Studies on Steroids. Part 37.[1] Synthesis of the Four Stereoisomers of 20,22-Epoxycholesterol

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All four stereoisomers of 20,22-epoxycholesterol were synthesized from (20*E*)-cholesta-5,20(22)-dien-3β-ol. The configurational assignments were based on the analogy with the corresponding 5,6-dihydro-derivatives, prepared by stereochemically unequivocal routes.

SEVERAL routes for the biosynthetic conversion of cholesterol into pregnenolone, a precursor of all steroid hormones, have been proposed.[2] Kraaipoel *et al.*[3] have recently claimed a new pathway which includes 20,22-didehydrocholesterol and 20,22-epoxycholesterol as intermediates. This scheme appears pertinent in view of our previous observations [4] on sitosterol dealkylation in insects, which proceeds through fucosterol and its 24,28-epoxide.

In order to examine whether or not the 20,22-epoxide can be an intermediate in the side-chain cleavage of cholesterol, we have now synthesized all four stereoisomers of 20,22-epoxycholesterol (19)—(22).

We first sought a stereochemically unambiguous synthetic route to the 5,6-dihydro-analogues (5), (6), (11), and (14). Our potential precursors of these compounds were the 20,22-dihydroxycholestanols, all four stereoisomers of which have been prepared recently by Hikino *et al.*[5] According to their procedure, the 20*R*,-22*S*- and 20*R*,22*R*-glycols (3) and (4) were obtained in 6 and 30% yield, respectively, from pregnanolone tetrahydropyranyl (Thp) ether (1), through the 22-vinyl alcohol (2). The glycol (3) was converted into the 22-mesylate, which in turn was treated with potassium hydroxide giving the 20*R*,22*R*-epoxide (5) with inversion of configuration at C-22. Similarly the glycol (4) was transformed into the 20*R*,22*S*-epoxide (6). However, although the other two epoxide isomers might also be prepared in an analogous manner from the 20*S*,22*R*- and 20*S*,22*S*-glycols, Hikino's method [5] for synthesizing these glycols seems unsatisfactory in view of the many steps required and the low overall yield. We therefore used (*E*)-cholest-20(22)-enol (7) as the starting compound for the synthesis of the epoxides (11) and (14). The olefin (7) was prepared by a Wittig reaction of pregnanolone Thp ether (1) with 4-methylpentyltriphenylphosphonium bromide under the conditions described by Schmit *et al.*,[6] followed by removal of the Thp group with acid. Epoxidation of the acetate (8) with *m*-chloroperbenzoic acid gave a diastereoisomeric mixture of 20,22-epoxides, which were separated by column chromatography on silica gel to give the less polar epoxide (10) and the more polar one (11) in the ratio 2 : 3. The assignment of the 20*R*-configuration to the minor product was based on its conversion by lithium aluminium hydride into (20*S*)-20-hydroxycholestanol.[7] In view of the *E*-configuration of the starting olefin (8) and the established *cis*-addition mechanism of epoxidation by peroxy-acids, the 22*R*-configuration should be assigned to (10). The major epoxidation product (11) was similarly transformed into (20*R*)-20-hydroxycholestanol,[7] indicating the 20*S*- and hence the 22*S*-stereochemistry of (11).

Oxidation of the olefin (8) with osmium tetraoxide gave a diastereoisomeric mixture of 20,22-glycols in the ratio 9 : 1, which was estimated by high-pressure liquid chromatography of their 3,22-dibenzoates. The major glycol (12) was also prepared from the 20*R*,22*S*-epoxide (6), by treatment with perchloric acid in tetrahydrofuran, in 38% yield.† Acetylation of (12) afforded (20*S*,22*S*)-5α-cholestane-3β,20,22-triol 3,22-diacetate,[5] establishing the stereochemistry of (12). The 20*R*- and 22*R*-configurations were therefore, assigned, to the minor

† Details of the acid-catalysed reaction of the 20,22-epoxides will be described elsewhere.

