Neighbouring Group Effects in Epoxide Ring Opening; *cis*-Epoxy-alcohols

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The relative importance of polar and steric influences on the course of the acid-catalysed opening of several epoxycholestanes bearing a vicinal *cis*-hydroxy- or -acetoxy-group has been investigated.

We have previously [1] reported that treatment of 3β,4β-epoxy-5β-cholestan-5-ol (1) and of 3α,4α-epoxy-5α-cholestan-5-ol (6) with lithium aluminium hydride affords stereospecifically the products of 'diequatorial' epoxide ring opening, namely 5β-cholestane-4β,5-diol and 5α-cholestane-4α,5-diol, respectively.[2] The behaviour of these *cis*-epoxy-alcohols is in contrast with that of the corresponding 3α,4α-epoxy-5α- and 3β,4β-epoxy-5β-cholestane.[3] The reversal of stereospecificity of the epoxide ring opening was explained [1] in terms of participation of the neighbouring hydroxy-group through the formation of a cyclic aluminium hydride salt which is subsequently attacked from the less hindered side by a second molecule of metal hydride. An alternative explanation is that the preferred attack at C(3) is the result of previous formation of a C(5)–$OAlH_3$ salt, as proposed for a similar reduction of a 9β,10β-epoxy-6β-hydroxy-steroid.[4]

We now report the behaviour of the same substrates (1) and (6) in the presence of hydrobromic or hydroiodic acid, *i.e.* under conditions of electrophilic assistance to the opening of the epoxide ring; [5] the investigation has been further extended to two other *cis*-epoxy-alcohols, (14) and (20), possessing secondary hydroxy-groups vicinal to di- and tri-substituted epoxide systems.

The reaction between 3β,4β-epoxy-5β-cholestan-5-ol (1) and hydrobromic acid in acetone proceeds with stereospecific cleavage of the C(3)–O bond and results in a mixture of the diequatorial hydroxy-bromohydrin (2a) and the corresponding bromo-acetonide (3). Compound (2a) was identified by formation of a monoacetate (2b) and subsequent reductive debromination with Raney nickel to give the known diol monoacetate (4).[1,6] Hydrolysis of compound (3) afforded the hydroxy-bromohydrin (2a). Upon treatment with hydroiodic acid, compound (1) gave only the diequatorial hydroxy-iodohydrin (5a), also characterised as the monoacetate (5b). The structures assigned to these compounds are unequivocally supported by their n.m.r. spectra [broad, unresolved multiplet at δ 4.29 for 3β-H and 4α-H in (5a); multiplet at δ 4.43 for 3β-H and doublet at δ 5.61 (J 10.5 Hz) for 4α-H in (5b)].

In contrast to the stereospecificity of the above reactions, the acid-catalysed opening of the epoxide ring in 3α,4α-epoxy-5α-cholestan-5-ol (6) proceeds by attack at either C(3) or C(4), to give diaxial and diequatorial products in practically equal amounts. Treatment of (6) with hydrobromic acid afforded, following chromatography on silica gel, 3β-bromo-5α-cholestane-4α,5-diol (7a) (the diequatorial product) and 4α,5-epoxy-5α-cholestan-3α-ol (9a),[7] formed through the intermediacy of 4β-bromo-5α-cholestane-3α,5-diol (8) (the diaxial product, which was not isolated). Compound (7a) was identified by acetylation (7b) and subsequent debromination to give the *cis*-diol monoacetate (10).[1,6] A similar reaction with hydroiodic acid afforded the hydroxy-iodohydrin (11) (the diequatorial product) and cholesta-3,5-diene (13), arising by spontaneous elimination of H_2O and HOI from the intermediate diaxial hydroxy-iodohydrin (12) under the acidic conditions. Such eliminations have already been encountered in diaxial iodohydrins.[8a,b]

The reason for the different behaviour of compounds (1) and (6) may be related to two factors: (*a*) the polar influence of the hydroxy-group leading to reinforcement of the nearby C(4)–O bond, which should be operative in both epoxy-alcohols, and (*b*) the different degree of steric hindrance to the attack of the nucleophile.

