960. *Aspects of Stereochemistry. Part IX.* The Formation of Fluorohydrins from the Cholesteryl 5 : 6-Epoxides and Boron Trifluoride–Ether Complex.*

By H. B. Henbest and T. I. Wrigley.

Whereas 6-ketones were the only crystalline products obtained from the reaction of unsubstituted 5 : 6-epoxysteroids with boron trifluoride–ether complex, the presence of substituents (acetoxy, chloro) at $C_{(3)}$ can cause diaxial fluorohydrins to be formed in good yields. The results are discussed in terms of the conformational and electrical effects of the nearby $C_{(3)}$-substituents.

In our previous paper on this topic,[1] reactions of boron trifluoride–ether complex with some aliphatic tri- and tetra-substituted epoxides of the steroid series were described, and the α- and β-5 : 6-epoxides were shown to yield 6-ketones by stereospecific hydrogen shifts. For the investigation of the effect of nearby groups on these reactions, the 3-substituted 5 : 6-epoxides were the obvious choice.

5α : 6α-*Epoxides.*—The following Table summarises the products obtained from various 5α : 6α-epoxides.

$C_{(3)}$ substituent	" Non-polar material "	6-Oxocoprostanes	Hydroxy-compounds
3α-OAc	—	Ketone (61%)	Oil (18%)
H	Oil (37%)	Ketone (34%)	Oil (20%)
3β-OAc	—	†	Fluorohydrin (74%) *
3β-Cl	—	†	Fluorohydrin (>45%)

* This yield was obtained (some unchanged material being allowed for) with a reaction time of 5 min. Longer reaction times caused the yield to fall: 41% (15 min.), 24% (120 min.).
† Although exact figures cannot be given, these yields are less than 5%.

The crystalline products were either 6-oxocoprostanes or diaxial fluorohydrins. The structures of the latter are discussed at the end of the paper.

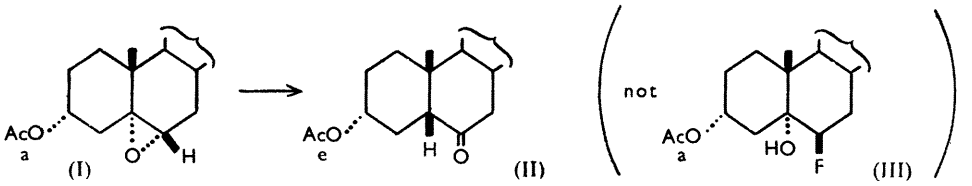
* Part VIII, *J.*, 1957, 4608.

[1] Henbest and Wrigley, *J.*, 1957, 4596.

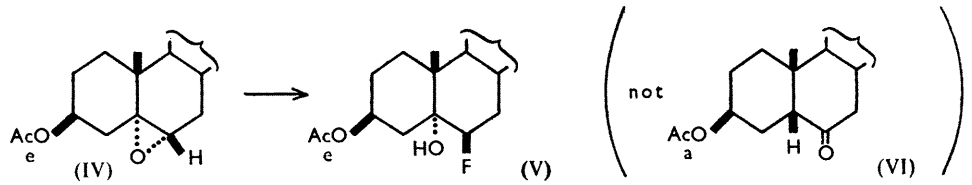
From two of the 3-substituted 5 : 6-epoxides, fluorohydrins are formed instead of a ketone as from the unsubstituted compound. In our earlier paper it was suggested that, in the production of the ketone from the 5 : 6-epoxide, the bond from oxygen to the more alkylated $C_{(5)}$-position was appreciably ionized in the transition state. As intramolecular electron-attracting groups have been shown [2,3] to slow down the rate of S_N solvolyses, the ionization necessary for the formation of 6-ketones from the epoxides containing acetoxy- or chloro-groups at $C_{(3)}$ may similarly be inhibited. The alternative reaction leading to fluorohydrin can then operate, this type of reaction involving dual attack of the Lewis acid and an external fluoride nucleophil. In accord with this picture, the configurations of the fluorohydrins are diaxial and they are formed at slower rates than are the 6-ketones from the unsubstituted epoxides. However, the mechanistic picture is not complete in that the precise origin and/or mode of attack of the fluoride nucleophil and the nature of the initial reaction product [? $>CF\cdot C(OBF_2)<$] have yet to be determined.

