REACTIONS OF EPOXIDES—II*

REARRANGEMENTS OF 3-ACETOXY-4,5-EPOXYCHOLESTANES WITH BORON TRIFLUORIDE

J. M. Coxon, M. P. Hartshorn and D. N. Kirk

University of Canterbury, Christchurch, New Zealand

Abstract—3β-Acetoxy-4α,5-epoxy-5α-cholestane is rearranged by boron trifluoride to give 3β-acetoxy-5β-cholestan-4-one (IV). Under similar reaction conditions the 3α-acetoxy-4β,5β-epoxide gives a stable 3α,5α-bridged ionic complex, and the 3β-acetoxy-4β,5β epoxide gives the fluorohydrin (X).

THE reaction between 3β-acetoxy-4α,5-epoxy-5α-cholestane (I) and boron trifluoride has been described by Julia and Lavaux. The product, originally[1] formulated as a fluorohydrin, and later[2] thought to be the 4β,5α-diol (IIa), was recently[3] shown to be the 4β-acetoxy-3β,5α-diol (IIb). The authors postulated a 3β,4β-bridged ionic structure (III) for the intermediate in this rearrangement, and have since demonstrated[4] that the migration of the acetoxy group from 3β- to the 4β- position through a cyclic intermediate is just one example among a group of reactions involving participation of a 3β-ester group in an "onium" reaction at the 4,5-positions. In the epoxide–boron trifluoride reaction, the formation of the diol (IIb) is clearly equivalent to an acid-catalysed hydrolysis of the epoxide, the extra oxygen atom coming from the aqueous solution used in hydrolysing the complex (III). This reaction, however, does not fit into the normal pattern of epoxide–boron trifluoride reactions[5] which usually lead to ketones, fluorohydrins, or olefinic compounds.

We therefore re-examined the reaction between the epoxide (I) and boron trifluoride (etherate) in benzene solution. The reaction mixture rapidly deposited a colourless gelatinous precipitate, and hydrolysis at this stage gave the rearranged diol (IIb) in good yield. However, when the reaction mixture was allowed to stand at room temperature the gelatinous precipitate slowly redissolved, giving a deep purple solution after several hours. Addition of aqueous sodium acetate at this point gave 3β-acetoxy-5β-cholestan-4-one (IV), the ketonic product derived by a normal rearrangement of the 4α,5α-epoxide system.[6]

The product (IV) was characterized by its IR spectrum which exhibited bands due to the α-acetoxy-ketone system. The Cotton curve ($a = -22$) had its extrema at 333 and 286 mμ, showing the acetoxy group to be axial.[7] The NMR spectrum was also

* Part I. Preceding paper.

[1] S. Julia and J-P. Lavaux, *C.R. Acad. Sci., Paris* **251**, 733 (1960).

[2] S. Julia, J-P. Lavaux, C. Moutonnier and B. Decouvelaere, *Bull. Soc. Chim. Fr.* 1997 (1961).

[3] S. Julia and J-P. Lavaux, *Bull. Soc. Chim. Fr.* 1238 (1963).

[4] S. Julia and B. Fürer, *C.R. Acad. Sci., Paris* **257**, 710 (1963).

[5] J. M. Coxon, M. P. Hartshorn and D. N. Kirk, preceding paper.

[6] H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.* 4596 (1957).

[7] C. Djerassi, O. Halpern, V. Halpern, O. Schindler and C. Tamm, *Helv. Chim. Acta* **41**, 250 (1958).

consistent with structure IV. The three protons of the acetate methyl group appeared at $\tau 7\cdot92$. Two protons were evident at lower field. One of these ($\tau 5\cdot08$) was a barely resolved triplet ($J = 2\cdot5$ c/s) which is assigned to the equatorial 3α-proton in an undistorted chair conformation of ring A.[8] The other low field signal ($\tau 7\cdot42$) is assigned to the 5β-proton, deshielded by its proximity to the 4-ketone. This band was broadened (width 7·8 c/s) by spin-spin coupling with the C-6 protons.

Confirmation of the structure (IV) was obtained by reducing the acetoxy ketone with calcium in liquid ammonia,[9] when 5β-cholestan-4-one[6] was obtained in excellent yield.