An additional model for studying neighbouring group effects is 2α,3α-epoxy-5α-cholestan-1α-ol (14a), which was prepared [9] by oxidation of 5α-cholest-2-en-1α-ol [10] with perbenzoic acid. While cleavage of the epoxide ring in 2α,3α-epoxy-5α-cholestane with various reagents invariably yields diaxial products,[11] the neighbouring *cis*-oriented hydroxy-group in (14a) leads to the loss of stereospecificity of nucleophilic attack. Treatment of compound (14a) with hydrobromic acid afforded a mix-

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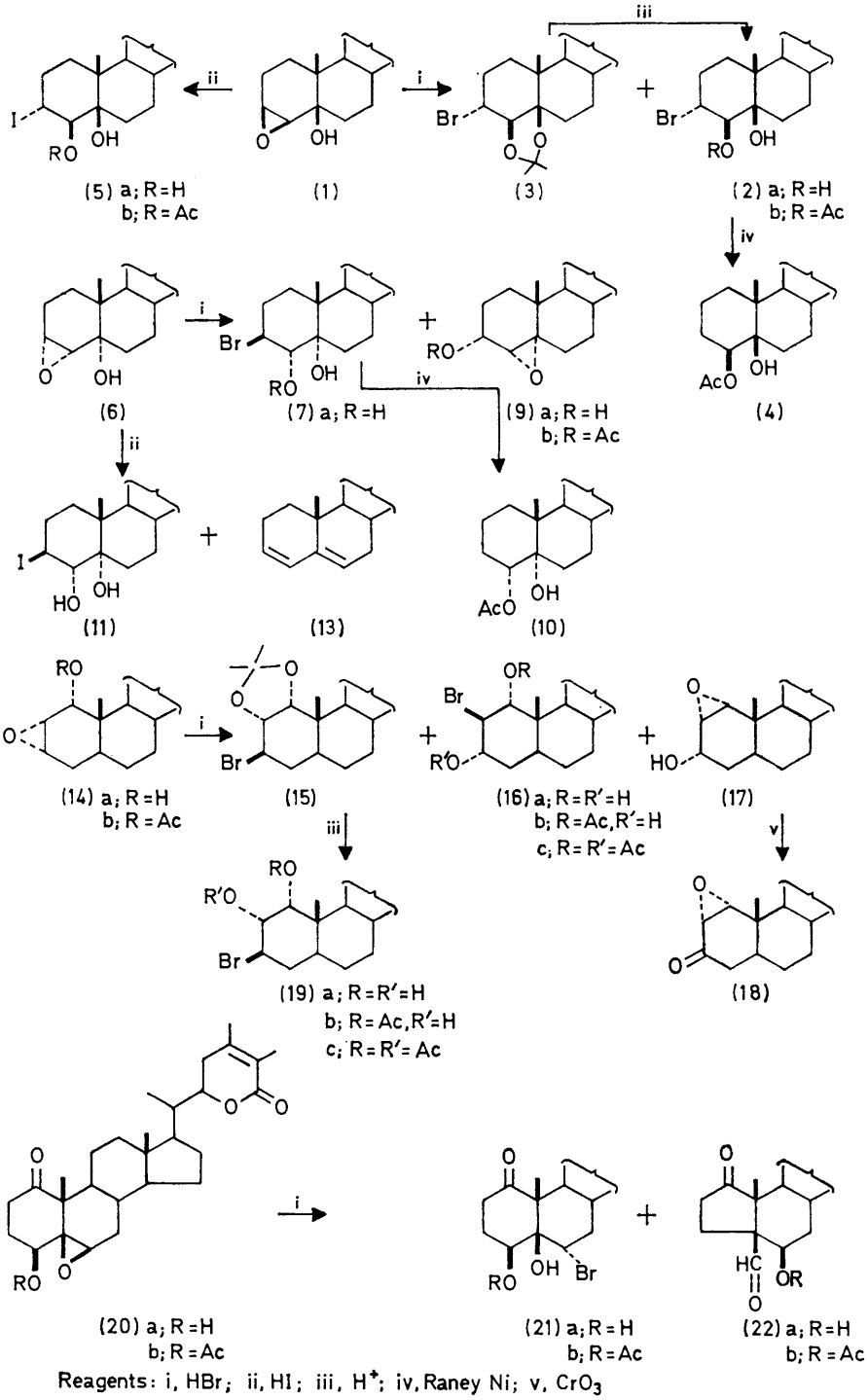
ture containing the bromo-acetonide (15) [cleavage of the C(3)–O bond] and the hydroxy-bromohydrin (16a) [cleavage of the C(2)–O bond]. The latter was partially converted during chromatography into the epoxy-alcohol (17), identified by comparison with an authentic sample [12] and by oxidation to 1α,2α-epoxy-5α-cholestan-3-one (18). Compound (16a) was converted quantitatively into (17) by treatment with base. The identification of the bromo-diol (16a) is based on its mode of formation as well as on n.m.r. data [in (16a), narrow multiplet at δ 3.99 for 1β-H and a slightly broader multiplet at δ 4.3 for 2α-H and 3β-H; in the corresponding diacetate (16c), narrow doublet at δ 4.97 ($J < 1.5$ Hz) for 1β-H, narrow double doublet at δ 4.12 (J 2 and <1.5



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Hz) for 2α-H, and narrow multiplet at δ 5.16 for 3β-H; upon irradiation of the δ 4.12 signal, the δ 4.97 doublet collapses to a singlet].

