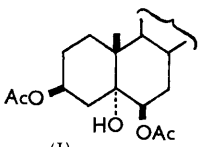
# 206. *Acid-catalysed Reactions of 6β-Substituted 5α-Hydroxysteroids.*

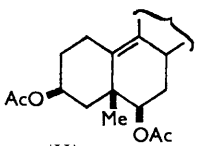
By J. W. Blunt, M. P. Hartshorn, and D. N. Kirk.

3β-Acetoxy-6β-fluorocholestan-5α-ol reacts with acetic anhydride–perchloric acid to give initially 3β,5α-diacetoxy-6β-fluorocholestane, but on prolonged reaction with the same reagents gives a 3α,5α-bridged carbonium ion as its perchlorate salt. The structure of this salt follows from the structures of its hydrolysis products, 3α-acetoxy-6β-fluorocholestan-5α-ol and 5α-acetoxy-6β-fluorocholestan-3α-ol. The reaction of the perchlorate salt with piperidine is described.

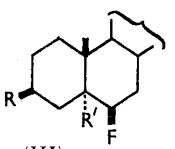
The abnormal product of dehydration of 3β,6β-diacetoxycholestan-5α-ol obtained by Westphalen,[1] using acetic anhydride–sulphuric acid, was shown by later workers [2] to be 3β,6β-diacetoxy-5β-methyl-19-norcholest-9-ene (II). It was found subsequently [3] that treatment of the triol diacetate (I) with acetic anhydride–potassium bisulphate gave Westphalen's diacetate (II) in better yield. A rearranged product was not obtained from the 6α-acetoxy-compound [4] or from compounds lacking a functional group at C-6.[5] Recently, it was shown that rearranged [6] products could also be obtained from compounds of the 6β-halogeno-5α-hydroxy-series. In view of this paper, and the report [7] that acetic anhydride–sulphuric acid could be used under milder conditions than those reported originally, we examined the dehydration of the 6β-fluoro-5α-hydroxy-system using acetic anhydride–perchloric acid.[8]



(I)

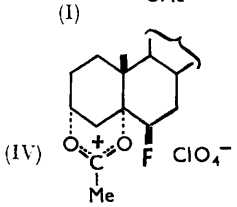


(II)

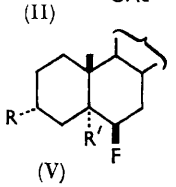


(III)

(a: R = OAc, R′ = OH)
(b: R = R′ = OAc)
(c: R = OH, R′ = OAc)

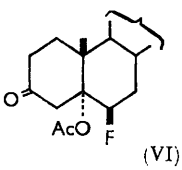


(IV)



(V)

(a: R = OAc, R′ = OH)
(b: R = OH, R′ = OAc)
(c: R = R′ = OAc)



(VI)

3β,5α-Diacetoxy-6β-fluorocholestane (IIIb) was formed on treatment (5 min.) of the fluorohydrin (IIIa) [9] with acetic anhydride containing catalytic amounts of perchloric acid. However, when the reaction time was increased to 24 hours, a crystalline, ether-insoluble, solid separated (yield *ca.* 20%). Since the acetic anhydride solution yielded a crude product the infrared spectrum of which was indistinguishable from the starting material, the quantity of perchloric acid used was increased to 1·1 mole. Under these conditions the yield of solid increased to 45%; a further 10% could be obtained by subsequent dilution of the acetic anhydride solution with ether.

[1] Westphalen, *Ber.*, 1915, **48**, 1064.
[2] (*a*) Bladon, Henbest, and Wood, *J.*, 1952, 2737; (*b*) Ellis and Petrow, *J.*, 1952, 2246, and references cited therein.
[3] Petrow, *J.*, 1939, 998.
[4] Davis and Petrow, *J.*, 1949, 2973.
[5] Aebli, Grob, and Schumacher, *Helv. Chim. Acta*, 1958, **41**, 774.
[6] Mihina, *J. Org. Chem.*, 1962, **27**, 2807.
[7] Shealy and Dodson, *J. Org. Chem.*, 1951, **16**, 1427.
[8] Blunt, Hartshorn, and Kirk, *Chem. and Ind.*, 1963, 1955.
[9] Henbest and Wrigley, *J.*, 1957, 4768.

