Neighbouring Group Effects in the Addition of Hypobromous Acid to Unsaturated Steroids

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The reaction of the stereoisomeric 3-hydroxy(or acetoxy)-5α-cholest-1-enes and 1-hydroxy(or acetoxy)-5α-cholest-2-enes with *N*-bromoacetamide was investigated. With one exception [formation of the bromo-diol (15a)], the reactions take place by initial formation of an α-oriented bromonium ion: the 2α,3α-ions are preferentially attacked at C(3) (β with respect to the neighbouring group), leading to *trans*-diequatorial products, whereas the 1α,2α-bromonium ions are invariably attacked at C(2) (α with respect to the neighbouring group), leading to diaxial products. In two instances, internal nucleophilic displacement by appropriately oriented hydroxy-groups leads to bromo-epoxides [compounds (3) and (16)].

THE addition of electrophilic agents to double bonds in steroidal molecules is controlled by electronic, polar, and steric factors, leading in most instances to *trans*-diaxial products. It is well known that addition of hypobromous acid to the disubstituted double bond of 5α-cholest-1-ene [1] and -2-ene [2] leads to the *trans*-diaxial bromohydrins (1α-bromo-2β-hydroxy- and 3α-bromo-2β-hydroxy-derivatives, respectively). In both instances, the initial electrophilic attack takes place from the less hindered, rear side of the molecule, through the transient formation of an α-oriented bridged bromonium ion, that is subsequently attacked in an antiparallel mode by the available nucleophilic hydroxy-group. In 5,6β-diacetoxy-5α-cholest-2-ene,[3] the ' top ' of the molecule is more accessible for the initial formation of the bromonium ion, and consequently the *trans*-diaxial 2β-bromo-3α-hydroxy-derivative is obtained. The conflict between electronic and steric factors is well illustrated in the addition of hypobromous acid to cholesteryl acetate, leading [4] to the 5α-bromo-6β-hydroxy-derivative (major product, anti-Markovnikov-type attack of an initial α-oriented bromonium ion). The influence of suitably placed neighbouring groups on the electrophilic addition to double bonds has been reviewed.[5a,b]

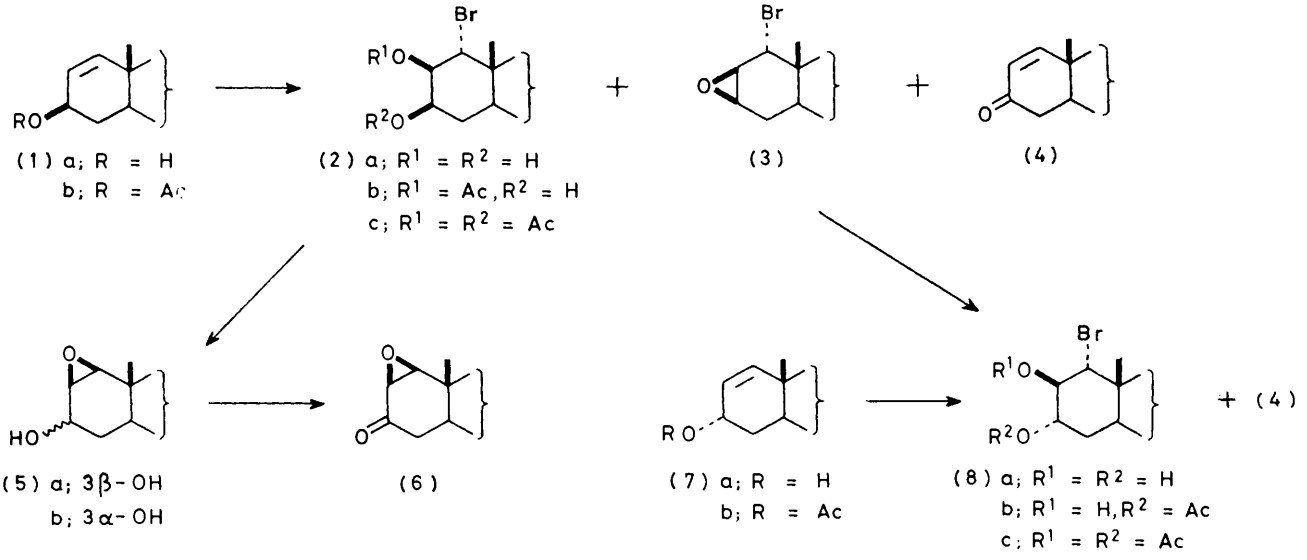
We now report the results obtained by addition of hypobromous acid to several steroidal allylic alcohols and acetates possessing disubstituted double bonds (Δ^1 and Δ^2). The reagent was generated from *N*-bromoacetamide in dioxan–water acidified with perchloric acid.

