28}H_{49}O_2$ (M^+ − CHO) requires *m/z*, 417.3732]; $\nu_{max.}$ ($CHCl_3$) 3 515, 1 724, 1 184, 1 099, and 1 088 cm^{-1}; δ_H 0.71 (3 H, s, 18-H_3), 1.04 (3 H, s, 19-H_3), 2.9—3.4 (1 H, m, 3α-H), 3.01 (1 H, exchanges with D_2O, OH), 3.29 (3 H, s, OMe), and 9.33 (1 H, s, CHO).

The derived *semicarbazone* (23 mg, 26%) was prepared by heating a mixture of the aldehyde (19) (80 mg), semicarbazide hydrochloride (170 mg), sodium acetate (350 mg), ethanol (3 ml), and water (7 ml) on a steam bath for 3 h, and had m.p. 200—202 °C (Found: C, 71.8; H, 10.9; N, 8.65; M^+, 503.4087. $C_{30}H_{53}N_3O_3$ requires C, 71.5; H, 10.6; N, 8.35%; M, 503.4087); $\nu_{max.}$ ($CHCl_3$) 3 545, 3 420, 3 365, and 1 696 cm^{-1}.

(b) 6α-Dimethoxymethyl-3β-methoxy-5α-cholestan-6β-ol (20) (see below) (46 mg) was heated on a steam bath for 1 h with acetic acid (2M; 5 ml) and ether (1 ml) to give, after work-up in the usual way, the aldehyde (19) (31 mg, 75%), identical (t.l.c., i.r., and n.m.r.) with a sample prepared as described in (a).

6α-*Dimethoxymethyl*-3β-*methoxy*-5α-*cholestan*-6β-*ol* (20).—A mixture of 6α-(1,3-dithian-2-yl)-3β-methoxy-5α-cholestan-6β-ol (18) (147 mg), mercury(II) chloride (519 mg), red mercury(II) oxide (150 mg), water (0.9 ml), and methanol (14.1 ml) was heated and stirred under reflux, under nitrogen, for 4 h. Dilute hydrochloric acid (5 ml) was added to the cooled mixture, and the suspension was stirred for 30 min and filtered. The residue was washed with methylene dichloride, and the filtrate was diluted with water and extracted with methylene dichloride. The combined extracts were washed with water, dried, and chromatographed (15 g column; chloroform as eluant). The early fractions afforded 6β-hydroxy-3β-methoxy-5α-cholestane-6α-carbaldehyde (19) (47 mg, 38%) as an oil, identical (t.l.c., n.m.r., i.r., and m.s.) with an authentic sample. Further elution gave 6α-*dimethoxymethyl*-3β-*methoxy*-5α-*cholestan*-6β-*ol* (20) (48 mg, 36%) as a glass (Found: M^+, 492.4186. $C_{31}H_{56}O_4$ requires M, 492.4178); $\nu_{max.}$ ($CHCl_3$) 3 600—3 300, 1 174, 1 157, 1 142, 1 090, and 1 070 cm^{-1}; δ_H 0.69 (3 H, s, 18-H_3), 1.01 (3 H, s, 19-H_3), 1.70 (1 H, exchanges with D_2O, OH), 2.9—3.3 (1 H, m, 3α-H), 3.36 (3 H, s, 3β-OMe), 3.53 (3 H, s, *Me*OCHOMe), 3.56 (3 H, s, MeOCHO*Me*), and 4.16 (1 H, s, $w_{\frac{1}{2}}$ 2 Hz, MeOC*H*OMe).

3β-*Methoxy*-6α-*methyl*-5α-*cholestan*-6β-*ol* (25).—(a) A solution of 3β-methoxycholestan-6-one (680 mg; 5α : 5β = 12 : 1) in ether (20 ml) was added to a solution of methylmagnesium iodide, prepared from magnesium (316 mg) and methyl iodide (0.9 ml), in ether (25 ml) and the mixture was heated under reflux for 4 h. Aqueous ammonium chloride was added, the ether layer was separated, and the aqueous fraction was extracted with ether. The combined organic solutions were washed with water, dried, and evaporated under reduced pressure. The residue was chromatographed (70 g column; chloroform as eluant) to yield 3β-*methoxy*-6α-*methyl*-5α-*cholestan*-6β-*ol* (25) (425 mg, 61%), m.p. 109—110 °C (from methanol); $[\alpha]_D^{40}$ +11.8° (*c* 1.52) (Found: C, 80.25; H, 11.8. $C_{29}H_{50}O_3$ requires C, 80.5; H, 12.1%); $\nu_{max.}$ 3 521 (sharp), 1 101, and 1 085 cm^{-1}; δ_H 0.68 (3 H, s, 18-H_3), 1.01 (3 H, s, 19-H_3), 1.16 (3 H, s, 6α-Me), 2.95—3.30 (1 H, m, 3α-H), and 3.36 (3 H, s, OMe).

