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ACID CATALYSED REACTIONS OF 5α-HYDROXY-STEROIDS—III*

THE WESTPHALEN REARRANGEMENT

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Abstract—A kinetic study of the Westphalen rearrangement has revealed that the reaction proceeds through a sulphate ester which gives rise to a C_6 carbonium ion. The effect of the 6β-substituent on the course of the reaction is described.

REACTION of 3β,6β-diacetoxycholestan-5α-ol (Ia) with acetic anhydride containing sulphuric acid[1] or potassium hydrogen[2] sulphate as an acidic catalyst has been shown to give the rearranged diacetate (IIa). In contrast, the use of other catalysts of varied acidity for the reaction in acetic anhydride, e.g. hydrogen chloride[3] or toluene-*p*-sulphonic acid[4] have been reported to give only the 5α-acetate (IIIa). In this work the use of perchloric acid, hydrofluoroboric acid or sulphoacetic acid in acetic anhydride has been shown to convert the 5α-hydroxy-compound (Ia) into the corresponding acetate (IIIa).

In view of the remarkable dependence[5] of the reaction path, dehydration or acetylation, on the nature of the acid catalyst we re-examined the reaction of the 5α-hydroxy-compound (Ia) with the sulphuric acid–acetic anhydride system. The possible intermediacy of the 5α-acetate (IIIa) in the sulphuric acid–acetic anhydride conversion of the 5α-hydroxy-compound (Ia) into the rearranged diacetate (IIa) was excluded by the recovery of the 5α-acetate (IIIa; *c*, 95%) from the treatment with that system at 45° for 2 hr. Under similar conditions the 5α-hydroxy-compound (Ia) was converted into the rearranged diacetate (IIa) in under 5 min.

The unlikely possibility, in view of the specificity of sulphuric acid or potassium hydrogen sulphate catalysis, that the dehydration of the 5α-hydroxy compound (Ia)

* Part I, J. W. Blunt, M. P. Hartshorn and D. N. Kirk, *J. Chem. Soc.* 1073 (1964); Part II, J. W. Blunt, F. W. Jones, M. P. Hartshorn and D. N. Kirk, *Tetrahedron Letters* 1399 (1964).

[1] T. Westphalen, *Chem. Ber.* **48**, 1064 (1915).

[2] V. Petrow, *J. Chem. Soc.* 998 (1939).

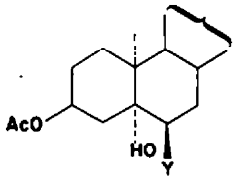
[3] Z. Hattori, *J. Pharm. Soc., Japan* **59**, 129 (1939); *Chem. Abstr.* **33**, 8622 (1939).

[4] [a] M. Davies and V. Petrow, *J. Chem. Soc.* 2536 (1949); [b] A. T. Rowland and H. R. Nace, *J. Amer. Chem. Soc.* **82**, 2833 (1960).

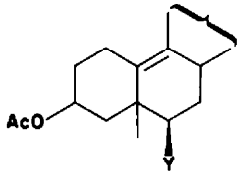
[5] Snatzke and Fehlhaber[6] showed that under forcing conditions (80° or 140°, ca. 30 min) $HClO_4$ and other acids can give rise to small yields of the Westphalen diacetate from either the 5-hydroxy compound (Ia) or the triacetate (IIIa). As we show that the 5-hydroxy compound is converted rapidly at 20° into the triacetate, the reactions reported must be considered to be those of the triacetate and not the 5-hydroxy compound. Snatzke's results therefore shed no light upon the *mechanism* of the Westphalen rearrangement, since we have demonstrated that the triacetate is inert even at 45°.

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

proceeded *via* protonation of the hydroxyl group followed by loss of water and the migration of the C_{19} methyl group was excluded by a comparison of the reactions of the 5α-hydroxy (Ia) and 5α-methoxy (IVa) compounds with sulphuric acid–acetic anhydride at 25°. While the reaction of the 5α-hydroxy compound (Ia) to give the rearranged diacetate (IIa) was complete in 1 min, the 5α-methoxy compound (IVa) was recovered unchanged (*c*, 90%) from the same system after 24 hr. If protonation of the C_5-oxygen atom, followed by loss of water or methanol, had been involved then the reactions of the 5α-hydroxy (Ia) and 5α-methoxy (IVa) compounds should have been similar.