3β-Hydroxy-5α-cholest-1-ene (1a) afforded 1α-bromo-2β,3β-dihydroxy-5α-cholestane (2a) [1] (*trans*-diaxial bromohydrin, major product), accompanied by 1α-bromo-2β,3β-epoxy-5α-cholestane (3) and 5α-cholest-1-en-3-one (4).[1] The structure (2a) is supported by formation of the diacetate (2c) and by treatment with base to give 1β,2β-epoxy-3β-hydroxy-5α-cholestane (5a).[1] The structure (3), characterised in the n.m.r. by a doublet (J 2 Hz) for 1β-H, a double doublet (J 4 and 2 Hz) for 2α-H, and a narrow multiplet for 3α-H, was ascertained by treatment with aqueous perchloric acid in acetone, leading to the quantitative formation of 1α-bromo-2β,3α-dihydroxy-

[1] H. B. Henbest and R. A. L. Wilson, *J. Chem. Soc.*, 1959, 4136.
[2] T. Nakano, M. Hasegawa, and C. Djerassi, *Chem. and Pharm. Bull.* (*Japan*), 1963, **11**, 465.
[3] P. Tsui and G. Just, *Canad. J. Chem.*, 1973, **51**, 3502.
[4] B. W. Cubberley and B. A. Marples, *J.C.S. Perkin*, 1974, 9, and references cited therein.
[5] (*a*) D. N. Kirk and M. P. Hartshorn, ' Steroid Reaction Mechanisms,' Elsevier, Amsterdam 1968, ch. 3.6; (*b*) J. G. Buchanan and Z. Sable, in ' Selective Organic Transformations,' ed. B. S. Thyagarajan, vol. 2, Wiley–Interscience, New York, 1972.

5α-cholestane (8a), alternatively obtained from compound (7a) by treatment with *N*-bromoacetamide.

Since the presence of a free hydroxy-group in compound (1a) is a necessary condition for the formation of compounds (3) and (4), the corresponding allylic acetate

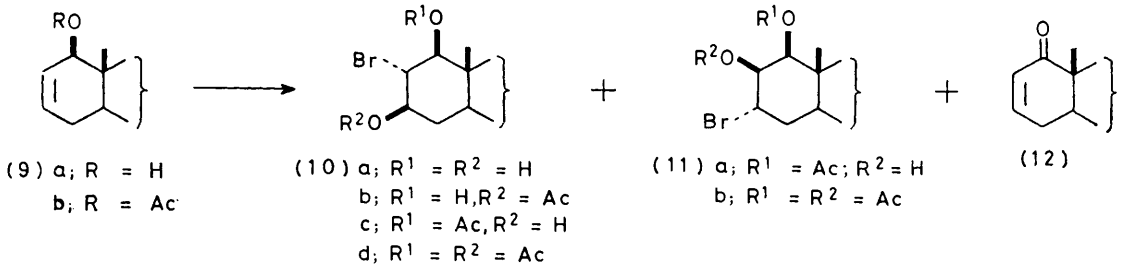


(1b) was expected to give only the diaxial bromohydrin. 3β-Acetoxy-5α-cholest-1-ene (1b) afforded however almost quantitatively 2β-acetoxy-1α-bromo-3β-hydroxy-5α-cholestane (2b), resulting from participation of the 3β-acetate in the displacement of the initial α-oriented bromonium ion, *via* an acetoxonium intermediate. Acetylation of compound (2b) gave the same diacetate (2c) as above.

3α-Hydroxy-5α-cholest-1-ene (7a) was obtained from the corresponding acetate (7b) [6] by treatment with a catalytic amount of barium methoxide in methanolic solution. In the presence of *N*-bromoacetamide, the allylic alcohol (7a) afforded a mixture of 1α-bromo-2β,3α-dihydroxy-5α-cholestane (8a) (*trans*-diaxial bromohydrin) and the enone (4). As expected, the enone (4), resulting from simple oxidation of compounds (1a) and (7a), is formed in larger proportion from the quasiaxial allylic alcohol (7a), than from the stereoisomeric quasi-equatorial allylic alcohol (1a).

The main product from 3α-acetoxy-5α-cholest-1-ene (7b) was the diaxial bromohydrin [3α-acetoxy-1α-bromo-2β-hydroxy-5α-cholestane (8b)], identified by formation of the same diacetate (8c) as obtained from compound (8a), and by treatment with base, leading to the hitherto unknown 1β,2β-epoxy-3α-hydroxy-5α-cholestane (5b). The relationship between the epoxy-alcohols (5a and b) was proved by oxidation to the same epoxy-ketone (6). Two minor products were also obtained from the reaction of the allylic acetate (7b) with *N*-bromoacetamide, but they have not yet been characterised.

