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REACTIONS OF 5α-HYDROXY STEROIDS—VII*

THE WESTPHALEN REARRANGEMENT OF SOME 3β-SUBSTITUTED-6β-ACETOXY-5α-HYDROXY CHOLESTANES

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Abstract—Product analyses and kinetic studies of the reactions of 3β-substituted-6β-acetoxy-5α-hydroxy cholestanes with H_2SO_4–Ac_2O–AcOH reveal a marked dependence of the reactions upon the nature of the 3β-substituent.

THE Westphalen rearrangement of the 5α-hydroxy steroid (Ia) has been shown[1] to proceed via the rate-determining heterolysis of the 5α-acetylsulphate (Ib) with formation of a C-5 carbonium ion. The rate of the rearrangment is markedly dependent upon the nature of the 6β-substituent (relative rates. 6β-F, 1; 6β-OCH_3, 3,300) consistent with slow carbonium ion formation at the adjacent C-5 position. The effect of the 6-substituent was also revealed by product analyses. The yield of the rearranged $\Delta^{9(10)}$-product (II) was greatest for the 6β-fluoro compound (Ic) where steric effects would be minimized and the electron withdrawing effect ($-I$) of the 6-substituent be at a maximum. As the substituent was changed from small size and large electronic effect progressively to large size and small electronic effect the yield of rearranged material dropped. This decrease in yield was off-set by increased yield of 5α-acetates and other minor products. In view of the dependence of the rate and course of the reaction on the nature of the 6β-substituent we have now examined the effect on reaction rate and product ratios of variations in the 3β-substituent.

The 3β-fluoro-5α-hydroxy compound (IIIa) was prepared from 3β-fluorocholest-5-ene via the 5α,6α-epoxide. Mild acid hydrolysis of the epoxide followed by acetylation using pyridine–acetic anhydride gave (IIIa). The 3β-chloro[2] (IIIb), 3β-methoxy[3] (IIIc) and the 3-deoxy[2] (IIId) compounds have all been described before.

The reaction of the 3β-fluoro compound (IIIa) with sulphuric acid–acetic acid–acetic anhydride gave only the rearranged material (IIa). The reaction of the 3β-chloro compound (IIIb) gave, in addition to a high yield of the rearranged compound (IIb), a small amount of an unsaturated material to which the 3β-chloro-5β-methyl-19-nor-$\Delta^{1(10)}$-structure (IVa) was assigned on the basis of IR and NMR spectroscopic evidence. In particular, the NMR spectrum exhibited signals at 4·02 (3α-H), 4·75

* Part VI, J. W. Blunt, M. P. Hartshorn and D. N. Kirk, *Tetrahedron Letters* 2125 (1966).

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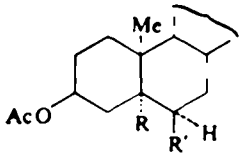
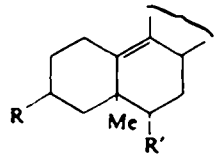
[1] J. W. Blunt, A. Fischer, M. P. Hartshorn, F. W. Jones, D. N. Kirk and S. W. Yoong, *Tetrahedron* **21**, 1567 (1965).

[2] I. M. Heilbron, W. Shaw and F. S. Spring, *Rec. Trav. Chim.* **57**, 529 (1938).

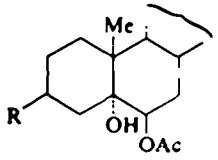
[3] V. Petrow, *J. Chem. Soc.* 1077 (1937).