I a Y, OAc
b Y, F
c Y, Cl
d Y, OCH_3
e Y, Br
f Y, I
g Y, $OCOCF_3$



II a Y, OAc
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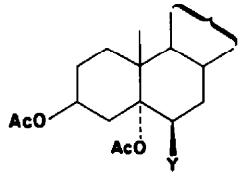
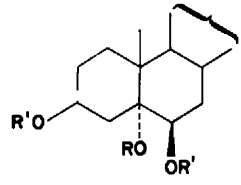
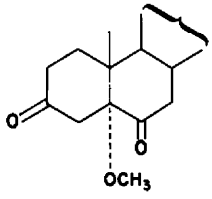
e Y, Br



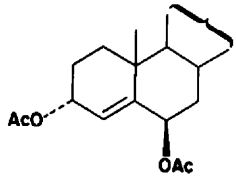
III a Y, OAc
b Y, OCH_3
c Y, Br
d Y, I



IV a R', Ac ; R, CH_3
b R', H ; R, CH_3
c R', Ac



V



VI

At this stage it seemed likely that the dehydration process of the 5α-hydroxy compound (Ia) proceeded *via* some derivative of the 5-hydroxy group which could only form in the sulphuric acid or potassium hydrogen sulphate–acetic anhydride medium. Loss of R—O^- from compound IVc would give a C_5 carbonium ion which could then rearrange with the loss of a proton from C_9 to give the diacetate (IIa). An indication that IVc is a sulphate ester was given by the reaction of cholesterol with sulphuric acid–acetic anhydride under the conditions used for the 5α-hydroxy (Ia), 5α-methoxy (IVa) comparison. After 1 min, cholesteryl hydrogen sulphate was isolated as the potassium salt in 75% yield in addition to a small amount of cholesteryl acetate (13%). The sulphonating properties of the sulphuric acid–acetic anhydride system are also revealed in the formation[7] of sulphoacetic acid from sulphuric acid–acetic anhydride alone and in the formation[8] of the 6-sulphonic acid on reaction of cholest-4-en-3-one with the system.

[7] T. F. Murray and W. O. Kenyon, *J. Amer. Chem. Soc.* **62**, 1230 (1940).
[8] A. Windaus and E. Kuhr, *Liebig's Ann.* **532**, 52 (1937).

KINETICS

The Westphalen rearrangement is characterized by a large positive shift in optical rotation due mainly to the formation of the rearranged diacetate (II), and the reaction was conveniently followed by observing this rotation change.

The by-products, the Δ^4-diacetates and compound IIIa, (Table 1) make a total contribution to the $[\alpha]_D$ of the product mixture of only $+2°$. The contribution to $[\alpha]_{546}$ is also expected to be small compared with the contribution of IIa of $+64°$ ($0{\cdot}66 \times 97°$). That this is so shown by the small difference between the contribution of IIa and the final value of the specific rotation for runs followed in the present work ($+71°$). It appears then that the rotation change in the course of a run is a good measure of the progress of the Westphalen rearrangement.

The results depicted in Figs. 2 and 3 indicate that the reaction being measured is first order in sulphuric acid and independent of steroid when steroid is in excess and first order in steroid and only slightly dependent on sulphuric acid when sulphuric acid is in excess. For some 43 runs carried out with $[Ac_2O] = 0{\cdot}5$ M and varied [Ia] (0·002–0·05 M) and $[H_2SO_4]$ (0·0008–0·17 M) rates varied from $0{\cdot}3 \times 10^{-6}$ to 30×10^{-6} mole l^{-1}. sec^{-1}. For these runs rate constants (k) were evaluated on the assumption that the rates were dependent, to the first power, on the concentration of the reactant present in lesser amount and independent of the concentration of the other reactant. A small correction to the rate constants of those runs in which sulphuric acid was in excess was made by subtracting the value 55×10^{-4} ($[H_2SO_4]$–[Ia]). This correction was made to remove the effect of the slight catalysis by sulphuric acid when it is in excess (see below). Values so obtained ranged from $4{\cdot}6 \times 10^{-4}$–$9{\cdot}2 \times 10^{-4}$ sec^{-1} but most values were grouped closely about the mean of $6{\cdot}2 \times 10^{-4}$ sec^{-1} which had a probable error of $\pm 0{\cdot}2 \times 10^{-4}$ sec^{-1}. The probable error in a single observation was $\pm 1 \times 10^{-4}$ sec^{-1}. Taking account of the large variations in concentrations and of the range of observed rates, it is clear that our deduction from Figs. 2 and 3 that the rate depends only on the lesser concentration of Ia or H_2SO_4 (at fixed, excess, $[Ac_2O]$) is consistent with the rates observed for all runs. The data for individual runs also support this conclusion concerning the dependence of rate on [Ia]. As already pointed out first order plots were obtained when the steroid concentration was less than that of sulphuric acid. Initial zeroth order plots were obtained when the steroid was in excess and these tended to first order when, in the course of the reaction, the steroid (Ia) concentration approached that of the sulphuric acid and then fell below it.