1β-Hydroxy-5α-cholest-2-ene (9a) afforded the diequatorial bromohydrin (10a) [2α-bromo-1β,3β-dihydroxy-5α-cholestane], accompanied by 5α-cholest-2-en-1-one (12). Acetylation of compound (10a) with acetic



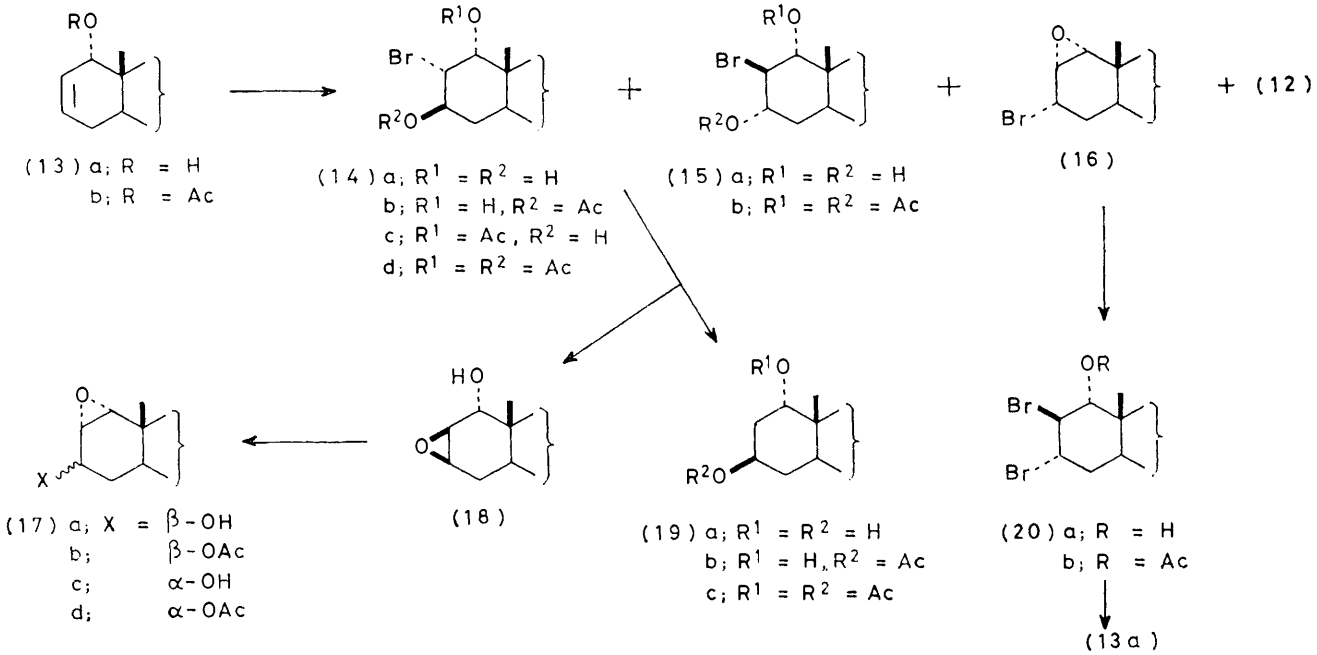
anhydride–pyridine for 24 h at room temperature afforded the 3-monoacetate (10b). Acetylation over longer periods of time afforded mixtures of the 3-monoacetate (10b) and the 1,3-diacetate (10d), the latter being identical with that obtained by acetylation of the bromohydrin (10c).

The main product from 1β-acetoxy-5α-cholest-2-ene (9b) was the diequatorial bromohydrin (10c), accompanied however by relatively small amounts of 1β-acetoxy-3α-bromo-2β-hydroxy-5α-cholestane (11a) (diaxial bromohydrin), identical with the product obtained

[6] J. G. H. Jones and B. A. Marples, *J. Chem. Soc.* (*C*), 1970, 1188.

by treatment with hydrobromic acid of 1β-acetoxy-2β,3β-epoxy-5α-cholestane.[7] The structure was confirmed by decoupling the n.m.r. spectrum of the diacetate (11b) (see Experimental section).

1α-Hydroxy-5α-cholest-2-ene (13a) afforded a mixture of *trans*-diequatorial (14a) and *trans*-diaxial (15a) bromohydrins, accompanied by the enone (12) and a



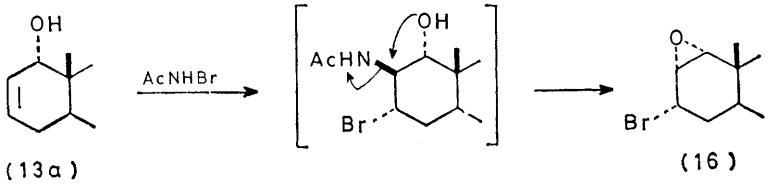
compound $C_{27}H_{45}BrO$ assigned the bromo-epoxide structure (16). The diequatorial bromohydrin [2α-bromo-1α,3β-dihydroxy-5α-cholestane (14a)], arising from an initial α-oriented bromonium ion, was isolated as the 3-monoacetate (14b). The 1α-hydroxy-group in this compound could not be acetylated with acetic anhydride in pyridine, even after 7 days at room temperature. The greater hindrance of the 1α-hydroxy-group in this bromohydrin (14b), as compared with that of the 1β-hydroxy-group in the bromohydrin (10a), can be explained by the effect of the neighbouring *cis*-bromo-substituent (in addition to the known fact that axial alcohols are more difficult to acetylate than their equatorial counterparts). Following treatment with Raney nickel, the bromohydrin (14b) was converted into 3β-acetoxy-1α-hydroxy-5α-cholestane (19b), that was easily acetylated to give the diacetate (19c). The latter was obtained alternatively by reduction with lithium aluminium hydride of the epoxy-alcohol (17a),[8] and subsequent acetylation.

