19-Hydroxy-steroids. Part 7.[1] Boron Trifluoride-catalysed Reactions of 19-Hydroxy- and 19-Acetoxy-5,6-epoxy-steroids

By **Harold Mastalerz** and **Peter Morand,*** Department of Chemistry, University of Ottawa, Ottawa, Ontario, Canada K1N 9B4

The effects of strong electron-withdrawing substituents at C-19 upon the boron trifluoride-catalysed reactions of 5,6-epoxy-steroids were examined. 3β-Acetoxy-5,6β-epoxy-5β-cholestan-19-ol (4) and 3β-acetoxy-5,6β-epoxy-19-hydroxy-5β-androstan-17-one (2) reacted with boron trifluoride gas in benzene with the loss of the C-10 groups as formaldehyde and subsequent dehydration to give the 1(10),5-dienes (16) and (17), respectively. 3β,19-Diacetoxy-5,6β-epoxy-5β-cholestane (5) and 3β,19-diacetoxy-5,6β-epoxy-5β-androstan-17-one (3) gave as the only rearrangement product the B-nor-5β-formyl-steroids (26) and (25). 3β-Acetoxy-5,6α-epoxy-5α-cholestan-19-ol (12) and its 19-acetate derivative (13) gave products arising from the participation of the 19-function in the epoxide opening.

SOME time ago we examined [2] the possible intermediacy of 5,6β-epoxy-3β,19-dihydroxy-5β-androstan-17-one (1) in the biosynthesis of estrone. Although this was ruled out by incubation experiments, we found that the 19-hydroxy-group had some rather interesting effects upon the reaction of the 5,6-epoxide, particularly with hydride reagents.[3] This led us to explore further the chemistry of C-19 substituted 5,6-epoxy-steroids and in this paper we report the boron trifluoride-catalysed reactions of such compounds in the cholestane and (in part) the androstane series.

It has been shown that the boron trifluoride-catalysed reactions of 5,6-epoxy-steroids are susceptible to changes in substituents at C-3,[4] C-17,[5] and to some extent C-10.[6] In the latter case, the effects of a C-10 [6a] ethyl or ethenyl [6b] group were examined. Although no clearly definable trends were established, it was found that the vinyl group, which would exert a $-I$ effect,[7] did appear to make C(5)–O cleavage more difficult and thereby allow nucleophilic attack by fluoride-donating species to compete more effectively. Since we were interested in observing the effect of groups which would be inductively more electron-withdrawing, it may be expected that fluorohydrin formation would become preponderant. In fact, it was found that the use of boron trifluoride gas [8] rather than its ether complex does give rise to a significant amount of product arising from C(5)–O cleavage.

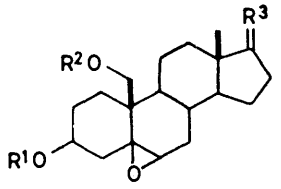
RESULTS

Preparation of the Epoxides.—The 5β,6β-epoxides in the cholestane [3] (4) and androstane [2] (2) series were readily available from the corresponding Δ^5-compounds, (8) and (10) respectively. However, the directive influence of the 19-hydroxy-group upon the epoxidation posed a problem in the preparation of the corresponding 5α,6α-epoxides. Epoxidation of the 19-acetate (9) with *m*-chloroperbenzoic acid gave a mixture of 5,6-epoxides (5α,6α : 5β, 6β *ca.* 3 : 1) but attempts [9] at selectively hydrolysing the 19-acetate function only resulted in the selective removal of the 3-acetyl group to give (14). This problem was overcome by using the 19-t-butyldimethylsilyl ether (11) which afforded, on epoxidation, a mixture of isomeric 5,6-epoxides [(15) : (6) *ca.* 2 : 1]. Subsequent desilylation with tetrabutylammonium fluoride gave the desired 3β-acetoxy-19-hydroxy-5,6α-epoxy-5α-steroid (12).

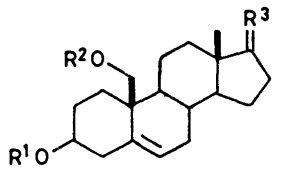
Boron Trifluoride-catalysed Reactions.—For these reactions it was found that the conditions under which the boron trifluoride gas was employed has a significant influence on the nature of the products obtained. In the first group of experiments a quantity of benzene was saturated with boron trifluoride gas and this solution was then added to a solution of the epoxide in benzene. Under these conditions, 19-hydroxy-5,6β-epoxy-5β-cholestane (4) gave, as the major product (47%), the known [10] 1(10),5-diene (16) ($\lambda_{max.}$ 243 nm). A second product (9%) was also isolated and it was identified as the 6β-19-methylenedioxy-steroid (18). This assignment was based mainly on its ^{1}H n.m.r. spectrum which showed a methylene quartet (δ_A 3.21, δ_B 3.99, J_{AB} 12 Hz) for the 19-methylene group, another methylene quartet (δ_A 4.59, δ_B 4.98, J_{AB} 8 Hz) for a methylene acetal, an apparent triplet [δ 4.43 (J 2 Hz)] assigned to the equatorial 6α-H, a multiplet [δ 5.25 ($W_{\frac{1}{2}}$ 18 Hz)] for the 3α-H, and a broadened singlet (δ 5.71) for the olefinic 4-H. The structure was confirmed by the following (Scheme 1) independent synthesis. Transdiaxial opening of the 19-hydroxy-5β,6β-epoxide (4) with hydrobromic acid followed by acetylation (acetic anhydride–perchloric acid) gave the triacetoxy-bromide (30). This was dehydrohalogenated by refluxing in pyridine to give the Δ^4-compound (31) which was then hydrolysed (methanolic sodium carbonate) to afford the triol (32). Initial attempts at converting this triol into a 6β,19-methylenedioxy-derivative under acidic conditions were apparently complicated by acid-catalysed dehydration of the allylic system. However, upon turning to basic, phase-transfer conditions,[11] the triol (32) was found to react with methylene chloride to give (33). This 6β,19-methylenedioxy-derivative presumably arises *via* initial formation of a 19-chloromethyl ether which would be best disposed for attack by the axial 6β-hydroxy-group. Acetylation of the crude 3β-alcohol (33) gave material identical with (18).

The corresponding 19-hydroxy-5,6β-epoxy-5β-androstan-17-one (2) similarly afforded the diene [12] (17) (30%) and the methylenedioxy-compound (19) (16%) upon treatment with boron trifluoride.