The products obtained when the 5α-hydroxy compounds (I) are treated with sulphuric acid in acetic anhydride are typical of a reaction involving an intermediate C–5 carbonium ion.[2] The proposed mechanism must accommodate this and the experimental observations made in this work, as well as the fact that sulphuric acid and hydrogen sulphate ion appear to be specific catalysts for the reaction. It seems likely that formation of the 5α-acetate (IIIa), when other acids are used as catalysts, involves nucleophilic attack of the 5α-hydroxy group on the acetyl function of the acetyl derivative of the catalytic acid. The alternative mechanism, involving carbonium ion formation and reaction of this with acetic acid would be expected to give rearrangement product (IIa) as well as 5α-acetate. We attribute the specificity of sulphuric acid in promoting rearrangement to the formation of the steroid sulphate

ester (VII) thus providing a better leaving group for carbonium formation. Formation of the sulphate ester should be a fast reaction relative to the ionization of the ester. The existence of an intermediate formed almost completely in a fast reaction between one molecule of hydroxy compound (I) and one molecule of sulphuric acid is demonstrated by the kinetic observation that the rate is dependent only of the concentration of the reactant present in lesser amount. If the intermediate were formed in the slow step, or if the equilibrium formation of intermediate favoured reactants rather than product, then the rate would be first order in both hydroxy compound (I) and sulphuric acid at all concentrations. Further evidence that an intermediate is formed rapidly is provided by the initial rotation values (determined by extrapolation of the chart record to $t = 0$). For runs in which $[H_2SO_4] > [Ia]$ and in which virtually all the hydroxy compound [Ia] would have been converted to intermediate the mean initial value of $[\alpha]_{546}$ was $-64°$. For runs in which $[H_2SO_4] <$ [Ia] not all of the hydroxy compound could have been converted into intermediate initially and indeed the initial $[\alpha]_{546}$ values tended towards the limiting value of $-52°$ found for hydroxy compound (Ia) in pure acetic acid. Thus, for runs for which $[H_2SO_4] < 0{\cdot}7[Ia]$ the mean initial $[\alpha]_{546}$ was $-57°$. Clearly these results are consistent with fast complete formation of an intermediate of $[\alpha]_{546} = -64°$. When there was insufficient sulphuric acid the observed rotation was lower because of the presence of the hydroxy compound of lower rotation ($-52°$).

However, intervention of a single intermediate is not sufficient to explain all of the kinetic data, since the rate is dependent on the acetic anhydride concentration. Even if acetic anhydride were required for fast formation of steroid sulphate, rate determining loss of sulphate would not lead to a kinetic dependence on acetic anhydride, provided that the anhydride is in excess. It is known that sulphuric acid reacts with acetic anhydride in fast reactions to form the monoacetyl and diacetyl sulphates.[9]