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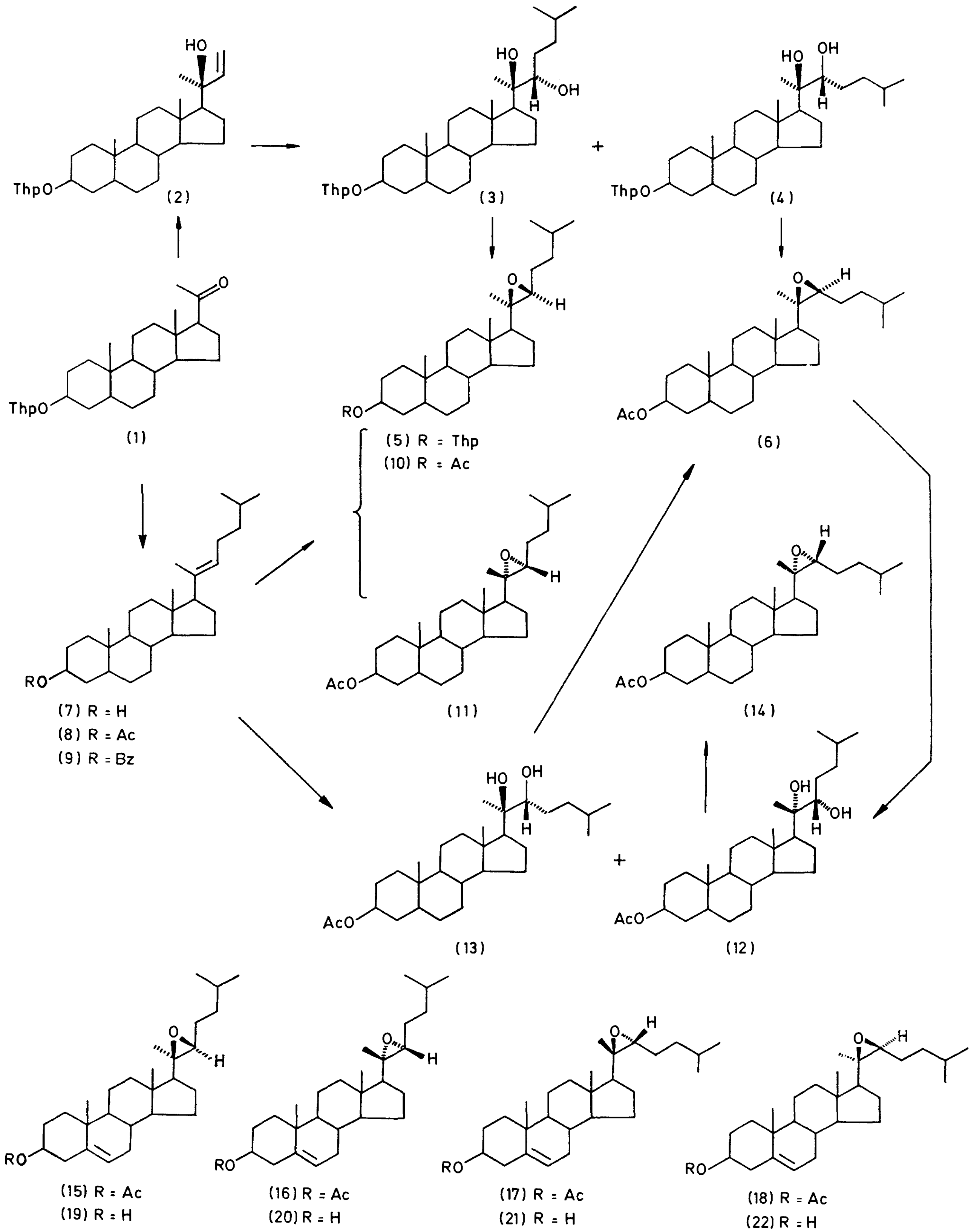
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glycol (13). It is noteworthy that electrophilic addition reactions (*i.e.* oxidations by peroxy-acid and osmium tetraoxide) of the (*E*)-20(22)-olefin (8) occurred preferentially from the *re-si*-face. This is in marked contrast with the observation[6] that catalytic hydrogenation occurred selectively on the *si-re*-face.

The 20*S*,22*R*-epoxide (14) was synthesized by mesylation of the glycol (12) followed by treatment with base. Further confirmation of the stereochemistry of compounds (6) and (14) came from their conversion by lithium aluminium hydride into (20*S*)- and (20*R*)-20-hydroxycholestanol,[7] respectively. All the four 20,22-epoxide stereoisomers, (6), (10), (11), and (14), were now in hand. Their ^{1}H n.m.r. spectra (Table 1) showed that

TABLE 1

^{1}H N.m.r. data [a]

Epoxide	13-Me	20-Me	22-H
(20*R*,22*S*) (6)	0.76	1.27	2.66 (dd, *J* 7 and 3 Hz)
(20*R*,22*R*) (10)	0.76	1.28	2.58 (t, *J* 6 Hz)
(20*S*,22*S*) (11)	0.65	1.28	2.92 (t, *J* 6 Hz)
(20*S*,22R) (14)	0.87	1.28	2.43 (t, *J* 6 Hz)