When the residues from the crystallization of the acetoxy-ketone (IV) were chromatographed on alumina, two products were obtained. One was the 4β-acetoxy-$3\beta,5\alpha$-diol (IIb). The other was a second acetoxy-ketone, also formed when the acetoxy-ketone (IV) was passed through an alumina column. The isomerized acetoxy-ketone was identified as 3β-acetoxy-5α-cholestan-4-one (V), despite an appreciable difference between its physical constants (m.p. 121·5°; $[\alpha]_D$ −7°) and published data for this compound (m.p. 117–118·5°; $[\alpha]_D$ −22·9°[10]). The position of the keto group and the configuration at C-5 were revealed by the formation of 5α-cholestan-4α-ol[11] and 5α-cholestan-4-one[12] when the acetoxy-ketone (V) was reduced with calcium in liquid ammonia. The 3β- configuration of the acetoxy group was apparent from the Cotton curve, with extrema at 305 and 267 mμ (equatorial OAc[7]), and a negative amplitude ($a = -81$), close to the value ($a = -91$[13]) for 5α-cholestan-4-one. The NMR spectrum showed one low-field proton ($\tau 4\cdot83$). This signal, assigned to the 3α-proton, confirms its axial conformation,[8] the chemical shift being distinctly smaller than that of the equatorial 3α-proton in the 5β-epimer ($\tau 5\cdot08$). The splitting pattern (quadruplet; $J = 6\cdot5$ and $11\cdot5$ c/s) reveals spin-spin coupling with two non-equivalent protons at C-2, due to a slight distortion of ring A from the pure chair conformation.[8] The 5α-proton signal could not be distinguished, and appeared to be masked by the acetate methyl peak ($\tau 7\cdot85$) which gave an integral corresponding to five or six protons between $\tau 7\cdot6$ and $\tau 7\cdot9$.

The formation of the acetoxy-ketone (IV) requires rupture of the C_5—O epoxide bond, and cannot proceed directly from the $3\beta,4\beta$-bridged structure (III). It is clear that the formation of the complex (III), although rapid, must be reversible. This would allow the slow formation of the acetoxy-ketone (IV) by a rearrangement proceeding from the simple epoxide–boron trifluoride coordination compound, even though this species is present in small concentration. As the precipitation of the complex (III) would further retard the rearrangement leading to the acetoxy-ketone, the reaction was also examined in dichloromethane as solvent. The complex (III) was not precipitated from this solution, although its formation was indicated by the isolation of the rearranged $3\beta,5\alpha$-diol (IIb) when the mixture was hydrolysed after 3 min. A deep blue colour developed rapidly when the reaction in dichloromethane was

[8] K. L. Williamson and W. S. Johnson, *J. Amer. Chem. Soc.* 83, 4623 (1961).
[9] J. H. Chapman, J. Elks, G. H. Phillipps and L. J. Wyman, *J. Chem. Soc.* 4344 (1956).
[10] S. Lieberman and D. K. Fukushima, *J. Amer. Chem. Soc.* 72, 5211 (1950).
[11] P. A. Plattner, T. Petrzilka and W. Lang, *Helv. Chim. Acta* 27, 513 (1944).
[12] L. Ruzicka, P. A. Plattner and M. Furrer, *Helv. Chim. Acta* 27, 727 (1944).
[13] C. Djerassi, W. Closson and A. E. Lippman, *J. Amer. Chem. Soc.* 78, 3163 (1956); C. Djerassi and W. Klyne, *J. Chem. Soc.* 2390 (1963).

allowed to continue, and the acetoxy-ketone (IV) was obtained after 1 hr in yield comparable with a 6 hr reaction in benzene.

Our studies of epoxide–boron trifluoride reactions were extended to include 3α-acetoxy- and 3β-acetoxy-4β,5-epoxy-5β-cholestanes. The fourth isomer, 3α-acetoxy-4α,5-epoxy-5α-cholestane, is difficult to prepare,[14] and was not examined.

The 3α-acetoxy-4β,5β-epoxide (VI)[15] reacted rapidly with boron trifluoride in benzene to give a semi-crystalline precipitate. Hydrolysis with aqueous sodium acetate at this stage afforded the 3α-acetoxy-4β,5α-diol (VIIa), which was hydrolysed by alkali to give the known 5α-cholestane-3α,4β,5-triol (VIIb).[16] When the reaction with boron trifluoride was prolonged, in the hope of obtaining a product of rearrangement of the epoxide, there was little change in the appearance of the mixture, and the 4β,5α-diol (VIIa) was obtained in over 50% yield even after 48 hr. Chromatography of the residual material from this reaction gave no identifiable products, and an attempt to isolate any ketones by the use of Girard's reagent P gave only traces of amorphous material. A reaction in dichloromethane, from which the complex was not precipitated, gave the diol (VIIa) as the only product isolated.