The infrared spectrum (in Nujol) of the crystalline solid revealed that the two acetoxy-groups in the starting material had either been modified or eliminated. In addition there were bands normally associated with the perchlorate ion.[10] Elemental analysis indicated the presence of six oxygen atoms which, the existence of the perchlorate ion being assumed, left two oxygen atoms to be placed. The evidence given below shows the salt to be the 3α,5α-bridged ion perchlorate (IV).

Hydrolysis of the perchlorate salt, using aqueous sodium hydrogen carbonate in boiling dioxan, gave a mixture of two hydroxy-acetates (Va and Vb), which could be separated by chromatography on deactivated alumina. Acetylation of each of these hydroxy-acetates gave the same diacetate (Vc). Mild oxidation of hydroxy-acetate (Vb) by chromic acid in acetone [11] gave a ketone (VI), which later was obtained by the following unambiguous route: the diacetate (IIIb) was hydrolysed by dilute sulphuric acid in methanol to give the 3β-hydroxy-5α-acetate (IIIc) which on oxidation with chromic acid in acetone gave the ketone (VI). As the hydroxy-acetate, obtained from the hydrolysis of the perchlorate salt, was not identical with the 3β-hydroxy-5α-acetate (IIIc) and yet gave the same ketone on oxidation, it was assigned the structure 5α-acetoxy-6β-fluorocholestan-3α-ol (Vb). The assignment of the 3α-acetoxy-5α-hydroxy-structure to the second hydroxy-acetate (Va) followed from the fact that it gave the same diacetate (Vc) on acetylation as did the hydroxy-acetate (Vb).

The isolation of 3α-hydroxy-5α-acetate and 5α-hydroxy-3α-acetate from the hydrolysis of the perchlorate salt (each hydroxy-acetate having an α-acetoxy-group) suggested that, in fact, the acetoxy-group in compounds (Va and Vb) had been involved in a 3,5-carbonium ion bridge, which, necessarily must have the α-configuration. The bridge formulated as (IV) would be stabilised by carbonium ion–oxonium ion mesomerism.

An analogous structure to the bridged carbonium ion, here isolated as the perchlorate salt, has been postulated [12] as an intermediate in the solvolysis of 3β-tosyloxy- (or 3β-methylsulphonyloxy-) 5α-acetoxy-compounds to give epicholesterol. The same type of bridge has been invoked [13] to explain the isolation of 5α-acetoxycholesta-3,6-dione as a minor product from the chromic acid oxidation of epicholesteryl acetate.

The mechanism of formation of the bridged carbonium ion is of interest, particularly in view of the fact that the fluorohydrin (IIIa) on reaction with acetic anhydride–potassium hydrogen sulphate was reported to yield mainly a Westphalen-type product. In the present work with acetic anhydride–perchloric acid, the acetylation of the 5α-hydroxy-group is presumed to proceed *via* acetyl perchlorate attack. Protonation of either the 3β-acetoxy- or 5α-acetoxy-group may occur under strongly acidic conditions. The normal loss of the 5α-substituent (as acetic acid in the case of a protonated 5α-acetoxy-group) to give an incipient carbonium ion at C-5, which could collapse either by proton loss from C-4 or C-6 or by skeletal rearrangement followed by proton loss, is hindered by the $-I$ effect of the 6β-fluoro-group. However, in acetic anhydride–perchloric acid there seems to be an alternative, lower energy pathway not involving a C-5 carbonium ion. Initial protonation of the 3β-acetoxy-group followed by the loss of acetic acid from C-3 combined with attack by the carbonyl oxygen of the 5α-acetoxy-group would give rise to the bridged carbonium ion (IV). In this scheme the 6β-fluoro-group would have the required effect of stabilising the $O–C_{(5)}$ bond.

The hydrolysis of the perchlorate salt, reported above to give the two hydroxy-acetates (Va and Vb), is presumed to occur *via* attack of the hydroxyl ion on the bridging carbon atom, followed by proton transfer with cleavage of a bridge C–O bond to give the *cis*-hydroxy-acetates (Va and Vb). Initial attack by hydroxyl ion on the bridging carbon