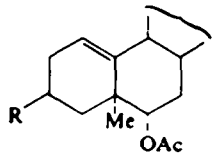
Ia R, OH
b R, OSO_2OAc
c R, OH; R', F
d R, OH; R', OAc
e R, OH; R', H
f R, OH; R', Me



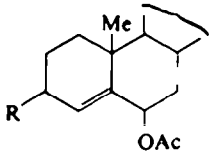
IIa R, F; R', OAc
b R, Cl; R', OAc
c R, OCH_3; R', OAc
d R, H; R', OAc



IIIa R, F
b R, Cl
c R, OMe
d R, H



IV a R, Cl
b R, OMe
c R, H
d R, OAc



Va R, Cl
b R, OAc
c R, F
d R, OMe
e R, H

(6α-H), 5·45 (1-H) and 1·27 ppm (5β-CH_3). Authentic 3β-chloro-6β-acetoxy-cholest-4-ene (Va), prepared by reaction of the 5α-hydroxy compound (IIIb) with thionyl chloride–pyridine, gave in contrast a NMR spectrum with signals at 4·20 (3α-H), 5·20 (6α-H), 5·70 (4-H) and 1·17 ppm (19-CH_3).

The reaction of the 3-deoxy compound (IIId) gave, in addition to the rearranged compound (IId) and the rearranged $\Delta^{1(10)}$-isomer (IVc), further fractions consisting largely of three compounds. GLC examination of this material allowed the identification of one compound as the 5α,6β-diacetate. The remaining compounds were not identified.

Finally the 3β-methoxy compound (IIIc) gave a moderate yield of the rearranged material (IIc). The other products isolated were the rearranged $\Delta^{1(10)}$-isomer (IVb), the 3β,6β-diacetoxy-Δ^4-compound (Vb) and a further unidentified compound. A late fraction from the chromatographic column was shown (NMR data) to consist of a mixture (1:1) of the 3α,6β-diacetoxy-cholest-4-ene and 3β-methoxy-5α,6β-diacetoxy cholestane. The 3β,6β- and 3α,6β-diacetoxy cholest-4-enes are considered to arise by reaction of 3β-methoxy-6β-acetoxy-cholest-4-ene (Vd) with sulphuric acid–acetic

TABLE 1. NMR SPECTRA (PPM)

(a) *3-Substituted-6β-acetoxycholest-4-enes*

3-Substituent	$C^{18}H_3$	$C^{19}H_3$	3α-H	6α-H	4-H
3β-chloro-(Va)	0·72	1·17	4·20(15)*	5·20(7)	5·70(4)
3β-acetoxy-(Vb)	0·74	1·16	5·20	5·20	5·55(4)
3β-fluoro-(Vc)	0·73	1·17	5·83 and 5·25	5·25	5·63(4)
3β-methoxy-(Vd)	0·72	1·11	3·67(16)	5·20(7)	5·67(4)
3-deoxy-(Ve)	0·73	1·09	–	5·20(6)	5·69(6)

(b) *Rearranged-$\Delta^{1(10)}$-compounds*

3-Substituent	$C^{18}H_3$	5β-CH_3	3α-H	6α-H	1-H
3β-chloro-(IVa)	0·67	1·27	4·01	4·75(12)*	5·45(13)
3β-methoxy-(IVb)	0·65	1·25	3·42	4·77(14)	5·37(11)
3-deoxy-(IVc)	0·65	1·25	—	4·67(12)	5·38(8)

(c) *Rearranged-$\Delta^{9(10)}$-compounds*

3-Substituent	$C^{18}H_3$	5β-CH_3	3α-H	6α-H
3β-fluoro-(IIa)	0·82	1·20	5·20 and 4·42	4·65(15)*
3β-chloro-(IIb)	0·82	1·30	4·33(9)	4·67(18)
3β-methoxy-(IIc)	0·78	1·17	3·43(10)	4·65(18)
3-deoxy-(IId)	0·82	1·05	–	4·67(19)

* Figure in parenthesis gives width at half-height in c/s.