The bromo-acetonide (15) on acid-catalysed hydrolysis gave the bromo-diol (19a), also characterised as the di-acetate (19c) [n.m.r. data: in (19a) broad multiplet at δ 3.87 for the overlap of 1β-H and 2β-H and broad multiplet at δ 4.25 for 3α-H; in (19c) the two-proton multiplet is shifted to δ 5.2, while the 3α-H multiplet remains almost unchanged (δ 4.21)]. The ratio of compound (15) to (16) + (17) is 1.1 : 1.

The reaction with the epoxy-acetate (14b) gave a mixture of acetoxy-bromohydrins. The ratio between the diaxial bromohydrin (16b) and the diequatorial bromohydrin (19b) is 1 : 2.5. The compounds were isolated following acetylation as the bromo-acetates (16c) and (19c), identical with the products of acetylation of the bromo-diols (16a) and (19a).

The fact that the epoxy-acetate (14b) affords a larger amount of diequatorial product than the corresponding epoxy-alcohol (14a) cannot be attributed to a steric factor since the ' top ' of the molecule is equally accessible to the nucleophile in both compounds. The difference may be assigned to the degree of reinforcement of the C(2)–O bond by the neighbouring substituent. Such an effect, which is controlled by polar and stereoelectronic factors, is more substantial when the substituent is acetoxy rather than hydroxy. This assumption is supported by the distribution of products of epoxide ring opening in the last model, having a 5β,6β-epoxy-4β-hydroxy- or -4β-acetoxy-system. The reactions were performed with derivatives (20a and b) of the naturally occurring steroidal lactone withaferin A.[13] Treatment of the epoxy-acetate (20b) with hydrobromic acid in acetic acid,[13] as well as in acetone, afforded stereospecifically the *trans*-diequatorial bromohydrin (21b) [maximum reinforcement of the C(5)–O bond next to the acetate group]. After similar treatment, the epoxy-alcohol (20a) gave an equimolecular mixture of the bromohydrin (21a) [cleavage of the C(6)–O bond] and the rearrangement product (22) [14] [formed by initial cleavage of the C(5)–O bond]. The same compound (22) was obtained by treatment of (20a) with sulphuric acid in acetic acid.[14]

The behaviour of the related *trans*-epoxy-alcohols and -acetates will be reported subsequently.

EXPERIMENTAL

M.p.s were taken with a Fisher–Johns apparatus. Optical rotations were recorded with an automatic Perkin-Elmer 141 polarimeter and refer to solutions in chloroform. I.r. spectra were recorded on a Perkin-Elmer Infracord 137 spectrophotometer and refer to solutions in chloroform; u.v. spectra were recorded on a Cary 14 instrument for solutions in ethanol; n.m.r. spectra were determined on a Varian A60 instrument for *ca.* 5% solutions in deuteriochloroform containing tetramethylsilane as internal standard. T.l.c. was carried out on plates of silica gel G (Merck) and spots were developed with iodine vapour. Column chromatography was done on silica gel (Merck). Mass spectra were taken under the direction of Dr. Z. Zaretskii with an Atlas CH4 instrument. Analyses were performed in the microanalytical laboratory of the Weizmann Institute, under the direction of Mr. R. Heller.

Treatment of 3β,4β-*Epoxy*-5β-*cholestan*-5-*ol* (1) *with Hydrobromic Acid.*—To a solution of compound (1) (200 mg) in acetone (200 ml), 45% hydrobromic acid in acetic acid (6 ml) was added dropwise; the mixture was kept for 1 h at room temperature, then neutralised with aqueous sodium hydrogen carbonate. Most of the solvent was removed, water was added, and the product was extracted with chloroform and chromatographed. Elution with hexane–ether (9.5 : 0.5) afforded 3α-*bromo*-4β,5-*isopropylidenedioxy*-5β-*cholestane* (3) (120 mg), m.p. 102—104° (from methanol), $[\alpha]_D$ +0.6° (*c* 0.5); δ 1.00 [s, C(10)Me], 1.50 and 1.58 (Me_2C), and 4.25 (m, 3-H + 4-H) (Found: C, 68.6; H, 9.6; Br, 15.4. $C_{30}H_{51}BrO_2$ requires C, 68.8; H, 9.8; Br, 15.3%).