Treatment of the bromohydrin (14b) with base was expected to give 2β,3β-epoxy-1α-hydroxy-5α-cholestane (18). This compound was undoubtedly formed; however it underwent an internal nucleophilic displacement by the anion of the axially oriented 1α-hydroxy-group to give the epoxy-alcohol (17a). The diaxial bromohydrin (15a), arising from a β-oriented bromonium ion, was isolated as the corresponding diacetate [1α,3α-diacetoxy-2β-bromo-5α-cholestane (15b)], and identified by comparison with an authentic sample.[9]

The 3α-bromo-1α,2α-epoxy-5α-cholestane structure assigned to compound (16) is based on the following data. The n.m.r. spectrum shows three sets of signals close to those exhibited by compound (17d),[10] a doublet (*J* 4 Hz) and a double doublet (*J* 4 and 1 Hz) ascribable to 1β-H and 2β-H, respectively, and a double triplet (*J* 9 and 1 Hz) for 3β-H. In contrast to other epoxides that are easily opened with perchloric acid in aqueous acetone solutions to the corresponding *trans*-diols, compound (16) remained unchanged when exposed to this reagent at room temperature, or after heating for 2 h at reflux. It is noteworthy however, that compounds (17c and d) behave in the same manner, in sharp contrast to the easy opening of the epoxide ring in compound (17b).[7] The structure (16) is supported by opening of the epoxide ring with hydrobromic acid, leading to 2β,3α-dibromo-1α-hydroxy-5α-cholestane (20a), characterised in the n.m.r. by two narrow multiplets for the equatorial 2α-H and 3β-H, and a narrow multiplet for 1β-H, as well as by a significant downfield shift of the C(10)Me signal (δ 1.23). As expected, treatment with Raney nickel of compound (20a) afforded the allylic alcohol (13a). The formation of the bromo-epoxide (16) may be interpreted in the same manner as proposed for the conversion of 5-hydroxy-5α-cholest-2-ene into 3α-bromo-2α,5-oxido-5α-cholestane.[11]

[7] E. Glotter and P. Krinsky, unpublished results.
[8] R. Albrecht and Ch. Tamm, *Helv. Chim. Acta*, 1957, **40**, 2216.
[9] E. Glotter, P. Krinsky, M. Rejtö, and M. Weissenberg, *J.C.S. Perkin I*, 1976, 1442.
[10] M. Weissenberg, D. Lavie, and E. Glotter, *Tetrahedron*, 1973, **29**, 353.
[11] P. Kocovsky and V. Cerny, *Coll. Czech, Chem. Comm.*, 1977, **42**, 353, and references cited therein.

In contrast to the allylic alcohol (13a), treatment of 1α-acetoxy-5α-cholest-2-ene (13b) with *N*-bromoacetamide afforded only 1α-acetoxy-2α-bromo-3β-hydroxy-5α-cholestane (14c) (diequatorial bromohydrin), which was smoothly acetylated to the bromodiacetate (14d).



(13a) (16)

Debromination of the latter with Raney nickel afforded the diacetate (19c).

Analysis of the results obtained in this work leads to the following observations. With one exception [(13a) ⟶ (15a)], the initial bromonium ion is α-oriented. The main mode of opening of the 2α,3α-bromonium ions involves nucleophilic attack at C(3) (β with respect to the original neighbouring hydroxy- or acetoxy-group), leading to a quasidiaxial bromohydrin in a boat-like ring A conformation, that undergoes subsequently a conformational change to the more stable diequatorial bromohydrin. The preferential nucleophilic attack of the bridged bromonium ion at the β-position with respect to the electronegative neighbouring group is in agreement with similar observations on the behaviour of 3-methoxycyclohexene;[12] this behaviour may be related to a certain degree of asymmetry of the bromonium ion, the bond towards the carbon atom α to the electronegative neighbouring group being stronger than the bond towards the carbon atom β to this group.[5a]

The nucleophilic attack on the 1α,2α-bromonium ions is invariably at C(2) (α with respect to the original neighbouring hydroxy- or acetoxy-group), in agreement with the general mode of electrophilic addition to steroidal 1-enes without neighbouring groups. This apparent discrepancy between the behaviour of 2α,3α- and 1α,2α-bromonium ions may be related to steric factors: axial, front side attack of a nucleophile at C(1) is sterically much more difficult than similar attack at C(2).