(b) A mixture of 6α-(1,3-dithian-2-yl)-3β-methoxy-5α-cholestan-6β-ol (18) (132 mg), W-5 Raney nickel [18] (5 g), and ethanol (10 ml) was stirred under nitrogen and heated under reflux for 5 h. After the mixture had cooled, dilute hydrochloric acid was added and the mixture was filtered through Celite and extracted with ether. The extract was washed with water, dried, and evaporated under reduced pressure to leave a semi-crystalline residue (84 mg). Chromatography (15 g

silica; chloroform as eluant) yielded 3β-methoxy-6α-methyl-5α-cholestan-6β-ol (25) (75 mg, 71%), identical (t.l.c., n.m.r., and i.r.) with material obtained as described in (a).

3β-*Methoxy*-6-*methylcholest*-5-*ene* (26).—Thionyl chloride (0.5 ml) was added to a solution of 3β-methoxy-6α-methyl-5α-cholestan-6β-ol (25) (274 mg) in ice-cold pyridine (5 ml). After 30 min the mixture was poured onto crushed ice, conc. HCl (5 ml) was added, and 3β-methoxy-6-methylcholest-5-ene (26) (217 mg, 83%), m.p. 97—99 °C (from methanol–chloroform) (lit.,[19] 101 °C), was isolated by extraction with ether.

5,6α-*Epoxy*-3β-*methoxy*-6β-*methyl*-5α-*cholestane* (28).—(a) A solution of 3β-methoxy-6-methylcholest-5-ene (26) (2.0 g) and 3-chloroperbenzoic acid (2.0 g) in ether (60 ml) was left at room temperature overnight. Ether (120 ml) was then added and the solution was washed successively with aqueous sodium hydrogensulphite, water, sodium hydrogencarbonate, and water, then dried, and evaporated under reduced pressure to afford a white solid (2.01 g) that was recrystallised from methanol to give 5,6α-*epoxy*-3β-*methoxy*-6β-*methyl*-5α-*cholestane* (28) (1.536 g, 75%) as needles, m.p. 123—124.5 °C; $[\alpha]_D^{20}$ −33.8° (*c* 1.02) (Found: C, 80.65; H, 12.05; M^+, 430.3804. $C_{29}H_{50}O_2$ requires C, 80.85; H, 11.7%; *M*, 430.3811); $\nu_{max.}$ 1 114, 1 105, 1 090, and 863 cm^{-1}; δ_H 0.62 (3 H, s, 18-H_3), 1.03 (3 H, s, 19-H_3), 1.28 (3 H, s, 6β-Me), 3.2—3.5 (1 H, m, 3α-H), and 3.36 (3 H, s, OMe).

(b) Thionyl chloride (1 ml) was added to a stirred suspension of 3β-methoxy-6α-methyl-5α-cholestane-5,6β-diol (15) (139 mg) in ice-cold pyridine (5 ml). After 30 min the mixture was poured onto crushed ice and dilute hydrochloric acid was added. 5,6α-Epoxy-3β-methoxy-6β-methyl-5α-cholestane (28) (122 mg, 95%), m.p. 125—126 °C (from methanol) was isolated by extraction with ether.