$$H_2SO_4 + Ac_2O \overset{K_1}{\rightleftharpoons} AcOSO_3H + AcOH \qquad (1)$$

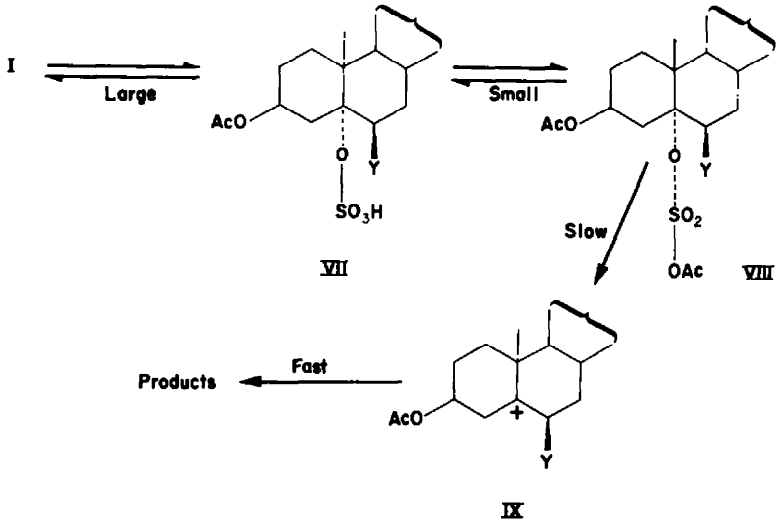
$$H_2SO_4 + 2Ac_2O \overset{K_2}{\rightleftharpoons} AcOSO_2OAc + 2AcOH \qquad (2)$$

The steroid hydrogen sulphate should likewise react with acetic anhydride to give the steroid acetyl sulphate (VIII). Acetyl sulphuric acid is much stronger as an acid than is sulphuric acid.[10] The acetyl sulphate in VIII should thus provide a much better leaving group than the hydrogen sulphate in VII and we propose that carbonium ion (IX) formation occurs from VIII.

Complete formation of acetyl sulphate (VIII) would lead to a rate independent of acetic anhydride when this is in excess. The rate dependence on acetic anhydride can be explained either by rate determining formation of acetyl sulphate (VIII) from hydrogen sulphate (VII) and acetic anhydride or by equilibrium formation of a small fraction of VIII followed by rate-determining loss of acetyl sulphate. It would be expected that formation of steroid acetyl sulphate (VIII) would be at comparable speed to formation of acetyl hydrogen sulphate and diacetyl sulphate from sulphuric acid itself, and therefore fast.[9] Furthermore, the marked sensitivity of the reaction to the electronic properties of the substituent group at C-6 is clearly indicative of

[9] E. A. Jeffery and D. P. N. Satchell, *J. Chem. Soc.* 1887 (1962).
[10] J. Russell and A. E. Cameron, *J. Amer. Chem. Soc.* **60**, 1345 (1938).

rate-determining carbonium ion formation. Formation of the acetyl derivative of VII might be expected to be insensitive to substituent effects as is acid catalysed esterification of carboxylic acids.[11] In addition, the reaction site is remote from the substituent, with at least three atoms interposed, thus substituent effects should be attenuated. In carbonium ion formation the reaction site and substituent are separated by only one carbon atom and this should lead to a greater sensitivity to the electronic effects of substituents. Using the rate data for the 6β-Cl (Ic), 6β-F (Ib) and 6β-MeO (Id) compounds and assuming that σ^* values for F—CH, Cl—CH, and CH_3O—CH are the same as the values listed[11] for F—CH_2, Cl—CH_2 and CH_3O—CH_2 respectively, a ρ^* value for the Westphalen rearrangement of −4·8 may be calculated. This value is to be compared with the values of −3·5 for solvolysis at 70° in acetic acid of secondary carbinyl *p*-bromobenzene sulphonates and −3·3 for solvolysis of tertiary alkyl chlorides in 80% ethanol at 25°.[12] Since the latter reactions involve carbonium ion formation in the rate-determining step we infer that the Westphalen rearrangement, even more sensitive to polar effects, does too. We therefore write the following reaction sequence.



It is pertinent to note at this point that when the effect of a saturated solution of potassium hydrogen sulphate in acetic anhydride on the 5α-hydroxy compound (Ia) was examined it was found that the rate of conversion of the alcohol (Ia) into the rearranged compound (IIa) was comparable with those reactions using sulphuric acid–acetic anhydride where the sulphuric acid:steroid ratio was low. This result may be rationalized if the small concentration of hydrogen sulphate ions in solution were involved in the equilibrium:—

$$HSO_4^- + Ac_2O \rightleftharpoons AcO{-}SO_2{-}O^- + AcOH.$$

and that the ion so formed, AcO-SO_2-O^-, may act as or give rise to a sulphonating agent in a manner similar to the species HO—SO_2—OAc or AcO—SO_2—OAc.