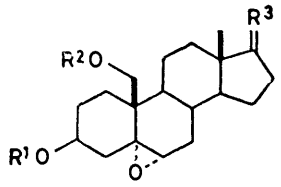
We next examined the reactions of the 19-acetoxy-5β,6β-epoxy-steroids. Treatment of the androstanone epoxide (3) with boron trifluoride, as described above, gave recovered starting material (19%), the fluorohydrin (22) (43%), and a third component obtained in an impure form after chromatography. The fluorohydrin was identified by its mass spectrum (*m/e* 424, molecular ion) and the simi-



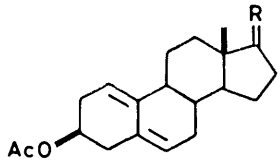
(1) $R^1 = R^2 = H, R^3 = O$
(2) $R^1 = Ac, R^2 = H, R^3 = O$
(3) $R^1 = R^2 = Ac, R^3 = O$
(4) $R^1 = Ac, R^2 = H, R^3 = H, C_8H_{17}$
(5) $R^1 = R^2 = Ac, R^3 = H, C_8H_{17}$
(6) $R^1 = Ac, R^2 = Si(Bu^t)(Me)_2, R^3 = H, C_8H_{17}$
(7) $R^1 = R^2 = H, R^3 = H, C_8H_{17}$



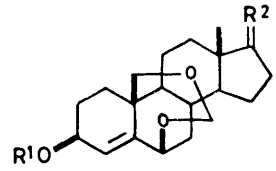
(8) $R^1 = Ac, R^2 = H, R^3 = H, C_8H_{17}$
(9) $R^1 = R^2 = Ac, R^3 = H, C_8H_{17}$
(10) $R^1 = Ac, R^2 = H, R^3 = O$
(11) $R^1 = Ac, R^2 = Si(Bu^t)(Me)_2, R^3 = H, C_8H_{17}$



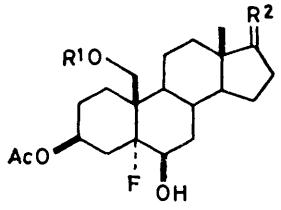
(12) $R^1 = Ac, R^2 = H, R^3 = H, C_8H_{17}$
(13) $R^1 = R^2 = Ac, R^3 = H, C_8H_{17}$
(14) $R^1 = H, R^2 = Ac, R^3 = H, C_8H_{17}$
(15) $R^1 = Ac, R^2 = Si(Bu^t)(Me)_2, R^3 = H, C_8H_{17}$



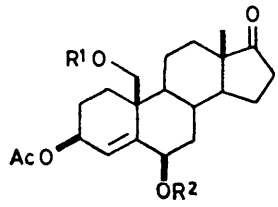
(16) $R = H, C_8H_{17}$
(17) $R = O$



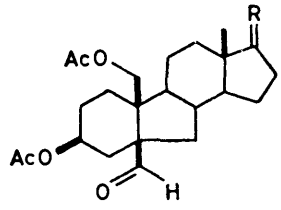
(18) $R^1 = Ac, R^2 = H, C_8H_{17}$
(19) $R^1 = Ac, R^2 = O$



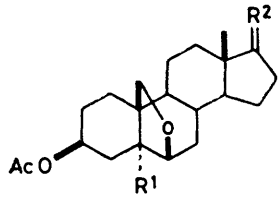
(20) $R^1 = H, R^2 = H, C_8H_{17}$
(21) $R^1 = Ac, R^2 = H, C_8H_{17}$
(22) $R^1 = Ac, R^2 = O$



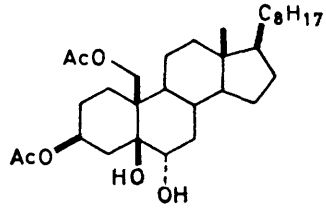
(23) $R^1 = R^2 = H$
(24) $R^1 = R^2 = Ac$



(25) $R = O$
(26) $R = H, C_8H_{17}$



(27) $R^1 = OH, R^2 = H, C_8H_{17}$
(28) $R^1 = F, R^2 = O$



(29)

larity in its spectral properties with the corresponding cholestane analogue which will be discussed subsequently. The third component was acetylated and re-chromatographed. This allowed for isolation of the 4-olefin (23) as its triacetate (24). The structure of the latter compound was verified by an independent synthesis from (2) (Scheme 1) using the same sequence that was employed in the preparation of the cholestane analogue (31).

The reaction of (3) was repeated, only this time the boron trifluoride gas was bubbled directly into a benzene solution of the epoxy-steroid. The fluorohydrin (22) was again obtained, albeit in a lesser amount (26%), together with a

mixture of olefinic material which was left unidentified, although the ^{1}H n.m.r. spectrum did indicate the presence of some of the 4-olefin (23), and a new product (16%). The ^{1}H n.m.r. spectrum of the latter compound indicated the presence of an aldehyde group (δ 9.70) consistent with the 5β-formyl-B-nor-structure (25). Further proof for this assignment of structure was obtained for the analogous cholestane and is presented below.

Similarly, when boron trifluoride gas was bubbled into a solution of 3β,19-diacetoxy-5,6β-epoxy-5β-cholestane (5), the fluorohydrin (21) (36%), the aldehyde (26) (21%), and a mixture of olefinic material were obtained. The structure of the fluorohydrin (21) was confirmed by its conversion (refluxing methanolic sodium carbonate) into the 5β,6β-epoxide (7). The aldehyde (26) and its androstane analogue (25) both had similar spectral properties but there remained some ambiguity regarding the nature of the A/B ring junction since the 3α-proton appeared as a multiplet having $W_{\frac{1}{2}}$ 15 Hz. The following chemical transformations (Scheme 2) were therefore carried out to obtain an unambiguous assignment. The aldehyde (26) was hydrolysed (methanolic sodium carbonate) to give a compound which existed in the form of a lactol, presumably (35). The ^{1}H n.m.r. spectrum showed a singlet for a lactol methine proton (δ 4.96), a quartet for the 19-methylene protons (δ_A 3.63, δ_B3.80, J_{AB} 10 Hz), and a multiplet for the 3α-proton [δ 3.96 ($W_{\frac{1}{2}}$ 16 Hz)]. Oxidation of the lactol (35) gave the keto-lactone (36) which was readily identifiable from its i.r. spectrum (1 769 and 1 725 cm^{-1}). This would confirm that the lactol was formed by cyclisation of the 19-hydroxy-group and the 5β-formyl-group and thereby establish the *cis* nature of the A/B ring junction.

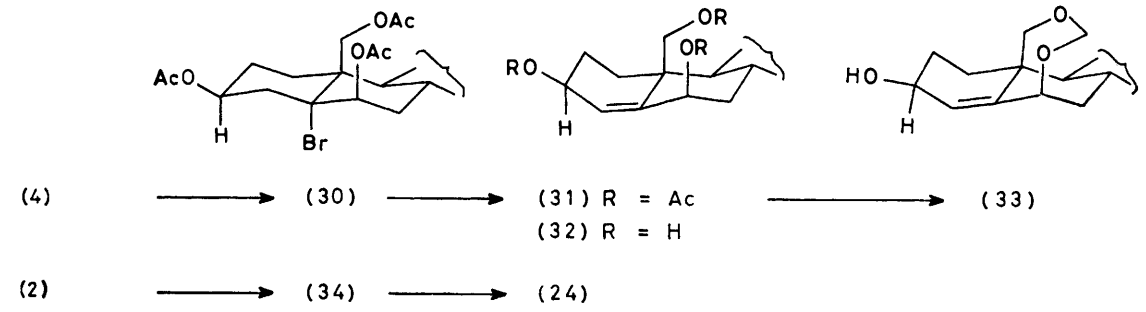
Lastly the boron trifluoride-catalysed reactions of the 5,6α-epoxy-5α-cholestanes were examined. The 19-hydroxy-5α,6α-epoxide (12) gave, as the major product (64%), the 6β,19-oxide (27) which had similar spectral and physical properties to those reported.[13] The 19-acetate (13) cleanly gave the known 5β,6α-diol (29) [14] in 95% yield.