3β-*Methoxy*-5-*methyl*-A-*homo*-B-*nor*-5β-*cholestan*-4a-*one* (29).—The epoxide (28) (319 mg), dry benzene (5 ml), and boron trifluoride–diethyl ether (0.4 ml) were shaken together for 30 s; aqueous sodium hydrogencarbonate was added and the product was extracted into ether. The extract was washed with aqueous sodium hydrogencarbonate and water, then dried, and evaporated under reduced pressure to afford 3β-*methoxy*-5-*methyl*-A-*homo*-B-*nor*-5β-*cholestan*-4a-*one* (29) (314 mg, 98%), m.p. 95—95.5 °C (from methanol); $[\alpha]_D^{20}$ −25.9° (*c* 1.27) (Found: C, 81.05; H, 11.75; M^+, 430.3818. $C_{29}H_{50}O_2$ requires C, 80.85; H, 11.7%; *M*, 430.3811); $\nu_{max.}$ 1 689 and 1 100 cm^{-1}; δ_H 0.67 (3 H, s, 18-H_3), 0.99 (3 H, s, 19-H_3), 1.21 (3 H, s, 5β-Me), 2.67 (1 H, dd, *J* 5 and 9.5 Hz, 4α-H), 2.89 (1 H, t, *J* 9.5 Hz, 4β-H), 3.06—3.40 (1 H, m, 3α-H), and 3.36 (3 H, s, OMe).

3β-*Methoxy*-5-*methyl*-A-*homo*-B-*nor*-5β-*cholestan*-4aβ-*ol* (30).—3β-Methoxy-5-methyl-A-homo-B-nor-5β-cholestan-4a-one (29) (388 mg) and lithium aluminium hydride (409 mg) were heated under reflux in ether (20 ml) for 2 h. Saturated aqueous ammonium chloride and dilute hydrochloric acid were added and the product, isolated by extraction with ether, was chromatographed (40 g column; chloroform as eluant) to yield 3β-*methoxy*-5-*methyl*-A-*homo*-B-*nor*-5β-*cholestan*-4aβ-*ol* (30) (331 mg, 85%) as a brittle glass which was purified by distillation (bath temperature 193 °C; 5×10^{-3} Torr), $[\alpha]_D^{20}$ 0° (*c* 1.06) (Found: C, 80.55; H, 12.25; M^+, 432.3963. $C_{29}H_{52}O_2$ requires C, 80.5; H, 12.1%; *M*, 432.3967); $\nu_{max.}$ (film) 3 445, 1 090, and 758 cm^{-1}; δ_H 0.66 (3 H, s, 18-H_3), 0.82 (3 H, s, 19-H_3), 0.99 (3 H, s, 5β-Me), 1.76 (1 H, exchanges with D_2O, OH), 3.35 (3 H, s, OMe), 3.3—3.6 (1 H, m, 3α-H), and 3.71 (1 H, d, *J* 7 Hz, 4aα-H).

Treatment with acetic anhydride and pyridine overnight at room temperature afforded a mixture of the alcohol (30) and the derived acetate (31). Comparison of the spectra of the alcohol and the mixture provided the following data for the acetate (31): (Found: M^+, 474.4070. $C_{31}H_{54}O_3$ requires *M*, 474.4073); $\nu_{max.}$ (film) 1 737 and 1 238 cm^{-1}; δ_H 0.66 (3 H, s, 18-H_3), 0.90 (3 H, s, 19-H_3), 0.96 (3 H, s, 5-Me), 2.09 (3 H, s, OAc), 3.08—3.40 (1 H, m, 3α-H), and 3.31 (3 H, s, OMe).

3β,6β-*Dimethoxy*-6α-*methyl*-5α-*cholestan*-5-*ol* (27).—Boron trifluoride–diethyl ether (0.5 ml) was added to a suspension of 5,6α-epoxy-3β-methoxy-6β-methyl-5α-cholestane (28) (289 mg) in methanol (5 ml) and the mixture was shaken until a solution had formed (2 min); water was added and the product was extracted into ether. The extract was washed with water, dried, and evaporated under reduced pressure. Chromatography (25 g column; chloroform as eluant) then gave a colourless gum, which was distilled (bath temperature 190 °C; 10^{-2} Torr) to afford 3β,6β-*dimethoxy*-6α-*methyl*-5α-*cholestan*-5-*ol* (27) (249 mg, 80%) (Found: C, 78.3; H, 11.9; M^+, 462.4075. $C_{30}H_{54}O_3$ requires C, 77.85; H, 11.75%; *M*, 462.4073); $\nu_{max.}$ (film) 3 480, 2 820, 1 095, and 1 080 cm^{-1}; δ_H 0.68 (3 H, s, 18-H_3), 1.09 (3 H, s, 19-H_3), 1.11 (3 H, s, 6α-Me), 1.31 (1 H, exchanges with D_2O, OH), 3.09 (3 H, s, 6β-OMe), 3.34 (3 H, s, 3β-OMe), and 3.4—3.7 (1 H, m, 3α-H).