The explanation of the failure of the epoxide (VI) to undergo a normal rearrangement appears to lie in the structure of its complex with boron trifluoride. This was shown to involve a 3α,5α-bridged acetonium ion by its reduction with lithium borohydride. The reduction proceeded with the addition of a hydride ion to the bridge carbon atom, giving 3α,5α-ethylidenedioxycholestan-4β-ol (VIIIa). The ethylidene-dioxy-bridge was hydrolysed by brief treatment with toluene-p-sulphonic acid in acetone to give the 3α,4β,5α-triol (VIIb). Oxidation of the 4β-hydroxy compound (VIIIa) with chromic acid–acetone gave the 4- ketone (VIIIb), characterized by a strongly negative Cotton curve (a = −93) similar to that of 5α-cholestan-4-one.[14] Since the 3,5-ethylenedioxy bridge is symmetrical about the 4- ketone, it would not be expected to affect the Cotton curve. The formation of the 4-ketone shows that the bridge links the 3α- and 5α-positions. The alternative 3α,4α-bridge, epimeric with structure III, is rendered unfavourable by the requirement of a 5β-configuration, which is found to involve large steric interactions across the α-face of the molecule (Dreiding models), while a 3α,5α-bridge is known to be a favourable structure.[17] The bridge would be formed in this case by nucleophilic attack of the acetoxy-carbonyl oxygen upon the 5α-position with rupture of the 5β-O bond. The rearrangement of this intermediate to give a 4-ketone would require migration of the 4α-hydrogen atom with rupture of the cis-related 5α-O bond, and is clearly unfavourable.

3β-Acetoxy-4β,5-epoxy-5β-cholestan (IX)[16] cannot form a bridged complex with participation of the 3β-acetoxy group, and was found to react in a normal manner with boron trifluoride, giving the fluorohydrin (X) after 2 min. Vigorous alkaline hydrolysis of the fluorohydrin, followed by acetylation, gave back the acetoxy-epoxide (IX). The hydroxyl group was shown to be at C-4 rather than C-5 by acetylation with acetic anhydride-pyridine. The formation of the fluorohydrin (X) is exactly analogous to the behaviour[5] of the 4α-methyl derivative of the epoxide (IX). Unlike the 4-methyl analogue, no other products could be isolated when the epoxide (IX) was allowed
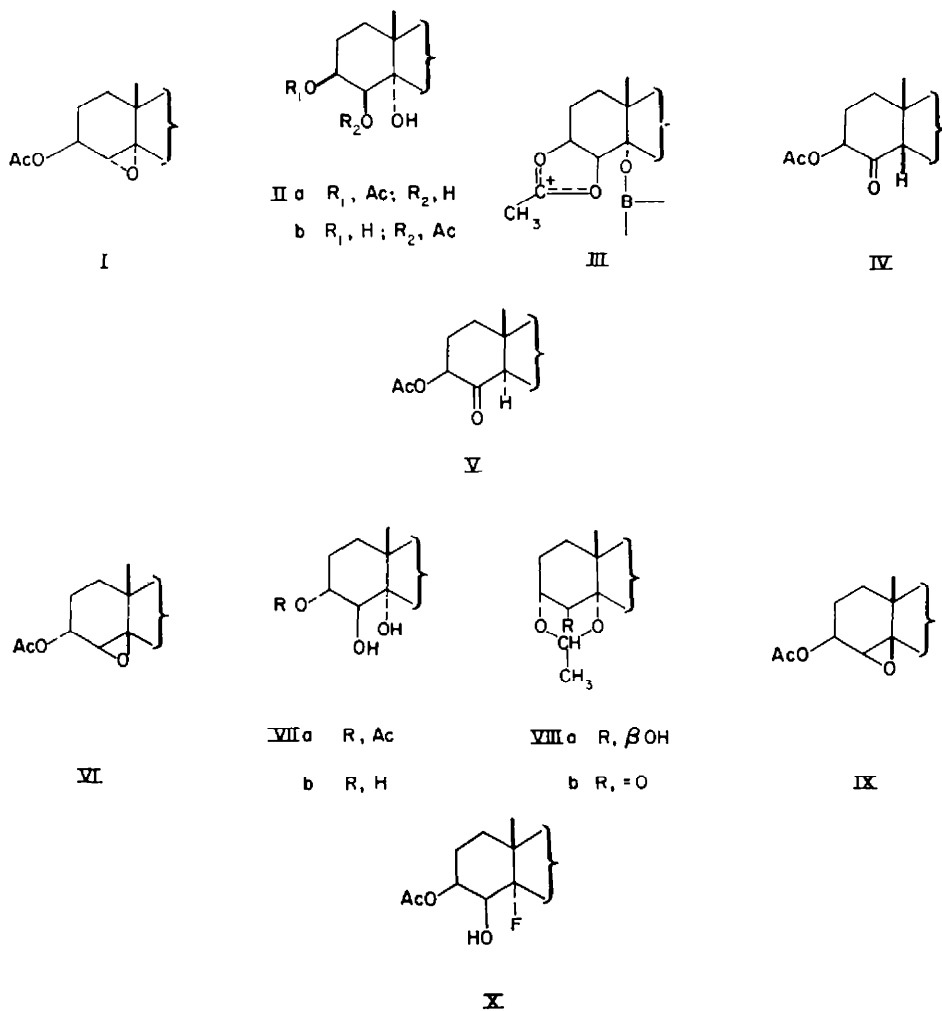
[14] P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta* **32**, 1070 (1949).
[15] D. J. Collins, *J. Chem. Soc.* 3919 (1959).
[16] P. A. Plattner, H. Heusser and A. B. Kulkarni, *Helv. Chim. Acta* **31**, 1822 (1948).
[17] J. W. Blunt, M. P. Hartshorn and D. N. Kirk, *J. Chem. Soc.* 1073 (1964).