TABLE 2. PRODUCTS OF THE REACTION OF 3-SUBSTITUTED-5α-HYDROXY-STEROIDS WITH H_2SO_4–AcOH–Ac_2O

3β-Substituent	$\Delta^{9(10)}$	$\Delta^{1(10)}$	Δ^4	Others	Total
3β-fluoro-(IIIa)	85	–	–	—	85
3β-chloro-(IIIb)	78	13	—	—	91
3β-methoxy-(IIIc)	52	5	21	13	91
3-deoxy-(IIId)	36	14	trace	25	75

acid–acetic anhydride; the ratio 3β:3α, 3:1, found here is consistent with our[4] equilibration studies of the diacetoxy cholest-4-enes. These structural assignments were supported by IR and NMR (cf. Table 1) spectra and by comparison of physical constants for compounds reported in the literature.

It is apparent (Table 2) that an efficient "Westphalen" rearrangement requires the presence of a strongly electron withdrawing substituent at C-3 as well as at the 6β-position. The variation in yield of the rearranged $\Delta^{1(10)}$-isomer however does not have a ready explanation in terms of the variation of substituents. In our earlier study[1] of the effects of variations in the 6β-substituent on the reaction with sulphuric acid–acetic acid–acetic anhydride no rearranged $\Delta^{1(10)}$-isomers were isolated. Snatzke and Fehlhaber[5] have however reported the isolation of a small quantity of the rearranged $\Delta^{1(10)}$-isomer (IVd) in a large scale reaction of the 5α-hydroxy compound (Id) with $KHSO_4$–acetic anhydride. It seems probable that the $\Delta^{1(10)}$-isomers were

[4] M. P. Hartshorn and D. N. Kirk, *Tetrahedron* **22**, 1415 (1966).

[5] G. Snatzke and H. Fehlhaber, *Liebig's Ann.* **676**, 188 (1964).

also formed in low yield in the 6β-substituent variation series and were present in the intermediate (gums) chromatographic fractions.

Kinetics

Rate measurements were made by following the change in rotation of the 5α-hydroxy steroid (III) in acetic acid containing acetic anhydride (0·5 M) and sulphuric acid (0·01 and 0·05 M). If the reasonable assumption is made that formation of the

TABLE 3. RATE DATA FOR REACTION OF 3-SUBSTITUTED-5α-HYDROXY STEROIDS WITH H_2SO_4–AcOH–Ac_2O

3-Substituent	10^5k sec^{-1} $[H_2SO_4]$ − 0·01	$k_{rel.}$	10^5k sec^{-1} $[H_2SO_4]$ = 0·05	$k_{rel.}$	$k_{rel.}$ (mean)
3-deoxy-(IIId)	1·7	13·2	—	—	13·2
3β-methoxy-(IIIc)	0·37	2·9	0·57	3·1	3·0
3β-fluoro-(IIIa)	0·16	1·25	0·23	1·25	1·25
3β-acetoxy-	0·13	1·00	0·18	1·00	1·00
3β-chloro-(IIIb)	0·084	0·66	0·11	0·58	0·62

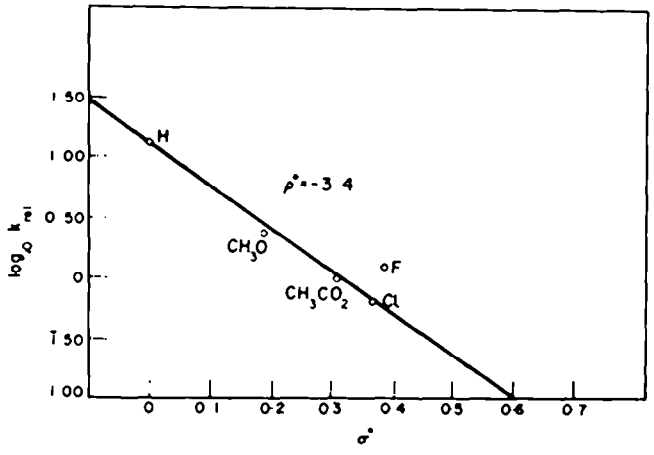


FIG. 1

minor products involves the same rate-determining step as formation of the rearranged $\Delta^{9(10)}$-compound (II), viz. formation of the C-5 carbonium ion, then the rotation is linearly related to the extent of reaction. Under the conditions used the reaction of the 5α-hydroxy compound (Id) has been shown[1] to be first order in steroid. Rate constants were therefore evaluated from Guggenheim plots of the run data and are shown in Table 3. The unsubstituted compound (IIId) reacted too rapidly for the runs to be followed at the higher acid concentration. For each of the other compounds a slight rate dependence on the sulphuric acid concentration was found even though the acid was in excess. This is consistent with the previous extensive[1] results for the 5α-hydroxy compound (Id).