[a] Determined with a JEOL JNM-4H-100 spectrometer, $CDCl_3$ as solvent, and Me_4Si as internal reference. We are indebed to Mr. K. Furihata, Institute of Applied Microbiology, University of Tokyo, for these measurements. The following signals are common to all four epoxides: δ 0.82 (3 H, s, 10-Me), 0.88 (6 H, d, *J* 6 Hz, 25-Me_2), 2.00 (3 H, s, Ac), and 4.68 (1 H, m, 3α-H).

the 13-Me and 22-H signals are characteristic of the configurations at C-20 and -22 configurations and thus may be of diagnostic value. Table 2 summarizes the ^{13}C n.m.r. spectra of the epoxides. The C-22 signals of

TABLE 2

^{13}C Chemical shifts [a]

Epoxide	C-17	C-20	C-21	C-22
(20*R*,22*S*) (6)	52.95	60.67	22.13	66.06
(20*R*,22*R*) (10)	56.21	59.65	17.09	59.85
(20*S*,22*S*) (11)	56.54	60.06	20.24	59.26
(20*S*,22*R*) (14)	50.09	60.57	22.57	64.60

[b] Determined with a JEOL PS/PFT-100 Fourier transform spectrometer at 25.3 MHz with $CDCl_3$ as solvent and Me_4Si as internal reference. We are indebted to Dr. A. Suzuki, Teijin Central Research Institute, for these measurements.

(10) and (11) appear at higher field (4—6 p.p.m.) than those of (6) and (14). In the molecules of (10) and (11), C-16 and/or C-13 could interact with the hydrogen atom on C-22, resulting in the observed shielding γ-effect.[8] Similarly the γ-effect of C-23 may be the cause of the shielding (3.5—6 p.p.m.) of the C-17 signals of (6) and (14) in comparison with (10) and (11). These ^{13}C n.m.r. data seem to support the configurational assignments mentioned above.

Having established syntheses of the four 20,22-epoxycholestanols, syntheses of the 5,6-didehydro-analogues was readily achieved. Oxidation of (*E*)-20,22-didehydrocholesterol acetate[6] with *m*-chloroperbenzoic acid occurred regioselectively at C-20(22) to give the 20*R*,22*R*-epoxide (15) (27%) and the 20*S*,22*S*-epoxide (16) (44%). Oxidation of the same olefin with osmium tetraoxide afforded a diastereoisomeric mixture of 20,22-glycols, which was directly transformed through the 22-mesylate into the 20,22-epoxides as described for the 5,6-dihydro-analogues. Column chromatography on silica gel gave the 20*S*,22*R*-epoxide (17) and the 20*R*,22*S*-epoxide (18) in 56 and 6% yields, respectively. The stereochemical assignments rest on analogy with the 5,6-dihydro-congeners, and were corroborated by n.m.r. analysis. Hydrolysis of the epoxy-acetates with potassium carbonate yielded the desired (20*R*,22*R*)-, (20*S*,-22*S*)-, (20*S*,22*R*)-, and (20*R*,22*S*)-20,22-epoxycholesterols (19)—(22).

Our recent experiments[1] have shown that none of these epoxides (19)—(22) nor (*E*)-20,22-didehydrocholesterol was significantly converted into pregnenolone on incubation with purified adrenocortical cytochrome P-450.

EXPERIMENTAL

M.p.s were determined with a hot-stage microscope. ^{1}H N.m.r. spectra were obtained with a Varian T-60 or a Hitachi R-24A spectrometer for solutions in $CDCl_3$ unless otherwise stated with Me_4Si as internal reference. Mass spectra were run on a Shimadzu-LKB 9000S spectrometer. Column chromatography was effected with silica gel (Wakogel C-200). 'The usual work-up' refers to dilution with brine, extraction with ethyl acetate, washing to neutrality, drying ($MgSO_4$), filtration, and evaporation under vacuum. The following abbreviations are used: THF, tetrahydrofuran; *m*-CPBA, *m*-chloroperbenzoic acid; Thp, tetrahydropyranyl; MCl, methanesulphonyl chloride.

(20S)-5α-*Norchol-22-ene*-3β,20-*diol* 3-*Thp Ether* (2).—A solution of vinyl bromide (53.7 g) in THF (100 ml) was added dropwise to a stirred mixture of magnesium (8.82 g) and a trace of iodine under argon. The mixture was stirred for 1 h and then cooled in ice–salt. To the resulting Grignard reagent was added dropwise a solution of pregnanolone Thp ether (1) (38.2 g) in THF (500 ml). Stirring was continued overnight and then aqueous NH_4Cl (20 g) was added with cooling (ice). The usual work-up followed by crystallization from acetone gave the 20-*vinyl alcohol* (2) (34 g), m.p. 146—148° (from acetone), δ 0.80 (6 H, s, 10- and 13-Me), 1.31 (3 H, s, 20-Me), 3.6 (1 H, m, 3α-H), 4.93 (1 H, dd, *J* 10 and 2 Hz, 23-H_a), 5.11 (1 H, dd, *J* 18 and 2 Hz, 23-H_b), and 5.97 (1 H, dd, *J* 18 and 10 Hz, 22-H), *m/e* 430 (M^+), 412 ($M - H_2O$), and 328 (M − ThpOH) (Found: C, 78.3; H, 10.8. $C_{28}H_{46}O_3$ requires C, 78.1; H, 10.8%).

