Steroids. Part XVIII.[1] Spontaneous Decomposition of 5α-Bromo-6β-hydroxy-steroids

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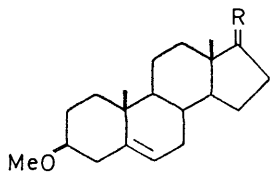
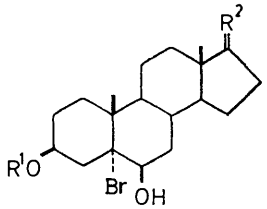
The rates of decomposition of steroidal 5α-bromo-6β-hydroxy-compounds are dependent on the nature of the 3-substituents. No major differences in stability are caused by variation of the C-17 substituents.

THE recent observation that 5α-bromo-6β-hydroxy-4,4-dimethyl-compounds spontaneously decompose to give the 5β,6β-epoxides [2] prompts us to report some of our results with related compounds. We have found that the 5α-bromo-6β-hydroxy-3β-methoxy-compounds (4)—(6) cannot be isolated from the usual reaction of the

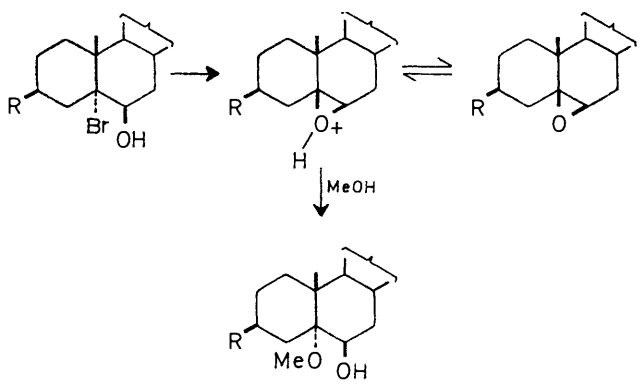


(1) R = β-C_8H_{17}, H
(2) R = O
(3) R = β-MeCO,H



(4) R^1=Me, R^2=β-C_8H_{17}, H
(5) R^1=Me, R^2=O
(6) R^1=Me, R^2=β-MeCO,H
(7) R^1=Ac, R^2=β-C_8H_{17}, H
(8) R^1=Ac, R^2=O
(9) R^1=Ac, R^2=β-MeCO,H

corresponding Δ^5-compounds (1),[3] (2),[4] and (3),[5] respectively, with *N*-bromoacetamide and perchloric acid in aqueous dioxan.[6] The corresponding 5β,6β-epoxide is a product in each case. Also, the 3β-acetoxy-5α-bromo-6β-hydroxy-compounds (7),[7] (8),[6] and (9) [8] are decomposed in methanol as shown in the Scheme.

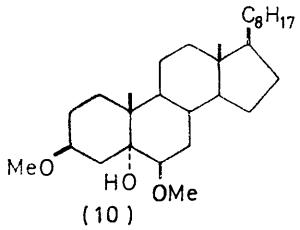


SCHEME

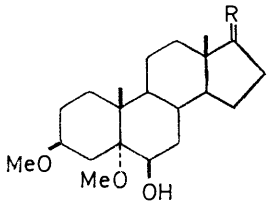
Qualitative monitoring of the reactions by t.l.c. showed no major differences in the reaction rates of the compounds (7)—(9).

[1] Part XVII, J. G. Ll. Jones and B. A. Marples, *J.C.S. Perkin I*, 1973, 1143.
[2] C. R. Eck, P. Kullberg, and B. Green, *J.C.S. Chem. Comm.*, 1972, 539.
[3] Y. F. Shealy and R. M. Dodson, *J. Org. Chem.*, 1951, **16**, 1427.
[4] A. Butenandt and W. Grosse, *Ber.*, 1936, **69**, 2776.
[5] A. Butenandt and W. Grosse, *Ber.*, 1937, **70**, 1446.
[6] V. Grenville, D. K. Patel, V. Petrow, I. A. Stuart-Webb, and D. M. Williamson, *J. Chem. Soc.*, 1957, 4105.
[7] J. Kalvoda, K. Heusler, H. Ueberwasser, G. Anner, and A. Wettstein, *Helv. Chim. Acta*, 1963, **46**, 1361.
[8] A. Bowers, R. Villotti, J. A. Edwards, E. Denot, and O. Halpern, *J. Amer. Chem. Soc.*, 1962, **84**, 3204.

