Neighbouring Group Effects in the Acid-catalysed Opening of Steroidal Epoxides

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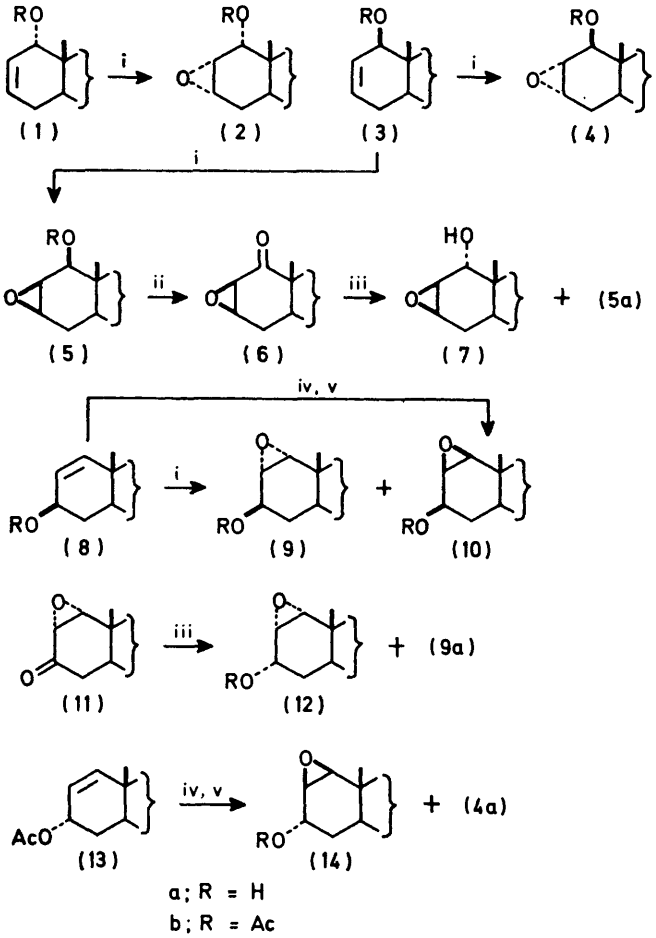
The hydrobromic-acid-induced opening of the epoxide ring in the stereoisomeric 1-hydroxy(or -acetoxy)-2,3-epoxy- and 3-hydroxy(or -acetoxy)-1,2-epoxy-5α-cholestanes was investigated. The results are evaluated with regard to the tendency to ' diaxial opening ' of the epoxide ring and the tendency of the nucleophile to attack at the carbon atom β with respect to the neighbouring group. The 2α,3α-epoxides give mixtures of diaxial and diequatorial products, whereas 2β,3β-epoxides give only diaxial products. All products obtained from 1,2-epoxides are diaxial. In several instances, the epoxide ring is displaced by an appropriately oriented acetoxy-group.

We have previously reported[1] that opening of the epoxide ring in several steroidal *cis*-epoxy-alcohols and -acetates is influenced by the neighbouring groups and leads to the preferential formation of *trans*-diequatorial products. In contrast to 2α,3α-epoxy-5α-cholestane, which reacts with hydrobromic acid to give almost quantitatively the diaxial 2β-bromo-3α-hydroxy-derivative, 2α,3α-epoxy-1α-hydroxy-5α-cholestane (2a) gives a 1.1 : 1 mixture of compound (15), resulting from ' diequatorial ' opening, and compounds (12a) and (16a), resulting from ' diaxial ' opening of the epoxide ring. This ratio is increased to 2.5 : 1 [compounds (17) and (16b), respectively] when the reaction is performed with the corresponding acetate (2b).[1b]

We now report the results obtained by treatment with

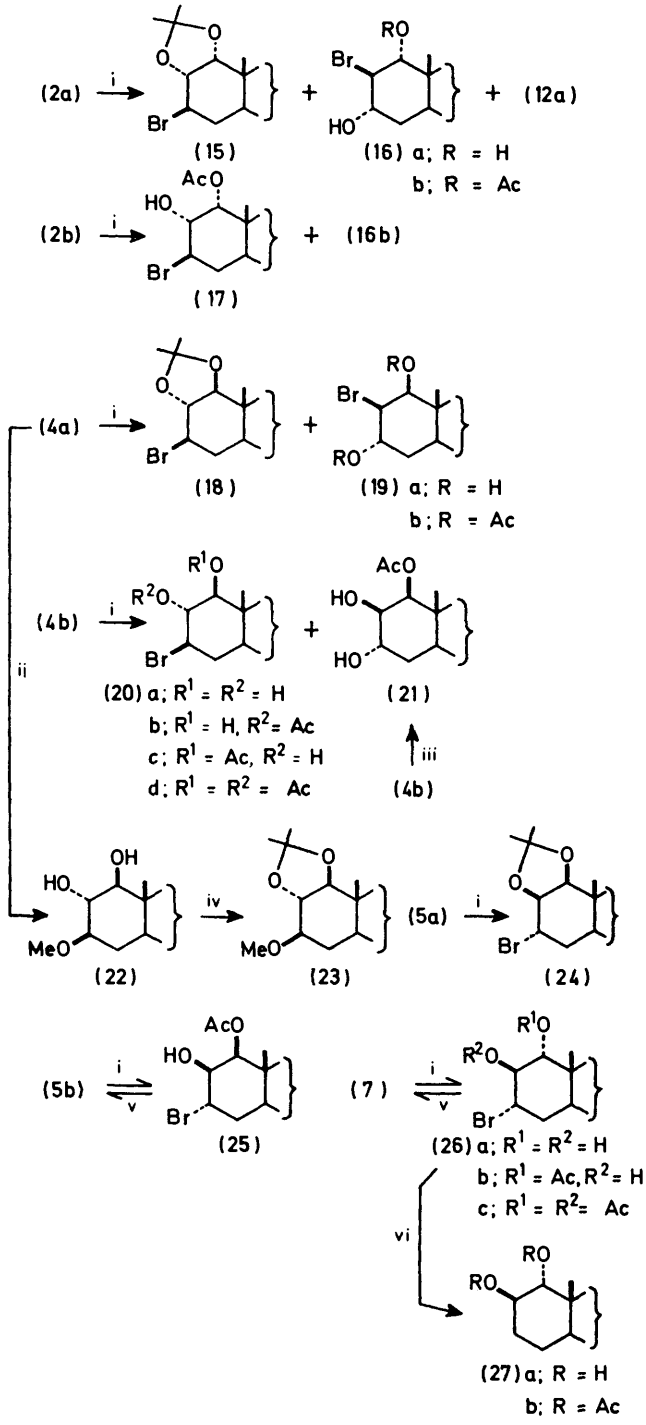
[1] (*a*) E. Glotter, S. Greenfield, and D. Lavie, *Tetrahedron Letters*, 1967, 5261; (*b*) E. Glotter, P. Krinsky, M. Rejtö, and M. Weissenberg, *J.C.S. Perkin I*, 1976, 1442.