The relative rates for the 3β-X compounds (III) cover a much smaller range than those of the 6β-X compounds. Plots of log $k_{rel.}$ against Taft's σ^* values are shown in Fig. 1. σ^* values for X—CH— groups (6β-X compounds) were assumed to be the

same as those listed by Taft[6] for the XCH_2— groups and σ^* for —CH(X)—CH_2— groups (3β-X compounds) were taken[7] as 1/2·8 of the values for the XCH_2— groups. σ^* for $AcOCH_2$ was taken[8] as 0·45 σ_I of AcO. The slopes (ρ^*) of the plots for 6β-X and 3β-X compounds were −3·6 and −3·4 respectively. The value of ρ^* for the 6β-X compounds has been changed (Fig. 2) with respect to our earlier report[1] (ρ^* −4·8) by the inclusion of rate data for the 6-deoxy (Ie) and 6β-methyl (If) compounds (cf. Table 4). While there is no evidence that the reaction for these compounds with

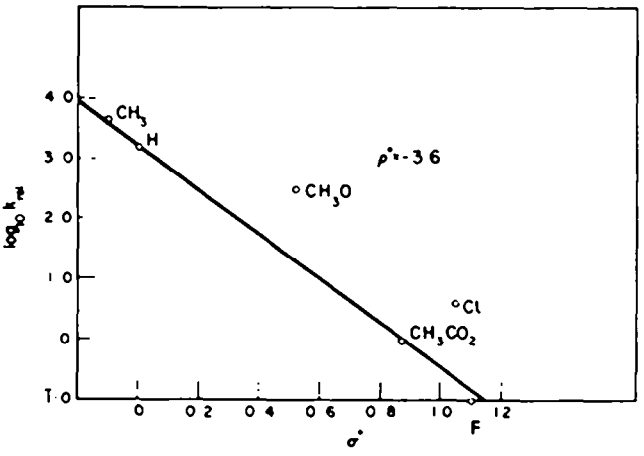


FIG. 2

TABLE 4. RATE DATA FOR REACTION OF 3β-ACETOXY-6β-SUBSTITUTED-5α-HYDROXY STEROIDS WITH H_2SO_4–AcOH–Ac_2O

6-Substituent	$k_{rel.}$
6β-methyl	4640
6-deoxy	1520
6β-methoxy	330
6β-fluoro	0·10
6β-acetoxy	1·00
6β-chloro	4·4

sulphuric acid–acetic acid–acetic anhydride to give non-rearranged olefins proceeds via the heterolysis of the 5α-acetylsulphate as opposed to the rate-determining loss of water from the protonated 5α-hydroxy group, the rates of reaction reported *do* represent the *upper* limit for the rate of formation of the C-5 carbonium ion from a 5α-acetylsulphate. These data necessitate the adjustment of the plot of log $k_{rel.}$ against σ^* for the 6β-X compounds and lead to a *maximum* value for ρ^* of −3·6. We conclude that in terms of the rate of formation of the C-5 carbonium ion the magnitude of the inductive effect (−*I*) exerted by substituents at C-3 or C-6 determines the rate of reaction. It would appear that the orientation of the substituent, equatorial at C-3 and axial at C-6, has no effect on the rate of formation of the C-5 carbonium ion.

[6] R. W. Taft, *Steric Effects in Organic Chemistry* p. 619. J. Wiley, New York (1956).
[7] R. W. Taft, *Steric Effects in Organic Chemistry* p. 592. J. Wiley, New York (1956).
[8] P. R. Wells, *Chem. Revs* 63, 182 (1963).