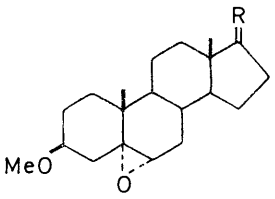
Attempted Preparation of the 5α-Bromo-6β-hydroxy-3β-methoxy-compounds.—We were unable to induce crystallisation of the crude reaction products from each of the compounds (1)—(3) with *N*-bromoacetamide and perchloric acid in aqueous dioxan.[6] From one such attempt in methanol, the product from cholesteryl methyl ether (1) gave, after t.l.c., the methoxylated compounds (11) and (10). The ^{1}H n.m.r. spectrum of compound (11), which is presumably derived from the bromohydrin (4) (Scheme), showed important signals at τ 6·15 (m, $W_{\frac{1}{2}}$ *ca.* 6 Hz, 6-H), 6·68 (s, 3-MeO), 6·88 (s, 5-MeO), and 6·5—7·0 (m, 3-H). The 3β,6β-dimethoxy-compound (10) showed characteristic n.m.r. signals at τ 6·68 (s, 3-MeO), 6·75 (s, 6-MeO), and 7·08 (m, $W_{\frac{1}{2}}$ *ca.* 6 Hz, 6-H), and was unequivocally identified by comparison with an authentic sample prepared by reaction of the 5α,6α-epoxide (14) [3] with boron trifluoride in methanol.[9] The compound (10) presumably originates in a similar manner since the 5α,6α-epoxide (14) is present in the crude bromohydrin reaction mixture (see later). Preparative t.l.c. of this crude product, without any attempt to induce crystallisation, gave a mixture of the 5α,6α-epoxide (14) and the 5β,6β-epoxide (17), and the 6α-bromo-5β-hydroxy-compound (26). Hydrolysis of the mixed epoxides gave the 5α,6β-diol (29).[10] Similar results were obtained by t.l.c. of the crude mixture from the reactions of the Δ^5-compounds (2) and (3) with *N*-bromoacetamide and perchloric acid in aqueous dioxan



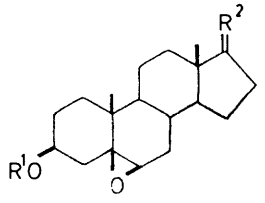
(10)



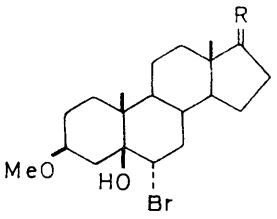
(11) R = β-C_8H_{17}, H
(12) R = O
(13) R = β-MeCO, H



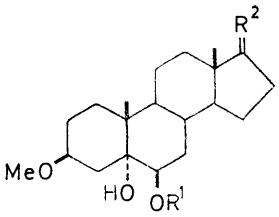
(14) R = β-C_8H_{17}, H
(15) R = O
(16) R = β-MeCO, H



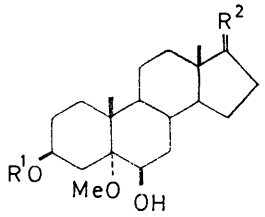
(17) R^1 = Me, R^2 = β-C_8H_{17}, H
(18) R^1 = Me, R^2 = O
(19) R^1 = Me, R^2 = β-MeCO, H
(20) R^1 = Ac, R^2 = β-C_8H_{17}, H
(21) R^1 = Ac, R^2 = O
(22) R^1 = Ac, R^2 = β-MeCO, H
(23) R^1 = H, R^2 = β-C_8H_{17}, H
(24) R^1 = H, R^2 = O
(25) R^1 = H, R^2 = β-MeCO, H



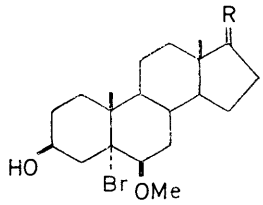
(26) R = β-C_8H_{17}, H
(27) R = O
(28) R = β-MeCO, H



(29) R^1 = H, R^2 = β-C_8H_{17}, H
(30) R^1 = H, R^2 = O
(31) R^1 = H, R^2 = β-MeCO, H
(32) R^1 = Ac, R^2 = O



(33) R^1 = H, R^2 = β-C_8H_{17}, H
(34) R^1 = H, R^2 = O
(35) R^1 = H, R^2 = β-MeCO, H
(36) R^1 = Ac, R^2 = β-C_8H_{17}, H
(37) R^1 = Ac, R^2 = O
(38) R^1 = Ac, R^2 = β-MeCO, H