to react for longer periods with boron trifluoride, although the yield of fluorohydrin fell sharply after a few minutes. It is noteworthy that the acetoxyketone (V), which might have been expected as a rearrangement product of the epoxide (IX) could not be detected.

EXPERIMENTAL

Rotations were measured at room temp for $CHCl_3$ solutions unless otherwise stated. IR spectra were recorded for CS_2 solutions unless otherwise stated. Alumina used for chromatography was Spence, Grade H, deactivated by the addition of 5% of 10% acetic acid. Light petroleum refers to the fraction of b.p. 50–70°. Boron trifluoride diethyl etherate was freshly distilled before use. O.R.D. curves (in methanol) were kindly determined by Prof. W. Klyne.

Reaction of 3β-acetoxy-4α,5-epoxy-5α-cholestane (I) with boron trifluoride

(a) A solution of the epoxide (1 g) in anhydrous benzene (15 ml) was treated with boron trifluoride etherate (1 ml). A colourless gelatinous precipitate appeared, and after 10 min 5% sodium acetate solution was added. The product, isolated by use of ether, was 4β-acetoxy-5α-cholestane-3β,5-diol (770 mg), m.p. 197–198° (from hexane). (lit.:[3] m.p. 198–199°).

(b) A reaction mixture as under (a) was stirred at intervals for 6 hr, and became deep purple. The product, isolated as above, crystallized from pentane to give 3β-*acetoxy-5β-cholestan-4-one* (435 mg), m.p. 108·5–109·5° (plates from methanol), [α]$_D$ +40° (c, 0·90, dioxan) ν_{max} 1748, 1721, 1224 cm^{-1} (α-acetoxy-ketone). O.R.D. [φ]$_{500}$ +196°, [φ]$_{333}$ −140°, [φ]$_{286}$ +2150, [φ]$_{273}$ +2090°, [φ]$_{238}$ +2300°. (Found: C, 78·2; H, 11·1. C$_{29}$H$_{48}$O$_3$ requires: C, 78·3; H, 10·9%).

The residual material (0·55 g) was adsorbed on to alumina (16 g). Elution with light petroleum-benzene (20:1) gave 3β-acetoxy-5α-cholestan-4-one (270 mg), m.p. 121·5–122° (prisms from methanol), [α]$_D$ −7° (c 1·30), ν_{max} 1759, 1737, and 1232 cm^{-1}, O.R.D. [φ]$_{305}$ −3400°, [φ]$_{267}$ +4700°, [φ]$_{234}$ +4250°. (Found: C, 78·6; H, 11·0. Calc. for C$_{29}$H$_{48}$O$_3$; C, 78·3; H, 10·9%). Elution with ether gave the 4β-acetoxy-3β,5α-diol (IIb) (170 mg), m.p. 197–198°.