(20R,22S)- *and* (20R,22R)-5α-*Cholestane*-3β,20,22-*triol* 3-*Thp Ethers*, (3) *and* (4).—The vinyl alcohol (2) (13.2 g) was ozonized in CH_2Cl_2 (660 ml) in the presence of pyridine (6.6 ml) with cooling (solid CO_2–acetone). Zinc powder (16.5 g) and acetic acid (33 ml) were added and the mixture was stirred for 1 h. Filtration and the usual work-up gave an amorphous product (12 g), δ 0.76 (s, 13-Me), 0.80 (s, 10-Me), 1.33 (s, 20-Me), and 9.55 (s, CHO). The presence of (1) as a by-product was shown by signals at δ 0.60 (s, 13-Me) and 2.11 (s, 20-Me). A solution of the crude ozonolysis product (12 g) in THF (200 ml) was added to the Grignard

[8] J. B. Stothers, 'Carbon-13 NMR Spectroscopy,' Academic Press, New York, 1972.

reagent prepared from isopentyl bromide (15.7 g), magnesium (2.53 g), THF (50 ml), and a trace of iodine. Stirring overnight, addition of NH_4Cl (11.3 g), and the usual work-up gave the crude product (15.3 g). Column chromatography with benzene–ethyl acetate (100 : 1) gave (20*S*)-20-isopentyl-5α-pregnane-3β,20-diol 3-Thp ether (2.87 g), m.p. 125—127° (from methanol), δ 0.79 (3 H, s, 13-Me), 0.83 (3 H, s, 10-Me), 0.87 (6 H, d, *J* 6 Hz, CMe_2), and 1.26 (3 H, s, 20-Me), *m/e* 456 (*M* − H_2O), 403 (*M* − C_5H_{11}), 372 (*M* − ThpOH − H_2O), and 301 (*M* − ThpOH − H_2O − C_5H_{11}). Further elution with benzene-ethyl acetate (50 : 1) gave the 20R,22S-*glycol* (3) (1.47 g), m.p. 198—200.5° (from methanol), δ 0.81 (3 H, s, 10-Me), 0.85 (3 H, s, 13-Me), 0.89 (6 H, d, *J* 6 Hz, 25-Me_2), 1.26 (3 H, s, 20-Me), and 3.24 (1 H, m, 22-H), δ (C_5D_5N) 0.78 (3 H, s, 10-Me), 0.88 (6 H, d, *J* 5 Hz, 25-Me_2), 1.12 (3 H, s, 13-Me), and 1.57 (3 H, s, 20-Me), *m/e* 486 (*M* − H_2O), 403 (*M* − C_6H_{13}), 385 (*M* − $C_6H_{13}O$ − H_2O), 301 (*M* − $C_6H_{13}O$ − ThpOH), and 283 (301 − H_2O) (Found: C, 76.4; H, 11.2. $C_{32}H_{56}O_4$ requires C, 76.15; H, 11.2%). Further elution with benzene–ethyl acetate (30 : 1) afforded the 20R,22R-*glycol* (4) (7.02 g), m.p. 153—154° (from methanol), δ 0.80 (3 H, s, 10-Me), 0.85 (3 H, s, 13-Me), 0.88 (6 H, d, *J* 6 Hz, 25-Me_2), and 1.19 (3 H, s, 20-Me), δ (C_5D_5N) 0.78 (3 H, s, 10-Me), 0.93 (6 H, d, *J* 5 Hz, 25-Me_2), 1.13 (3 H, s, 13-Me), and 1.48 (3 H, s, 20-Me) (Found: C, 76.1; H, 11.2%).