(39) R = O
(40) R = β-C_8H_{17}, H

(Table 1). The ^{1}H n.m.r. spectra of the α- and β-epoxide mixtures showed characteristic signals for the 6β-H and the 6α-H at τ *ca.* 7·1 (d, *J ca.* 4 Hz) and 6·95 (d, *J ca.* 2·5 Hz) respectively.[11] The mechanism whereby the α-epoxides are produced is not known. It seems doubtful that the 6β-bromo-5α-hydroxy-compounds, the obvious precursors, would account for all of the α-epoxide produced in each case. The ^{1}H n.m.r. spectra of the 6α-bromo-5β-hydroxy-compounds (26)—(28) showed important bands at τ *ca.* 5·5—6·0 (m, 6-H), 5·6 (s, 5-OH), and 6·3 (m, $W_{\frac{1}{2}}$ *ca.* 9 Hz, 3-H). The mass spectra of compounds (26) and (28) showed no molecular ions; that of compound (27) showed a weak molecular

TABLE 1

Products from compounds (1)—(3) with *N*-bromoacetamide and perchloric acid in aqueous dioxan

Δ^5-Compound	Epoxide mixture	6α-Bromo-5β-hydroxy-compound	Epoxides hydrolysis product
(1)	(14) + (17)	(26)	(29) [a]
(2)	(15) + (18)	(27)	(30) [b]
(3)	(16) + (19)	(28)	(31) [c]

[a] Ref. 10. [b] Converted into the acetate (32). [c] Ref. 22.

[9] A. Bowers, E. Denot, R. Urquiza, and L. M. Sanchez-Hidalgo, *Tetrahedron*, 1960, **8**, 116.

[10] V. Petrow, *J. Chem. Soc.*, 1937, 1077.

[11] A. D. Cross, *J. Amer. Chem. Soc.*, 1962, **84**, 3206.

ion. All had intense peaks corresponding to $[M - Br]^+$ and $[M - HBr]^+$. It is likely that these compounds are formed by diequatorial cleavage of the intermediate 5α,6α-bromonium ion.[12]

Methanolysis of the 3β-Acetoxy-5α-bromo-6β-hydroxy-compounds.—The low stability of the 3β-methoxy-5α-bromo-6β-hydroxy-compounds (4)—(6) contrasts with that reported for the corresponding 3β-acetoxy-compounds (7),[7] (8),[6] and (9).[8] We find that the cholestane derivative (7) and the androstane (8) are rapidly decomposed in boiling methanol to give the 3β,6β-dihydroxy-5α-methoxy-compounds (33)[13] and (34), respectively. Quantities of the corresponding 3β-acetoxy-compounds (36)[14] and (37)[15a] were also isolated. T.l.c. monitoring of the decomposition of compound (8) in methanol at 45°, indicated that the 3β-acetoxy-5β,6β-epoxide (21)[16] was the first-formed product (Scheme). After the disappearance of the bromohydrin (8), the reaction mixture was shown by t.l.c. to contain the 3β-acetoxy-5α-methoxy-compound (37), its hydrolysed derivative (34), and the 3β-hydroxy-5β,6β-epoxide (24).[17] It is apparent, from these reactions in methanol, that the 3β-acetoxy-5α-bromo-6β-hydroxy-compounds are more labile than has previously been indicated. For example, methanol is reported to be a suitable solvent for crystallisation of compound (8).[18] We were encouraged to attempt to examine the relative stabilities of the bromohydrins (7)—(9) by the observation[19] that the androstane derivative (39) readily decomposes, unlike the cholestane (40). Also, we[20] and others[21] have shown that long-range effects of C-17 substituents can be important. However, a comparison of stabilities in methanol was felt to be unsatisfactory owing to the generation of hydrogen bromide as the reactions proceed. Accordingly, we examined the reactions in methanol saturated with sodium hydrogen carbonate at reflux and at 45°. This method is also not altogether satisfactory, since we cannot completely exclude the possibility of the reactions being partially base-catalysed and proceeding through the 6β-alkoxides. However, the low solubility and weak basicity of sodium hydrogen carbonate suggested that these would not be major reactions. This conclusion was supported by the production, at reflux, of solvolysis products in addition to epoxides from compounds (7)—(9) (Table 2). It is apparent that proton removal from the first-formed protonated epoxide (Scheme), and attack by the solvent occur at similar rates. The yields of epoxides *versus* solvolysis products were variable owing to the heterogeneity of the system and the resultant variability of the efficiency of the proton removal process. T.l.c. monitoring of these reactions showed that, in each case, the bromohydrin had disappeared after *ca.* 20 min, thereby not allowing any reasonable estimate of reactivity differences. Accordingly, similar reaction mixtures were shaken

TABLE 2

Methanolysis of the bromohydrins (7)—(9) with sodium hydrogen carbonate at reflux