DISCUSSION

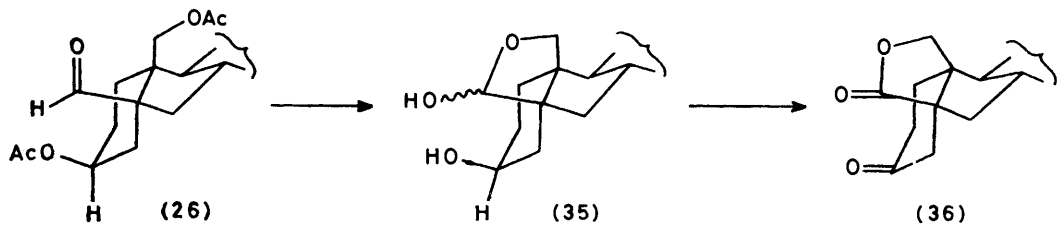
The major products which were obtained from the 19-hydroxy-5β,6β-epoxides (4) and (2) were the dienes (16) and (17). These products are best rationalised (Scheme 3) as being derived from a C-5 carbocation (37). This could have been formed by direct opening of the epoxide by boron trifluoride or by protonation by a boron trifluoride-complexed 19-hydroxy-group. The latter course seems likely, since the existence of hydrogen bonding between the 19-hydroxy-group and the 5β,6β-epoxide has been demonstrated.[15] As well, there remains the possibility [16] that the epoxide is initially converted into a fluorohydrin and that this species subsequently reacts with boron trifluoride to give the observed product. To test this, some of the fluorohydrin (20) was prepared by treating the epoxide (4) with boron trifluoride–ether complex.[17] When treated with boron trifluoride gas, the fluorohydrin (20) was recovered unchanged, thereby ruling out its possible involvement.

Once an open carbocation at C-5 has been formed (Scheme 3), the 10-hydroxymethylene group would be suitably placed such that fragmentation with the loss of formaldehyde could occur. The allylic alcohol (39) thus formed was not observed but would be expected, under the reaction conditions, to be readily dehydrated to the diene, (16) or (17). The latter step has been demonstrated [18] with similar $\Delta^{5(10)}$-6β-hydroxy-steroids which undergo facile dehydration with protic acids to give 1(10),5-dienes.

The methylenedioxy-compounds (18) and (19), the compounds obtained on treatment of the 19-hydroxy-5β,6β-epoxides with boron trifluoride, could also be derived from the carbocation (37). The loss of a proton from C-4 would give rise to the diol (38), which in turn



SCHEME 1



SCHEME 2

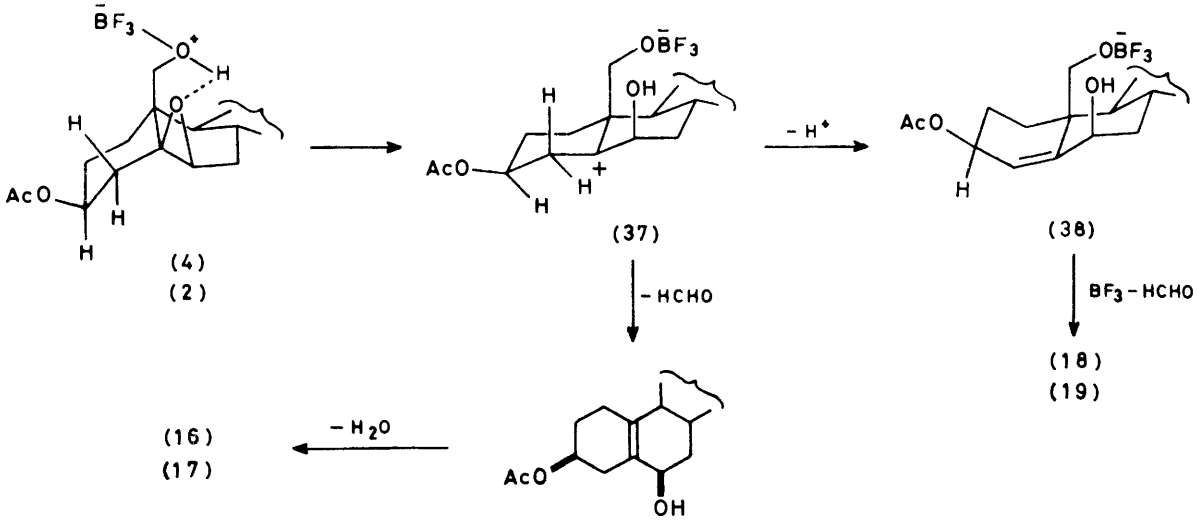
could react with the formaldehyde present to give (18) or (19).

In the case of the 19-acetoxy-5β,6β-epoxides (5) and (3), the presence of the 19-acetate group prevented fragmentation involving the C-10 substituent and its $-I$ effect favoured the formation of fluorohydrin. The only rearrangement products observed were the aldehydes (26) and (25). These would have been formed by migration [16] of the C-6–C-7 bond along the α-face of a C-5 carbocation derived from the 5β,6β-epoxides. Again, the possibility of a fluorohydrin precursor was ruled out since (22), upon treatment with boron trifluoride, gave only the 6β,19-oxide (28) (25%), apart from recovered starting material (58%). Evidently, the 3β- and 19-acetate groups sufficiently suppress ionisation of the 5α-fluoride such that the only reaction which does occur is the boron trifluoride-catalysed displacement of the 19-acetate function by the 6β-alcohol group.

The relative yields of products obtained from the androstane epoxide (3) when the two different methods of introducing boron trifluoride were used appear to reflect the fact that epoxide rearrangements can follow different paths with different reagent systems,[19] in this case the variable being the concentration of Lewis acid present. When a saturated solution of boron trifluoride in benzene is added to the epoxide, the amount of boron trifluoride would be less. A good portion of it would be complexed with the other functional groups present in the molecule and, even though the necessary precautions were taken, with traces of water which may have been present. This would diminish its overall reactivity as shown by the amount of fluorohydrin obtained together with unreacted starting material. With the direct introduction of boron trifluoride gas an excess of reagent would be present, allowing for the interaction of the epoxide with uncomplexed Lewis acid. This would appear to account for the appearance of rearrangement product, namely the aldehyde (25), under these conditions but not the former ones.