hydrobromic acid of all the stereoisomeric 1-hydroxy-(or -acetoxy)-2,3-epoxy- and 3-hydroxy-(or -acetoxy)-1,2-epoxy-5α-cholestanes. The preparation of these compounds is summarised in Scheme 1. Treatment of



SCHEME 1 Preparation of epoxy-alcohols and acetates; reagents: i, $PhCO_3H$; ii, CrO_3 (Jones reagent); iii, $NaBH_4$; iv, AcNHBr; v, NaOH

1α-hydroxy-5α-cholest-2-ene (1a) with peroxybenzoic acid affords quantitatively the 2α,3α-epoxy-derivative (2a),[1b] whereas 1β-hydroxy-5α-cholest-2-ene (3a) [2] gives a 2.5 : 1 mixture of 2α,3α-epoxy- (4a) and 2β,3β-epoxy-1β-hydroxy-5α-cholestane (5a). Epoxidation of the allylic acetate (3b) gives only the 2α,3α-epoxy-derivative (4b). Mild oxidation of the *cis*-epoxy-alcohol (5a) affords in good yield 2β,3β-epoxy-5α-cholestan-1-one (6); the analogous androstane derivative was previously obtained [3] in trace amounts by treatment of 17β-acetoxy-5α-androst-2-en-1-one with hydrogen peroxide in alkaline medium. Reduction with sodium borohydride of the epoxy-ketone (6) gives a 1 : 2 mixture of *cis*- (5a) and *trans*-epoxy-alcohol (7a). Since epoxidation of 3β-hydroxy-5α-cholest-1-ene (8a) gives a 1 : 2 mixture of the 1α,2α- (9a) and 1β,2β-epoxide (10a),[4] the latter was prepared by treatment of the allylic alcohol (8a) with *N*-bromoacetamide, followed by epoxide ring closure in the presence of alkali.[4,5] The steroisomeric 3β-hydroxy-



SCHEME 2 Reactions of 1-hydroxy(or -acetoxy)2,3-epoxy-5α-cholestanes; reagents: i, HBr in Me_2CO; ii, *p*-$MeC_6H_4{\cdot}SO_3H$ in MeOH; iii, $HClO_4$ in Me_2CO; iv, *p*-$MeC_6H_4{\cdot}SO_3H$ in Me_2CO solution; v, silica gel; vi, Raney nickel

[2] (*a*) Ch. Tamm and R. Albrecht, *Helv. Chim. Acta*, 1959, **42**, 2172; (*b*) M. Weissenberg and E. Glotter, *J.C.S. Perkin I*, 1977, 988.

[3] H. Tada and Y. K. Sawa, *J. Org. Chem.*, 1968, **33**, 3347.

[4] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1957, 1958; R. Albrecht and Ch. Tamm, *Helv. Chim. Acta*, 1957, **40**, 2216.

[5] E. Glotter and P. Krinsky, preceeding paper.

and 3α-hydroxy-1α,2α-epoxycholestanes [(9a) and (12a)] were obtained by reduction with sodium borohydride of the epoxy-ketone (11).[6] Finally, treatment of 3α-acetoxy-5α-cholest-1-ene [7] with *N*-bromoacetamide and subsequent ring closure of the bromohydrin afforded 1β,2β-epoxy-3α-hydroxy-5α-cholestane (14a).[5] This epoxy-alcohol was accompanied by small amounts of the isomeric compound (4a), resulting from internal nucleophilic displacement of the 1β,2β-epoxide by the anion of the axially oriented 3α-hydroxy-group. Such ' epoxide migrations ' are often encountered in carbohydrate and cyclitol epoxides.[8]

The behaviour of 1-hydroxy(or -acetoxy)-2,3-epoxycholestanes in the presence of hydrobromic acid in acetone solution is summarised in Scheme 2. 2α,3α-Epoxy-1β-hydroxy-5α-cholestane (4a) gives a 1 : 2.5 mixture of the bromo-acetonide (18) and the bromo-diol (19a). The assignment of structure (19a) (2β-bromo-1β,3α-dihydroxy-5α-cholestane) is based on the n.m.r. pattern of the corresponding diacetate (19b) (see Experimental section). The easy acetylation of the 1β-OH group in compound (19a) is in sharp contrast with the inertness of the same group in compounds (20a and b). The structure (18) was confirmed by acid-catalysed hydrolysis to 3β-bromo-1β,2α-dihydroxy-5α-cholestane (20a). Although it is well known that acetonides are easily obtained from *cis*-glycols, there seem to be less examples pointing to similar behaviour of *trans*-diequatorial glycols.[9]

In contrast to the above bidirectional opening of the epoxide ring, methanolysis of compound (4a) in the presence of a trace of toluene-*p*-sulphonic acid afforded only 1β,2α-dihydroxy-3β-methoxy-5α-cholestane (22), resulting from ' diequatorial ' opening of the epoxide ring. The *trans*-diequatorial system in this compound (22) was easily converted into the corresponding acetonide (23).