	Products (typical % yield)	
Bromohydrin	β-Epoxide	6β-Hydroxy-5α-methoxy-compound
(7)	(20) [a] (7)	(33) [b] (13)
	(23) [a] (2)	(36) [c] (53)
(8)	(21) [d] (12)	(34) (18)
	(24) [a] (34)	(37) [e] (36)
(9)	(22) [f] (6)	(35) (21)
	(25) [a] (29)	(38) [g] (28)

[a] Ref. 17. [b] Ref. 13. [c] Ref. 14. [d] Ref. 16. [e] Ref. 15*a*. [f] Ref. 23. [g] Ref. 15*b*.

vigorously at 45°. Under these conditions, the bromohydrins (7)—(9) gave only the β-epoxides (20)—(22), respectively. Work-up and preparative t.l.c. after 1 h gave an estimate of the degree of reaction, though the unchanged bromohydrins (7)—(9) could not be isolated in a pure state as they decomposed to β-epoxide to some extent on the silica gel. Table 3 gives the yields of

TABLE 3

Methanolysis of the bromohydrins (7)—(9) with sodium hydrogen carbonate at 45°

Bromohydrin	% β-Epoxide after 1 h	Estimated total reaction time (h)
(7)	71	1·75
(8)	49	2·0
(9)	52	1·5

β-epoxides isolated, and the times for complete reaction which were estimated by t.l.c. These qualitative data suggest that there are no major differences in the reactivities of the bromohydrins (7)—(9).

Discussion.—Two main points emerge from this work. The 5α-bromo-6β-hydroxy-3β-methoxy-steroids are very unstable, and the 3β-acetoxy-compounds, though readily isolable, are methanolysed fairly rapidly. No major differences in methanolysis rates are brought about by variation of the C-17 substituents. The spontaneous decomposition of the bromohydrins involves the ionisation of the C(5)–Br bond, and thus a likely accumulation of positive charge at C-5. A 3-methoxy-substituent is less likely inductively to inhibit this process than a 3-acetoxy-substituent, and this could account for the lower stability of the 3-methoxy-compounds. Similar effects have been reported by us in steroidal 5,6-epoxide rearrangements.[20]

[12] J. G. Ll. Jones and B. A. Marples, *J. Chem. Soc.* (*C*), 1968, 2698.
[13] J. W. Blunt, A. Fischer, M. P. Hartshorn, F. W. Jones, D. N. Kirk, and S. W. Yoong, *Tetrahedron*, 1965, **21**, 1567.
[14] P. Morand and M. Kaufman, *J. Org. Chem.*, 1969, **34**, 2175.
[15] (*a*) R. Pappo and L. N. Nysted, U.S.P. 3,157,643 (*Chem. Abs.* 1965, **62**, 1720f); (*b*) R. Pappo and R. T. Nicholson, U.S.P. 3,159,619 (*Chem. Abs.*, 1965, **62**, 6540f).
[16] L. Ruzicka and A. C. Muhr, *Helv. Chim. Acta*, 1944, **27**, 503.
[17] M. Kocor, P. Lenkowski, A. Mironowicz, and L. Nowak, *Bull. Acad. polon. Sci. Sér. Sci. chim.*, 1966, **14**, 79.
[18] M. Akhtar and D. H. R. Barton, *J. Amer. Chem. Soc.*, 1964, **86**, 1528.
[19] S. Julia, B. Decouvelaere, and F. Engelmann, *Bull. Soc. chim. France*, 1966, 2277.
[20] I. G. Guest and B. A. Marples, *J.C.S. Perkin I*, 1973, 900.
[21] R. T. Blickenstaff and K. Sophasan, *Tetrahedron*, 1972, **28**, 1945.

EXPERIMENTAL

Solutions were dried over anhydrous sodium sulphate and solvents were removed *in vacuo* on a rotary evaporator. Plates (1 m × 0·5 mm thick) of Kieselgel PF 254 (Merck) were used for preparative t.l.c.

I.r. spectra were determined with Perkin-Elmer 237 and 257 spectrophotometers. ^{1}H N.m.r. spectra were determined, for solutions in deuteriochloroform (unless specified otherwise), at 60 MHz with a Perkin-Elmer R10 spectrometer. Mass spectra were recorded with A.E.I. MS 902 and MS 12 spectrometers. Rotations were measured for solutions in chloroform at 22° with a Bendix polarimeter 143C. M.p.s were measured with a Kofler hot-stage apparatus.