The second factor required to explain the present results is that reactions leading to less favourable molecular conformations are prohibited. The reactions will be discussed in terms of these electrical and conformational factors.

Compared with the unsubstituted 5α : 6α-epoxide, the 3α-acetoxy-compound (I) gave a higher yield of a 6-ketone (*i.e.* II), the reaction being assisted by the change of the acetate conformation from axial (a) to equatorial (e). However, the rate of reaction of the substituted epoxide was slower, in line with the general suggestion that ionization of the $C_{(5)}$–O bond would be more difficult. Formation of the diaxial fluorohydrin (III) is probably discouraged because increase of compression (of 3α- and 5α-axial substituents) would be involved.



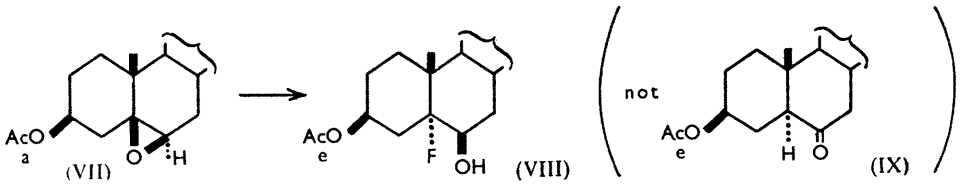
In contrast, the 3β-acetoxy-epoxide (IV) gave very little ketone (*i.e.* VI), the fluorohydrin (V) being the major product. In this case, formation of a ketone is inhibited for both conformational and electrical reasons. Similarly, the 3β-chloro-analogue of (IV) also gave a fluorohydrin, the infrared absorption of the total reaction product showing that very little ketone was produced.



5β : 6β-*Epoxides.*—The reactions of only two compounds have been studied but here again the introduction of an acetoxy-substituent at $C_{(3)}$ profoundly alters the course of reaction. Thus, whereas the unsubstituted 5β : 6β-epoxide afforded a 6-ketone (cholestan-6-one), the diaxial fluorohydrin (VIII) was obtained from the 3β-acetoxy-compound (VII). Formation of either the fluorohydrin (VIII) or the ketone (IX) can derive assistance from the change of acetate conformation from axial to equatorial, and so the difficulty in ionizing the $C_{(5)}$–O bond, necessary for the production of the ketone (IX), is decisive in this case. The rate of reaction of the substituted epoxide (VII) was slower than that of the

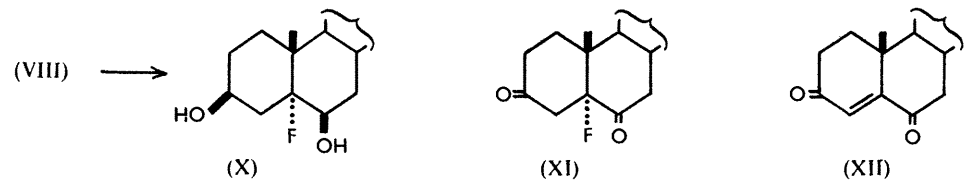
[2] Brown, Kharasch, and Chao, *J. Amer. Chem. Soc.*, 1940, **62**, 3435.
[3] Streitwieser, jun., *ibid.*, 1956, **78**, 4935.

unsubstituted compound, agreeing with the general suggestion that the slower reaction leading to a fluorohydrin becomes of importance only when the normally more rapid ionization-hydrogen shift reaction is inhibited.



Structures of Reaction Products.—Apart from the usual evidence, the proof of structure of the 5β-6-ketone (II) followed from its epimerisation by alkali to the known 5α-6-ketone.

The hydroxyl group (infrared evidence) in the fluorohydrin (V) was resistant to normal



acetylation and therefore was 5α- in configuration. The *trans*-arrangement of $C_{(5)}$ and $C_{(6)}$ substituents was confirmed by treatment of the fluorohydrin with potassium *tert.*-butoxide whereupon the initial α-epoxide formed. The rotation of the fluorohydrin was also similar to that of the related known chlorohydrin. [This fluorohydrin is unusual in that its infrared spectrum contained a second (weaker) carbonyl band at 1713 cm.$^{-1}$ in addition to the usual acetate band at 1733 cm.$^{-1}$. Experiments (to be reported later) have shown that the new band arises from appreciable intermolecular association.]