1β-Acetoxy-2α,3α-epoxy-5α-cholestane (4b) afforded two compounds (20b and c) resulting from ' diequatorial ' opening of the epoxide, and a compound (21) obtained by displacement of the epoxide ring by the *trans*-oriented acetoxy group, *via* an acetoxonium ion intermediate. The same compound (21) was obtained by treatment of the epoxy-acetate (4b) with aqueous perchloric acid in acetone solution. The diequatorial bromohydrin (20c) (1β-acetoxy-3β-bromo-2α-hydroxy-5α-cholestane, showing a doublet n.m.r. signal, *J* 9 Hz, for 1α-H) was accompanied by small amounts of the isomeric 2α-acetoxy-3β-bromo-1β-hydroxy-5α-cholestane (20b) (double doublet for 2β-H, *J* 11 and 10 Hz); the latter was formed under the conditions of the reaction by internal acid-catalysed transesterification of compound (20c). Indeed, when treated with hydrobromic acid in acetone solution, compound (20c) was partially converted into compound (20b). Although the 1β-hydroxy-group in (20b) is equatorially oriented, its hindrance is remarkable. Whereas this compound could not be acetylated with acetic anhydride in pyridine at room temperature, the 2α-hydroxy-group in compound (20c) was easily acetylated to give the bromo-diacetate (20d) (doublet for 1α-H, *J* 10 Hz, triplet for 2β-H, *J* 10 Hz). Acetylation of the bromo-diol (20a) afforded only the monoacetate (20b).

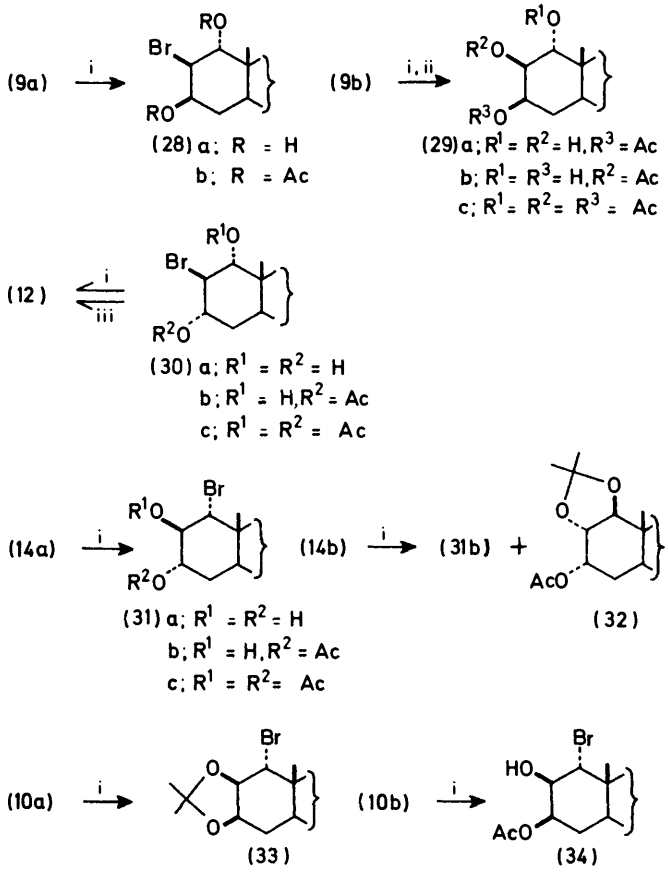
The opening of the epoxide ring in compounds (5a and b) is stereospecific. 2β,3β-Epoxy-1β-hydroxy-5α-cholestane (5a) gives the bromo-acetonide (24), whereas the corresponding acetate (5b) gives 1β-acetoxy-3α-bromo-2β-hydroxy-5α-cholestane (25), identical with the bromohydrin obtained [5] by treatment of 1β-acetoxy-5α-cholest-2-ene (3b) with *N*-bromoacetamide. This behaviour is also characteristic of the *trans*-epoxy-alcohol (7a) and its acetate (7b). The former gave only the *trans*-diaxial bromohydrin (26a) (3α-bromo-1α,2β-dihydroxy-5α-cholestane) whereas the latter gave the corresponding 1-monoacetate (26b). Both compounds were acetylated to the same diacetate (26c), which was subsequently debrominated with Raney nickel to 1α,2β-diacetoxy-5α-cholestane (27b); hydrolysis afforded the known diol (27a).[10]

The behaviour of the 3-substituted 1,2-epoxycholestanes is summarised in Scheme 3. The opening of the 1α,2α-epoxide system in the epoxy-alcohols (9a) and (12a) is stereospecific and follows the same pattern as in 1α,2α-epoxycholestane.[11] 1α,2α-Epoxy-3β-hydroxy-5α-cholestane (9a) afforded 2β-bromo-1α,3β-dihydroxy-5α-cholestane (28a), which was acetylated to give the diacetate (28b). The isomeric 1α,2α-epoxy-3α-hydroxy-5α-cholestane (12a) afforded 2β-bromo-1α,3α-dihydroxy-5α-cholestane (30a). In the presence of silica gel, the bromohydrin (30a) was reconverted into the original epoxy-alcohol (12a).

In the *trans*-epoxy-acetate (9b), the epoxide ring was displaced by the acetoxy-group *via* an acetoxonium ion, which was cleaved in both directions, to give an easily separable mixture of 3β-acetoxy-1α,2β-dihydroxy- (29a) and 2β-acetoxy-1α,3β-dihydroxy-5α-cholestane (29b). Both compounds afforded the same triacetate (29c). The same displacement takes place on treatment of compound (9b) with aqueous perchloric acid in acetone; however the cleavage of the acetoxonium intermediate is unidirectional, leading only to compound (29b). The *cis*-relationship between the functional groups in the epoxy-acetate (12b) prevents the participation of the acetate in the opening of the epoxide ring; the behaviour of this compound is unexceptional, yielding the 3α-acetoxy-2β-bromo-1α-hydroxy-derivative (30b). In the presence of silica gel, the starting epoxy-acetate (12b) was re-formed.

[6] M. Weissenberg, D. Lavie, and E. Glotter, *Tetrahedron*, 1973, **29**, 353.
[7] J. G. Ll. Jones and B. Marples, *J. Chem. Soc.* (C), 1970, 1188.
[8] S. J. Angyal, V. Bender, and J. H. Curtin, *J. Chem. Soc.* (*C*), 1966, 798, and references cited therein.
[9] See for instance T. Abe and A. Kambegawa, *Chem. and Pharm. Bull.* (*Japan*), 1973, **21**, 1295.
[10] C. W. Davey, E. L. McGinnis, J. M. McKeown, G. D. Meakins, M. W. Pemberton, and R. N. Young, *J. Chem. Soc.* (*C*), 1968, 2674.
[11] T. Nakano, M. Hasegawa, and C. Djerassi, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 465.