Attempted Preparation of 5-Bromo-3β-methoxy-5α-cholestan-6β-ol (4), *5-Bromo-6β-hydroxy-3β-methoxy-5α-androstan-17-one* (5), *and 5-Bromo-6β-hydroxy-3β-methoxy-5α-pregnan-20-one* (6).—Aqueous perchloric acid (60%; 0·4 ml) was added to a stirred solution of the 3β-methoxy-Δ^5-compound (1), (2), or (3) in redistilled dioxan (50 ml) at 15—20°. *N*-Bromoacetamide (0·4 g) was added during 5 min, after which the mixture was allowed to warm to room temperature. After a further 2 h, the solution was cooled to 5°, and aqueous sodium thiosulphate (10%; 25 ml) was added. After being shaken for 10 min, the mixture was extracted with chloroform, and the extracts were washed with aqueous sodium hydrogen carbonate solution and dried. Removal of the solvent gave the crude product.

Preparative t.l.c. of the crude product from 3β-methoxycholest-5-ene (1) (0·5 g), in ethyl acetate–benzene (1 : 5), gave 6α-*bromo*-3β-*methoxy*-5β-*cholestan*-5-*ol* (26) (100 mg), m.p. 163—165° [from dichloromethane–ether–petroleum (b.p. 40—60°)], $[\alpha]_D$ +18° (*c* 0·9), $\nu_{max.}$ 3460 cm^{-1} (OH), τ 5·4—5·8 (m, 6-H), 5·61 (s, 5-OH), 6·3 (m, $W_{\frac{1}{2}}$ *ca.* 9 Hz, 3-H), 6·65 (s, OMe), 9·04 (s, 10-Me), and 9·33 (s, 13-Me) {Found: $[M - Br]^+$ (78%) 417; $[M - HBr]^{+\cdot}$ (100%) 416·3641. $C_{28}H_{49}BrO_2$ requires 417; 416·3654}, and an impure fraction (154 mg) containing the 5α,6α-epoxide (14) and the 5β,6β-epoxide (17). Further t.l.c. of this fraction in ether–petroleum (b.p. 40—60°) (1 : 1) gave a mixture (50 mg) of the epoxides (14) and (17), τ 6·68 (s, 3-OMe), 6·5—6·9 (m, 3-H), 6·95 (d, *J ca.* 2·5 Hz, 6α-H), 7·1 (d, *J ca.* 4 Hz, 6β-H), 8·96 [s, 10-Me (5α)], 9·02 [s, 10-Me (5β)], 9·36 [s, 13-Me (5β)], and 9·39 [s, 13-Me (5α)].

Preparative t.l.c. of the crude product from 3β-methoxyandrost-5-en-17-one (2) (0·4 g) in ether–petroleum (b.p. 40—60°) (3 : 2) gave 6α-*bromo*-5-*hydroxy*-3β-*methoxy*-5β-*androstan*-17-*one* (27) (65 mg), m.p. 187—189° [from dichloromethane–ether–petroleum (b.p. 40—60°)], $[\alpha]_D$ +73° (*c* 0·55), $\nu_{max.}$ 3460 (OH) and 1740 cm^{-1} (C=O), τ 5·3—5·8 (m, 6-H), 5·57 (s, 5-OH), 6·30 (m, $W_{\frac{1}{2}}$ *ca.* 9 Hz, 3-H), 6·65 (s, OMe), 9·01 (s, 10-Me), and 9·14 (s, 13-Me), M^+ (1%) 398, 400, $[M - Br]^+$ (100%) 319·2273, $[M - HBr]^{+\cdot}$ (60%) 318 ($C_{20}H_{31}BrO_3$ requires $[M - Br]^+$ 319·2273) (Found: C, 60·5; H, 7·9. $C_{20}H_{31}BrO_3$ requires C, 60·15; H, 7·8%), and two fractions (49 mg and 230 mg) which contained the 5α,6α-epoxide (15) and the 5β,6β-epoxide (18). The smaller and less polar fraction was not purified further; further t.l.c. of the larger and more polar fraction in ether–petroleum (b.p. 40—60°) (1 : 1; 6 runs) yielded more (88 mg) of the mixed epoxides (15) and (18), τ 6·5—7·0 (m, 3-H), 6·65 (s, OMe), 6·9 (d, *J ca.* 2·5 Hz, 6α-H), 7·02 (d, *J ca.* 4 Hz, 6β-H), 8·93 [s, 10-Me (5α)], 8·99 [s, 10-Me (5β)], 9·15 [s, 13-Me (5β)], and 9·18 [s, 13-Me (5α)].