In spite of efforts to isolate the steroid 5α-hydrogen sulphate ester at no time

[11] Taft, in Newman, *Steric Effects in Organic Chemistry*. J. Wiley, New York (1956).
[12] A. Streitwieser, *J. Amer. Chem. Soc.* **78**, 4938 (1956).

could any such material be separated. All such attempts resulted in the isolation only of the starting material and products of the "Westphalen" reaction. These observations are consistent with the literature report[13] that sulphonate esters of tertiary alcohols revert to the alcohol when attempts are made to isolate them.

In the course of the above work the 5α-methoxy compound (IVa) was required. Treatment of the 3β-acetoxy-5,6β-epoxide with boron trifluoride etherate in anhydrous methanol gave the 5α-methoxy-3β,6β-diol (IVb) which on acetylation gave the required compound IVa. The location of the methoxy-group in the diol (IVb) was confirmed by oxidation of the diol under mild conditions to the 5α-methoxy-3,-6-diketone (V) which on alkaline treatment at 20° was converted smoothly into the known Δ^4-3,6-diketone.

6β-Substituted-5α-hydroxy compounds required for this study which had not hitherto been described were prepared as follows. Reaction of cholesterol-α-epoxide with methanol–boron trifluoride gave the 6β-methoxy-3β,5α-diol which was converted into the corresponding 3β-acetate (Id) by mild acetylation conditions. The 6β-iodo-5α-hydroxy compound (If) was prepared from cholesteryl-α-epoxy acetate by reaction with concentrated aqueous hydrogen iodide in acetone solution.

3β-Acetoxy-6β-trifluoroacetoxycholestan-5α-ol (Ig) was prepared by reaction of 3β-acetoxy-cholestan-5α,6β-diol with trifluoroacetic anhydride in pyridine.

In the preparative "Westphalen" reactions the product was isolated when the reaction was indicated to be complete by a maximum positive value of the rotation of the reaction mixture. The product compositions are summarized in Table 1. It is pertinent at this point to indicate that reaction with sulphuric acid in a mixture of acetic anhydride–acetic acid at 25° is less destructive and more conducive to complete isolation of reaction products than previously reported procedures involving treatment with sulphuric acid–acetic anhydride[14] at 45° or with potassium hydrogen sulphate–acetic anhydride[2,15] at 80–100°. In addition, the colour changes which take place in the course of the reactions are not related to the formation of the rearranged material as such but result mainly by interaction of by-products with the sulphuric acid–acetic anhydride–acetic acid system. It seems probable that the Δ^4-products and similar unsaturated material may be the steroidal substrates concerned.

The reaction of the 6β-fluoro compound (Ib) gave only the corresponding rearranged material (IIb). In all other cases the situation was more complicated. The 6β-chloro compound (Ic) gave, in addition to a high yield of the rearranged material (IIc), a small amount of 4β-acetoxycholest-5-en-3β-ol. The origin of this material and the Δ^4-3,6-diacetates reported below will be discussed in a subsequent paper.

The reaction of the 6β-acetoxy compound (Ia) gave in addition to the rearranged diacetate (IIa) three further compounds, namely the 3β,5α,6β-triacetate (IIIa) and two isomeric diacetates. These diacetates were identified as the Δ^4-3β,6β-diacetate (14%) and Δ^4-3α,6β-diacetate (VI) (5%) from their IR and NMR spectra and by comparison with physical constants reported in the literature.

In the case of the 6β-methoxy compound (Id), the yield of the rearranged product

[13] N. C. Deno and M. S. Newman, *J. Amer. Chem. Soc.* **72**, 3852 (1950).
[14] Y. Shealy and R. Dodson, *J. Org. Chem.* **16**, 1427 (1951).
[15] J. S. Mihina, *J. Org. Chem.* **27**, 2807 (1962).

(IId) was markedly reduced with a corresponding increase in the amount of 3β,5α-diacetate (IIIb) isolated. In addition the presence of a small quantity (7%) of Δ⁴-3β,6β-diacetate was detected.