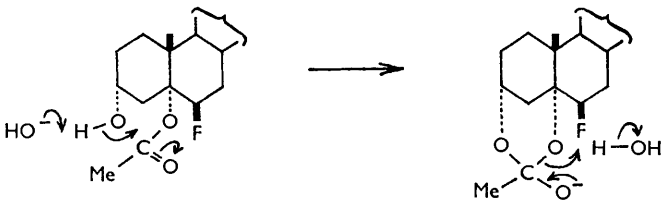
[10] Cross, " Introduction to Practical Infrared Spectroscopy," Butterworths, London, 1960.
[11] Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, **39**.
[12] Plattner and Lang, *Helv. Chim. Acta*, 1944, **27**, 1872; Plattner, Furst, Koller, and Lang, *ibid.*, 1948, **31**, 1455.
[13] Tarlton, Fieser, and Fieser, *J. Amer. Chem. Soc.*, 1953, **75**, 4423.

atom is necessary because initial attack either at C-5 or C-3 would probably lead to *trans*-hydroxy-acetates which were not found.

During the study of the hydrolysis of the perchlorate salt, it was found that while the total yield of hydroxy-acetates (Va and Vb) remained constant at *ca.* 95%, the relative yields of the hydroxy-acetates were markedly dependant upon the reaction time as shown in the Table.

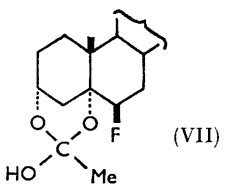
| Reaction time | Relative yields of 3α-acetoxy-5α-alcohol (Va) | 3α-hydroxy-5α-acetate (Vb) |
|---|---|---|
| 2 min. ..... | 1 | 9 |
| 30 min. ..... | 2·5 | 7·5 |
| 2 hr. ..... | 6 | 4 |

The qualitative relation between the reaction times and the relative amounts of the hydroxy-acetates isolated from the hydrolyses suggested that under the hydrolytic conditions the 3α-hydroxy-5α-acetoxy-compound (Vb) was being converted into the 3α-acetoxy-5α-hydroxy-compound (Va). Accordingly, when pure hydroxy-acetate (Vb) was treated under the same hydrolytic conditions for 4 hours, it was converted virtually quantitatively into the second hydroxy-acetate (Va). The transference of the acetoxy-group is visualised as proceeding thus:

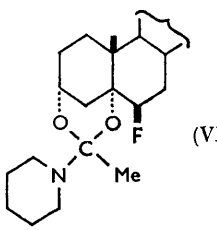



It seems likely then that in the hydrolysis of the perchlorate salt the initial attack of hydroxyl ion gives rise to the cyclic orthoacetate (VII). The initial predominant formation of the 5α-acetoxy-3α-hydroxy-compound (Vb) by breakdown of the cyclic orthoacetate may be rationalised in terms of kinetically-controlled preferred protonation of the 3α-oxygen atom rather than the 5α-oxygen atom, protonation of the 5α-oxygen atom being rendered relatively unfavourable as a result of the $-I$ effect of the adjacent 6β-fluoro-substituent. However, conditions allowing equilibration between the two hydroxy-acetates must ultimately lead to a preponderance of the isomer (Va), that is more favoured thermodynamically.

Reaction of the perchlorate salt (IV) with piperidine also occurs by attack of the base on the bridge carbon atom. Piperidinium perchlorate was isolated and the infrared spectrum of the steroidal product exhibited no band characteristic of acetoxy-groups. However, mild hydrolysis of this material gave only the 5α-acetoxy-3α-hydroxy-compound




(VII)




(VIII)

(Vb). These observations may be rationalised in terms of the formation of the cyclic system (VIII) which on subsequent hydrolysis could then give rise to the hydroxy-acetate (Vb).

## Experimental

Rotations were measured for chloroform solutions at room temperature. Infrared spectra were recorded for carbon disulphide solutions, except where otherwise stated. The alumina used for chromatography was P. Spence, grade " H," which had been treated with 5% of 10% acetic acid. Light petroleum refers to the fraction of b. p. 50—70°.

3β,5α-*Diacetoxy*-6β-*fluorocholestane* (IIIb).—Perchloric acid (0·1 c.c., 60%) was added to a suspension of the fluorohydrin (IIIa) (1 g.) in acetic anhydride (25 c.c.), and the mixture kept at 20° for 5 min. The crude product, isolated *via* ether, was adsorbed on alumina (100 g.). Elution with light petroleum–benzene (6 : 1) gave a gum which on crystallisation (methanol) afforded the *diacetate* (IIIb) (550 mg.) as needles, m. p. 123—124°, $[\alpha]_D$ 0° (*c* 1·0) (Found: C, 73·7; H, 10·4; F, 3·65. $C_{31}H_{51}FO_4$ requires C, 73·5; H, 10·1; F, 3·8%); $\nu_{max.}$ 1730 and 1232 cm.$^{-1}$ (OAc).