Opening of the 1β,2β-epoxide ring in the epoxy-alcohol (14a) afforded the same bromo-diol (31a) as obtained from 3α-hydroxy-5α-cholest-1-ene by treatment with *N*-bromoacetamide.[5] The stereoisomeric epoxy-alcohol (10a) affords a bromo-*cis*-glycol, which is quantitatively transformed into the corresponding bromo-acetonide (33). Whereas 3β-acetoxy-1β,2β-epoxy-5α-cholestane (10b) is stereospecifically transformed into the 3β-acetoxy-1α-bromo-2β-hydroxy-derivative (34), the



SCHEME 3 Reactions of 3-hydroxy(or -acetoxy)-1,2-epoxy-5α-cholestanes; reagents: i, HBr in Me_2CO; ii, $HClO_4$ in Me_2CO; iii, silica gel

stereoisomeric 3α-acetoxy-1β,2β-epoxy-5α-cholestane (14b) gives the *trans*-diaxial bromohydrin (31b), accompanied by small amounts of the acetoxy-acetonide (32). Compound (31b) is identical with that obtained by treatment of 3α-acetoxy-5α-cholest-1-ene (13) with *N*-bromoacetamide.[5] Compound (32), resulting from initial displacement of the epoxide by the neighbouring acetoxy-group, is an additional example of an acetonide formed from a *trans*-diequatorial glycol.

The products obtained from 1-hydroxy-(or -acetoxy)-2α,3α-epoxides reflect two contradictory tendencies: (*a*) the tendency to form diaxial products, involving nucleophilic attack at C(2) (α with respect to the neighbouring group) from the ' top ' of the molecule; (*b*) the tendency of the nucleophile to attack at C(3) (β with respect to the neighbouring group), resulting in *trans*-diequatorial products. This tendency is in agreement with similar observations concerning the electrophilic addition to α-substituted unsaturated compounds,[5,12] and with the opening of the epoxide ring in simple α-substituted epoxycyclohexanes.[12] The ratio of *trans*-diaxial to *trans*-diequatorial products may be substantially modified not only by changing the neighbouring group (hydroxy or acetoxy), but also by changing the solvent and the acidic reagent [for instance, formation of compound (22)]. An additional factor is encountered in the *trans*-epoxy-acetate (4b), in which the acetoxy-group is favourably disposed for internal displacement of the epoxide.

In 1-hydroxy-(or -acetoxy)-2β,3β-epoxides, the above two tendencies work in the same direction and result in stereospecific opening of the epoxide ring. In the epoxy-acetate (7b) the epoxide is not displaced by the acetoxy-group, although the latter is suitably disposed for this purpose.

In the 3-substituted 1α,2α-epoxides, attack at the β-position with respect to the neighbouring group would imply the sterically unfavourable approach of the nucleophile at C(1), from the ' top ' of the molecule. The reactions are therefore stereospecific, taking place by nucleophilic attack at the alternative position C(2), in agreement with the tendency to form diaxial products [in the *trans*-epoxy-acetate (9b) only the internal nucleophilic attack is operative]. As a general feature, the displacement of an epoxide by a neighbouring *trans*-oriented acetoxy-group seems to be strongly dependent upon the conditions of the reaction.[13]

The behaviour of the 3-substituted 1β,2β-epoxy-steroids is similar to that of the stereoisomeric 2β,3β-compounds; nucleophilic attack at C(1) from the rear of the molecule, leading to *trans*-diaxial products, is in agreement with the tendency to attack the epoxide at the β-position with respect to the neighbouring group, and is also sterically favourable. The only exception is the formation of the acetoxy-acetonide (32), *via* an intermediate acetoxonium ion.

EXPERIMENTAL

M.p.s were taken with a Fisher–Johns apparatus. Optical rotations were recorded with an automatic Perkin-Elmer polarimeter and refer to solutions in chloroform. N.m.r. spectra were determined with a Varian NV-14 instrument (60 MHz) for solutions in deuteriochloroform. Mass spectra were taken with a Varian MAT 731 instrument. T.l.c. was carried out on chromatoplates of silica gel G (Merck) and spots were developed with iodine vapour. Column chromatography was performed on silica gel 60 (Merck, 70—230 mesh). Petroleum refers to the fraction of b.p. 60—80 °C. Analyses were performed in the microanalytical laboratory of the Weizmann Institute, under the direction of Mr. R. Heller.

[12] J. G. Buchanan and Z. Sable, in ' Selective Organic Transformations,' ed. B. S. Thyagarajan, vol. 2, Wiley–Interscience, New York, 1972.

[13] T. H. Campion, G. A. Morisson, and J. B. Wilkinson, *J.C.S. Perkin I*, 1976, 2508; P. Vita-Finzi, Y. Kashman, E. Glotter, and D. Lavie, *Tetrahedron*, 1968, **24**, 5847.

Preparation of Epoxy-alcohols and Acetates.—The following compounds were prepared according to literature indications: compounds (2a and b);[1b] (9a and b);[6] (10a);[4,5] (12a and b);[6] and (14a).[5]

Treatment of 1β-*Hydroxy*-5α-*cholest*-2-*ene*[2,5] (3a) *with Peroxybenzoic Acid.*—To a solution of compound (3a) (7.5 g) in benzene (75 ml) a solution of perbenzoic acid in benzene (10% excess) was added. After 24 h at room temperature, the solution was washed with dilute sodium carbonate solution, then with water, dried (Na_2SO_4), and evaporated. The crude product (7.3 g) was chromatographed [silica gel (500 g)]. Elution with petroleum–ether (82 : 18) gave compound (5a) (1.5 g), followed by mixtures of (5a) and (4a) (150 mg) and then by compound (4a) (3.8 g). 2α,3α-*Epoxy*-1β-*hydroxy*-5α-*cholestane* (4a) had m.p. 115—117 °C (from methanol); $[\alpha]_D$ +18° (*c* 0.6); δ 0.76 [s, C(10)Me], 2.93 (d, *J* 4 Hz, 2β-H), 3.2 (narrow m, 3β-H), and 3.63 (narrow m, 1α-H) (Found: C, 80.5; H, 11.5. $C_{27}H_{46}O_2$ requires C, 80.55; H, 11.5%). Acetylation with acetic anhydride–pyridine overnight at room temperature gave 1β-*acetoxy*-2α,3α-*epoxy*-5α-*cholestane* (4b), m.p. 140—142 °C (from methanol); $[\alpha]_D$ +19.5° (*c* 0.6); δ 0.82 [s, C(10)Me], 2.01 (OAc), 2.55 (d, *J* 4 Hz, 2β-H), 3.0 (narrow m, 3β-H), and 4.58 (s, 1α-H) (Found: C, 78.5; H, 11.0. $C_{29}H_{48}O_3$ requires C, 78.3; H, 10.9%). 2β,3β-*Epoxy*-1β-*hydroxy*-5α-*cholestane* (5a) had m.p. 122—123 °C (from methanol); $[\alpha]_D$ +11° (*c* 1.2); δ 0.87 [s, C(10)Me], 3.17 (dd, *J* 4.5 and 3 Hz, 3α-H), 3.37 (dd, *J* 4.5 and 3 Hz, 2α-H), and 3.61 (dd, *J* 11 and 3 Hz; after addition of D_2O, d, *J* 3 Hz, 1α-H) (Found C, 80.5; H, 11.5. $C_{27}H_{46}O_2$ requires 80.55; H, 11.5%). Acetylation afforded 1β-*acetoxy*-2β,3β-*epoxy*-5α-*cholestane* (5b), m.p. 95—97 °C (from methanol); $[\alpha]_D$ −7.3° (*c* 0.5); δ 1.0 [s, C(10)Me], 2.11 (OAc), 3.28 (overlap, narrow m, 2α- and 3α-H), and 4.88 (d, *J* 2.5 Hz, 1α-H) (Found: C, 78.4; H, 11.05. $C_{29}H_{48}O_3$ requires C, 78.3; H, 10.9%).