In addition to the influence of the neighbouring groups as shown above, there are two instances when a neighbouring hydroxy-group participates in the reaction by displacing the bridged bromonium ion [compounds (3) and (16)]; the formation of the bromo-epoxide (16) involves (if the explanation is correct) two displacements. It is noteworthy that the 1β-hydroxy-2-ene (9a) does not yield any bromo-epoxide, although the initial bromonium ion is formed from the rear of the molecule. This may well be due to the diminished conformational flexibility of compound (9a) in which the 1β-hydroxy-group cannot assume the quasiaxial orientation necessary to displace the bromonium ion.

Participation of neighbouring acetate groups *via* intermediate acetoxonium ions is possible only if the acetate, *trans* with respect to the bromonium ion, can assume a quasiaxial orientation. Such a participation is indeed observed in the reaction (1b) ⟶ (2b). Concerning the formation of compound (11a), there is no clear-cut evidence whether it is formed *via* an acetoxonium ion or by external nucleophilic attack at C(2).

[12] R. A. Bannard, A. A. Casselman, and L. R. Hawkins, *Canad. J. Chem.*, 1965, **43**, 2398; see also ref. 5*b*.

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. 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.

Reaction of Allylic Alcohols and Acetates with N-Bromoacetamide.—A solution of allylic alcohol or acetate (500 mg) in pure dioxan (30 ml) containing aqueous 4% perchloric acid (6 ml) was flushed with nitrogen for *ca.* 15 min. Dioxan was filtered before use through a column of basic alumina, Woelm activity I. Freshly recrystallised *N*-bromoacetamide (250 mg) was then added and the solution was stirred during 3 h under nitrogen at room temperature. To the ice-cooled solution, aqueous 10% sodium thiosulphate was added until disappearance of the yellow colour; ice–water was then added, and the crude product was collected by filtration or extracted with methylene chloride, and subjected to chromatography on silica (50 g).

Treatment of 3β-hydroxy-5α-cholest-1-ene (1a). Elution with petroleum gave *1α-bromo-2β,3β-epoxy-5α-cholestane* (3) (75 mg), m.p. 115—116 °C (from acetone–methanol); $[\alpha]_D$ +132° (*c* 1.1); δ 1.02 [s, C(10)Me], 3.25 (m, $W_{\frac{1}{2}}$ 11 Hz, 3α-H), 3.58 (dd, *J* 4 and 2 Hz, 2α-H), and 4.48 (d, *J* 2 Hz, 1β-H). (Found: C, 69.5; H, 9.8; M^+, 464/466. $C_{27}H_{45}BrO$ requires C, 69.65; H, 9.75%; *M*, 465.5). Elution with petroleum–ether (9 : 1) gave 5α-cholest-1-en-3-one (4) (95 mg) identified by comparison with an authentic sample. Elution with methylene chloride gave 1α-bromo-2β,3β-dihydroxy-5α-cholestane (2a) (300 mg), m.p. 186 °C (lit.,[1] 186—188°). Acetylation with acetic anhydride–pyridine, overnight at room temperature gave the *diacetate* (2c), m.p. 152—154 °C (from methanol); $[\alpha]_D$ +28° (*c* 0.9); δ 1.13 [s, C(10)Me], 2.0 and 2.1 (2 OAc), 4.25 (d, *J* 3 Hz, 1β-H), and 5.55 (overlapped multiplets, 2α- and 3α-H). (Found: C, 65.4; H, 9.2; M^+, 566/568. $C_{31}H_{51}BrO_4$ requires C, 65.6; H, 9.05%; *M*, 567.6).

Alternatively, the crude product (600 mg) obtained from the reaction of compound (1a) with *N*-bromoacetamide was dissolved in methanolic 5% potassium hydroxide (25 ml) and heated to reflux during 2 h. After cooling, the solution

was neutralised with dilute hydrochloric acid (1 : 4), water was added, and the product was filtered off and chromatographed as above. Elution with petroleum gave compound (3); elution with petroleum–ether (9 : 1) gave compound (4); further elution with petroleum–ether (4 : 1) gave 1β,2β-epoxy-3β-hydroxy-5α-cholestane (5a) (240 mg), m.p. 170—171 °C (from methanol) [lit.,[1] 173—176 °C (from acetone)]; $[\alpha]_D$ +54° (*c* 1.5); δ 0.91 [s, C(10)Me], 3.25 (narrow) (1α- and 2α-H), and 3.90br (m, 3α-H) (Found: C, 80.4; H, 11.4. Calc. for $C_{27}H_{46}O_2$: C, 80.5; H, 11.5%).

Treatment of 3β-*acetoxy*-5α-*cholest*-1-*ene* (Ib). The crude product showed one spot on a chromatoplate and was purified by direct crystallisation. 2β-*Acetoxy*-1α-*bromo*-3β-*hydroxy*-5α-*cholestane* (2b) had m.p. 122—124 °C (from methanol), $[\alpha]_D$ +35° (*c* 1); δ 1.06 [s, C(10)Me], 2.1 (OAc), 4.31 (d, *J* 3 Hz, 1β-H), 4.4br (m, 3α-H), and 5.4 (dd, *J* 4 and 3 Hz, 2α-H) (Found: C, 66.2; H, 9.4; M^+, 524/526. $C_{29}H_{49}BrO_3$ requires C, 66.3; H, 9.4%; *M*, 525.6). Acetylation afforded a diacetate identical with compound (2c).