*Isolation of the Bridged Carbonium Ion Perchlorate Salt* (IV).—A solution of the diacetate (IIIb) (730 mg.) in acetic anhydride (18 c.c.) containing perchloric acid (0·19 c.c.; 60%) was kept at 20° for 24 hr. Filtration afforded the *perchlorate salt* (IV) (416 mg.), m. p. 159—160° (decomp.) (Found: C, 63·7; H, 8·6; Cl, 6·7. $C_{29}H_{48}ClFO_6$ requires C, 63·6; H, 8·8; Cl, 6·5%); $\nu_{max.}$ (Nujol) 1109, 1098, 1085, and 1075 cm.$^{-1}$ ($ClO_4^-$).

A further sample of the salt (84 mg.; m. p. 160—161°) was obtained by dilution of the above filtrate with ether, when more solid was deposited. The residue was poured into saturated aqueous sodium hydrogen carbonate and the crude product, isolated by use of ether, was adsorbed on alumina (20 g.). Elution with light petroleum–benzene (3 : 1) gave a gum (170 mg.), the infrared spectrum of which was indistinguishable from that of the starting material.

Elution with benzene gave 5α-*acetoxy*-6β-*fluorocholestan*-3α-*ol* (Vb) (32 mg.) which crystallised (methanol) as needles, m. p. 82—85° and 131—132°, $[\alpha]_D$ +5° (*c* 1·0) (Found: C, 72·5; H, 10·8; F, 4·4. $C_{29}H_{51}FO_4$ (*i.e.*, the monohydrate) requires C, 72·2; H, 10·7; F, 3·9%); $\nu_{max.}$ 3584 and 3497 cm.$^{-1}$ (OH), 1733 and 1239 cm.$^{-1}$ (OAc).

*Hydrolysis of the Perchlorate Salt* (IV).—The salt (200 mg.) in pure dioxan (32 c.c.) containing saturated aqueous sodium hydrogen carbonate (1·1 c.c.) was heated under reflux for 30 min. The crude product, isolated by use of ether, was adsorbed on alumina (10 g.). Elution with light petroleum–benzene (1 : 1) and crystallisation (methanol) gave 3α-*acetoxy*-6β-*fluorocholestan*-5α-*ol* (47 mg.) as needles, m. p. 113—114°, $[\alpha]_D$ −24° (*c* 1·0) (Found: C, 75·4; H, 10·8; F, 4·2. $C_{29}H_{49}FO_3$ requires C, 75·1; H, 10·6; F, 4·1%); $\nu_{max.}$ 3503 cm.$^{-1}$ (OH), 1741 and 1215 cm.$^{-1}$ (OAc).

Elution with benzene–ether (10 : 1) and crystallisation (methanol) gave 5α-acetoxy-6β-fluorocholestan-3α-ol (120 mg.) as needles, m. p. 82—85° and 131—132°, $[\alpha]_D$ +5° (*c* 1·0), $\nu_{max.}$ 3584 and 3497 cm.$^{-1}$ (OH), 1733 and 1239 cm.$^{-1}$ (OAc).

5α-*Acetoxy*-6β-*fluorocholestan*-3β-*ol* (IIIc).—A solution of 3β,5α-diacetoxy-6β-fluorocholestane (420 mg.) in methanol (50 c.c.) containing sulphuric acid (10 c.c.; 4N) was heated under reflux for 30 min. The product, isolated by use of ether, was adsorbed on alumina (30 g.). Elution with light petroleum–benzene (1 : 1) and crystallisation from methanol gave unchanged diacetate (195 mg.) as needles, m. p. 123—124°.

Elution with benzene–ether (1 : 1) gave the *hydroxyacetate* (IIIc) as a gum (170 mg.) which crystallised (methanol) as needles (135 mg.), m. p. 156—157°, $[\alpha]_D$ +2° (*c* 1·0) (Found: C, 75·2; H, 10·9; F, 4·0. $C_{29}H_{49}FO_3$ requires C, 75·1; H, 10·6; F, 4·1%); $\nu_{max.}$ 3509 cm.$^{-1}$ (OH), 1730 and 1232 cm.$^{-1}$ (OAc).