Epoxidation of 1β-*Acetoxy*-5α-*cholest*-2-*ene* (3b).—Acetylation of the allylic alcohol (3a) with acetic anhydride–pyridine, overnight at room temperature, gave compound (3b), which showed one spot on a chromatoplate and was subjected without further purification to epoxidation as described above. The crude product (1 g) was chromatographed [silica gel (50 g)]. Elution with benzene gave unchanged material (3b) (180 mg), followed by 1β-acetoxy-2α,3α-epoxy-5α-cholestane (4b), m.p. 140—142 °C.

Oxidation of the Epoxy-alcohol (5a) *to* 2β,3β-*Epoxy*-5α-*cholestan*-1-*one* (6).—To a solution of compound (5a) (1 g) in acetone (400 ml), a solution of Jones reagent was added dropwise, with stirring, at *ca.* 20 °C. After 20 min, the excess of reagent was destroyed with a few drops of methanol, most of the solvent was removed, water was added, and the product was collected by filtration. 2β,3β-*Epoxy*-5α-*cholestan*-1-*one* (6) had m.p. 86—88 °C (from ethanol); $[\alpha]_D$ +139° (*c* 0.6); δ 1.20 [s, C(10)Me], 3.20 (d, *J* 4 Hz, 2α-H), and 3.51 (t, *J* 4 Hz, 3α-H) (Found: C, 81.0; H, 10.9. $C_{27}H_{44}O_2$ requires C, 80.95; H, 11.05%).

Reduction of Compound (6) *with Sodium Borohydride.*—To a solution of compound (6) (500 mg) in methanol (100 ml), sodium borohydride (250 mg) was added over a few min. The solution was stirred for 2 h at room temperature, then neutralised with dilute hydrochloric acid, and most of the solvent was removed under reduced pressure; water was added and the product was extracted with ethyl acetate. The solution was dried (Na_2SO_4), the solvent removed, and the product chromatographed [silica gel (200 g)]. Elution with petroleum–ether (85 : 15) gave compound (5a) (100 mg), followed by mixtures of (5a) and (7a) (75 mg), and then by 2β,3β-*epoxy*-1α-*hydroxy*-5α-*cholestane* (7a) (200 mg), m.p. 140—141 °C (from methanol); $[\alpha]_D$ +67° (*c* 0.7); δ 0.83 [s, C(10)Me], 3.16 (overlap, narrow m, 2α- and 3α-H), and 3.95 (narrow m, 1β-H) (Found: C, 80.3; H, 11.4. $C_{27}H_{46}O_2$ requires C, 80.55; H, 11.5%). Acetylation gave 1α-acetoxy-2β-3β-epoxy-5α-cholestane (7b) which could not be crystallised; δ 0.83 [s, C(10)Me], 2.02 (OAc), 3.0 (overlap, 2α- and 3α-H), and 5.05 (narrow, m, 1β-H).

Treatment of 3β-*Hydroxy*-5α-*cholest*-1-*ene* (8a) *with Perbenzoic Acid.*—Compound (8a) (1 g) in benzene (12 ml) was treated with a benzene solution of perbenzoic acid as described above. The crude product showed one spot on a chromatoplate; according to n.m.r. it was however a 1 : 2 mixture of compounds (9a)[6] and (10a).[4,5] Pure compound (10a) was prepared as described in ref. 5. Acetylation afforded 3β-acetoxy-1β,2β-epoxy-5α-cholestane, δ 0.93 [s, C(10)Me], 2.08 (OAc), 3.2 (overlap, narrow m, 1α- and 2α-H), and 5.1br (m, 3α-H). The compound was used without further purification in the reaction with hydrobromic acid.

Acetylation of 1β,2β-epoxy-3α-hydroxy-5α-cholestane[5] (14a) afforded the *acetate* (14b), m.p. 85—86 °C (from methanol); δ 0.86 [s, C(10)Me], 2.1 (OAc), 3.13 (overlap, narrow m, 1α- and 2α-H), and 5.31 (narrow m, 3β-H) (Found: C, 78.4; H, 10.9. $C_{29}H_{48}O_3$ requires C, 78.3; H, 10.9%).

General Procedure for the Reaction of Epoxy-alcohols and Acetates with Hydrobromic Acid.—To a solution of epoxy-alcohol or epoxy-acetate (300 mg) in acetone (250 ml), 45% hydrobromic acid in acetic acid (9 ml) was added, dropwise at 0 °C. The solution was kept for 1 h at this temperature, then neutralised with aqueous sodium hydrogen carbonate. Most of the solvent was removed, water was added, and the product was isolated by filtration or by extraction with dichloromethane. The crude product was then chromatographed or directly crystallised, as specified for each particular reaction.