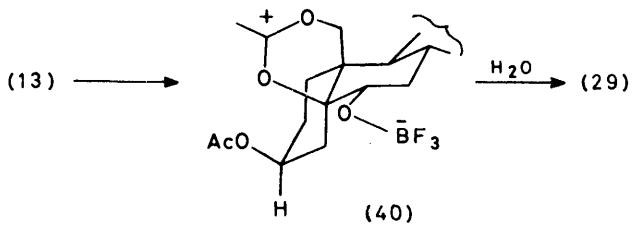
The reactions of the α-epoxides (12) and (13) essentially parallel those found with protic acids,[20] namely that neighbouring-group participation directs the course of epoxide opening. For (12), the 19-hydroxy-group is suitably situated for diaxial opening of the boron trifluoride-complexed epoxide to give the 6β,19-oxide (27). In the case of (13), attack by the 19-acetate group upon C-5 leads to an acetoxonium ion intermediate (40) [21] (Scheme 4) which, upon hydrolysis, gives rise to the observed diequatorial alcohol (29).

It can therefore be seen that the presence of a strong



SCHEME 3

$-I$ group at C-19 significantly alters the course of boron trifluoride-catalysed reactions of 5β,6β-epoxy-steroids. Most notable is the extent to which rearrangement is suppressed. The contraction of the B-ring, observed in



the case of the 19-acetates, (3) and (5), is the only process of this type that seems to be favoured. Other possible modes of rearrangement, such as those leading to 6-keto-compounds [22] or 1(10 → 5)-*abeo*-compounds [5] were not observed. It remains difficult to determine whether the effect of the C-17 substituent is a factor when comparing the yields of material obtained from the 5β,6β-epoxy-cholestanes with those obtained from the corresponding androstan-17-ones. Rather than being a long-range

transmission effect, the observed variations in yields may be due simply to differences in BF_3 concentrations which are inevitable when using BF_3 in the gaseous phase.

The C-19 alcohols underwent fragmentive loss of the C-10 substituent, a process which has the features of a Grob fragmentation, although the two bonds being broken are not in the usual *anti*-periplanar arrangement. This type of fragmentation involving β-substituted epoxides is of interest to us since it may be operative in the biosynthesis of certain sesquiterpenes,[23] and we also believe that it may be the mode in which the angular methyl group at C-10 is eliminated in estrone biosynthesis.[12] In a future paper, we will communicate our findings on the acid-catalysed reactions of 19-substituted-4,5-epoxyandrostane-3,17-diones, which may be involved in such a process.

EXPERIMENTAL

Melting points were determined on a Hoover Uni-Melt apparatus. Optical rotations are for chloroform solutions using a Perkin-Elmer 141 polarimeter. U.v. spectra are for solutions in ethanol obtained on a Perkin-Elmer 202 spectrophotometer. I.r. spectra were recorded on a Beckman IR-8 spectrophotometer using chloroform solutions. Hydrogen-1 n.m.r. spectra were obtained on Varian T-60 or H-100 instruments using deuteriochloroform as solvent and tetramethylsilane as internal standard. Mass spectra were recorded with an AEI MS902S spectrometer. The silica gel used for column chromatography was from Baker (60—200 mesh). T.l.c. was performed on Merck pre-coated Silica Gel 60 F-254 plates. Light petroleum used was of the boiling range 30—60 °C. Microanalyses were carried out by Galbraith Laboratories, Knoxville, Tenn. 37921, U.S.A.

3β-19-*Diacetoxy*-5,6β-*epoxy*-5β-*androstan*-17-*one* (3).—3β-Acetoxy-5,6β-epoxy-19-hydroxy-5β-androstan-17-one (2) [2] was acetylated (acetic anhydride–pyridine) to give the *diacetate* (3), m.p. 133—134 °C (prisms from light petroleum); $[\alpha]_D$ +26° (*c* 5.7); $\nu_{max.}$ 1 735 cm^{-1}; δ 0.87 (s, 3 H, 18-Me), 2.00 and 2.08 (6 H, 2 × OAc), 3.07 (s, 1 H, 6α-H), 4.33 (q, 2 H, δ_A 4.09, δ_B 4.58, J_{AB} 12 Hz, 19-CH_2), and 4.67 (m, 1 H, $W_{\frac{1}{2}}$ 24 Hz, 3α-H); *m/e* 404 (M^+) (Found: C, 68.35; H, 7.85. $C_{23}H_{32}O_6$ requires C, 68.29; H, 7.98%).

3β-*Acetoxy*-5,6α-*epoxy*-5α-*cholestan*-19-*ol* (12).—A solution of 3β-acetoxycholest-5-en-19-ol (8) (12 g) in dimethylformamide (50 ml) containing t-butyldimethylsilyl chloride [24] (4.82 g) and imidazole (4.60 g) was stirred at room temperature for 20 h. Water (50 ml) was then added and the suspension extracted with methylene chloride (3 × 100 ml). The organic extracts were washed with water (2 × 50 ml) and brine (50 ml), dried (sodium sulphate), and the solvent removed. Chromatography on silica gel (eluting with hexane) gave 3β-acetoxy-19-t-butyldimethylsilyloxycholest-5-ene (11) (13.87 g) as a white solid; $\nu_{max.}$ 1 735 cm^{-1}; δ *ca.* 0 (s, Me_2Si) 0.82 (s, Bu^tSi), 1.97 (s, 3 H, OAc), 3.64 (q, 2 H, δ_A 3.57, δ_B 3.71, J_{AB} 11 Hz, 19-CH_2), 4.58 (m, 1 H, $W_{\frac{1}{2}}$ 22 Hz, 3α-H), and 5.56 (m 1 H, 6-H); *m/e* 498 (M^+ − HOAc). The silyl ether (11) (13.64 g) was dissolved in methylene chloride (50 ml) and treated with a solution of *m*-chloroperbenzoic acid (5.5 g, 85%) in methylene chloride (60 ml). After standing at room temperature for 1 h, it was worked up in the usual manner. This left an oil (14.7 g) which was taken up in tetrahydrofuran (15 ml) and a solution of tetrabutylammonium fluoride (47 ml, 1M in tetrahydrofuran, *ca.* 5 mol % water) was added. After 3 h, the solution was poured into water (60 ml) and extracted with methylene chloride. The solvent was removed and the residual semi-solid was chromatographed on silica gel (250 g) [eluting with ethyl acetate–hexane (3 : 7)] affording 3β-*acetoxy*-19-*t-butyldimethylsilyloxy*-5,6β-*epoxy*-5β-*cholestane* (6) (2.48 g), m.p. 97—98 °C (needles from acetone); $\nu_{max.}$ 1 730 cm^{-1}; δ 0.10 (s, 6 H, Me_2Si), 0.92 (s, 6 H, Bu^tSi), 2.00 (s, 3 H, OAc), 2.92 (s, 1 H, 6α-H), 3.72 (s, 2 H, 19-CH_2), 4.82 (m, 1 H, $W_{\frac{1}{2}}$ 24 Hz, 3α-H) (Found: C, 73.3; H, 10.75. $C_{35}H_{62}O_4Si$ requires C, 73.11; H, 10.87%) [a sample of this compound on treatment with tetrabutylammonium fluoride for 43 h gave material which was identical (t.l.c. and ^1H n.m.r.) with (4)]: 3β-acetoxy-5,6β-epoxy-5β-cholestan-19-ol (4) (1.74 g) which was identical (t.l.c. and ^1H n.m.r.) with authentic material: and 3β-acetoxy-5,6α-epoxy-5α-cholestan-19-ol (12) (6.78 g), m.p. 186—188 °C; $[\alpha]_D$ −47° (lit.,[3] m.p. 184—186 °C, $[\alpha]_D$ −57°).