5-*Acetoxy*-3β-*methoxy*-5α-*cholestan*-6β-*ol* (33).—A solution of acetyl chloride (40 ml) in chloroform (60 ml) was added to a stirred mixture of 3β-methoxy-5α-cholestane-5,6β-diol (32) (4.02 g) and freshly distilled *N*,*N*-dimethylaniline (40 ml) in chloroform (30 ml), and the mixture was heated under reflux for 24 h. When cool, the mixture was poured into a mixture of crushed ice and conc. hydrochloric acid and extracted with methylene dichloride. The extract was washed with 2M-hydrochloric acid and water, then dried and evaporated under reduced pressure. Chromatography of the residue on alumina (305 g, grade 5) afforded the derived diacetate. This was stirred overnight at room temperature with sodium hydroxide (3.06 g) in methanol (50 ml). The mixture was diluted with water and extracted with ether, and the extract was washed with water and dried. Evaporation under reduced pressure and recrystallisation from methanol gave 5-acetoxy-3β-methoxy-5α-cholestan-6β-ol (33) (2.24 g, 51%), m.p. 171.5—173 °C (lit.,[20] 171 °C); δ_H 0.69 (3 H, s, 18-H_3), 1.20 (3 H, s, 19-H_3), 2.02 (3 H, s, OAc), 2.36 (1 H, br, exchanges with D_2O, OH), 2.84—3.40 (2 H, m, 3α- and 4α-H), 3.31 (3 H, s, OMe), and 4.66 (1 H, m, $w_{\frac{1}{2}}$ 9 Hz, 6α-H).

5,6β-*Epoxy*-3β-*methoxy*-5β-*cholestane* (34).—(a) 5-Acetoxy-3β-methoxy-5α-cholestan-6β-ol (33) (490 mg) was heated under reflux with sodium hydroxide (650 mg) in ethanol (20 ml) for 3 h. Water was added and the mixture was extracted into ether. The extract was washed with water, dried, evaporated under reduced pressure, and chromatographed (15 g column; chloroform as eluant) to yield 5,6β-*epoxy*-3β-*methoxy*-5β-*cholestane* (34) (411 mg, 96%), m.p. 86—87 °C (from light petroleum); $[\alpha]_D^{20}$ +6.3° (*c* 1.2) (Found: C, 80.95; H, 11.5; M^+, 416.3644. $C_{28}H_{48}O_2$ requires C, 80.7; H, 11.6%; *M*, 416.3654); δ_H 0.64 (3 H, s, 18-H_3), 0.99 (3 H, s, 19-H_3), 3.04 (1 H, d, *J* 2 Hz, 6α-H), 3.1—3.6 (1 H, m, 3α-H), and 3.32 (3 H, s, OMe).

(b) 5-Fluoro-3β-methoxy-5α-cholestan-6β-yl acetate (40) (see below) (68 mg) and sodium hydroxide (120 mg) were heated under reflux in ethanol (8 ml) for 2.5 h. The mixture was cooled, diluted with brine (75 ml), and extracted with ether. The extract was washed with brine, dried, and evaporated under reduced pressure to leave 5,6β-epoxy-3β-methoxy-

5β-cholestane (34) (59 mg, 91%), m.p. 82—84 °C (from methanol), identical (n.m.r. and mixed m.p.) with material prepared as described in (a).

Reaction of 5,6β-*Epoxy*-3β-*methoxy*-5β-*cholestane* (34) *with Methylmagnesium Iodide*.—(a) *In ether*. Solutions of 5,6β-epoxy-3β-methoxy-5β-cholestane (330 mg) and methylmagnesium iodide [from magnesium (122 mg) and methyl iodide (2 ml)] in ether (10 ml and 6 ml respectively) were mixed and heated under reflux for 3 h under nitrogen. The organic products were isolated by extraction with ether and separated by chromatography (50 g column; chloroform as eluant). Four components were isolated.