Treatment of 2α,3α-*Epoxy*-1β-*hydroxy*-5α-*cholestane* (4a) *with Hydrobromic Acid.*—The crude product was chromatographed [silica gel (80 g)]. Elution with dichloromethane gave 3β-*bromo*-1β,2α-*isopropylidenedioxy*-5α-*cholestane* (18) (115 mg), m.p. 140—142 °C (from methanol); $[\alpha]_D$ +4.6° (*c* 0.9); δ 0.83 [s, C(10)Me], 1.4 (CMe_2), 3.08 (d, *J* 9 Hz, 1α-H), 3.66 (dd, *J* 9 and 10 Hz, 2β-H), and 4.0br (m, 3α-H) (Found: C, 68.7; H, 9.9%; M^+, 522/524. $C_{30}H_{51}BrO_2$ requires C, 68.8; H, 9.8%; *M*, 523.6). Further elution with benzene–ethyl acetate (7 : 3) gave 2β-*bromo*-1β,3α-*dihydroxy*-5α-*cholestane* (19a) (250 mg), m.p. 185—187 °C (from methanol); $[\alpha]_D$ +14.4° (*c* 0.6) (Found: C, 67.1; H, 9.8%; M^+, 482/484. $C_{27}H_{47}BrO_2$ requires C, 67.05; H, 9.8%; *M*, 483.5). Acetylation of compound (19a) with acetic anhydride–pyridine, overnight at room temperature, afforded 1β,3α-diacetoxy-2β-bromo-5α-cholestane (19b), that could not be crystallised; δ 1.18 [s, C(10)Me], 2.10 (2 OAc), 4.48 (m, $W_{\frac{1}{2}}$ 10 Hz, 2α-H), 4.75 (d, *J* 5 Hz, 1α-H), and 5.26 (m, $W_{\frac{1}{2}}$ 6 Hz, 3β-H).

Hydrolysis of the Isopropylidene Derivative (18).—A few crystals of toluene-*p*-sulphonic acid were added to a solution of compound (18) (50 mg) in methanol (20 ml). The solution was heated to reflux for 2 h, then cooled and neutralised with aqueous sodium hydrogen carbonate; most of the solvent was removed and the product (20a) was extracted with dichloromethane. 3β-Bromo-1β,2α-dihydroxy-5α-cholestane (20a) showed one spot on a chromatoplate

Acetylation as above afforded 2α-*acetoxy*-3β-*bromo*-1β-*hydroxy*-5α-*cholestane* (20b), m.p. 188—189 °C (from acetone–methanol); $[\alpha]_D$ −15° (*c* 0.6); δ 0.89 [s, C(10)Me], 2.06 (OAc), 3.31 (m; after addition of D_2O d, *J* 10 Hz, 1α-H), 3.83br (m, 3α-H), and 4.98 (dd, *J* 11 and 10 Hz, 2β-H) (Found: M^+, 524.287 8/526.286 0. $C_{29}H_{49}BrO_3$ requires *M*, 524.289 1/526.287 5).

Formation of 1β,2α-*Dihydroxy*-3β-*methoxy*-5α-*cholestane* (22).—A few crystals of toluene-*p*-sulphonic acid were added to a solution of compound (4a) (100 mg) in methanol (50 ml) and the solution was heated to reflux for 2 h. After neutralisation with aqueous sodium hydrogen carbonate most of the solvent was removed, water was added, and the *product* (22) was collected by filtration (80 mg) and purified by chromatography (elution with ethyl acetate); m.p. 120—121 °C (from hexane); $[\alpha]_D$ −9° (*c* 0.5); δ 0.86 [s, C(10)Me] and 3.4 (OCH_3) (Found: C, 77.1; H, 11.4. $C_{28}H_{50}O_3$ requires C, 77.35; H, 11.6%).

Formation of 1β,2α-*Isopropylidenedioxy*-3β-*methoxy*-5α-*cholestane* (23).—To a solution of compound (22) (25 mg) in acetone (25 ml), 45% hydrobromic acid in acetic acid (0.5 ml) was added and the solution was kept for 4 days at room temperature. After neutralisation with aqueous sodium hydrogen carbonate, the *product* (23) was isolated by filtration; m.p. 108—109 °C (from methanol); $[\alpha]_D$ −11.8° (*c* 0.5); δ 0.85 [s, C(10)Me], 1.36 (CMe_2), 3.06 (d, *J* 9 Hz, 1α-H), and 3.4 (OCH_3) (Found: C, 78.5; H, 11.6%; M^+, 474. $C_{31}H_{54}O_3$ requires C, 78.4; H, 11.5%; *M*, 474.7).

Treatment of 1β-*Acetoxy*-2α,3α-*epoxy*-5α-*cholestane* (4b) *with Hydrobromic Acid*.—The crude product was chromatographed [silica gel (100 g)]. Elution with dichloromethane gave compound (20b) (17 mg); elution with benzene–ethyl acetate (7 : 3) gave 1β-*acetoxy*-3β-*bromo*-2α-*hydroxy*-5α-*cholestane* (20c) (115 mg), m.p. 175—177 °C (from hexane); $[\alpha]_D$ −2° (*c* 0.9); δ 1.0 [s, C(10)Me], 2.06 (OAc), 3.5—4.2 (overlap, 2β- and 3α-H), and 4.75 (d, *J* 9 Hz, 1α-H) (Found: C, 66.4; H, 9.35; M^+, 524/526. $C_{29}H_{49}BrO_3$ requires C, 66.3; H, 9.4%; *M*, 525.6). Further elution with benzene–ethyl acetate (3 : 2) gave 1β-*acetoxy*-2β,3α-*dihydroxy*-5α-*cholestane* (21) (200 mg), m.p. 202—203 °C (from hexane); $[\alpha]_D$ +14° (*c* 0.7); δ 1.10 [s, C(10)Me], 2.10 (OAc), 3.9 (overlap m, 2α- and 3β-H), and 4.93 (d, *J* 4 Hz, 1α-H) (Found: C, 75.4; H, 11.0%; M^+, 462. $C_{29}H_{50}O_4$ requires C, 75.3; H, 10.9%; *M*, 462.7).

Acetylation of compound (20c) with acetic anhydride–pyridine, overnight at room temperature, afforded 1β,2α-diacetoxy-3β-bromo-5α-cholestane (20d), which could not be crystallised; δ 1.06 [s, C(10)Me], 1.13 and 1.20 (2 OAc), 4.0br (m, 3α-H), 4.78 (d, *J* 10 Hz, 1α-H), and 5.23 (t, *J* 10 Hz, 2β-H).