The presence of a secondary hydroxyl group in the fluorohydrin (VIII) was demonstrated by acetylation and oxidation, and the *trans*-disposition of groups by the formation of cholesterol β-epoxide on treatment with alkali. The 3 : 6-diol (X) was best prepared by reductive hydrolysis of the acetate (VIII) with lithium aluminium hydride. Oxidation of the diol gave the diketone (XI) from which hydrogen fluoride was eliminated on treatment with alumina to yield the known cholest-4-ene-3 : 6-dione (XII).

The presence of fluorine in the fluorohydrins (V) and (VIII) was confirmed by elemental analyses. These were determined at the University of Birmingham by arrangement with Professor M. Stacey, whom we thank.

Experimental

General directions are as given before.[1]

3α-*Acetoxycoprostan*-6-*one* (II).—A solution of 3α-acetoxy-5α : 6α-epoxycholestane (1·93 g.) and boron trifluoride–ether complex (1·4 c.c.) in benzene (31 c.c.) was kept at 20° for 14 hr. The product was isolated with benzene and chromatographed on deactivated alumina (125 g.). Elution with benzene gave 3α-*acetoxycoprostan*-6-*one* (1·24 g.; 61%), m. p. 142—143° (from methanol), $[\alpha]_D$ −21° (Found: C, 78·1; H, 10·75. $C_{29}H_{48}O_3$ requires C, 78·35; H, 10·9%). Infrared absorption (in CS_2): carbonyl peaks at 1733 (acetate) and 1703 cm.$^{-1}$ (6-ketone). Elution with ether–benzene (1 : 3) gave an oil (0·28 g.; 18%) which showed hydroxyl absorption in the infrared region.

A similar experiment, with only 5 min. reaction time, gave starting material (20%), the 6-ketone (37%), and the non-crystalline hydroxy-compound (15%).

3α-Acetoxycoprostan-6-one (76 mg.) in benzene (3 c.c.) was adsorbed on to alumina (5 g.) impregnated with potassium hydroxide. After 16 hr. the steroid was eluted with ether to give

3α-hydroxycholestan-6-one (67 mg.), m. p. 157—159° (from aqueous methanol), $[\alpha]_D$ 0°. Acetylation gave the 3α-acetate, m. p. 102—105° (from aqueous acetone), $[\alpha]_D$ −10°. (Lit. values for the alcohol, m. p. 159—160°, $[\alpha]_D$ +3°; for the acetate, m. p. 107—108°, $[\alpha]_D$ −4°.)

3β-*Acetoxy*-6β-*fluorocholestan*-5α-*ol* (V).—Boron trifluoride–ether complex (0·9 c.c.) was added to a solution of 3β-acetoxy-5α : 6α-epoxycholestane (1·12 g.) in benzene (20 c.c.) at 20°. After 5 min. the product (1·08 g.) was isolated and then chromatographed on deactivated alumina (30 g.). Benzene–light petroleum (1 : 1, 80 c.c.) eluted starting material (161 mg., 18%), m. p. 94—97°. Benzene (200 c.c.) eluted 3β-*acetoxy*-6β-*fluorocholestan*-5α-*ol* (638 mg., 62%); elution with benzene–ether (9 : 1) gave gummy material (20%). Crystallisation from methanol afforded the pure fluorohydrin, m. p. 207—209°, $[\alpha]_D$ −21° (Found: C, 74·75; H, 10·8; F, 4·0. $C_{29}H_{49}O_3F$ requires C, 75·0; H, 10·55; F, 4·3%).

Prolongation of the reaction time caused the solution to become blue and the yield of fluorohydrin obtained by chromatography to fall (see Table).

The fluorohydrin was recovered from treatment with acetic anhydride and pyridine at 20° for 24 hr. Solutions of the fluorohydrin (175 mg.) in *tert.*-butyl alcohol (12 c.c.) and N-potassium *tert.*-butoxide in *tert.*-butyl alcohol (4 c.c.) were mixed and then kept at 20° for 16 hr. Crystallisation from methanol gave 5α : 6α-epoxycholestan-3β-ol (110 mg.), m. p. and mixed m. p. 140—141°; infrared absorption identical with that of an authentic sample.