However, the nature and orientation, e.g. OAc at C-6,[1,4] of the substituent does control the distribution of the C-5 carbonium ion among the various subsequent reaction paths.

EXPERIMENTAL

Rotations (chf. solns at room temp); IR spectra (CS_2 solns unless otherwise stated, on a Perkin–Elmer 221 spectrometer); alumina used for chromatography (P. Spence, Grade H, deactivated by addition of 5% of 10% AcOH); light petroleum, b.p. 50–70°; NMR spectra (60 Mc in CCl_4 with chf. and TMS as internal standards)

3β-Fluoro-6β-acetoxycholestan-5α-ol. (IIIa)

3β-Fluorocholest-5-ene (25 g) in ether (125 ml) was treated with an ethereal soln of monoperphthalic acid (275 ml; $3{\cdot}6 \times 10^{-4}$ mole/ml) and the soln kept at 0° for 2 days. Isolation by means of ether and crystallization from acetone gave the crude 5,6-epoxide (22·4 g), m.p. 83–85°. Hydrolysis of the epoxide (22·4 g) with perchloric acid (0·5 ml; 60%) in acetone (150 ml) and water (35 ml) at 20° for 3 hr gave, after isolation of the steroid, a gum. Acetylation of the gum with pyridine (200 ml) and Ac_2O (20 ml) at 100° for 12 hr and isolation by means of ether gave a crude product which was absorbed onto alumina (500 g). Elution with light petroleum–benzene (4:1) gave the *5α-hydroxy compd* (12 g) as needles from pentane, m.p. 147·5–148°, $[\alpha]_D$ −20° (*c* 1·16). (Found: C, 75·0; H, 10·6; F, 3·9. $C_{29}H_{49}O_3F$ requires C, 74·8; H, 10·6; F, 4·1%.)

Reactions of 5α-hydroxy-3-substituted compds with H_2SO_4–AcOH–Ac_2O

(a) 3β-*Fluoro*-(IIIa). To a soln of steroid (1 g) in AcOH (40 ml) and Ac_2O (5 ml) at 30° was added H_2SO_4–AcOH (0·25M; 15 ml). Isolation after 48 min by means of pentane gave a gum (994 mg) which was adsorbed onto alumina (100 g). Elution with light petroleum gave the *rearranged* $\Delta^{9(10)}$-compd (IIa) (821 mg) which crystallized from MeOH as needles, m.p. 84–85°, $[\alpha]_D$ +87° (*c* 0·89), ν_{max} 1738 and 1240 cm^{-1}. (Found: C, 78·2; H, 10·7; F, 3·9. $C_{29}H_{47}O_2F$ requires C, 78·0; H, 10·5%.)

(b) 3β-*Chloro*-(IIIb). To a soln of steroid (1·5 g) in AcOH (60 ml) and Ac_2O (7 ml) at 30° was added H_2SO_4–AcOH (0·25M; 15 ml). Isolation after 67 min by means of pentane gave a gum (1·498 g) which was adsorbed onto alumina (150 g). Elution with light petroleum gave the *rearranged* $\Delta^{9(10)}$-*compd* (IIb) (1·132 g) which crystallized from MeOH as needles, m.p. 87–88°, $[\alpha]_D$ +86° (*c* 0·86), ν_{max} 1740 and 1239 cm^{-1}. (Found: C, 75·4; H, 10·4; Cl, 8·0. $C_{29}H_{47}O_2Cl$ requires C, 75·2; H, 10·2; Cl, 7·7%.)

Elution with light petroleum–benzene (19:1) gave the *rearranged* $\Delta^{1(10)}$-*compd* (186 mg) which crystallized from acetone as needles, m.p. 105–106°, $[\alpha]_D$ +8° (*c* 0·38), ν_{max} 1740 and 1239 cm^{-1}. (Found: C, 75·3; H, 10·3; Cl, 7·8. $C_{29}H_{47}O_2Cl$ requires; C, 75·2; H, 10·2; Cl, 7·7%.)