(20R,22R)-20,22-*Epoxy*-5α-*cholestan*-3β-*yl Thp Ether* (5).—The 20*R*,22*S*-glycol (3) (63 mg) was treated with MsCl (43 μl) in pyridine (0.8 ml) at 0 °C overnight. The usual work-up gave the crude 22-mesylate, δ 0.78 (3 H, s, 13-Me), 0.83 (3 H, s, 10-Me), 0.88 (6 H, d, *J* 6 Hz, 25-Me_2), 1.32 (3 H, s, 20-Me), 3.08 (3 H, s, mesyl), and 4.43 (1 H, m, 22-H). This (82 mg) was refluxed with KOH (34 mg) in methanol (50 ml) for 8 min. The usual work-up gave the 20R,22R-*epoxide* (5) (53 mg), m.p. 134—135.5° (from acetone), δ 0.77 (3 H, s, 13-Me), 0.83 (3 H, s, 10-Me), 0.89 (6 H, d, *J* 6 Hz, 25-Me_2), 1.28 (3 H, s, 20-Me), and 2.63 (1 H, t, *J* 6 Hz, 22-H) (Found: M^+, 486.409. $C_{32}H_{54}O_3$ requires *M*, 486.407).

(20R,22S)-20,22-*Epoxy*-5α-*cholestan*-3β-*yl Acetate* (6).—The 20*R*,22*R*-glycol (4) (2.3 g) was treated with MsCl (1.39 ml) in pyridine (31 ml) at 0 °C overnight. The usual work-up gave the crude 22-mesylate, which was then treated with 3N-HCl (0.2 ml) in methanol (250 ml) for 2 h. The usual work-up gave the crude 3-alcohol (1.95 g), which was then refluxed with KOH (680 mg) in methanol (100 ml) for 10 min. The usual work-up and column chromatography with benzene gave the epoxy-alcohol (844 mg), m.p. 75—78° (from hexane), δ 0.75 (3 H, s, 13-Me), 0.79 (3 H, s, 10-Me), 0.88 (6 H, d, *J* 6 Hz, 25-Me_2), 1.27 (3 H, s, 20-Me), 2.70 (1 H, dd, *J* 6 and 3 Hz, 22-H), and 3.54 (1 H, m, 3α-H), *m/e* 402 (M^+), 387 (*M* − Me), 384 (*M* − H_2O), and 331 (*M* − C_5H_{11}). This was acetylated with acetic anhydride–pyridine to give the *epoxy-acetate* (6), m.p. 134—135° (from hexane); for n.m.r. see Tables 1 and 2; *m/e* 444 (M^+) (Found: C, 78.2; H, 10.9. $C_{29}H_{48}O_3$ requires C, 78.3; H, 10.9%).

(E)-5α-*Cholest*-20(22)-*en*-3β-*ol* (7).—A freshly prepared solution of sodium pentyloxide in benzene (2.9N, 19.3 ml) was added to 4-methylpentyltriphenylphosphonium bromide (23.9 g). Benzene (80 ml) was added and the mixture was refluxed in argon for 20 min. To this stirred solution, pregnanolone Thp ether (1) (9 g) in benzene (250 ml) was added. After refluxing overnight, the resulting precipitate was filtered off and the filtrate was worked up as usual. The crude product in hexane–benzene (4 : 6) was passed through a short column of silica gel to give the 20(22)-olefin Thp ether, m.p. 87—89° (from methanol), *m/e* 470 (M^+) and 386 (*M* − ThpOH). This was treated with 2N-HCl (0.2 ml) in methanol (300 ml) to give the *olefin* (7) (5.7 g), m.p. 116—118° (from methanol), δ 0.51 (3 H, s, 13-Me), 0.81 (3 H, s, 10-Me), 0.87 (6 H, d, *J* 6 Hz, 25-Me_2), 1.61br (3 H, s, 20-Me), 3.6 (1 H, m, 3α-H), and 5.19 (1 H, t, *J* 7 Hz, 22-H), *m/e* 386 (M^+), 371 (*M* − Me), and 353 (*M* − Me − H_2O) (Found: C, 84.05; H, 12.1. $C_{27}H_{46}O$ requires C, 83.9; H, 12.0%). Acetylation with acetic anhydride–pyridine gave the *acetate* (8), m.p. 92—93.5° (from methanol), *m/e* 428 (M^+), 413 (*M* − Me), 368 (*M* − AcOH), and 353 (*M* − AcOH − Me) (Found: C, 81.4; H, 11.3. $C_{29}H_{48}O_2$ requires C, 81.25; H, 11.3). Benzoylation with benzoyl chloride–pyridine gave the *benzoate* (9), m.p. 121—123° (from acetone), *m/e* 490 (M^+).