Reactions with Boron Trifluoride.—Method A. The epoxide (1 g) was dissolved in dry benzene (50 ml) and a solution of dry benzene (25 ml), which had been saturated with boron trifluoride gas, was added. The mixture was stirred for 10 min. and the reaction was then stopped by the addition of an aqueous solution of sodium hydrogencarbonate (50 ml, 5%). The organic layer was diluted with diethyl ether (75 ml), separated, washed with water (3 × 50 ml) and brine (50 ml), dried (anhydrous sodium sulphate), and the solvents removed.

Method B. Boron trifluoride gas was bubbled directly into a solution of the epoxide (1 g) in dry benzene (100 ml) until a brownish gel, indicative of the epoxide–boron trifluoride complex, was formed. In those instances where such a gel was not formed, the gas was bubbled into the solution for 2 min. The reaction was stopped after 5 min and worked up as above.

Reaction of 3β-*Acetoxy*-5,6β-*epoxy*-5β-*cholestan*-19-*ol* (4) *with Boron Trifluoride.*—The 5β,6β-epoxide (4) (2 g) was treated with boron trifluoride according to method A. Chromatography on silica gel (eluting with benzene) gave 3β-acetoxy-19-norcholesta-1(10),5-diene (16) (840 mg), m.p. 74—76 °C (prisms from methanol–ether), $\lambda_{max.}$ 243 nm (lit.,[10] m.p. 74–75 °C, $\lambda_{max.}$ 240 nm) (Found: C, 81.35; H, 10.85. $C_{28}H_{44}O_2$ requires C, 81.49; H, 10.73%): and 3β-*acetoxy*-6β,19-*methylenedioxycholest*-4-*ene* (18) (193 mg), m.p. 121—122 °C (needles from methanol–ether); $\nu_{max.}$ 1 735 cm^{-1} (acetate C=O); δ 2.05 (s, 3 H, OAc), 3.60 (q, 2 H, δ_A 3.21, δ_B 3.99, J_{AB} 12 Hz, 19-CH_2), 4.43 (t, 1 H, *J ca.* 2 Hz, 6α-H), 4.79 (q, 2 H, δ_A 4.59, δ_B 4.98, J_{AB} 8 Hz, OCH_2O), 5.25 (m, 1 H, $W_{\frac{1}{2}}$ *ca.* 18 Hz, 3α-H), and 5.71 (s, 1 H, 4-H); *m/e* 412 (M^+ − HOAc) (Found: C, 76.7; H, 10.45. $C_{30}H_{44}O_4$ requires C, 76.23; H, 10.24%).

Reaction of 3β-*Acetoxy*-19-*hydroxy*-5,6β-*epoxy*-5β-*androstan*-17-*one* (2) *with Boron Trifluoride.*—Similarly, the androstanone (2) (1 g) afforded (method A) 3β-*acetoxy*-19-*norandrosta*-1(10),5-*dien*-17-*one* (17) (260 mg), m.p. 115 °C (prisms from benzene–ether); $\lambda_{max.}$ 240 nm; $\nu_{max.}$ 1 735 cm^{-1} (acetate CO and 17-CO); δ 0.89 (s, 3 H, 18-Me), 2.02 (s, 3 H, OAc), 5.01 (m, 1 H, $W_{\frac{1}{2}}$ 18 Hz, 3α-H), and 5.31—5.58 (m, 2 H, 1-H and 4-H) (Found: C, 76.45; H, 8.3. $C_{20}H_{26}O_3$ requires C, 76.40; H, 8.34%): and 3β-*acetoxy*-6β,19-*methylenedioxyandrost*-4-*en*-17-*one* (19) (143 mg), m.p. 160—161 °C (prisms from methanol); $\nu_{max.}$ 1 740 cm^{-1} (acetate CO and 17-CO); δ 0.97 (s, 3 H, 18-Me), 2.08 (s, 3 H, OAc), 3.64 (q, 2 H, δ_A 3.28, δ_B 4.00, J_{AB} 12 Hz, 19-CH_2), 4.50 (m, 1 H, $W_{\frac{1}{2}}$ *ca.* 6 Hz, 6α-H), 4.81 (q, 2 H, δ_A 4.62, δ_B

5.00, J_{AB} 7 Hz, OCH_2O), 5.12 (m, 1 H, $W_{\frac{1}{2}}$ *ca.* 18 Hz, 3α-H), and 5.76 (s, 1 H, 4-H) (Found: C, 70.7; H, 8.20. $C_{22}H_{30}O_5$ requires C, 70.56; H, 8.08%).

Synthesis of 3β-*Acetoxy*-6β,19-*methylenedioxycholest*-4-*ene* (18).—Hydrobromic acid (0.43 ml, 50%) was added to an ice-cooled solution of 3β-acetoxy-5,6β-epoxy-5β-cholestan-19-ol (4) (1.17 g) and this was stirred for 15 min. Acetic anhydride (10 ml) followed by perchloric acid (3 drops, 70%) were added and the solution was left for 1 h. Water was then added and 5-bromo-3β,6β,19-triacetoxy-5α-cholestane (30) (1.25 g) separated as an oily precipitate; δ 2.02, 2.08, and 2.13 (9 H, 3 × OAc), 4.57 (s, 2 H, 19-CH_2), 5.33 (m, $W_{\frac{1}{2}}$ *ca.* 8 Hz, 6α-H), and 5.47 (m, $W_{\frac{1}{2}}$ *ca.* 24 Hz, 3α-H). The crude bromide (30) (1.25 g) was taken up in pyridine (10 ml) and refluxed for 6 h. Water was added and 3β,6β,19-*triacetoxycholest*-4-*ene* (31) (870 mg) separated, m.p. 138—139 °C (needles from acetone-water); $\nu_{max.}$ 1 730 cm^{-1} (acetate C=O); δ 1.99 (s, 3 H, OAc), 2.07 (s, 6 H, 2 × OAc), 4.50 (q, 2 H, δ_A 4.19, δ_B 4.48, J_{AB} 11 Hz, 19-CH_2), 5.23 (m, 2 H, 3α-H, 6α-H), and 5.80 (d, 1 H, *J* 2 Hz, 4-H) (Found: C, 72.55; H, 9.65. $C_{33}H_{52}O_6$ requires C, 72.76; H, 9.62%). A suspension of the triacetate (31) (750 mg) and sodium carbonate (700 mg) in methanol (50 ml) was refluxed for 7 h. Work-up afforded *cholest*-4-*ene*-3β,6β,19-*triol* (32) (424 mg), m.p. 209—211 °C (needles from ethyl acetate); *m/e* 400 ($M^+ - H_2O$) (Found: C, 77.6; H, 11.1. $C_{27}H_{46}O_3$ requires C, 77.47; H, 11.08%). A solution of the triol (32) (183 mg) and benzyltriethylammonium chloride (50 mg) in methylene chloride (20 ml) was added to a solution of potassium hydroxide (15 ml, 50%) and the mixture refluxed for 2 h. The organic phase was separated, washed with water, dried (sodium sulphate), and the solvent removed. The residual oil was chromatographed on silica gel [eluting with ethyl acetate–hexane (1 : 1)] affording 6β,19-methylenedioxycholest-4-en-3β-ol (33) as an oil; δ 3.61 (q, 2 H, δ_A 3.15, δ_B 4.07, J_{AB} 12 Hz, 19-CH_2), 4.23 (m, 3α-H), 4.46 (m, 6α-H), 4.79 (q, 2 H, δ_A 4.65, δ_B 4.93, J_{AB} 8 Hz, OCH_2O), and 5 80 (s, 1 H, 4-H), which was taken directly and acetylated (acetic anhydride–pyridine) to give the acetate (18) (53 mg), m.p. 118—120 °C, mixed m.p. 118—121 °C, identical (t.l.c. and ^1H n.m.r.) with that previously obtained.