Preparative t.l.c. of the crude product from 3β-methoxypregn-5-en-20-one (3) (0·5 g) in ethyl acetate–benzene (1 : 5) gave 6α-*bromo*-5-*hydroxy*-3β-*methoxy*-5β-*pregnan*-20-*one* (28) (30 mg), m.p. 170—173° [from dichloromethane–ether–petroleum (b.p. 40—60°)], $\nu_{max.}$ 3460 (OH) and 1720 cm^{-1} (C=O), τ 5·3—5·8 (m, 6-H), 5·60 (s, 5-OH), 6·30 (m, $W_{\frac{1}{2}}$ *ca.* 9 Hz, 3-H), 6·65 (s, OMe), 7·80 (s, MeCO), 9·03 (s, 10-Me), and 9·40 (s, 13-Me) {Found: $[M - Br]^+$ (53%) 347·2575; $[M - HBr]^{+\cdot}$ (28%) 346, $[MeCO]^+$ (100%) 43. $C_{22}H_{35}BrO_3$ requires $[M - Br]^+$ 347·2586}, and an impure fraction (178 mg) containing the 5α,6α-epoxide (16) and the 5β,6β-epoxide (19). Further t.l.c. of this fraction in ether–petroleum (b.p. 40—60°) (1 : 1) gave a mixture (85 mg) of the epoxides (16) and (19), τ 6·69 (s, 3-OMe), 6·4—6·9 (m, 3-H), 6·94 (d, *J ca.* 2·5 Hz, 6α-H), 7·09 (d, *J ca.* 4 Hz, 6β-H), 7·91 (s, MeCO), 8·96 [s, 10-Me (5α)], 9·02 [s, 10-Me (5β)], 9·41 [s, 13-Me (5β)], and 9·43 [s, 13-Me (5α)].

3β,6β-*Dimethoxy*-5α-*cholestan*-5-*ol* (10) *and* 3β,5-*Dimethoxy*-5α-*cholestan*-6β-*ol* (11).—A dry methanolic solution of the crude products from the reaction of the 3β-methoxy-Δ^5-compound (1) (0·5 g) with *N*-bromoacetamide–perchloric acid was heated under reflux for 30 min. The solution was diluted with ether, washed with sodium hydrogen carbonate solution, and dried. Removal of the solvent, followed by preparative t.l.c. in ether–petroleum (b.p. 40—60°) (1 : 1), gave the 3β,6β-*dimethoxy-compound* (10) (120 mg), m.p. 130—132° (from methanol), $[\alpha]_D$ −28° (*c* 0·8), $\nu_{max.}$ 3450 (OH) and 1090 cm^{-1} (C–O), τ 6·2—6·6 (m, 3-H), 6·68 (s, 3-OMe), 6·75 (s, 6-OMe), 7·08 (m, $W_{\frac{1}{2}}$ *ca.* 6 Hz, 6-H), 8·92 (s, 10-Me), and 9·33 (s, 13-Me) (Found: C, 77·5; H, 11·7. $C_{29}H_{52}O_3$ requires C, 77·6; H, 11·7%), and the 3β,5α-*dimethoxy-compound* (11) (200 mg), m.p. 144—146° (from methanol), $[\alpha]_D$ −10° (*c* 1·85), $\nu_{max.}$ 3430 (OH) and 1080 cm^{-1} (C–O), τ 6·16 (m, $W_{\frac{1}{2}}$ *ca.* 6 Hz, 6-H), 6·68 (s, 3-OMe), 6·88 (s, 5-OMe), 6·5—7·0 (m, 3-H), 8·83 (s, 10-Me), and 9·33 (s, 13-Me) (Found: C, 77·8; H, 11·8. $C_{29}H_{52}O_3$ requires C, 77·6; H, 11·7%).

Treatment of a solution of 5,6α-epoxy-3β-methoxy-5α-cholestane [3] (0·5 g) in methanol (20 ml) with boron trifluoride–ether complex (0·5 ml) at room temperature for 1·5 h, followed by normal work-up and preparative t.l.c., gave the 3β,6β-dimethoxy-compound (10) (270 mg), m.p. 128—130°, $[\alpha]_D$ −28°.

Hydrolysis of 3β-*Methoxy*-5,6-*epoxide Mixtures*.—A solution of the epoxide mixture in methyl ethyl ketone (25 ml) was treated with aqueous perchloric acid (60%; 5 drops) and set aside at room temperature for 5 min. The mixture was diluted with ether, washed with sodium hydrogen carbonate solution, and dried. Removal of the solvent gave the crude 5α,6β-diol which was purified by preparative t.l.c. in ethyl acetate.

The mixture of epoxides (14) and (17) (45 mg) gave 3β-methoxy-5α-cholestane-5,6β-diol (29) (25 mg), m.p. 151—153° (from methanol), $[\alpha]_D$ −4·4° (lit.,[10] m.p. 154°, $[\alpha]_D$ −4·8°).