(20R,22R)- *and* (20S,22S)-20,22-*Epoxy*-5α-*cholestan*-3β-*yl Acetates*, (10) *and* (11).—*m*-CPBA (85%, 2.5 g) was added to a stirred solution of the olefin (8) (3.5 g) in CH_2Cl_2 (80 ml). Stirring was continued for 2 h. The usual work-up and column chromatography with hexane–benzene (1 : 9) gave the 20R,22R-*epoxide* (10) (0.86 g), m.p. 119—120.5° (from hexane); for n.m.r. see Tables 1 and 2; *m/e* 444 (M^+), 429 (*M* − Me), 426 (*M* − H_2O), 384 (*M* − AcOH), and 355 (*M* − C_5H_{11} − H_2O) (Found: C, 78.45; H, 10.85. $C_{29}H_{48}O_3$ requires C, 78.3; H, 10.9%). Further elution with the same solvent gave the 20S,22S-*epoxide* (11) (1.36 g), m.p. 116—119° (from hexane); for n.m.r. see Tables 1 and 2; *m/e* 444 (M^+) (Found: C, 78.3; H, 11.0%).

Treatment of the 20R,22S-*Epoxide* (6) *with Perchloric Acid*.—The 20*R*,22*S*-epoxide (6) (414 mg) was treated with 3% $HClO_4$ (16 ml) in THF (100 ml) at room temperature for 3 h. The usual work-up and column chromatography with benzene gave 5α-cholest-20(21)-ene-3β,20-diol 3-acetate (109 mg), m.p. 150—155° (from methanol), $\nu_{max.}$ 3 570 (OH), 1 720 (acetyl), and 900 cm^{-1} (exocyclic methylene), δ 0.58 (3 H, s, 13-Me), 0.82 (3 H, s, 10-Me), 0.87 (6 H, d, *J* 6 Hz, 25-Me_2), 2.0 (3 H, s, Ac), 4.0 (1 H, m, 22-H), 4.7 (1 H, m, 3α-H), 4.96br (1 H, s, 21-H_a), and 5.30br (1 H, s, 21-H_b). Further elution with benzene afforded the 20S,22S-*glycol* (12) (157 mg), δ 0.82 (3 H, s, 10-Me), 0.85 (3 H, s, 13-Me), 0.89 (6 H, d, *J* 6 Hz, 25-Me_2), 1.07 (3 H, s, 21-Me), 2.01 (3 H, s, Ac), 3.70 (1 H, m, 22-H), and 4.7 (1 H, m, 3α-H), δ (C_5D_5N) 0.76 (3 H, s, 10-Me), 0.96 (6 H, d, *J* 5 Hz, 25-Me_2), 1.08 (3 H, s, 13-Me), 1.32 (3 H, s, 21-Me), 2.02 (3 H, s, Ac), and 4.04 (1 H, m, 3α-H). Acetylation of the glycol (12) gave the 3,22-diacetate, m.p. 124—126° (from methanol) (lit.,[4] 125—126.5°), δ 0.81 (3 H, s, 10-Me), 0.90 (3 H, s, 13-Me), 1.05 (3 H, s, 21-Me), 1.96 (3 H, s, Ac), 2.04 (3 H, s, Ac), 4.65 (1 H, m, 3α-H), and 5.13 (1 H, m, 22-H).

Oxidation of the Benzoate (9) *with Osmium Tetraoxide*.—OsO_4 (38.1 mg) was added to a solution of the benzoate (9) (50 mg) in diethyl ether (1 ml) containing pyridine (32 μl). The mixture was stirred at room temperature for 40 min. Ether was evaporated off and the residue was stirred with a mixture of $NaHSO_3$ (140 mg), water (3.1 ml), and pyridine (4.2 ml) overnight. The usual work-up gave the crude 20,22-glycols (51 mg), δ 0.86 (6 H, s, 10- and 13-Me_2), 0.90 (6 H, d, *J* 6 Hz, 25-Me_2), 1.06 (3 H, s, 21-Me), 3.72 (1 H, m, 22-H), 4.88 (1 H, m, 3α-H), and 7.48 and 8.07 (5 H, m, aromatic). These were treated with benzoyl chloride–pyridine to give the 3,22-dibenzoates, which were analysed by high-pressure liquid chromatography (Shimadzu–DuPont 830; column of Zorbax SiL 25 × 0.25 cm; solvent CH_2Cl_2;

pressure, 84 kg cm^{-2}); two peaks appeared at t_R 6.7 and 8.8 min (9 : 1).

(20S,22R)-20,22-*Epoxy-5α-cholestan-3β-yl Acetate* (14).—(*a*) The 20*S*,22*S*-glycol (12) (103 mg) was treated with MsCl (63 μl) in pyridine (1.2 ml) at 0 °C overnight. The usual work-up gave the crude 22-mesylate, δ 0.88 (3 H, s, 13-Me), 3.13 (3 H, s, mesyl), and 4.95 (1 H, m, 22-H). This (87 mg) was refluxed with K_2CO_3 (30 mg) in methanol (3 ml) for 5 min. The usual work-up followed by column chromatography with hexane–benzene (4 : 1) gave the 20S,22R-*epoxide* (14) (31 mg), m.p. 159.5—161° (from hexane); for n.m.r. see Tables 1 and 2; *m/e* 444 (M^+) (Found: C, 78.3; H, 10.9. $C_{29}H_{48}O_3$ requires C, 78.3; H, 10.9%).