The product composition of the reaction of the 6β-bromo compound (Ie) was similar to that for the 6β-methoxy compound, in that both the rearranged material (IIe) and the 3β,5α-diacetate (IIIc) were obtained in moderate yield. However, in

TABLE 1. PRODUCTS OF THE REACTION OF 5α-HYDROXY-6β-SUBSTITUTED STEROIDS WITH H_2SO_4—Ac_2O—AcOH

6β-Substituent	Δ⁹·¹⁰-product	5α-acetate	Δ⁴-compounds	others	Total
F	81	none found	none found	2	83
Cl	72	none found	9*	13	94
AcO	66	5	19	5	95
CH_3O-	38	40	7	3	88
Br-	22	24	8(+6*)	12	74
I-	none found	37	25	26	88

* transformed on alumina to 4β-acetoxycholest-5-en-3β-ol.

addition the Δ⁴-3β,6β- and Δ⁴-3α,6β-diacetates were identified in 5% and 3% yields respectively, as well as the 3β-hydroxy compound (6%) reported above in the 6β-chloro-reaction.

Finally the 6β-iodo compound (If) gave a moderate yield of the 3β,5α-diacetate (IIId) but no rearranged material could be detected. However, an iodine containing unstable material was obtained (ca. 10%) which decomposed spontaneously before constructive efforts towards its identification could be made. The reaction of the 6β-iodo compound with sulphuric acid–acetic anhydride in acetic acid was characterized by the liberation of ca. 30% of the initial iodine content as molecular iodine which was estimated by titration with sodium thiosulphate. In accord with this observation cholesteryl acetate (16·5%) was isolated, presumably formed by loss of I^+ from the intermediate C_5-carbonium ion (IX). In addition the Δ⁴-3β,6β-diacetate (15%) and the Δ⁴-3α,6β-diacetate (10%) were isolated.

Now that a more complete study (cf. Ref. 15) has been made of the effects of changing both the physical size of the 6β-substituent and its accompanying electronic effects certain general conclusions may be drawn. First, the yield of rearranged material can be seen to be greatest in the case of the 6β-fluoro compound (Ib) where steric effects might be considered to be at a minimum and the electron withdrawing effect (−I) of the C_6-substituent at a maximum. As the substituent is changed from this case of small size and large electronic effect (−I) progressively to large size and relatively small electronic effect (−I) the yields of rearranged material drops. This decrease in yield is counterbalanced by an increase in yield of the 5α-acetate and assorted minor products. As the yield of 5α-acetate is only significant in the cases of 6β-methoxy, 6β-bromo and 6β-iodo compounds, each of these substituents being notably[16] capable of neighbouring group participation, a reasonable explanation may be offered. If these groups do participate and in effect assist the heterolytic rate-determining step by stabilizing the C_5-carbonium ion so formed then the necessary 5β,6β-bridge so implied would shield the C_5-carbonium ion from the C_{19} migration

[16] B. Capon, *Quart. Rev.* **18**, 45 (1964).

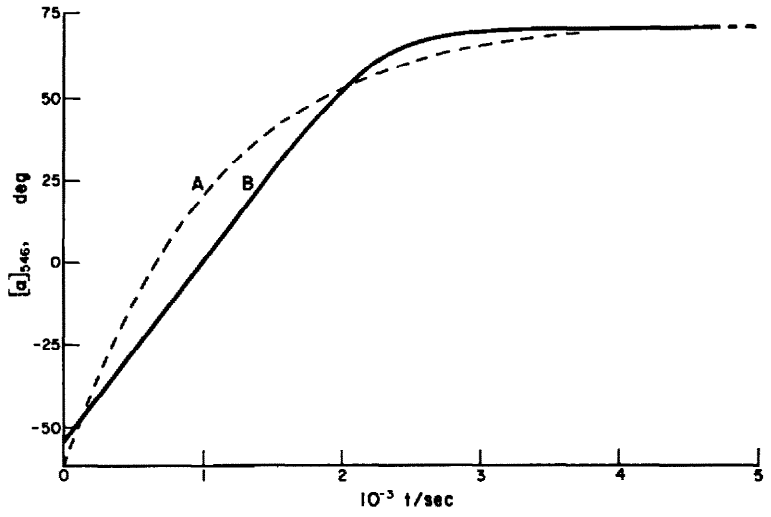


FIG. 1. A Reaction of 0·01 M 3β,6β-diacetoxycholestan-5α-ol with 0·056 M H_2SO_4 and 0·5 M Ac_2O. B Reaction of 0·053 M 3β,6β-diacetoxycholestan-5α-ol with 0·005 M H_2SO_4 and 2 M Ac_2O.