The mixture of epoxides (15) and (18) (88 mg) gave 5,6β-dihydroxy-3β-methoxy-5α-androstan-17-one (30) (40 mg), m.p. 261—264°. Acetylation with an excess of acetic anhydride in pyridine followed by normal work-up gave 6β-acetoxy-5-hydroxy-3β-methoxy-5α-androstan-17-one (32), m.p. 193—195° [from acetone–petroleum (b.p. 40—60°)], $[\alpha]_D$ +7·9° (*c* 0·75), $\nu_{max.}$ 3480 (OH), 1740 (C=O), 1225 (C–O), and 1095 cm^{-1} (C–O), τ 5·23 (m, $W_{\frac{1}{2}}$ *ca.* 6 Hz, 6-H), 6·3—6·7 (m, 3-H), 6·68 (s, OMe), 7·92 (s, OAc), 8·92 (s, 10-Me), and 9·10 (s, 13-Me) (Found: C, 69·5; H, 9·2. $C_{22}H_{34}O_5$ requires C, 69·8; H, 9·05%).

The mixture of epoxides (16) and (19) (85 mg) gave 5,6β-dihydroxy-3β-methoxy-5α-pregnan-20-one (31) (65 mg), m.p. 194—196° (from methanol), $[\alpha]_D$ +25° (*c* 1·0) (lit.,[22] m.p. 192—194°, $[\alpha]_D$ +39·3°), $\nu_{max.}$ 3440 (OH), 1705 (C=O), and 1090 cm^{-1} (C–O), τ 6·2—6·7 (m, 3-H), 6·48 (m, 6-H), 6·68 (s, OMe), 7·90 (s, MeCO), 8·84 (s, 10-Me), and 9·36 (s, 13-Me).

Decomposition of the 3β-*Acetoxy-bromohydrins* (7) *and* (8) *in Methanol.*—A solution of 3β-acetoxy-5-bromo-5α-cholestan-6β-ol (7) (200 mg) in dry methanol (32 ml) was heated under reflux for 2 h. The solution was diluted with water and extracted with ether. The extracts were washed with sodium hydrogen carbonate solution and dried. Removal of the solvent gave the crude product (150 mg), which after t.l.c. in ethyl acetate–benzene (1 : 5) gave 5-methoxy-5α-cholestane-3β,6β-diol (33) (110 mg), m.p. 197—199° (from methanol), $[\alpha]_D$ 0·5° (*c* 1·4) (lit.,[13] m.p. 198—199°, $[\alpha]_D$ 0°), and 3β-acetoxy-5-methoxy-5α-cholestan-6β-ol (36) (15 mg), m.p. 149—151° (from methanol), $[\alpha]_D$ −23·8° (*c* 1·58) (lit.,[14] m.p. 152—154°, $[\alpha]_D$ −119°). The very large difference in $[\alpha]_D$ between compounds (33) and (36) seems unreasonable in the light of comparison of the figures for compounds (34) and (37), and (35) and (38).

A solution of 3β-acetoxy-5-bromo-6β-hydroxy-5α-androstan-17-one (8) (100 mg) in dry methanol (12·5 ml) was heated under reflux for 1 h and worked up as before. Preparative t.l.c. of the crude product (60 mg) in ethyl acetate–benzene (2 : 1) gave 3β-6β-*dihydroxy-5-methoxy-5α-androstan-17-one* (34) (20 mg), m.p. 251—252° (from methanol), $[\alpha]_D$ +34° (*c* 0·25), $\nu_{max.}$ 3440 (OH), 1740 (C=O), and 1080 cm^{-1} (C–O) (Found: $[M]^{+\cdot}$ 336·2312. $C_{20}H_{32}O_4$ requires 336·2301), and 3β-acetoxy-6β-hydroxy-5-methoxy-5α-androstan-17-one (37) (30 mg), m.p. 198—200° (from methanol), $[\alpha]_D$ +13° (*c* 0·95) (lit.,[15a] m.p. 201—203°).

A solution of the bromohydrin (8) (200 mg) in dry methanol (25 ml) was shaken in a water-bath at 45°. T.l.c. showed that 3β-acetoxy-5,6β-epoxy-5β-androstan-17-one (18) was formed initially. After 7 h the bromohydrin (8) had disappeared and the products were 3β,6β-dihydroxy-5-methoxy-5α-androstan-17-one (34), 3β-acetoxy-6β-hydroxy-5-methoxy-5α-androstan-17-one (37), and 3β-hydroxy-5,6β-epoxy-5β-androstan-17-one (24).