(*b*) OsO_4 (787 mg) was added to a solution of the acetate (8) (1.1 g) in diethyl ether (22 ml) containing pyridine (0.7 ml). The mixture was stirred at room temperature for 1 h. Ether was evaporated off and the residue was stirred with a mixture of $NaHSO_3$ (2.8 g), water (62 ml), and pyridine (84 ml) overnight. The usual work-up gave the crude 20,22-glycol, which was treated with MsCl (0.6 ml) in pyridine (10 ml) at 0 °C overnight. The resulting 22-mesylate (1.30 g) was refluxed with K_2CO_3 (375 mg) in methanol (40 ml) for 20 min. The usual work-up and column chromatography with hexane–benzene (1 : 9) gave the 20S,22R-*epoxide* (14) (330 mg) and the 20R,22S-*epoxide* (6) (50 mg).

Reduction of the Epoxides (6), (10), (11), *and* (14) *with Lithium Aluminium Hydride*.—A mixture of the 20*S*,22*S*-epoxide (11) (90 mg) and $LiAlH_4$ (80 mg) was refluxed in THF (3 ml) overnight. The usual work-up followed by crystallization from ethanol gave (20*R*)-5α-cholestane-3β,-20-diol (60 mg), m.p. 121—123° (lit.,[7] 125—127°), δ 0.80 (3 H, s, 10-Me), 0.84 (3 H, s, 13-Me), 0.87 (6 H, d, *J* 6 Hz, 25-Me_2), 1.12 (3 H, s, 21-Me), and 3.6 (1 H, m, 3α-H), *m/e* 386 ($M - H_2O$), 371 ($M - Me - H_2O$), 353 ($M - Me - 2H_2O$), and 301 ($M - H_2O - C_6H_{13}$). Similar reduction of the 20*R*,22*R*-epoxide (10) afforded (20*S*)-5α-cholestane-3β,20-diol,[7] δ 0.79 (3 H, s, 13-Me), 0.81 (3 H, s, 10-Me), 0.87 (6 H, d, *J* 6 Hz, 25-Me_2), 1.27 (3 H, s, 21-Me), and 3.55 (1 H, m, 3α-H). The 20*S*,22*R*-epoxide (14) and the 20*R*,22*S*-epoxide (6) yielded in analogous manner the 20*R*- and the 20*S*-alcohol, respectively.

(20R,22R)- *and* (20S,22S)-20,22-*Epoxycholest-5-en-3β-yl Acetates*, (15) *and* (16).—To a stirred solution of (20*E*)-cholesta-5,20(22)-dien-3β-yl acetate[6] (852 mg) in CH_2Cl_2 (50 ml) was added *m*-CPBA (344 mg) dropwise with cooling (ice–salt). Stirring for 2 h and the usual work-up gave a crystalline product (929 mg). Column chromatography with benzene–hexane (9 : 1) gave the 20R,22R-*epoxide* (15) (242 mg), m.p. 93—96° (from methanol), δ 0.78 (3 H, s, 13-Me), 0.87 (6 H, d, *J* 6 Hz, 25-Me_2), 1.00 (3 H, s, 10-Me), 1.28 (3 H, s, 20-Me), 1.99 (3 H, s, Ac), 2.55 (1 H, m, 22-H), 4.5 (1 H, m, 3α-H), and 5.35 (1 H, m, 6-H) (Found: C, 78.5: H, 10.5. $C_{29}H_{46}O_3$ requires C, 78.7; H, 10.5%). Further elution with the same solvent afforded the 20S,22S-*epoxide* (16) (384 mg), m.p. 90—92° (from methanol), δ 0.68 (3 H, s, 13-Me), 0.88 (6 H, d, *J* 6 Hz, 25-Me_2), 1.00 (3 H, s, 10-Me), 1.28 (3 H, s, 20-Me), 1.99 (3 H, s, Ac), 2.91 (1 H, m, 22-H), 4.5 (1 H, m, 3α-H), and 5.35 (1 H, m, 6-H) (Found: C, 78.6; H, 10.5%).