The early fractions afforded 6α-*iodo*-3β-*methoxy*-5β-*cholestan*-5-*ol* (35) (50 mg, 12%), m.p. 150—155 °C (needles, from methanol–chloroform); $[\alpha]_D^{18}$ +23.7° (*c* 0.85) [Found: C, 61.6; H, 8.95; I, 23.3; *m/z*, 417.3732. $C_{28}H_{49}IO_2$ requires C, 61.75; H, 9.05; I, 23.3%; *m/z* 417.3751 ($M^+ - I$)]; *m/z*, 417 ($M^+ - I$) and 416 ($M^+ - HI$); $\nu_{max.}$ 3 490 and 1 087 cm^{-1}; δ_H 0.66 (3 H, s, 18-H_3), 0.99 (3 H, s, 19-H_3), 3.36 (3 H, s, OMe), 3.69 (1 H, m, $w_{\frac{1}{2}}$ 7 Hz, 3α-H), 4.41 (1 H, exchanges with D_2O, OH), and 4.72 (1 H, dd, *J* 4.5 and 13 Hz, 6β-H).

The next fractions gave unchanged starting material (98 mg, 30%), which was followed by 3β-*methoxy*-4aα-*methyl*-A-*homo*-B-*nor*-5β-*cholestan*-4aβ-*ol* (43) (53 mg, 15%), m.p. 105—107 °C (from methanol); $[\alpha]_D^{40}$ +21.2° (*c* 1.19) (Found: C, 80.5; H, 12.0; M^+, 432.3972. $C_{29}H_{52}O_2$ requires C, 80.5; H, 12.1; *M*, 432.3967); $\nu_{max.}$ 3 480 and 1 078 cm^{-1}; δ_H 0.68 (3 H, s, 18-H_3), 0.99 (3 H, s, 19-H_3), 1.16 (3 H, s, 4aα-Me), 3.34 (3 H, s, OMe), 3.56 (1 H, m, $w_{\frac{1}{2}}$ 11 Hz, 3α-H), and 4.30 (1 H, exchanges with D_2O, OH).

Further elution provided 3β-methoxy-6α-methyl-5α-cholestan-6β-ol (25) (38 mg, 11%), identical (t.l.c., n.m.r., and i.r.) with the samples obtained as described in earlier experiments.

(b) *In benzene*. A solution of 5,6β-epoxy-3β-methoxy-5β-cholestane (34) (395 mg) in benzene (10 ml) was added to a solution of methylmagnesium iodide in ether (10 ml) [prepared from magnesium (240 mg) and methyl iodide (4 ml)], and the ether was removed by distillation. Benzene (10 ml) was added and the mixture was heated under reflux under nitrogen for 6 h. The reaction mixture was worked up in the usual way to give, after chromatography (50 g column; chloroform as eluant), 3β-methoxy-4aα-methyl-A-homo-B-nor-5β-cholestan-4aβ-ol (43) (143 mg, 35%), identical with material obtained as described in (a), and 3β-methoxy-6α-methyl-5α-cholestan-6β-ol (25) (66 mg, 16%), identical (t.l.c., n.m.r., and i.r.) with an authentic sample.

5-*Chloro*-3β-*methoxy*-5α-*cholestan*-6β-*ol* (41).—Dry hydrogen chloride was bubbled through a solution of 5,6β-epoxy-3β-methoxy-5β-cholestane (34) (98 mg) in chloroform (10 ml) for 45 min. The solution was stirred overnight, then diluted with methylene dichloride, washed with water, dried and evaporated under reduced pressure to give 5-*chloro*-3β-*methoxy*-5α-*cholestan*-6β-*ol* (41) (104 mg, 97%), m.p. 155—157 °C (from light petroleum–methylene dichloride); $[\alpha]_D^{20}$ −29.4° (*c* 1.73) (Found: C, 74.25; H, 10.9; Cl, 8.0; M^+, 452.3430. $C_{28}H_{49}ClO_2$ requires C, 74.2; H, 10.9; Cl, 7.8%; *M*, 452.3421); $\nu_{max.}$ 3 510, 1 090, and 1 055 cm^{-1}; δ_H 0.68 (3 H, s, 18-H_3), 1.27 (3 H, s, 19-H_3), 3.39 (3 H, s, OMe), 3.65—4.05 (1 H, m, 3α-H), and 3.95 (1 H, m, $w_{\frac{1}{2}}$ 6-Hz, 6α-H).