Elution with hexane–ether (9 : 1) afforded 3α-*bromo*-5β-*cholestane*-4β,5-*diol* (2a) (90 mg), m.p. 160—162° (from methanol), $[\alpha]_D$ +10° (*c* 0.6); δ 0.96 [s, C(10)Me] and 4.23 (m, 3-H + 4-H) (Found: C, 66.9; H, 9.7; Br, 16.5. $C_{27}H_{47}BrO_2$ requires C, 67.1, H, 9.8; Br, 16.5%).

Hydrolysis of the Isopropylidene Derivative (3).—A few crystals of toluene-*p*-sulphonic acid were added to a solution of compound (3) (60 mg) in methanol (20 ml). The solution was kept for 3 days at room temperature, then neutralised with sodium hydrogen carbonate; most of the solvent was removed and the product was extracted with chloroform and crystallised from methanol. It was identical with compound (2a).

Reductive Debromination of 3α-*Bromo*-5β-*cholestane*-4β,5-*diol* 4-*Acetate* (2b).—Acetylation of compound (2a) with acetic anhydride in pyridine, overnight at room temperature, afforded the *monoacetate* (2b), m.p. 133—134° (from methanol), $[\alpha]_D$ +29.5° (*c* 0.4); δ 0.96 [s, C(10)Me], 4.35 (m, 3-H), and 5.62 (d, *J* 10 Hz, 4-H) (Found: C, 66.2; H, 9.4; Br, 15.2. $C_{29}H_{49}BrO_3$ requires C, 66.1; H, 9.2; Br, 15.4%).

To a solution of (2b) (70 mg) in absolute ethanol (30 ml) 2 teaspoonfuls of Raney nickel were added and the mixture was heated to reflux with stirring during 6 h. The catalyst was filtered off, the solvent removed, and the residue dissolved in benzene, filtered through silica gel, and crystallised from methanol to give the hydroxy-acetate (4), m.p. and mixed m.p. 115—117°.[1,6]

Treatment of Compound (1) *with Hydroiodic Acid.*—To a solution of the epoxy-alcohol (1) (150 mg) in acetone (60 ml) and chloroform (6 ml), 57% hydroiodic acid (6 ml) was added. After stirring overnight at room temperature, water was added and the product was extracted with chloroform; the solution was washed with dilute sodium thiosulphate solution, and then with water. The crude product was chromatographed; elution with hexane–ether (9 : 1) gave 3α-*iodo*-5β-*cholestane*-4β,5-*diol* (5a) (160 mg), m.p. 174—176° (from methanol), $[\alpha]_D$ +4° (*c* 0.7); δ 0.94 [s, C(10)Me] and 4.29 (m, 3-H + 4-H) (Found: C, 61.1; H, 9.0. $C_{27}H_{47}IO_2$ requires C, 61.1; H, 8.8%). The *monoacetate* (5b) had m.p. 145—147° (from methanol), $[\alpha]_D$ +10° (*c* 0.7); δ 0.96 [s, C(10)Me], 4.43 (m, 3-H), and 5.61 (d, *J* 10.5 Hz, 4-H) (Found: C, 61.0; H, 8.7. $C_{29}H_{49}IO_3$ requires C, 60.8; H, 8.6%).

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[14] D. Lavie, Y. Kashman, E. Glotter, and N. Danieli, *J. Chem. Soc.* (*C*), 1966, 1757.

Treatment of 3α,4α-*Epoxy*-4α-*cholestan*-5-*ol* (6) *with Hydrobromic Acid*.—The reaction was carried out as described for compound (1), but at 5—10 °C. Following chromatography two products were isolated. Elution with hexane–ether (9.5 : 0.5) gave 3β-*bromo*-5α-*cholestane*-4α,5-*diol* (7a) (109 mg), m.p. 152—153° (from methanol), $[\alpha]_D$ +48.5° (*c* 0.5); δ 1.00 [s, C(10)Me], 3.73 (d, *J* 10 Hz, 4-H), and 4.42 (m, 3-H) (Found: C, 67.3; H, 9.7; Br, 16.4. $C_{27}H_{47}BrO_2$ requires C, 67.1; H, 9.8; Br, 16.5%). Elution with hexane–ether (8 : 2) gave 4α,5-epoxy-5α-cholestan-3α-ol (9a) (104 mg), m.p. 91—92° (from methanol), $[\alpha]_D$ +85° (*c* 1.0); δ 1.01 [s, C(10)Me], 3.2 (d, *J* 4.5 Hz, 4-H), and 4.07 (m, 3-H).