(20S,22R)- *and* (20R,22S)-20,22-*Epoxycholest-5-en-3β-yl Acetates*, (17) *and* (18).—OsO_4 (1.0 g) was added in one portion to a stirred solution of (20*E*)-cholesta-5,20(22)-dien-3β-yl acetate[6] (1.7 g) in diethyl ether (60 ml) with cooling (ice–salt). Stirring was continued at −10 °C for 1 h and then at 15 °C for 45 min. Ether was evaporated off and the residue was stirred with a mixture of $NaHSO_3$ (3.5 g), water (77 ml), and pyridine (105 ml). Stirring at 15 °C for 45 min and the usual work-up gave the crude 20,22-glycol (1.90 g), δ 0.87 (3 H, s, 13-Me), 0.90 (3 H, d, *J* 6 Hz, 25-Me_2), 1.01 (3 H, s, 10-Me), 1.05 (3 H, s, 20-Me), 2.01 (3 H, s, Ac), 3.7 (1 H, m, 22-H), 4.6 (1 H, m, 3α-H), and 5.35 (1 H, m, 6-H). This (1.16 g) was treated with MsCl (0.75 ml) in pyridine (7 ml) at −10 °C overnight. The usual work-up and then refluxing with K_2CO_3 (280 mg) in methanol (40 ml) for 15 min, followed by column chromatography with benzene–hexane (2 : 1), afforded unchanged olefin (27 mg). Further elution with benzene–hexane (9 : 1) gave the 20S,-22R-*epoxide* (17) (650 mg), m.p. 147.5—148.5° (from methanol), δ 0.87 (3 H, s, 13-Me), 0.90 (3 H, d, *J* 6 Hz, 25-Me_2), 1.01 (3 H, s, 10-Me), 1.28 (3 H, s, 20-Me), 2.00 (3 H, s, Ac), 4.6 (1 H, m, 3α-H), and 5.35 (1 H, m, 6-H) (Found: C, 78.8; H, 10.55. $C_{29}H_{46}O_3$ requires C, 78.7; H, 10.5%); and the 20R,22S-*epoxide* (18) (70 mg), m.p. 161—163° (from methanol), δ 0.78 (3 H, s, 13-Me), 0.88 (3 H, d, *J* 6 Hz, 25-Me_2), 1.00 (3 H, s, 10-Me), 1.98 (3 H, s, acetyl), 4.5 (1 H, m, 3α-H), and 5.35 (1 H, m, 6-H).

Hydrolysis of the Epoxy-acetates (15)—(18).—The 20*R*,-22*R*-epoxy-acetate (15) (40 mg) was heated at 70 °C in a mixture of K_2CO_3 (0.3 g), water (1.5 ml), and methanol (10 ml) for 15 min. The usual work-up gave (20R,22R)-20,22-*epoxycholest-5-en-3β-ol* (19) (35 mg), m.p. 133—134° (from methanol), δ 0.75 (3 H, s, 13-Me), 0.88 (6 H, d, *J* 6 Hz, 25-Me_2), 0.99 (3 H, s, 10-Me), 1.28 (3 H, s, 20-Me), 2.55 (1 H, m, 22-H), 3.5 (1 H, m, 3α-H), and 5.35 (1 H, m, 6-H) (Found: C, 80.9; H, 11.1. $C_{27}H_{44}O_2$ requires C, 80.95; H, 11.1%). Similar hydrolysis of compounds (16)—(18) afforded, respectively, the 20S,22S-*epoxide* (20), m.p. 133—134.5° (from methanol), δ 0.68 (3 H, s, 13-Me), 0.89 (6 H, d, *J* 6 Hz, 25-Me_2), 1.00 (3 H, s, 10-Me), 1.29 (3 H, s, 20-Me), 2.92 (1 H, m, 22-H), 3.5 (1 H, m, 3α-H), and 5.30 (1 H, m, 6-H) (Found: C, 80.9; H, 11.15%), the 20S,22R-*epoxide* (21), m.p. 134—135.5° (from methanol), δ 0.88 (3 H, s, 13-Me), 0.89 (6 H, d, *J* 6 Hz, 25-Me_2), 1.00 (3 H, s, 10-Me), 1.29 (3 H, s, 20-Me), 3.5 (1 H, m, 3α-H), and 5.33 (1 H, m, 6-H) (Found: C, 81.15; H, 11.1%), and the 20R,22S-*epoxide* (22), δ 0.78 (3 H, s, 13-Me), 0.89 (6 H, d, *J* 6 Hz, 25-Me_2), 1.00 (3 H, s, 10-Me), 1.27 (3 H, s, 20-Me), 2.65 (1 H, m, 22-H), 3.5 (1 H, m, 3α-H), and 3.35 (1 H, m, 6-H) (Found: M^+, 400.329. $C_{27}H_{44}O_2$ requires *M*, 400.334).

[6/550 *Received, 22nd March*, 1976]