5α-*Acetoxy*-6β-*fluorocholestan*-3-*one* (VI).—(i) *From* 5α-*acetoxy*-6β-*fluorocholestan*-3α-*ol* (Vb). Chromic acid (1·1 mole; 8N) was added to a solution of the alcohol (34 mg.) in acetone (5 c.c.). Reaction after 5 min. gave a product, which crystallised (acetone) to give the *ketone* as needles (14 mg.), m. p. 156—157°, $[\alpha]_D$ +13° (*c* 1·0) (Found: C, 75·3; H, 10·4; F, 5·0. $C_{29}H_{47}FO_3$ requires C, 75·3; H, 10·2; F, 4·1%); $\nu_{max.}$ 1715 cm.$^{-1}$ (C=O), 1736, 1227, and 1209 cm.$^{-1}$ (OAc).

(ii) *From* 5α-*acetoxy*-6β-*fluorocholestan*-3β-*ol* (IIIc). Chromic acid (8N) oxidation of the alcohol (110 mg.) gave a product which crystallised as needles (76 mg.), m. p. 156—157°, $[\alpha]_D$ +12° (*c* 1·0). This product was identical with that obtained by method (i) above (mixed m. p. and infrared spectrum).

3α,5α-*Diacetoxy*-6β-*fluorocholestane* (Vc).—(i) *From* 3α-*acetoxy*-6β-*fluorocholestan*-5α-*ol* (Va). Perchloric acid (0·02 c.c., 60%) was added to a solution of the alcohol (30 mg.) in a mixture of

acetic anhydride (0·8 c.c.) and carbon tetrachloride (0·3 c.c.). After 1 min., the reaction was quenched with aqueous sodium hydrogen carbonate solution, and the crude product isolated by use of ether. Crystallisation from methanol gave the *diacetate* as plates (28 mg.), m. p. 130·5—131°, $[\alpha]_D$ −19° (*c* 1·05) (Found: C, 73·6; H, 10·4; F, 3·6. $C_{31}H_{51}FO_4$ requires C, 73·5; H, 10·1; F, 3·8%); $\nu_{max.}$ 1733 and 1242 cm.$^{-1}$ (OAc).

(ii) *From* 5α-*acetoxy*-6β-*fluorocholestan*-3α-*ol* (Vb). The alcohol (20 mg.) was converted by the above method into the diacetate (14 mg.), m. p. and mixed m. p. 130—131°, $[\alpha]_D$ −16° (*c* 1·08).

3α-*Acetoxy*-6β-*fluorocholestan*-5α-*ol* (Va) *from* 5α-*Acetoxy*-6β-*fluorocholestan*-3α-*ol* (Vb).—A solution of the hydroxy-acetate (Vb) (53 mg.) in dioxan (9 c.c.) containing aqueous sodium hydrogen carbonate (0·25 c.c.) was heated under reflux for 4 hr. Isolation by use of ether, followed by adsorption on alumina (10 g.), and elution with benzene–ether (10 : 1) gave a gum (55 mg.), which crystallised (methanol) to give hydroxy-acetate (Va) as needles (45 mg.), m. p. 113—114°, $[\alpha]_D$ −24° (*c* 1·03).

*Reaction of the Perchlorate Salt* (IV) *with Piperidine.*—To a solution of the perchlorate salt (40 mg.) in piperidine (0·5 c.c.) was added dry ether (5 c.c.), the deposited solid, m. p. 130—132°, was identical (infrared spectrum) with authentic piperidinium perchlorate. Removal of excess of piperidine and ether from the filtrate at 20 mm. gave an oil (54 mg.), the infrared spectrum of which exhibited no bands characteristic of acetoxy-groups.

Brief warming of this oil with dioxan (1 c.c.) containing aqueous sodium hydrogen carbonate (0·02 c.c.), and isolation by use of ether gave a gum (40 mg.) from which only 5α-acetoxy-6β-fluorocholestan-3α-ol (26 mg.), m. p. 82—85° and 131—132°, $[\alpha]_D$ +4° (*c* 1·03), was obtained by chromatography on alumina.

Microanalyses were carried out by Dr. A. D. Campbell and his associates at the University of Otago.

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