Treatment with acetic anhydride and pyridine at room temperature gave the derived *acetate* (42), m.p. 116—118 °C (needles, from methanol); $[\alpha]_D^{20}$ −61° (*c* 1.04) (Found: C, 73.0; H, 10.0; Cl, 7.65. $C_{30}H_{51}ClO_3$ requires C, 72.75; H, 10.4; Cl, 7.15%); *m/z*, 434 (M^+, ^{35}Cl); $\nu_{max.}$ 1 741, 1 240, 1 110, 1 093, and 1 035 cm^{-1}; δ_H 0.69 (3 H, s, 18-H_3), 1.24 (3 H, s, 19-H_3), 2.07 (3 H, s, OAc), 3.36 (3 H, s, OMe), 3.65—3.95 (1 H, m, 3α-H), and 5.14 (1 H, m, $w_{\frac{1}{2}}$ 6 Hz, 6α-H).

Reaction of 5,6β-*Epoxy*-3β-*methoxy*-5β-*cholestane* (34) *with Dilute Hydrochloric Acid*.—A solution of 5,6β-epoxy-3β-methoxy-5β-cholestane (108 mg) in ether (5 ml) was heated under reflux with 2M hydrochloric acid (4 ml) for 4 h, then the mixture was stirred vigorously overnight. From the organic layer there was isolated, after chromatography (10 g column; chloroform as eluant), 6α-*chloro*-3β-*methoxy*-5β-*cholestan*-5-*ol* (36) (18 mg, 15%), m.p. 153—154 °C (needles, from methanol); $[\alpha]_D^{16}$ +19.7° (*c* 0.12) (Found: C, 74.4; H, 11.15; Cl, 7.85; M^+, 452.3413. $C_{28}H_{49}ClO_2$ requires C, 74.2; H, 10.9; Cl, 7.8%; *M*, 452.3421); $\nu_{max.}$ ($CHCl_3$) 3 440 cm^{-1}; δ_H 0.66 (3 H, s, 18-H_3), 0.97 (3 H, s, 19-H_3), 3.36 (3 H, s, OMe), 3.70 (1 H, m, $w_{\frac{1}{2}}$ 9 Hz, 3α-H), 4.31 (1 H, exchanges with D_2O, OH), and 4.29 (1 H, dd, *J* 4 and 12 Hz, 6β-H).

Further elution yielded 5-chloro-3β-methoxy-5α-cholestan-6β-ol (41) (75 mg, 64%), identical with material obtained as described in the preceding experiment.

Reaction of 5,6β-*Epoxy*-3β-*methoxy*-5β-*cholestane* (34) *with Boron Trifluoride–Diethyl Ether*.—(a) *Using ether as solvent*. The epoxide (34) (207 mg) was stirred in dry ether (4 ml) with boron trifluoride–diethyl ether (0.5 ml) for 5 min. The reaction was quenched by the addition of water, and the organic products were isolated by extraction with ether. Chromatography [25 g column; chloroform–ethyl acetate (9 : 1) as eluant] afforded, from the early fractions, 5-*fluoro*-3β-*methoxy*-5α-*cholestan*-6β-*ol* (39) (49 mg, 23%), m.p. 155—157 °C (needles, from methanol); $[\alpha]_D^{18}$ −2.6° (*c* 0.43) (Found: C, 77.05; H, 11.45; F, 4.2; M^+, 436.3721. $C_{28}H_{49}FO_2$ requires C, 77.0; H, 11.3; F, 4.35%; *M*, 436.3716); $\nu_{max.}$ 3 505 (sharp), 1 091, and 1 084 cm^{-1}; δ_H 0.69 (3 H, s, 18-H_3), 1.14 (3 H, s, 19-H_3), 1.81 (1 H, exchanges with D_2O, OH), 3.38 (3 H, s, OMe), 3.3—3.75 (1 H, m, 3α-H), and 3.74 (1 H, m, $w_{\frac{1}{2}}$ 11 Hz, 6α-H).