Opening of the epoxide ring in the bromo-epoxide (3). A solution of compound (3) (50 mg) in acetone (4 ml) containing aqueous 7% perchloric acid (0.1 ml) was kept overnight at room temperature. Water was then added and the product (35 mg) was collected by filtration. 1α-*Bromo*-2β,3α-*dihydroxy*-5α-*cholestane* (8a) had m.p. 173—174 °C (from methanol–methylene chloride); $[\alpha]_D$ +69° (*c* 0.5); δ 1.15 [s, C(10)Me], 3.91 (m, 3β-H), 4.23 (m, $W_{\frac{1}{2}}$ 5 Hz, 1β-H), and 4.58 (m, $W_{\frac{1}{2}}$ 8 Hz, 2α-H) (Found: C, 67.0; H, 9.8. $C_{27}H_{47}BrO_2$ requires C, 67.05; H, 9.8%). Acetylation afforded the diacetate (8c), m.p. 101—102 °C (from methanol); δ 1.05 [s, C(10)Me], 2.05 and 2.08 (2 OAc), 4.16 (m, $W_{\frac{1}{2}}$ 5 Hz, 1β-H), 4.86 (m, $W_{\frac{1}{2}}$ 7 Hz, 3β-H), and 5.41 (m, $W_{\frac{1}{2}}$ 6 Hz, 2α-H).

Treatment of 3α-*hydroxy*-5α-*cholest*-1-*ene* (7a). Compound (7a) was obtained by hydrolysis of the acetate (7b) [6] (experiment by Dr. Y. Rabinsohn). To a solution of this compound (150 mg) in methanol (30 ml), N-barium methoxide in methanol (1 ml) was added. After 2.5 h at room temperature, the solution was evaporated in vacuum to small volume (without heating), water was added, and the product (7a) was extracted with methylene chloride. It showed one spot on a chromatoplate and was subjected (80 mg) without further purification to reaction with *N*-bromoacetamide.

Elution with petroleum–ether (95 : 5) gave the enone (4) (55 mg); elution with petroleum–ether (1 : 1) gave compound (8a) (20 mg).

Treatment of 3α-*acetoxy*-5α-*cholest*-1-*ene* (7b).[6] Elution with petroleum–ether (4 : 1) gave an unidentified product (100 mg) which could not be purified. Elution with petroleum–ether (7 : 3) gave 3α-*acetoxy*-1a-*bromo*-2β-*hydroxy*-5α-*cholestane* (8b) (280 mg), m.p. 178—180 °C (from methanol); $[\alpha]_D$ +56.3° (*c* 0.6); δ 1.13 [s, C(10)Me], 2.08 (OAc), 4.16 (m, $W_{\frac{1}{2}}$ 5 Hz, 1β-H), 4.56 (m, $W_{\frac{1}{2}}$ 9 Hz, 2α-H), and 4.83 (m, $W_{\frac{1}{2}}$ 6 Hz, 3β-H) (Found: C, 66.4; H, 9.4. $C_{29}H_{49}BrO_3$ requires C, 66.3; H, 9.4%). Acetylation afforded the diacetate (8c). Further elution with petroleum–ether (1 : 1) gave an unidentified product (35 mg) which could not be purified.

Formation of 1β,2β-*epoxy*-3α-*hydroxy*-5α-*cholestane* (5b) *from compound* (8b). A solution of compound (8b) (1 g) in methanolic 5% potassium hydroxide (60 ml) was heated to reflux during 1 h, then cooled and neutralised with dilute hydrochloric acid (1 : 4); water was added and the product collected by filtration. The crude product was filtered through a column of silica and crystallised twice from methanol to give the *epoxy-alcohol* (5b), m.p. 148—149 °C; $[\alpha]_D$ +7° (*c* 0.6); δ 0.86 [s, C(10)Me], 3.1 (narrow) (m, 1α- and 2α-H), and 4.31 (m, $W_{\frac{1}{2}}$ 8 Hz, 3β-H) (Found: C, 80.5; H, 11.6. $C_{27}H_{46}O_2$ requires C, 80.5; H, 11.5%). The mother liquors contained an inseparable mixture of epoxy-alcohol (5b) and the isomeric 2α,3α-*epoxy*-1β-*hydroxy*-5α-*cholestane* [7] (identified by t.l.c. and n.m.r.).