Synthesis of 3β,6β,19-*Triacetoxyandrost*-4-*en*-17-*one*(24).—Similarly, 3β-acetoxy-19-hydroxy-5,6β-epoxy-5β-androstan-17-one (2) afforded 5-bromo-3β,6β,19-triacetoxy-5α-androstan-17-one (34); δ 0.90 (s, 3 H, 18-Me), 2.03, 2.10, and 2.17 (9 H, 3 × OAc), 4.61 (q, 2 H, δ_A 4.53, δ_B 4.69, J_{AB} 13 Hz, 19-CH_2), 5.33 (m, $W_{\frac{1}{2}}$ *ca.* 8 Hz, 6α-H), and 5.43 (m, $W_{\frac{1}{2}}$ *ca.* 24 Hz, 3α-H); *m/e* 525/527 (M^+), which was dehydrobrominated to the 4-*olefin* (24), m.p. 132—133 °C (needles from ether–light petroleum); $\nu_{max.}$ 1 735 cm^{-1} (acetate CO and 17-CO); δ 0.95 (s, 3 H, 18-Me), 2.02 (s, 3 H, OAc), 2.08 (s, 6 H, 2 × OAc), 4.36 (q, 2 H, δ_A 4.30, δ_B 4.42, J_{AB} 12 Hz, 19-CH_2), 5.20 (m, 2 H, 3α- and 6α-H), 5.88 (s, 1 H, 4-H); *m/e* 386 (M^+ — HOAc) (Found: C, 67.4; H, 7.75. $C_{25}H_{34}O_7$ requires C, 67.24; H, 7.68%).

Reaction of 3β,19-*Diacetoxy*-5,6β-*epoxy*-5β-*androstan*-17-*one* (3) *with Boron Trifluoride*.—The epoxide (3) (1.4 g) was treated with boron trifluoride according to method A, but in this case the reaction was allowed to proceed for 45 min before work-up. The residual oil was chromatographed on silica gel (180 g) [eluting with mixtures of ethyl acetate–hexane varying from (1 : 4) to (3 : 7)]. This afforded starting material (266 mg) [which was identical (t.l.c. and ^1H n.m.r.) with authentic material]: 3β-19-*diacetoxy*-5-*fluoro*-5α-*androstan*-17-*one* (22) (633 mg), m.p. 109—111 °C (prisms from ether–light petroleum); $[\alpha]_D$ +27° (*c* 8.1); $\nu_{max.}$ 3 500 (OH) and 1 735 cm^{-1} (acetate CO and 17 CO); δ 0.88 (s, 3 H, 18-Me), 2.02 and 2.08 (6 H, 2 × OAc), 3.72 (m, 1 H, $W_{\frac{1}{2}}$ 8 Hz, 6α-H), 4.52 (q, 2 H, δ_A 4.40, δ_B 4.64, J_{AB} 14 Hz, 19-CH_2) and 5.03 (m, 1 H, $W_{\frac{1}{2}}$ 22 Hz, 3α-H); *m/e* 424 (M^+) (Found: C, 64.85; H, 7.55. $C_{23}H_{33}FO_6$ requires C, 65.07; H, 7.84%), and a white solid (308 mg) which consisted predominantly of 3β,19-diacetoxy-6β-hydroxyandrost-4-en-17-one (23); δ 0.91 (s, 3 H, 18-Me), 2.08 and 2.05 (6 H, 2 × OAc), 4.29 (t, 3 H, *J ca.* 3 Hz, 6α-H), 4.50 (q, 2 H, δ_A 4.44, δ_B 4.56, J_{AB} 11 Hz, 19-CH_2), 5.23 (m, 1 H, $W_{\frac{1}{2}}$ 20 Hz, 3α-H), and 5.69 (d, 1 H, *J ca.* 2 Hz, 4-H). This last component was acetylated (acetic anhydride–pyridine) and rechromatographed to give 3β,6β,19-triacetoxyandrost-4-en-17-one (24) which was identical (t.l.c. and ^1H n.m.r.) with material prepared independently.

The 5β,6β-epoxide (3) (250 mg) was treated with boron trifluoride according to method B. The resulting oil was chromatographed on silica gel (60 g) [eluting with mixtures of ethyl acetate–hexane varying from (1 : 4) to (2 : 3)]. This afforded 3β,19-*diacetoxy*-5-*formyl*-B-*nor*-5β-*androstan*-17-*one* (25) (41 mg) as an oil; $[\alpha]_D$ +60° (*c* 20.5); $\nu_{max.}$ 2 830 (CHO) and 1 735 cm^{-1} (acetate CO, CHO, and 17-CO); δ 0.88 (s, 3 H, 18-Me), 2.05 (s, 6 H, 2 × OAc), 4.07 (s, 2 H, 19-CH_2), 5.08 (m, 1 H, $W_{\frac{1}{2}}$ 15 Hz, 3α-H), and 9.70 (s, 1 H, CHO); *m/e* 404 (M^+) (Found: C, 68.35; H, 8.1. $C_{23}H_{32}O_6$ requires C, 68.27; H, 7.98%): 3β,19-diacetoxy-5-fluoro-6β-hydroxy-5α-androstan-17-one (22) (69 mg) which was identical (t.l.c. and ^1H n.m.r.) with authentic material: and a mixture (52 mg) of olefinic material. The latter material was unidentified although a ^1H n.m.r. spectrum of the mixture was consistent with the presence of the 4-olefin [possibly (23)].