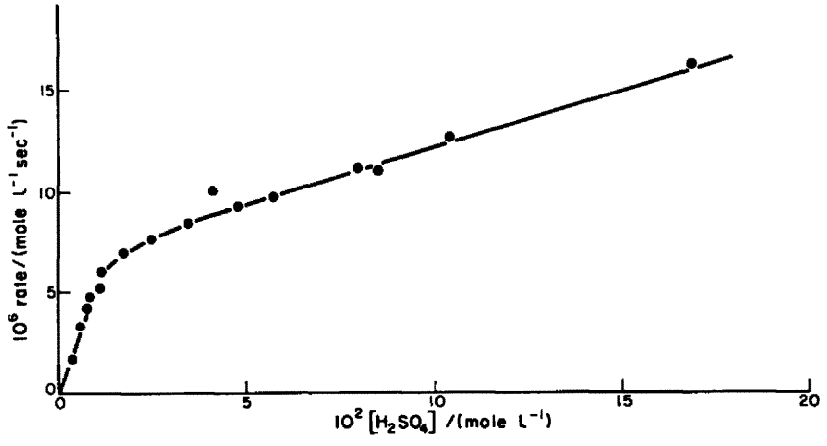


FIG. 2. Rate plot for reaction of 0·01 M 3β,6β-diacetoxycholestan-5α-ol with H_2SO_4 and 0·5 M Ac_2O.

and allow the weakly basic acetic acid molecule to approach from the α-face to form the 5α-acetate. At the present time no explanation can be offered for the variability in yield of the Δ^4-products. Such an explanation may in fact be forthcoming from work at present in progress on these ill-understood 3β,6β-disubstituted Δ^4-compounds. Further work has been undertaken to separate the electronic and steric factors by studying appropriately substituted 6β-phenyl derivatives.

EXPERIMENTAL

Rotations were measured for $CHCl_3$ solutions at room temp. IR spectra were recorded for CS_2 solutions. Alumina used for chromatography was Peter Spence, Grade H, deactivated by the addition of 5% of 10% acetic acid. Light petroleum refers to the fraction of b.p. 50–70°.

Acetylation of 3β,6β-diacetoxy-5α-hydroxycholestane (Ia)

To a solution of the steroid (6 g) in acetic anhydride (20 ml) and CCl_4 (5 ml) was added $HClO_4$ (60%; 0·1 ml) or hydrofluoroboric acid (42%; 0·1 ml) and the solution kept at 25° for 2 min. Isolation in the usual manner gave a crude product which crystallized from MeOH to give the triacetate as needles (5·7 g), m.p. 147–149°.

Reactions with sulphuric acid–acetate anhydride

(a) *With 3β,6β-diacetoxy-5α-hydroxycholestane.* H_2SO_4 (36 N; 0·05 ml) was added to a solution of the steroid (1 g) in acetic anhydride (5 ml) and CCl_4 (2 ml) and the solution kept at 45° for 5 min. The crude product, isolated in the usual manner, on crystallization from MeOH gave IIa (450 mg) as needles, m.p. 125–127°. Lit.[3] m.p. 128°.

(b) *With 3β,5α,6β-triacetoxycholestane.* The steroid (1 g) was treated with the above system at 45° for 2 hr. The crude material, isolated in the usual manner, on crystallization from MeOH gave starting material (950 mg) as needles, m.p. 148–150°.

Reaction of 3β,6β-diacetoxy-5α-methoxycholestane (IVa) *with sulphuric acid–acetic anhydride*

To a solution of the steroid (48 mg) in CCl_4 (1 ml) was added H_2SO_4 (36 N; 9·1 mg; 1 mole) in acetic anhydride (4 ml) and the resulting solution kept at 25° for 24 hr. No significant change in specific rotation occurred during this time. The crude product (44 mg), isolated in the usual manner, was identified by comparison of its IR spectrum with the starting material, and on crystallization from MeOH gave needles, m.p. and m.m.p. 112–113°.

Cholesteryl hydrogen sulphate

To a solution of cholesterol (1 g) in CCl_4 (15 ml) was added H_2SO_4 (36 N; 0·15 ml) in acetic anhydride (20 ml) and the whole kept at 20° for 1 min. Pyridine (2 ml) was added and the suspension diluted with ether–pentane (100 ml; 1:1). Filtration allowed the separation of the pyridinium salt of cholesteryl hydrogen sulphate, m.p. 155–160°. Lit[17] m.p. 158–160; 175–178 (in capillary). The pyridinium salt in water (20 ml) was treated with KI (2·5 g) in water (20 ml). The deposited solid, the potassium salt (980 mg), was isolated by filtration, m.p. 224–230° (dec). Lit[17] m.p. 226–227° (dec), 210°, 239° (dec).