(c) The epoxide (1 g) in anhydrous dichloromethane (15 ml) was treated with boron trifluoride etherate (1 ml). After 1 hr the deep red solution was treated with sodium acetate solution, and the product isolated as before. Crystallization from pentane gave 3β-acetoxy-5β-cholestan-4-one (580 mg) m.p. 108·5–109·5°.

Reduction of 3β-acetoxy-5β-cholestan-4-one (IV) *with calcium-liquid ammonia*

The acetoxy ketone (50 mg) in anhydrous toluene (10 ml) was added to a stirred solution of Ca (100 mg) in liquid ammonia (40 ml), and stirring was continued for 5 min. Ammonium chloride was added to decolourize the solution, and after evaporation of the ammonia the product was isolated by use of ether. The crude material was oxidized in acetone solution with 8N chromic acid, and isolated by use of ether, giving 5β-cholestan-4-one (35 mg) m.p. 108–109° (acetone), [α]$_D$ +42° (c 0·78) (lit.:^{4} m.p. 108–110°, [α]$_D$ +44°).

Isomerization of 3β-acetoxy-5β-cholestan-4-one (IV)

The acetoxyketone (100 mg) in light petroleum was adsorbed on to alumina (3 g). After 30 min, elution with light petroleum-benzene (10:1) gave V (85 mg), m.p. 121·5–122°.

Reduction of 3β-acetoxy-5α-cholestan-4-one (V)

The acetoxyketone (50 mg) was reduced as described above for the 5β-isomer. The crude product crystallized from acetone to give 5α-cholestan-4α-ol (19 mg), m.p. 185–187°, [α]$_D$ +8° (c 0·80). (lit.:^{11} m.p. 187–187·5°, [α]$_D$ +10·7°). The residual material was oxidized with chromic acid–acetone to give 5α-cholestan-4-one (12 mg), m.p. 98–99°, [α]$_D$ +26° (c 0·88) (lit.:^{12} m.p. 99–99·5°, [α]$_D$ +29·5°).

Reaction of 3α-acetoxy-4β,5-epoxy-5β-cholestane (VI) *with boron trifluoride*

(a) The epoxide (500 mg) in benzene (10 ml) was treated with boron trifluoride etherate (0·5 ml), giving a gelatinous precipitate in 1 min. After 1 hr sodium acetate aq was added and the product was isolated by use of ether. Trituration with pentane gave 3α-*acetoxy-5α-cholestane-4β,5-diol* (360 mg) which crystallized from acetone in rods, m.p. 190–191°, [α]$_D$ +72° (c 0·99), ν_{max} (in Nujol) 3425, 3338, 1702, 1282, 1274 cm^{-1} (Found: C, 75·5; H, 10·9. C$_{29}$H$_{50}$O$_4$ requires: C, 75·3; H, 10·9%).

(b) A reaction mixture as in (a) was left for 48 hr, and gave 3α-acetoxy-5α-cholestane-4β,5-diol (262 mg) after working up as above. Chromatography of the remaining material (240 mg) on alumina (25 g) gave an unidentified product (28 mg) m.p. 250–254° (no significant IR absorption bands) eluted by light petroleum. No other solid compounds could be isolated.

(c) The epoxide (280 mg) and boron trifluoride etherate (0·28 ml) were allowed to react in dichloromethane (3 ml) for 24 hr, giving a deep blue solution. The product, isolated as in (a), was the 4β,5α-diol (115 mg) m.p. 190–191°.

Hydrolysis of 3α-acetoxy-5α-cholestane-4β,5-diol (VIIa)

The diol (90 mg) and KOH (180 mg) in 95% methanol (15 ml) were heated under reflux for 1 hr. The cooled solution deposited 5α-cholestane-3α,4β,5-triol (68 mg), m.p. 282–285° from ethanol [α]$_D$ +41° (c 0·84 in pyridine) (lit.:^{16} m.p. 295–297°, [α]$_D$ −43·5°).