Reaction of 3β,19-*Diacetoxy*-5,6β-*epoxy*-5β-*cholestane* (5) *with Boron Trifluoride*.—The 5β,6β-epoxide (5) (627 mg) was treated with boron trifluoride according to method B. Chromatography on silica gel (120 g) [eluting initially with hexane and then mixtures of ethyl acetate–hexane up to 1 : 4] afforded a mixture of olefinic compounds (67 mg) which were left unidentified: 3β,19-diacetoxy-5-formyl-B-nor-5β-cholestane (26) (132 mg) as an oil; $\nu_{max.}$ 2 740 (CHO) and 1 730 cm^{-1} (acetate CO and CHO); δ 0.66 (s, 3 H, 18-Me), 2.03 (s, 6 H, 2 × OAc), 4.02 (s, 2 H, 19-CH_2), 5.04 (m, 1 H, $W_{\frac{1}{2}}$ 15 Hz, 3α-H), and 9.62 (s, 1 H, CHO); *m/e* 502 (M^+): and 3β,19-*diacetoxy*-5-*fluoro*-5α-*cholestan*-6β-*ol* (21) (234 mg) as an oil; $[\alpha]_D$ −3° (*c* 12.5); $\nu_{max.}$ 1 735 cm^{-1} (acetate CO); δ 0.67 (s, 3 H, 18-Me), 2.01 and 2.06 (6 H, 2 × OAc), 3.71 (m, 1 H $W_{\frac{1}{2}}$ 8 Hz, 6α-H), 4.46 (q, 2 H, δ_A 4.34, δ_B 4.57, J_{AB} 13 Hz, 19-CH_2), and 5.02 (m, 1 H, $W_{\frac{1}{2}}$ 23 Hz, 3α-H); *m/e* 522 (M^+) (Found: C, 71.1; H, 9.9. $C_{31}H_{51}FO_5$ requires C, 71.20; H, 9.84%). The identity of the fluorohydrin (21) was confirmed by its conversion (refluxing methanolic sodium carbonate, 12 h) to 5,6β-epoxy-5β-cholestane-3β,19-diol (7), m.p. 177—178 °C (ether–light petroleum); $\nu_{max.}$ 3 520 cm^{-1} (OH); δ 0.70 (s, 3 H, 18-Me), 3.07 (s, 1 H, 6α-H), 3.72 (m, 1 H, $W_{\frac{1}{2}}$ *ca.* 24 Hz, 3α-H), 3.85 (q, 2 H, δ_A 3.55, δ_B 4.15, J_{AB} 12 Hz, 19-CH_2); *m/e* 400 ($M^+ - H_2O$). This was identical (t.l.c. and ^1H n.m.r.) with material obtained by hydrolysing (methanol, sodium carbonate) the 3β-acetoxy-5β,6β-epoxide (4).

Conversion of 3β,19-*Diacetoxy*-5-*formyl*-B-*nor*-5β-*cholestane* (26) *to* B-*Nor*-5β-*cholestan*-3-*one*-5β,19-*carbolactone* (36).—The aldehyde (26) (44 mg) was hydrolysed (methanol, sodium carbonate). After work-up, the residual oil was chromatographed on silica gel (18 g) [eluting with ethyl

acetate–hexane mixtures varying from (3 : 7) to (2 : 3)]. This afforded 5-formyl-B-nor-5β-cholestane-3β,19-diol (35) (21 mg) as a white solid; $\nu_{max.}$ 3 400 cm^{-1} (OH); δ 0.67, (s, 3 H, 18-Me), 3.72 (q, 2 H, δ_A 3.63, δ_B 3.80, J_{AB} 10 Hz, 19-CH_2), 3.96 (m, 1 H, $W_{\frac{1}{2}}$ 16 Hz, 3α-H), and 4.96 (s, 1 H, lactol methine); *m/e* 400 ($M^+ - H_2O$). The lactol (35) (15 mg) was dissolved in methylene chloride (1 ml) and this solution was added to a solution of the chromium trioxide–pyridine complex [25] (1 ml, 0.02M in methylene chloride) and left for 10 min. The resulting suspension was transferred onto a short column of Florosil and eluted with diethyl ether. The solvent was removed and the residual solid chromatographed on silica gel (5 g) [eluting with ethyl acetate–hexane (3 : 17)] to afford the *lactone* (36) (7 mg), m.p. 140—141 °C (needles from acetone–water); $\nu_{max.}$ 1 769 (γ-lactone), and 1 725 cm^{-1} (3-CO); δ 0.67 (s, 3 H, 18-Me), 2.64 (q, 2 H, δ_A 2.47, δ_B 2.81, J_{AB} 16 Hz, 4-CH_2), and 4.16 (q, 2 H, δ_A 4.01, δ_B 4.29, J_{AB} 10 Hz, 19-CH_2); *m/e* 414 (M^+) (Found: C, 77.7; H, 10.15. $C_{27}H_{42}O_3$ requires C, 78.21; H, 10.21%).

Reaction of 3β-*Acetoxy*-5,6α-*epoxy*-5α-*cholestan*-19-*ol* (12) *with Boron Trifluoride*.—The 5α,6α-epoxide (12) (190 mg) was treated with boron trifluoride according to method B. Column chromatography on silica gel (20 g) [eluting with ethyl acetate–hexane (1 : 4)] gave 3β-acetoxy-6β,19-epoxy-5α-cholestan-5-ol (27) (122 mg), m.p. 160—161 °C; $[\alpha]_D$ +4° (*c* 15.1) (lit.,[13] m.p. 162—163 °C, $[\alpha]_D$ +9°); δ 0.70 (s, 3 H, 18-Me), 2.02 (s, 3 H, OAc), 3.70 (m, 1 H, $W_{\frac{1}{2}}$ 5 Hz, 6α-H), 3.80 (s, 2 H, 19-CH_2), and 4.98 (m, 1 H, $W_{\frac{1}{2}}$ 24 Hz, 3α-H); *m/e* 460 (M^+).

Reaction of 3β,19-*Diacetoxy*-5,6α-*epoxy*-5α-*cholestane* (13) *with Boron Trifluoride*.—The epoxide (13) (250 mg) was treated with boron trifluoride according to method B. Work-up afforded 3β,19-diacetoxy-5β-cholestane-5,6α-diol (29) (249 mg) as an amorphous solid (t.l.c. pure); $[\alpha]_D$ +46° (*c* 16.1) (lit.,[14] +39°); $\nu_{max.}$ 3 600 (OH), 1 735 cm^{-1} (acetate CO); δ 2.05 and 2.09 (6 H, 2 × OAc), 3.95 (q, 1 H, *J* 12 and 4 Hz, 6β-H), 4.33 (s, 2 H, 19-CH_2), and 5.27 (m, 1 H, $W_{\frac{1}{2}}$ 7 Hz, 3α-H); *m/e* 502 (M^+).