(c) 3β-*Methoxy*-(IIIc). To a soln of the steroid (1·5 g) in AcOH (70 ml) and Ac_2O (7 ml) at 30° was added H_2SO_4–AcOH (0·25M; 15 ml). Isolation after 10 min by means of pentane gave a gum (1·421 g) which was adsorbed onto alumina (150 g). Elution with light petroleum gave a gum (172 mg), $[\alpha]_D$ +62° (*c* 1·17), ν_{max} 1737 and 1239 cm^{-1}. Further elution with light petroleum gave the rearranged $\Delta^{9(10)}$-compd (IIc) (753 mg) which crystallized from acetone as needles, m.p. 120–122°, $[\alpha]_D$ +94° (*c* 0·93). Lit.[9] values m.p. 121·5–122·5°, $[\alpha]_D$ +166·6° (!).

Elution with light petroleum–benzene (9:1 and 4:1) gave a gum (67 mg), $[\alpha]_D$ +1° (*c* 0·93), ν_{max} 1737 and 1246 cm^{-1} to which the rearranged $\Delta^{1(10)}$-structure was assigned (see Table 1 for NMR data).

Elution with light petroleum–benzene (3:2 and 1:1 gave 3β,6β-diacetoxycholest-4-ene (Vb) (250 mg) which crystallized as needles from MeOH, m.p. and m.m.p.[4] 132–134°, $[\alpha]_D$ −8° (*c* 0·82).

Finally elution with light petroleum–benzene (1:1) gave a mixture (161 mg), the NMR spectrum of which[4] was consistent with a mixture (1:1) of 3α,6β-diacetoxycholest-4-ene and 3β-methoxy-5α,6β-diacetoxycholestane.

(d) 3-*Deoxy*-(IIId). To a soln of the steroid (1·0 g) in AcOH (56 ml) and Ac_2O (4 ml) at 30° was added H_2SO_4–AcOH (0·25M; 5 ml). Isolation after 2 min by means of ether gave a gum (770 mg) which was adsorbed onto alumina (100 g). Elution with light petroleum gave a gum (345 mg), $[\alpha]_D$ +70° (*c* 0·83) to which the *rearranged* $\Delta^{9(10)}$-*structure* (IId) was assigned (NMR data). (Found: C, 80·9; H, 11·3. $C_{29}H_{48}O_2$ requires C, 81·3; H, 11·2%.)

[9] V. Petrow, *J. Chem. Soc.* 1077 (1937).

Further elution with light petroleum gave the *rearranged* $\Delta^{1(10)}$*-compd* (IVc) (138 mg) which crystallized from MeOH as needles, m.p. 125–127°, $[\alpha]_D$ −23·5° (*c* 0·7), ν_{max} 1737, 1678 and 1236 cm^{-1}. (Found: C, 80·8; H, 11·3. $C_{29}H_{44}O_3$ requires C, 81·3; H, 11·2%.)

Finally elution with light petroleum–benzene (7:3 to 1:1) gave a gum (253 mg), shown by TLC to consist mainly of three compounds.

3β-Fluoro-6β-acetoxycholest-4-ene (Vc)

A soln of the 5α-hydroxy compd (1·35 g) in pyridine (10 ml) containing $SOCl_2$ (3 ml) was kept at −15° for 30 min. Isolation by means of pentane and crystallization from pentane gave the *3β-fluoro-*Δ^4*-compd* (Vc; 1·01 g) as needles, m.p. 97–98°, $[\alpha]_D$ −19° (*c* 1·70) (Found: C, 78·1; H, 10·1; F, 4·2. $C_{29}H_{47}O_2F$ requires: C, 78·0; H, 10·5; F, 4·3%.)

Kinetics

The method described previously was used, in which the rotation (sodium *D*) of the reaction mixture was monitored continuously with a recording polarimeter.

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