3α,5α-*Ethylidenedioxycholestan-4β-ol* (VIIIa)

The 3α-acetoxy-4β,5β-epoxide (VI: 500 mg) in benzene (10 ml) was treated with boron trifluoride etherate (0·5 ml). After 5 min the mixture was stirred vigorously while a sat. solution of LiBH₄ in anhydrous tetrahydrofuran was added dropwise, until gas evolution ceased (3 min). The mixture was then treated with water, and the product isolated with the use of pentane. Trituration with pentane gave the 3α,5α-*ethylidenedioxy-compound* (180 mg), m.p. 153–155° (needles from methanol), $[\alpha]_D$ +26° (c 1·05, dioxan), ν_{max} 3614 (OH), 1142 and 1083 cm⁻¹ (C.O.C.). (Found: C, 78·2; H, 11·4. $C_{29}H_{50}O_3$ requires: C, 78·0; H, 11·3%).

The residual material was adsorbed on to alumina (12 g). Elution with light petroleum–benzene (1:1) gave unreacted epoxide (100 mg) m.p. 68–69°. Elution with benzene gave the 3α,5α-ethylidene-dioxy-compound (214 mg) m.p. 151–154° (total yield 76%).

The ethylidenedioxy-compound (50 mg) in acetone (5 ml) was warmed with toluene-*p*-sulphonic acid (10 mg) and water (0·2 ml) for 2 min. The solution rapidly deposited 5α-cholestane-3α,4β,5-triol, m.p. 280–285°.

3α,5α-*Ethylidenedioxycholestan-4-one* (VIIIb)

The 4β-hydroxy compound (VIIIa; 100 mg) in acetone (5 ml) was treated with a slight excess of 8N chromic acid and the mixture was at once diluted with water. The 4-*ketone*, isolated with the use of ether, formed plates, m.p. 96–97° (from methanol), $[\alpha]_D$ +39° (c 0·89), ν_{max} 1735 (C:O), 1126 and 1096 cm⁻¹ (C.O.C.), O.R.D. $[\phi]_{400}$ +110°, $[\phi]_{330}$ −3200°, $[\phi]_{273}$ −6060° (infl), $[\phi]_{232}$ +12,830°. (Found: C, 78·4; H, 11·1. $C_{29}H_{48}O_3$ requires: C, 78·3; H, 10·9%).

3β-*Acetoxy-4β,5-epoxy-5β-cholestane* (IX)

This epoxide was prepared by epoxidation of 3β-hydroxycholest-4-ene with monoperphthalic acid, and acetylation of the crude β-epoxy-alcohol. It crystallized from methanol as needles, m.p. 97–98°, $[\alpha]_D$ −3° (c 1·0). (lit.:¹⁶ m.p. 89–90°, $[\alpha]_D$ −21·8°, −20·3°).

3β-*Acetoxy-5α-fluorocholestan-4β-ol* (X)

3β-Acetoxy-4β,5-epoxy-5β-cholestane (650 mg) in anhydrous benzene (6·5 ml) was treated with boron trifluoride etherate (0·65 ml) for 5 min at 20°, then the solution was poured into NaHCO₃ aq. The product, isolated by use of ether, was adsorbed from light petroleum–benzene (20:1) on to deactivated alumina (26 g). Elution with light petroleum–benzene (4:1) gave oily fractions (44 mg) showing only acetoxy-absorption in the IR.

The *fluorohydrin* (X), eluted by light petroleum–benzene (1:1),was an amorphous solid (379 mg), m.p. 169–175°, $[\alpha]_D$ +7 (c 0·94), ν_{max} 3610, 3472, 1739, and 1238 cm⁻¹. (Found: C, 75·1; H, 11·0; F, 3·8. $C_{29}H_{49}FO_3$ requires: C, 74·9; H, 10·6; F, 4·1%).

Hydrolysis of the fluorohydrin (X)

The fluorohydrin (38 mg) and KOH (0·1 g) in methanol (5 ml) were heated under reflux for 3 hr. The product, extracted with the use of ether, was treated with pyridine (1 ml) and acetic anhydride (0·5 ml) for 16 hr at 20°, giving IX, m.p. and m.m.p. 96–98°, IR spectrum identical with an authentic sample.

3β,4β-*Diacetoxy-5-fluoro-5α-cholestane*

The fluorohydrin (X; 50 mg) in pyridine (1 ml) and acetic anhydride (2 ml) was heated at 90° for 3 hr. The *diacetate*, isolated by use of ether, formed needles, m.p. 137–139° (methanol), $[\alpha]_D$ +17° (c 0·63), ν_{max} 1754, 1745, 1236, and 1218 cm⁻¹ (Found: C, 73·1; H, 10·2; F, 3·2. $C_{31}H_{50}O_4F$ requires: C, 73·45; H, 10·15; F, 3·75%).