Conversion of Compound (20c) *into* (20b).—To a solution of compound (20c) (20 mg) in acetone (20 ml), 10 drops of hydrobromic acid in acetic acid were added. After 2 h at 0 °C the solution was worked up as described above and the product was isolated by extraction with dichloromethane. It showed two spots on a chromatoplate with the same R_F values as compounds (20b and c). The n.m.r. spectrum showed the presence of a *ca.* 1 : 1 mixture of these compounds.

Treatment of the Epoxy-acetate (4b) *with Perchloric Acid*.—To a solution in acetone (7 ml) of compound (4b) (100 mg), aqueous 7% perchloric acid (0.2 ml) was added. The solution was kept overnight at room temperature, then water was added, and the product (21) was collected by filtration; m.p. and mixed m.p. 202—203 °C.

Treatment of 2β,3β-*Epoxy*-1β-*hydroxy*-5α-*cholestane* (5a) *with Hydrobromic Acid*.—The crude product (320 mg) showed one spot on a chromatoplate and was purified by crystallisation. 3α-*Bromo*-1β,2β-*isopropylidenedioxy*-5α-*cholestane* (24) had m.p. 106—108 °C; $[\alpha]_D$ +93.7° (*c* 0.8); δ 0.83 [s, C(10)Me], 1.35 and 1.48 (CMe_2), and 3.75—4.4 (partially overlapped signals) (Found: C, 68.8; H, 9.6. $C_{30}H_{51}BrO_2$ requires C, 68.8; H, 9.8%).

Treatment of 1β-*Acetoxy*-2β,3β-*epoxy*-5α-*cholestane* (5b) *with Hydrobromic Acid*.—The crude product did not show detectable amounts of unchanged material (t.l.c. and n.m.r. evidence) and was chromatographed [silica gel (100 g)]. Elution with petroleum–ether (85 : 15) gave compound (5b) (50 mg), followed by 1β-*acetoxy*-3α-*bromo*-2β-*hydroxy*-5α-*cholestane* (25) (90 mg), m.p. 166—168 °C (from hexane); $[\alpha]_D$ +61.4° (*c* 0.5), identical with a minor component obtained by treatment of compound (3b) with *N*-bromoacetamide [5] (Found: C, 66.3; H, 9.5%; M^+ 524/526. Calc. for $C_{29}H_{49}BrO_3$: C, 66.3; H, 9.4%; *M*, 525.6).

Treatment of 2β,3β-*Epoxy*-1α-*hydroxy*-5α-*cholestane* (7a) *with Hydrobromic Acid*.—Attempted chromatography of the crude product through silica gel afforded mixtures of compound (7a) and 3α-bromo-1α,2β-dihydroxy-5α-cholestane (26a). When the crude product was kept for 48 h on silica gel, only the epoxy-alcohol (7a) was obtained. Acetylation of the crude compound (26a) afforded 1α,2β-diacetoxy-3α-bromo-5α-cholestane (26c), that could not be crystallised; δ 1.00 [s, C(10)Me], 2.06 and 2.10 (2 OAc), 4.25 (narrow m, 3β-H), 4.73 (narrow m, 1β-H), and 5.16 (narrow m, 2α-H).

Reduction of Compound (26c).—To a solution of this compound (50 mg) in ethanol (20 ml) 1 teaspoonful of Raney nickel was added, and the mixture was heated to reflux with stirring during 4 h. The catalyst was filtered off and the solvent was removed; the crude product (27b) (35 mg) showed one spot on a chromatoplate; it had δ 1.00 [s, C(10)Me], 2.08 (2 OAc), and 4.83 (overlap, narrow m, 1β- and 2α-H). Compound (27b) was hydrolysed by heating to reflux for 2 h with methanolic 2% potassium hydroxide (10 ml). After work-up, the crude product crystallised from methanol; 1α,2β-dihydroxy-5α-cholestane (27a) had m.p. 150—152 °C (lit.,[10] 151—152 °C).

Treatment of 1α-*Acetoxy*-2β,3β-*epoxy*-5α-*cholestane* (7b) *with Hydrobromic Acid*.—The crude 1α-acetoxy-3α-bromo-2β-hydroxy-5α-cholestane (26b) showed one spot on a chromatoplate, but could not be crystallised; δ 1.05 [s, C(10)Me], 2.08 (OAc), 4.25 (overlap, narrow m, 2α- and 3β-H), and 4.68 (narrow m, 1β-H). Acetylation with acetic anhydride and pyridine gave the diacetate (26c).

Treatment of 1α,2α-*Epoxy*-3β-*hydroxy*-5α-*cholestane* (9a) *with Hydrobromic Acid*.—The crude product (320 mg) showed one spot on a chromatoplate. 2β-*Bromo*-1α,3β-*dihydroxy*-5α-*cholestane* (28a) had m.p. 160—162 °C (from hexane); $[\alpha]_D$ +21.5° (*c* 1.1); δ 1.16 [s, C(10)Me], 3.9br (m, 3α-H), 4.11 (m, $W_{\frac{1}{2}}$ 9 Hz, 2α-H), and 4.53 (m, $W_{\frac{1}{2}}$ 8 Hz, 1β-H) (Found: C, 67.0; H, 9.6. $C_{27}H_{47}BrO_2$ requires C, 67.05; H, 9.8%). Acetylation gave 1α,3β-*diacetoxy*-2β-*bromo*-5α-*cholestane*, m.p. 103—105 °C (from methanol); $[\alpha]_D$ +20° (*c* 0.6); δ 1.25 [s, C(10)Me], 2.06 (2 OAc), 4.46 (narrow m, 2α-H), 4.96br (m, 3α-H), and 5.16 (d, *J* 3 Hz, 1β-H) (Found: C, 65.4; H, 9.05. $C_{31}H_{51}BrO_4$ requires C, 65.6; H, 9.05%).