The *monoacetate* (7b) had m.p. 202—204°, $[\alpha]_D$ +64.7° (*c* 0.4); δ 1.07 [s, C(10)-Me], 4.41 (m, 3-H), and 5.30 (d, *J* 10 Hz, 4-H) (Found: C, 66.2; H, 9.2; Br, 15.15. $C_{29}H_{49}BrO_3$ requires C, 66.3; H, 9.4; Br, 15.2%). The monoacetate (9b) had m.p. 92—94° (lit.,[15] 91—92°); δ 1.02 [s, C(10)Me], 3.21 (d, *J* 4 Hz, 4-H), and 5.18 (m, 3-H) (Found: M^+, 444. $C_{29}H_{48}O_3$ requires *M*, 444.6).

Reductive Debromination of Compound (7b).—The reaction was carried out as described for compound (2b). The product was identical with an authentic sample of 5α-cholestane-4α,5-diol 4-acetate.[1,6]

Treatment of Compound (6) *with Hydroiodic Acid*.—The reaction was performed with compound (6) (100 mg) as described for (1). Following chromatography, two products were separated. Elution with hexane gave cholesta-3,5-diene (13) (47 mg), m.p. 76—78° (lit.,[16] 79°); δ 0.94 [s, C(10)Me] and 5.65 (m, 3-H, 4-H, and 6-H); $\lambda_{max.}$ 228 (ε 18 100), 235 (19 200), and 243 nm (12 300). Elution with hexane–ether (9.5 : 0.5) gave 3β-*iodo*-5α-*cholestane*-4α,5-*diol* (11), m.p. 156—158° (decomp.), $[\alpha]_D$ +55° (*c* 0.5); δ 1.00 [s, C(10)Me], 3.75 (d, *J* 10 Hz, 4-H), and 4.4 (m, 3-H) (Found: C, 61.3; H, 8.75. $C_{27}H_{47}IO_2$ requires C, 61.1; H, 8.9%).

2α,3α-*Epoxy*-5α-*cholestan*-1α-*ol* (14a).—Reduction of 1α,2α-epoxy-5α-cholestan-3-one with hydrazine hydrate according to ref. 17 afforded 5α-cholest-2-en-1α-ol, m.p. 100—103°. To a solution of the latter (1 g) in benzene (50 ml), a solution of perbenzoic acid in benzene was added (10% excess). After 24 h at room temperature, the excess of reagent was removed by washing with aqueous 5% sodium carbonate solution, then with water; the *product* (14a) crystallised from methanol; m.p. 94—95°, $[\alpha]_D$ +71° (*c* 1.0); δ 0.68 [s, C(10)Me], 3.4 (m, 1-H and 3-H), and 3.74 (dd, 2-H) (Found: C, 80.4; H, 11.4. $C_{27}H_{46}O_2$ requires C, 80.5; H, 11.5%). The acetate (14b) could not be induced to crystallise; δ 0.78 [C(10)Me], 3.29 (m, 3-H), 3.48 (dd, *J* 3.5 and 5 Hz, 2-H), and 4.75 (d, *J* 5 Hz, 1-H), M^+ 444.