Decomposition of the 3β-*Acetoxy-bromohydrins* (7)—(9) *in Methanol–Sodium Hydrogen Carbonate.*—(a) *At reflux.* A solution of the bromohydrin (200 mg) in methanol (25—30 ml) saturated with sodium hydrogen carbonate (100 mg) was heated under reflux for 1 h. The mixture was diluted with water and extracted with ether. The extracts were washed with aqueous sodium hydrogen carbonate solution, dried, and evaporated to yield the crude product which was separated into its components by preparative t.l.c. in ethyl acetate–benzene (1 : 3).

The bromohydrin (7) gave 5,6β-epoxy-5β-cholestan-3β-yl acetate (20) (12 mg), m.p. 110—112° (from methanol), $[\alpha]_D$ 0° (*c* 1·09) (lit.,[17] m.p. 109—112°, $[\alpha]_D$ 0°), 5,6β-epoxy-5α-cholestan-3β-ol (23) (3 mg), m.p. 128—129° (from methanol), $[\alpha]_D$ +7·8° (*c* 0·7) (lit.,[17] m.p. 128—131°, $[\alpha]_D$ +9°), 3β-acetoxy-5-methoxy-5α-cholestan-6β-ol (36) (97 mg),[14] and 5-methoxy-5α-cholestane-3β,6β-diol (33) (21 mg).[13]

The bromohydrin (8) gave 3β-acetoxy-5,6β-epoxy-5β-androstan-17-one (21) (20 mg), m.p. 185—187° [from acetone–petroleum (b.p. 40—60°)], $[\alpha]_D$ +40·5° (*c* 2·67) (lit.,[16] m.p. 186—187°, $[\alpha]_D$ +41°), 5,6β-epoxy-3β-hydroxy-5β-androstan-17-one (24) (49 mg), m.p. 158—160° [from acetone–petroleum (b.p. 40—60°)], $[\alpha]_D$ +56° (*c* 1·78) (lit.,[17] m.p. 161—164°, $[\alpha]_D$ +58°), 3β-acetoxy-6β-hydroxy-5-methoxy-5α-androstan-17-one (37) (64 mg), m.p. 198—200° (from methanol), $[\alpha]_D$ +13·2° (*c* 0·95) (lit.,[15a] m.p. 201—203°), and 3β,6β-dihydroxy-5-methoxy-5α-androstan-17-one (34) (29 mg).

The bromohydrin (9) gave 3β-acetoxy-5,6β-epoxy-5β-pregnan-20-one (22) (10 mg), m.p. 133—135° (from acetone–petroleum), $[\alpha]_D$ +51° (*c* 2·15) (lit.,[23] m.p. 133—135°, $[\alpha]_D$ +52°), 5,6β-epoxy-3β-hydroxy-5β-pregnan-20-one (25) (42 mg), m.p. 178—180° (from acetone–petroleum), $[\alpha]_D$ +66° (*c* 0·68) (lit.,[17] m.p. 180—184°, $[\alpha]_D$ +68°), 3β-acetoxy-6β-hydroxy-5-methoxy-5α-pregnan-20-one (38) (50 mg), m.p. 229—230° (from methanol), $[\alpha]_D$ +21° (*c* 1·03) (lit.,[15b] m.p. 234—236°), and 3β-6β-*dihydroxy-5-methoxy-5α-pregnan-20-one* (35) (33 mg), m.p. 235—237° (from methanol), $[\alpha]_D$ +44·2° (*c* 0·6), τ 6·0—6·4 (m, 3-H and 6-H), 6·19 (s, OMe), 7·95 (s, MeCO), 8·95 (s, 10-Me), and 9·37 (s, 13-Me) (Found: C, 72·1; H, 10·0. $C_{22}H_{36}O_4$ requires C, 72·5; H, 9·95%).

(b) *At* 45°. A 0·0187M-solution of the bromohydrin (200 mg) in dry methanol saturated with sodium hydrogen carbonate (100 mg) was immersed and shaken in a water-bath at 45° for 1 h. Work-up in the usual manner afforded a mixture of 5β,6β-epoxide and starting material, which was separated by preparative t.l.c. in ethyl acetate–benzene (1 : 5).

The bromohydrins (7)—(9) gave the corresponding 3β-acetoxy-5β,6β-epoxides (20)—(22) (120, 80, and 86 mg, respectively) and starting material contaminated with the epoxide (16, 60, and 49 mg, respectively). These experiments were repeated and the disappearance of the starting material was followed by t.l.c. (see Table 3).

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