3β-*Acetoxy*-5α-*fluorocholestan*-6β-*ol* (VIII).—A solution of 3β-acetoxy-5β : 6β-epoxycholestane (0·9 g.) in benzene (25 c.c.) was treated with boron trifluoride–ether complex (0·4 c.c.). The reaction (followed polarimetrically) was completed in 30 min. and the product was then isolated with ether. The solution in hot methanol was filtered to remove some sparingly soluble material (60 mg.) and cooled to give the *fluorohydrin* (0·69 g.), m. p. 160—170°. The pure compound had m. p. 171—172°, $[\alpha]_D$ −9° (Found: C, 74·9; H, 10·65; F, 4·05. $C_{29}H_{49}O_3F$ requires C, 75·0; H, 10·55; F, 4·3%). Treatment of the compound with alkali, as described for the previous fluorohydrin, gave 5β : 6β-epoxycholestan-3β-ol, m. p. and mixed m. p. 131—133°.

Acetylation of the fluorohydrin at 20° gave 3β : 6β-*diacetoxy*-5α-*fluorocholestane*, double m. p. 124—125°, 160—161°, $[\alpha]_D$ −20° (Found: C, 73·6; H, 10·2. $C_{31}H_{51}O_4F$ requires C, 73·5; H, 10·1%).

The fluorohydrin (0·9 g.) in acetone (40 c.c.) was oxidised with 8N-chromic acid. The product was isolated with ether and chromatographed on deactivated alumina (25 g.). Light petroleum eluted 3β-*acetoxy*-5α-*fluorocholestan*-6-*one* (0·79 g.), m. p. 122—124° (from methanol), $[\alpha]_D$ −1° (Found: C, 75·5; H, 10·35. $C_{29}H_{47}O_3F$ requires C, 75·4; H, 10·15%): infrared absorption (in CS_2), carbonyl bands at 1735 (acetate) and 1703 cm.$^{-1}$ (6-ketone).

5α-*Fluorocholestane*-3 : 6-*dione* (XI).—A solution of 3β-acetoxy-5α-fluorocholestan-6β-ol (0·33 g.) and lithium aluminium hydride (96 mg.) in dry ether (20 c.c.) was heated under reflux. Isolation with ether yielded 5α-fluorocholestane-3β : 6β-diol (0·28 g.), m. p. 196—197° (from ethyl acetate), $[\alpha]_D$ +13°. [Acetylation of the diol gave 3β : 6β-diacetoxy-5α-fluorocholestane, m. p. and mixed m. p. 124—125° and 160—161°.] The diol (0·22 g.) in acetone (8 c.c.) was treated dropwise with 8N-chromic acid until a yellow colour persisted. Isolation with ether and crystallisation from methanol afforded 5α-*fluorocholestane*-3 : 6-*dione* (0·14 g.), m. p. 143—144°, $[\alpha]_D$ +10° (Found: C, 77·9; H, 10·5. $C_{27}H_{43}O_2F$ requires C, 77·5; H, 10·3%). The compound showed no appreciable absorption in the ultraviolet region and gave a carbonyl band (1720 cm.$^{-1}$) but no hydroxyl band in the infrared spectrum.

A solution of the fluoro-diketone (36 mg.) in benzene was adsorbed on to alumina (5 g.). After 12 hr. the steroid was eluted with ether (30 c.c.). Crystallisation from methanol gave cholest-4-ene-3 : 6-dione, m. p. and mixed m. p. 124—126°.

3β-*Chloro*-6β-*fluorocholestan*-5α-*ol*.—Boron trifluoride–ether complex (0·5 c.c.) was added to a solution of 3β-chloro-5α : 6α-epoxycholestane (0·6 g.) in benzene (20 c.c.) at 20°. After 18 min. the product was isolated with ether: it showed negligible carbonyl absorption near 1700 cm.$^{-1}$. Two crystallisations from methanol–acetone afforded 3β-*chloro*-6β-*fluorocholestan*-5α-*ol* (278 mg.), m. p. 129—131°, $[\alpha]_D$ 0° (Found: C, 73·85; H, 10·7; Cl, 8·1. $C_{27}H_{46}OClF$ requires C, 73·55; H, 10·45; Cl, 8·05%): infrared spectrum (in CS_2), hydroxyl peak at 3580 cm.$^{-1}$.

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