Preparation of 3β-*Acetoxy*-5-*fluoro*-5α-*cholestane*-6β,19-diol (20).—Boron trifluoride–diethyl ether complex (2.5 ml) was added to a solution of 3β-acetoxy-5,6β-epoxy-5β-cholestan-19-ol (4) (2.5 g) in a benzene–diethyl ether mixture (250 ml, 1 : 1). This was left for 15 min and then worked up in the usual manner. Column chromatography on silica gel (200 g) [eluting with ethyl acetate–hexane (20 : 80)] afforded the *fluorohydrin* (20) (820 mg) contaminated with a small amount of unidentified material. Repated crystallisation from methylene chloride–light petroleum gave pure material, m.p. 148—149 °C; $\nu_{max.}$ 3 340 (OH) and 1 730 cm^{-1} (acetate CO); δ 0.57 (s, 3 H, 18-Me), 2.02 (s, 3 H, OAc), 3.55—4.62 (m, 3 H, 19-CH_2 and 6α-H), and 5.15 (m, 1 H, $W_{\frac{1}{2}}$ 24 Hz, 3α-H); *m/e* 476,* 462 ($M^+ - H_2O$), and 420 ($M^+ - HOAc$) (Found: C, 72.25; H, 10.5. $C_{29}H_{49}FO_4$ requires C, 72.48; H, 10.28%). A sample of the fluorohydrin (20) was cleanly converted (refluxing methanolic sodium carbonate, 10 h) into the 5β,6β-epoxide (7) which was identical (t.l.c. and ^1H n.m.r.) with authentic material.

Reaction of 3β-*Acetoxy*-5-*fluoro*-5α-*cholestane*-6β,19-*diol* (20) *with Boron Trifluoride*.—The fluorohydrin (20) (127 mg) was treated with boron trifluoride according to method B. After work-up, analysis of the product (t.l.c. and ^1H n.m.r.) revealed only the presence of unreacted starting material.

Reaction of 3β,19-*Diacetoxy*-5-*fluoro*-6β-*hydroxy*-5α-*androstan*-17-*one* (22) *with Boron Trifluoride*.—The fluorohydrin (22) (242 mg) was treated with boron trifluoride according to method B. Column chromatography on silica gel (50 g) [eluting with ethyl acetate–hexane (1 : 4)] afforded 3β-*acetoxy*-5-*fluoro*-6β,19-*expoxy*-5α-*androstan*-17-*one* (28) (52 mg), m.p. 186—187 °C (plates from acetone–water); $\nu_{max.}$ 1 740 cm^{-1} (acetate CO and 17-CO); δ 0.83 (s, 3 H, 18-Me), 1.92 (s, 3 H, OAc), 3.78 (s, 2 H, 19-CH_2), and 4.90 (m, 1 H, $W_{\frac{1}{2}}$ 24 Hz, 3α-H); *m/e* 364 (M^+) (Found: C, 69.1; H, 7.8. $C_{21}H_{29}FO_4$ requires C, 69.22; H, 8.02%): and unreacted fluorohydrin (140 mg) which was identical (t.l.c. and ^1H n.m.r.) with authentic material.

We thank the Ontario government and the National Research Council of Canada for graduate scholarships (to H. M.). Financial support for this work from the Natural Sciences and Engineering Research Council of Canada is gratefully acknowledged, as well as the technical assistance of M. Kalapurackal and L. Lompa-Krzymien in the preparation of some of the compounds reported in this paper.

[0/304 *Received*, 25*th February*, 1980]

* The peak at highest *m/e* was 476 although the fragmentation did not appear to originate from this ion. The peaks corresponding to the loss of water and acetic acid appear to be derived from the molecular ion (*m/e* 480) even though the latter was not observed. It is suggested that the peak at 476 originates from some recombination sequence in the mass spectrometer.

REFERENCES

[1] Part 6. P. Morand, and A. Van Tongerloo, *Steroids*, 1973, **21**, 65.
[2] P. Morand, D. G. Williamson, D. S. Layne, L. Lompa-Krzymien, and J. Salvador, *Biochemistry*, 1975, **14**, 635.
[3] P. Morand and M. Kaufman, *Canad. J. Chem.*, 1971, **49**, 3185.
[4] (*a*) I. G. Guest and B. A. Marples, *J. Chem. Soc.* (*C*), 1970, 1626; (*b*) J. M. Coxon, M. P. Hartshorn, and B. L. S, Sutherland, *Tetrahedron Letters*, 1969, 4029 and previous papers in this series.
[5] I. G. Guest and B. A. Marples, *J.C.S. Perkin I*, 1973, 900.
[6] (*a*) I. G. Guest and B. A. Marples, *J. Chem. Soc.* (*C*), 1971, 576; (*b*) B. W. Cubberley, I. G. Guest, J. G. Ll. Jones, and B. A. Marples, *J.C.S. Perkin I*, 1977, 1916.
[7] E. S. Gould, 'Mechanisms and Structure in Organic Chemistry,' Holt, Rinehart, and Winston, New York, 1959, p. 207.
[8] J. W. ApSimon, R. R. King, and J. J. Rosenfeld, *Canad. J. Chem.*, 1969, **47**, 1989.
[9] P. Morand and M. Kalapurackal, unpublished work.
[10] Y. Watanabe and Y. Mizuhara, *J.C.S. Chem. Comm.*, 1973, 752.
[11] E. V. Demlow and J. Schmidt, *Tetrahedron Letters*, 1976, 95.
[12] P. Morand, M. Kalapurackal, L. Lompa-Krzymien, and A. Van Tongerloo, *J. Theor. Biol.*, 1976, **56**, 503.
[13] P. Kočovský and V. Černý, *Coll. Czech. Chem. Comm.*, 1979, **44**, 226.
[14] J. Joska and J. Fajkoš, *Coll. Czech. Chem. Comm.*, 1978, **43**, 3433.
[15] R. R. Fraser, M. Kaufman, P. Morand, and G. Govil, *Canad. J. Chem.*, 1969, **47**, 403.
[16] B. N. Blackett, J. M. Coxon, M. P. Hartshorn, and K. E. Richards, *Tetrahedron*, 1969, **25**, 4999.
[17] J. Fried and N. A. Abraham, 'Organic Reactions in Steroid Chemistry,' eds. J. Fried and J. A. Edwards, Van Nostrand–Reinhold, New York, 1972, vol. 1, p. 423.
[18] R. Ginsing and A. D. Cross, *J. Org. Chem.*, 1966, **31**, 1761.
[19] D. N. Kirk and M. P. Hartshorn, 'Steroid Reaction Mechanisms,' Elsevier, Amsterdam, 1968, p. 365.
[20] P. Kočovský and V. Černý, *Coll. Czech. Chem. Comm.*, 1979, **44**, 1496.
[21] A. Guida and M. Mousseron-Canet, *Bull. Soc. chim. France II*, 1973, 1098.
[22] Ref. 19, p. 362.
[23] F. Dorn and D. Arigoni, *Experimentia*, 1974, **30**, 851.
[24] E. J. Corey and A. Venkateswarlu, *J. Amer. Chem. Soc.*, 1972, **94**, 6190.
[25] R. W. Ratcliffe, *Org. Synth.*, 1976, **55**, 84.