Treatment of 1β-*hydroxy*-5α-*cholest*-2-*ene* (9a). Compound (9a), m.p. 82 °C, was prepared by reduction with lithium aluminium hydride of 5α-cholest-2-en-1-one (12),[13] or by oxidation with Jones reagent of the epoxy-alcohol (5a) and subsequent reduction with hydrazine hydrate of 1β,2β-epoxy-5α-cholestan-3-one (6),[8] as described for the isomeric 1α,2α-epoxy-ketone.[14]

Chromatography of the crude product from the reaction with *N*-bromoacetamide gave, on elution with petroleum–ether (4 : 1), the enone (12) (170 mg); further elution with petroleum–ether (7 : 3) gave 2α-*bromo*-1β,3β-*dihydroxy*-5α-*cholestane* (10a) (200 mg), which could not be crystallised. Acetylation with acetic anhydride and pyridine, overnight at room temperature, gave 3β-acetoxy-2α-bromo-1β-hydroxy-5α-cholestane (10b) which could not be crystallised; δ 0.90 [s, C(10)Me], 2.08 (OAc), 3.48 (dd, *J* 10 and 2 Hz; after addition of D_2O, d *J* 10 Hz, 1α-H), 4.08 (t, *J* 10 Hz, 2β-H), and 5.03br (m, 3α-H). Acetylation for 3 days at room temperature gave a mixture of monoacetate (10b) and diacetate (10d).

Treatment of 1β-*acetoxy*-5α-*cholest*-2-*ene* (9b). Elution with petroleum–ether (7 : 3) gave 1β-*acetoxy*-2α-*bromo*-3β-*hydroxy*-5α-*cholestane* (10c) (330 mg), m.p. 159—160 °C (from methanol); $[\alpha]_D$ +37° (*c* 1.1); δ 0.95 [s, C(10)Me], 2.08 (OAc), 3.8br (m, 3α-H), 4.05 (t, *J* 10 Hz, 2β-H), and 5.00 (d, *J* 10 Hz, 1α-H) (Found: C, 66.4; H, 9.3; M^+, 524/526. $C_{29}H_{49}BrO_3$ requires C, 66.25; H, 9.4%; *M*, 525.6). Further elution with the same solvent mixture gave 1β-acetoxy-3α-bromo-2β-hydroxy-5α-cholestane (11a) (25 mg), which could not be crystallised; δ 1.11 [s, C(10)Me], 2.08 (OAc), 4.18 (narrow) (m, 3β-H), and 4.35 (narrow) (m, 2α-H). Acetylation of compound (10c) with acetic anhydride and pyridine, overnight at room temperature, gave 1β,3β-*diacetoxy*-2α-*bromo*-5α-*cholestane* (10d), m.p. 112—114 °C (from methanol); $[\alpha]_D$ +25° (*c* 0.8); δ 0.96 [s, C(10)Me], 2.08 (2 OAc), 4.06 (t, *J* 10 Hz, 2β-H), 5.00 (d, *J* 10 Hz, 1α-H), and 5.0br (m, 3α-H) (Found: C, 65.7; H, 9.0, M^+, 566/568. $C_{31}H_{51}BrO_4$ requires C, 65.6; H, 9.05%; *M*, 567.6). Acetylation of compound (11a) gave 1β,2β-diacetoxy-3α-bromo-5α-cholestane (11b), which could not be crystallised; δ 1.08 [s, C(10)Me], 1.98 and 2.06 (2 OAc), 4.23 (narrow) (m, 3β-H), 5.21 (d, *J* 3.6 Hz, 1α-H), and 5.41 (narrow) (m, 2α-H). This spectrum was decoupled with a Brucker WH-270 instrument. Irradiation at δ 4.23 caused the δ 5.41 signal to become a doublet, *J* 3.6 Hz; irradiation at δ 5.41 caused the δ 5.21 signal to become a singlet and the δ 4.23 signal to become narrower.

Treatment of 1α-*hydroxy*-5α-*cholest*-2-*ene* (13a).[9] The crude product was acetylated with acetic anhydride and pyridine, overnight at room temperature, and then chromatographed (100 g silica). Elution with petroleum gave compound (16) (50 mg), followed by 5α-cholest-2-en-1-one (12) (70 mg). 3α-*Bromo*-1α,2α-*epoxy*-5α-*cholestane* (16) had m.p. 138—139 °C (from acetone); $[\alpha]_D$ +14° (*c* 0.5); δ 0.96

[13] (*a*) Ch. Tamm and R. Albrecht, *Helv. Chim. Acta*, 1959, **42**, 2177; (*b*) M. Weissenberg and E. Glotter, *J.C.S. Perkin I*, 1977, 988.

[14] M. P. Cava and B. R. Vogt, *J. Org. Chem.*, 1965, **30** 3775.