Later fractions yielded a mixture (145 mg) of 5-fluoro-3β-methoxy-5α-cholestan-6β-ol and a more polar product. The mixed fraction was acetylated [acetic anhydride (1 ml) and pyridine (2 ml) for 16 h at room temperature] and the derived acetates were separated by chromatography [20 g column; chloroform–light petroleum (1 : 1) as eluant]. In this way 3β-methoxy-5β,14β-dimethyl-18,19-dinor-8α,9β,10α-cholest-13(17)-en-6β-yl acetate (38) (16 mg), identical (t.l.c. and n.m.r.) with an authentic sample (see next experiment) was obtained, followed by 5-*fluoro*-3β-*methoxy*-5α-*cholestan*-6β-*yl acetate* (40) (83 mg), m.p. 76—77 °C (hexagonal plates, from methanol); $[\alpha]_D^{24}$ −34.4° (*c* 1.06) (Found: C, 75.0; H, 10.95; F, 4.0; M^+, 478.3824. $C_{30}H_{51}FO_3$ requires C, 75.25; H, 10.75; F, 3.95%; *M*, 478.3822); $\nu_{max.}$ 1 751, 1 237, 1 101, and 1 042 cm^{-1}; δ_H 0.69 (3 H, s, 18-H_3), 1.11 (3 H, s, 19-H_3), 2.06 (3 H, s, OAc), 3.35 (3 H, s, OMe), 3.3—3.75 (1 H, m, 3α-H), and 4.91 (1 H, m, $w_{\frac{1}{2}}$ 12 Hz, 6α-H).

(b) *Using benzene as solvent*. The epoxide (34) (734 mg) and boron trifluoride–diethyl ether (0.75 ml) were shaken together in dry benzene (15 ml) for 5 min, then water and ether were added and the organic fraction was washed with water, dried, and evaporated under reduced pressure. Chromatography (75 g column; chloroform as eluant) afforded a mixture of 5-fluoro-3β-methoxy-5α-cholestan-6β-ol (39) and 3β-methoxy-5β,14β-dimethyl-18,19-dinor-8α,9β,10α-cholest-13(17)-en-6β-ol (37) (528 mg). A sample of this mixture (504 mg) was acetylated by warming on a steam-bath with acetic anhydride (3 ml) and pyridine (5 ml) for 2 h. The resulting mixture of acetates was chromatographed [75 g column; chloroform–ethyl acetate (1 : 1) as eluant] to afford 3β-*methoxy*-5β,14β-*dimethyl*-18,19-*dinor*-8α,9β,10α-*cholest*-13(17)-*en*-6β-*yl acetate*

(38) (219 mg, 28%) as an oil which was distilled *in vacuo* (bath temperature 193 °C; 10^{-2} Torr); $[\alpha]_D^{20}$ +10.8° (*c* 0.86) (Found: C, 78.15; H, 10.85; M^+, 458.3742. $C_{30}H_{50}O_3$ requires C, 78.55; H, 11.0%; *M*, 458.3760); *m/z* 458 (M^+) and 345 (100%, $M^+ - C_8H_{17}$); $\nu_{max.}$ (film) 2 850, 1 741, 1 369, 1 245, 1 096, and 1 023 cm^{-1}; δ_H 0.84 (6 H, d, *J* 6 Hz, 26- and 27-H_3), 0.91 (3 H, s, 14β-Me), 0.95 (3 H, d, *J* 8 Hz, 21-H_3), 1.09 (3 H, s, 5β-Me), 2.06 (3 H, s, OAc), 2.34 (1 H, m, 20-H; irradiation at this frequency caused the doublet at δ 0.95 to collapse to a singlet), 3.29 (3 H, s, OMe), 3.48 (1 H, m, $w_{\frac{1}{2}}$ 8.5 Hz, 3α-H), and 4.56 (1 H, t, *J* 8 Hz, 6α-H). Later fractions gave 5-fluoro-3β-methoxy-5α-cholestan-6β-yl acetate (40) (134 mg, 17%), identical n.m.r. and t.l.c.) with material obtained as described in (a).