Treatment of 3β-*Acetoxy*-1α,2α-*epoxy*-5α-*cholestane* (9b) *with Hydrobromic Acid*.—The crude product was chromatographed [silica gel (100 g)]. Elution with benzene–ethyl

acetate (4 : 1) gave 3β-*acetoxy*-1α,2β-*dihydroxy*-5α-*cholestane* (29a) (75 mg), m.p. 211—213 °C (from hexane); $[\alpha]_D$ +29° (*c* 0.8); δ 1.01 [s, C(10)Me], 2.08 (OAc), 3.83 and 4.06 (narrow m, 1β- and 2α-H), and 5.0br (m, 3α-H) (Found: C, 75.15; H, 10.7. $C_{29}H_{50}O_4$ requires C, 75.3; H, 10.9%). Further elution with benzene–ethyl acetate (7 : 3) gave 2β-*acetoxy*-1α,3β-*dihydroxy*-5α-*cholestane* (29b) (150 mg), m.p. 88—90 °C (from hexane); $[\alpha]_D$ +25° (*c* 0.6); δ 0.90 [s, C(10)Me], 2.08 (OAc), 3.83 (narrow m, 1β-H), 4.0br (m, 3α-H), and 5.05 (dd, *J* 4 and 3 Hz, 2α-H) (Found: C, 73.6; H, 10.9. $C_{29}H_{50}O_4$,0.5H_2O requires C, 73.8; H, 10.9%). Acetylation of compounds (29a) and (29b) afforded the same triacetate 1α,2β,3β-*triacetoxy*-5α-*cholestane* (29c), m.p. 150—152 °C (from methanol); $[\alpha]_D$ +13° (*c* 0.8); δ 1.02 [s, C(10)Me], 1.96 (OAc), 2.08 (2 OAc), 4.9 (d, *J* 3 Hz, 1β-H), 5.1br (m, 3α-H), and 5.13 (narrow m, 2α-H) (Found: C, 72.6; H, 10.0. $C_{33}H_{54}O_6$ requires C, 72.5; H, 9.95%).

Treatment of Compound (9b) *with Perchloric Acid.*—The reaction was performed as described for the epoxy-acetate (4b). The crude product was purified by chromatography; elution with benzene–ethyl acetate (4 : 1) gave compound (29b), m.p. and mixed m.p. 88—90 °C.

Treatment of 1α,2α-*Epoxy*-3α-*hydroxy*-5α-*cholestane* (12a) *with Hydrobromic Acid.*—The crude product did not show detectable amounts of unchanged material (t.l.c. and n.m.r. evidence). Chromatography [silica gel (75 g); elution with benzene–ethyl acetate (9 : 1)] afforded 2β-bromo-1α,-3α-dihydroxy-5α-cholestane [16] (30a) (150 mg), m.p. and mixed m.p. 173—175 °C (from methanol), followed by compound (12a) (140 mg).

Treatment of 3α-*Acetoxy*-1α,2α-*epoxy*-5α-*cholestane* (12b) *with Hydrobromic Acid.* The crude product showed one spot on a chromatoplate [on attempted chromatography the product was partially converted into the starting epoxy-acetate (12b)] and was purified by direct crystallisation. 3α-Acetoxy-2β-bromo-1α-hydroxy-5α-cholestane (30b) had m.p. 128—130 °C (from methanol); $[\alpha]_D$ +56° (*c* 0.8); δ 1.18 [s, C(10)Me], 2.08 (OAc), 3.9 (narrow m, 1β-H), 4.25 (narrow m, 2α-H), and 5.25 (narrow m, 3β-H). Acetylation gave 1α,3α-diacetoxy-2β-bromo-5α-cholestane [16] (30c), m.p. and mixed m.p. 167—168 °C (from methanol).

Treatment of 1β,2β-*Epoxy*-3α-*hydroxy*-5α-*cholestane* (14a) *with Hydrobromic Acid.*—The crude product showed one spot on a chromatoplate and was purified by direct crystallisation to give 1α-bromo-2β,3α-dihydroxy-5α-cholestane [5] (31a), m.p. and mixed m.p. 173—174 °C.

Treatment of 3α-*Acetoxy*-1β,2β-*epoxy*-5α-*cholestane* (14b) *with Hydrobromic Acid.*—The crude product was chromatographed [silica gel (100 g)]. Elution with petroleum–ether (85 : 15) gave 3α-*acetoxy*-1β,2α-*isopropylidenedioxy*-5α-*cholestane* (32) (40 mg), m.p. 158—159 °C (from methanol); $[\alpha]_D$ +31° (*c* 0.5); δ 0.85 [s, C(10)Me], 1.35 (CMe_2), 2.08 (OAc), 3.58 (very narrow m, 1α- and 2β-H), and 5.36 (narrow m, 3β-H) (Found: C, 76.6; H, 10.9%; M^+ − 15, 487; M^+ − 60, 442. $C_{32}H_{54}O_4$ requires C, 76.45; H, 10.85%; *M*, 502.7). Further elution with the same solvent gave 3α-acetoxy-1α-bromo-2β-hydroxy-5α-cholestane [5] (31b) (270 mg), m.p. and mixed m.p. 178—180 °C.

Treatment of 1β,2β-*Epoxy*-3β-*hydroxy*-5α-*cholestane* (10a) *with Hydrobromic Acid.*—The crude product (330 mg) showed one spot on a chromatoplate. 1α-*Bromo*-2β,3β-*isopropylidenedioxy*-5α-*cholestane* (33) had m.p. 123—125 °C (from methanol); $[\alpha]_D$ +68° (*c* 0.9); δ 1.15 [s, C(10)Me], 1.31 and 1.50 (CMe_2), 4.4br (m, 3α-H), 4.50 (d, *J* 2 Hz, 1β-H), and 4.66 (dd, *J* 5 and 2 Hz, 2α-H) (Found: C, 68.7; H, 9.8%; M^+, 522/524. $C_{30}H_{51}BrO_2$ requires C, 68.8; H, 9.8%; *M*, 523.6).

Treatment of 3β-*Acetoxy*-1β,2β-*epoxy*-5α-*cholestane* (10b) *with Hydrobromic Acid.*—Direct crystallisation of the crude product (320 mg) gave 3β-*acetoxy*-1α-*bromo*-2β-*hydroxy*-5α-*cholestane* (34), m.p. 135—138 °C (from methanol); $[\alpha]_D$ +45° (*c* 0.8); δ 1.18 [s, C(10)Me], 2.06 (OAc), 4.28 (d, *J* 3 Hz, 1β-H), 4.4 (narrow m, 2α-H), and 5.4br (m, 3α-H) (Found: C, 66.45; H, 9.55. $C_{29}H_{49}BrO_3$ requires C, 66.3; H, 9.4%).

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