[s, C(10)Me], 3.15 (dd, *J* 4 and 1 Hz, 2β-H), 3.47 (d, *J* 4 Hz, 1β-H), and 4.26 (dt, *J* 9 and 1 Hz, 3β-H) (Found: C, 69.8; H, 9.5; M^+, 464/466. $C_{27}H_{45}BrO$ requires C, 69.65; H, 9.75%; *M*, 465.5). Elution with petroleum–ether (9 : 1) gave 3β-*acetoxy*-2α-*bromo*-1α-*hydroxy*-5α-*cholestane* (14b) (200 mg), m.p. 164—166 °C (from methanol); $[\alpha]_D$ −17° (*c* 1); δ 0.86 [s, C(10)Me], 2.08 (OAc), 3.87 (narrow) (m; after addition of D_2O, d, *J* 2.5 Hz, 1β-H), 4.43 (dd, *J* 11 and 2.5 Hz, 2β-H), and 5.23br (m, 3α-H) (Found: C, 66.4; H, 9.4. $C_{29}H_{49}BrO_3$ requires C, 66.25; H, 9.4%). Elution with petroleum–ether (4 : 1) gave 1α,3α-diacetoxy-2β-bromo-5α-cholestane (15b) [9] (130 mg), m.p. and mixed m.p. 169—170 °C (from methanol).

Treatment of 1α-*acetoxy*-5α-*cholest*-2-*ene* (13b). Elution with methylene chloride gave 1α-*acetoxy*-2α-*bromo*-3β-*hydroxy*-5α-*cholestane* (14c) (360 mg), m.p. 183—184 °C (from methanol); $[\alpha]_D$ +18° (c, 0.7). (Found: C, 66.3; H, 9.6. $C_{29}H_{49}BrO_3$ requires C, 66.25; H, 9.4%). Acetylation gave 1α 3β-diacetoxy-2α-bromo-5α-cholestane (14d), which could not be crystallised; δ 0.95 [s, C(10)Me], 2.10 and 2.18 (2 OAc), 4.35 (dd, *J* 11 and 3 Hz, 2β-H), 5.2 (m, 3α-H), and 5.41 (d, *J* 3 Hz, 1β-H).

Formation of 1α,2α-*epoxy*-3β-*hydroxy*-5α-*cholestane* (17a) *from compound* (14b). A solution of compound (14b) (40 mg) in methanolic 2% potassium hydroxide (5 ml) was heated to reflux during 1 h. The solution was cooled and neutralised with dilute hydrochloric acid (1 : 4), water was added, and the product was collected by filtration. It was identical with an authentic sample of compound (17a).[10]

Reduction of compound (14b) *with Raney nickel.* To a solution of compound (14b) (50 mg) in ethanol (10 ml), Raney nickel (*ca.* 500 mg) was added, and the mixture was heated to reflux during 4 h. The crude product (19b) showed one spot on a chromatoplate: δ 0.81 [s, C(10)Me], 2.03 (OAc), 3.85 (narrow) (m, 1β-H), and 5.1br (m, 3α-H). Hydrolysis of crude compound (19b) by heating to reflux with methanolic 2% potassium hydroxide during 0.5 h, gave after work-up 1α,3β-dihydroxy-5α-cholestane (19a), m.p. 155 °C (from ethanol) (lit.,[8] 155 °C), identical with the product obtained by reduction with lithium aluminium hydride of compound (17a). Similarly, reduction with Raney nickel of compound (14d) (50 mg) afforded 1α,3β-diacetoxy-5α-cholestane (19c); hydrolysis as above gave the diol (19a).

Attempted epoxide ring opening in compounds (16), (17c), *and* (17d). To a solution of compound (16) (50 mg) in acetone (4 ml), aqueous 7% perchloric acid (0.1 ml) was added. The compound remained unchanged after 24 h at room temperature, or after 2 h heating to reflux. No reaction occurred when dioxan was substituted for acetone as solvent. The reaction was repeated (in acetone solution at room temperature) with compounds (17c and d). They remained unchanged.

Reaction of the bromo-epoxide (16) *with hydrobromic acid to give* 2β,3α-*dibromo*-1α-*hydroxy*-5α-*cholestane* (20a). A solution of compound (16) (35 mg) in acetone (35 ml) containing 40% hydrobromic acid in acetic acid (1 ml) was stirred during 1 h at 0 °C. Aqueous 5% sodium hydrogen carbonate was then added until the mixture was slightly alkaline, most of the solvent was evaporated off, water was added, and the product (20a) was extracted with methylene chloride. It showed one spot on a chromatoplate; δ 1.23 [s, C(10)Me], 4.21 (narrow) (m; after addition of D_2O, d, *J* 2.5 Hz, 1β-H), 4.53 (narrow) (m, 2α-H), and 4.8 (narrow) (m, 3β-H). Acetylation afforded 1α-acetoxy-2β,3α-dibromo-5α-cholestane (20b); δ 1.28 [s, C(10)Me], 2.10 (OAc), 4.3—4.5 (partially overlapped multiplets, 2α- and 3β-H), and 5.23 (d, *J* 2.5 Hz, 1β-H). Reduction of compound (20a) (30 mg) in ethanol solution (8 ml) with Raney nickel (*ca.* 200 mg), as described above, gave 1α-hydroxy-5α-cholest-2-ene (13a), m.p. and mixed m.p. 103—104 °C (from acetone).[13b]

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