Treatment of Compound (14a) *with Hydrobromic Acid*.—The reaction was performed with (14a) (250 mg) at −5 °C as described for other epoxy-alcohols. Elution of the chromatographic column with hexane–ether (9.5 : 0.5) gave 3β-*bromo*-1α,2α-*isopropylidenedioxy*-5α-*cholestane* (15) (150 mg), m.p. 118—120°, $[\alpha]_D$ −7.7° (*c* 0.4); δ 0.90 [s, C(10)Me], 1.35 and 1.53 (CMe_2), and 4.08 (m, 1-H, 2-H, and 3-H) (Found: C, 69.0; H, 9.7; Br, 15.25. $C_{30}H_{51}BrO_3$ requires C, 68.8; H, 9.8; Br, 15.25%). Elution with hexane–ether (9 : 1) afforded 2β-bromo-5α-cholestane-1α,3α-diol (16a) (100 mg), m.p. 173—175° (from methanol), $[\alpha]_D$ +31° (*c* 0.6); δ 1.15 [s, C(10)Me], 3.99 (narrow m, 1-H), and 4.3 (m, 2-H and 3-H) (Found: C, 67.2; H, 9.65; Br, 16.4. $C_{27}H_{47}BrO_2$ requires C, 67.1; H, 9.8; Br, 16.5%). The *diacetate* (16c) had m.p. 167—168° (from methanol), $[\alpha]_D$ +35.5° (*c* 0.8); δ 1.21 [s, C(10)Me], 4.12 (dd, 2-H), 4.97 (d, 1-H), and 5.16 (m, 3-H) (Found: C, 65.3; H, 8.8; Br, 14.2. $C_{31}H_{51}BrO_4$ requires C, 65.6; H, 9.05; Br, 14.1%). Further elution with hexane–ether (8 : 2) gave 1α,2α-epoxy-5α-cholestan-3α-ol (17) (15 mg), m.p. 133—135° (lit.,[12] 134—135°), $[\alpha]_D$ +7.5° (*c* 1.0); δ 0.84 [s, C(10)Me], 3.23 (d, *J* 4 Hz, 1-H), 3.36 (t, *J* 4 Hz, 2-H), and 4.05 (m, 3-H) (Found: C, 80.7; H, 11.4. Calc. for $C_{27}H_{46}O_2$: C, 80.55; H, 11.5%).

Hydrolysis of the Isopropylidene Derivative (15).—The reaction was carried out with compound (15) (120 mg) as described for (3). The crude product crystallised from methanol to give 3β-*bromo*-5α-*cholestane*-1α,2α-*diol* (19a), m.p. 150—152°, $[\alpha]_D$ *ca.* 0° (*c* 1.0); δ 0.85 [s, C(10)Me], 3.87 (m, 1-H and 2-H), and 4.25br (m, 3-H) (Found: C, 67.2; H, 9.65; Br, 16.4. $C_{27}H_{47}BrO_2$ requires C, 67.1; H, 9.8; Br, 16.5%).

The diacetate (19c) had m.p. 140—142°, $[\alpha]_D$ +24.5° (*c* 0.8); δ 0.99 [s, C(10)Me], 4.21br (m, 3-H), and 5.2 (m, 1-H and 2-H).

Oxidation of Compound (17) *to* 1α,2α-*Epoxy*-5α-*cholestan*-3-*one* (18).—The oxidation was performed with Jones reagent in acetone, at 5—10 °C. The excess of reagent was destroyed with a few drops of methanol, the solvent was removed, and the crude product, in hexane solution, was filtered through silica. The product had m.p. and mixed m.p. 125—127° (from ethanol–ether).

Preparation of the Epoxy-alcohol (17) *by Treatment of Compound* (16a) *with Base*.—To a solution of (16a) (50 mg) in methanol (30 ml), a methanolic 2% solution of sodium methoxide (30 ml) was added. After 24 h at room temperature, the solution was neutralised with dilute hydrochloric acid (1 : 4), most of the solvent was removed, and the product was extracted with chloroform. The crude product (40 mg) crystallised from methanol; m.p. and mixed m.p., 133—135°.

Treatment of 2α,3α-*Epoxy*-5α-*cholestan*-1α-*yl Acetate* (14b) *with Hydrobromic Acid*.—The reaction was performed with (14b) (200 mg) as described above. The crude product, which showed only one spot on a chromatoplate, was acetylated and then chromatographed. Elution with hexane–ether (9.5 : 0.5) afforded a product (180 mg) identical with the bromo-diacetate (19c). Further elution with the same solvent gave a second product (70 mg), identical with the bromo-diacetate (16c).

Treatment of 2,3-*Dihydro*-27-*deoxywithaferin A* (20a) *with Hydrobromic Acid*.—The crude product obtained as described for similar reactions was acetylated to give a mixture of (21b) and (22b), which was separated on a column of silica gel H (Merck) by elution with benzene–ethyl acetate (1 : 4). The bromohydrin (21b) and the rearrangement product (22b) were identified by comparison with authentic samples.[13,14] The ratio (*ca.* 1 : 1) was determined by integration of the n.m.r. spectrum of the mixture before chromatography. When the monoacetate (20b) was treated with hydrobromic acid in acetone, only the bromohydrin (21b) [13] was obtained.

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