3β-*Methoxy*-5β,14β-*dimethyl*-18,19-*dinor*-8α,9β,10α-*cholest*-13(17)-*en*-6β-*ol* (37).—Lithium aluminium hydride (292 mg) and 3β-methoxy-5β,14β-dimethyl-18,19-dinor-8α,9β,10α-cholest-13(17)-en-16β-yl acetate (38) (148 mg) were heated under reflux in ether (20 ml) for 2.5 h. Ice-cold dilute hydrochloric acid was added and the mixture was extracted with ether. The extract was washed with brine, dried, and evaporated under reduced pressure to afford 3β-*methoxy*-5β,14β-*dimethyl*-18,19-*dinor*-8α,9β,10α-*cholest*-13(17)-*en*-6β-*ol* (37) (116 mg, 86%), m.p. 81—85 °C (needles, from methanol); $[\alpha]_D^{20}$ +16.0° (*c* 1.11) (Found: C, 80.35; H, 11.45; M^+, 416.3648. $C_{28}H_{48}O_2$ requires C, 80.7; H, 11.6%; *M*, 416.3654); *m/z* 416 (M^+) and 303 (100%, $M^+ - C_8H_{17}$); $\nu_{max.}$ 3 550—3 200, 1 096, and 1 021 cm^{-1}; δ_H 0.83 (6 H, d, *J* 6 Hz, 26- and 27-H_3), 0.91 (3 H, s, 14β-Me), 0.96 (3 H, d, *J* 9 Hz, 21-H_3), 1.01 (3 H, s, 5β-Me), 1.7—1.9 (1 H, exchanges with D_2O, OH), 2.38 (1 H, m, 20-H; irradiation here caused the doublet at δ 0.96 to collapse to a singlet), 3.24 (1 H, dd, *J* 6 and 10 Hz, 6α-H), 3.30 (3 H, s, OMe), and 3.51 (1 H, m, $w_{\frac{1}{2}}$ 8 Hz, 3α-H).

Acknowledgements

We thank the S.R.C. for the award of a research studentship to A. W. B.

References

1 C. E. Cook, R. C. Corley, and M. E. Wall, *Tetrahedron Lett.*, 1965, 891; *J. Org. Chem.*, 1968, **33**, 2789; J. D. Ballantine and P. J. Sykes, *J. Chem. Soc. C*, 1970, 731.
2 G. A. Morrison and J. B. Wilkinson, *Tetrahedron Lett.*, 1975, 2713.
3 J. R. Shanklin, C. R. Johnson, J. Ollinger, and R. M. Coates, *J. Am. Chem. Soc.*, 1973, **95**, 3429.
4 E. J. Corey and D. Seebach, *J. Org. Chem.*, 1966, **31**, 4097.
5 H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1957, 1958.
6 *Cf.* W. Z. Chow, D. C. Huang, and Huang-Minlon, *Tetrahedron*, 1966, **22**, 1053.
7 For a related rearrangement of a spiro-epoxyoctalone, see P. Geetha, K. Narasimhan, and S. Swaminathan, *Tetrahedron Lett.*, 1979, 565.
8 M. Nussim and Y. Mazur, *Tetrahedron*, 1968, **24**, 5337.
9 J. W. Blunt, M. P. Hartshorn, and D. N. Kirk, *Tetrahedron*, 1965, **21**, 559.
10 J. N. Coxon, M. P. Hartshorn, and W. J. Rae, *Tetrahedron*, 1970, **26**, 1091.
11 D. N. Kirk and V. Petrow, *J. Chem. Soc.*, 1960, 4657.
12 B. W. Cubberley and B. A. Marples, *J. Chem. Soc., Perkin Trans. 1*, 1974, 9.
13 M. Chuman, *J. Chem. Soc. Jpn., Pure Chem. Section*, 1949, **70**, 253 (*Chem. Abstr.*, 1951, **45**, 6651d); Y. Urushibara and M. Chuman, *Bull. Chem. Soc. Jpn.*, 1949, **22**, 69.
14 I. G. Guest and B. A. Marples, *J. Chem. Soc. C*, 1970, 1626.
15 E. J. Corey and M. Chaykovsky, *J. Am. Chem. Soc.*, 1965, **87**, 1353.
16 K. Sjöberg, *Tetrahedron Lett.*, 1966, 6383.
17 J. H. Beynon, I. M. Heilbron, and F. S. Spring, *J. Chem. Soc.*, 1937, 406.
18 R. Mozingo, *Org. Synth.*, 1955, Coll. Vol. III, 181.
19 G. Just and E. Lee-Ruff, *Can. J. Chem.*, 1966, **44**, 2587.
20 C. R. Narayanan and M. R. Sarma, *Tetrahedron Lett.*, 1968, 1553.

Received 10*th May* 1983; *Paper* 3/739