The filtrate from the separation of the pyridinium salt gave cholesteryl acetate (136 mg) m.p. 114–115°.

3β,6β-Dihydroxy-5α-methoxycholestane (IVb)

Boron trifluoride etherate (1 ml) was added to 3β-acetoxy-5,6β-epoxycholestane (1 g) in anhydrous MeOH (15 ml) and the solution kept at 40° for 1 hr. Dilution with water gave the *diol* (820 mg), which on crystallization from MeOH afforded needles, m.p. 198–199°, $[\alpha]_D$ 0° (*c*, 0·78), ν_{max} 3610 and 1080 cm^{-1}. (Found: C, 75·1; H, 11·3. $C_{28}H_{50}O_3.CH_3OH$ requires: C, 74·6; H, 11·7%.)

3β,6β-Diacetoxy-5α-methoxycholestane (IVa)

A solution of the diol (700 mg) in acetic anhydride (3 ml) and pyridine (5 ml) was heated at 100° for 3 hr. Isolation by use of ether gave a crude product which on crystallization from MeOH gave the *diacetate* (560 mg) as needles, m.p. 113–115°, $[\alpha]_D$ −45° (*c*, 1·11), ν_{max} 1745, 1242 and 1077 cm^{-1}. (Found: C, 73·8; H, 10·5. $C_{32}H_{54}O_5$ requires: C, 74·1; H, 10·5%.)

5α-Methoxycholestan-3,6-dione (V)

Oxidation of the diol (50 mg) with chromic acid in acetone[18] gave the *diketone* (38 mg) as needles from MeOH m.p. 125–126°, $[\alpha]_D$ −2° (*c*, 0·55) ν_{max} 1721 and 1070 cm^{-1}. (Found: C, 77·8; H, 10·9. $C_{28}H_{46}O_3$ requires: 78·1; H, 10·8%.)

Cholest-4-en-3,6-dione

A solution of the methoxy-diketone (20 mg) in MeOH (2 ml) containing KOH (10 mg) was kept at 20° for 30 min. Neutralization of the solution with acetic acid followed by dilution with

[17] J. McKenna and J. K. Norymberski, *J. Chem. Soc.* 3889 (1957); A. E. Sobel and P. E. Spoerri, *J. Amer. Chem. Soc.* 63, 1259 (1941).

[18] K. Bowden, I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.* 39 (1946).

water to crystallization gave the conjugated ketone (12 mg), m.p. 123–124°, ν_{max} 1685, 1600 and 870 cm^{-1}, Lit.[19] m.p. 124–125°.

3β-Acetoxy-5α-hydroxy-6β-methoxycholestane (Id)

Boron trifluoride etherate (2 ml) was added to a solution of cholesterol-α-epoxide (4 g) in anhydrous MeOH (100 ml) initially at 45° and the mixture then allowed to cool during 6 hr. Isolation in the usual manner, acetylation using pyridine–acetic anhydride at 20°, and crystallization from MeOH gave the *6β-methoxy-compound* (Id; 3·17 g) as needles, m.p. 124–125°, $[\alpha]_D$ −33·5 (*c*, 0·94), ν_{max} 3584, 3484, 1733, 1715, 1240, 1095 cm^{-1}. (Found: C, 75·7; H, 11·1 $C_{30}H_{52}O_4$ requires: C, 75·6; 11·0%.)

3β-Acetoxy-6β-trifluoroacetoxycholestan-5α-ol (Ig)

Prepared from the 6β-hydroxy compound by reaction with trifluoroacetic anhydride in pyridine at 0°, m.p. 151–151·5°, prisms from MeOH. (Found: C, 66·9; H, 9·0; F, 10·0. $C_{31}H_{49}F_3O_5$ requires: C, 66·6; H, 8·8; F, 10·2%.) ν_{max}(Nujol) 3410(OH), 1783(O.CO.CF$_3$), 1714(associated OAc), 1218 and 1170 cm^{-1}. ν_{max}(CS$_2$) 3450(OH), 1781(O.CO.CF$_3$), 1734, 1711(OAc), 1200 and 1167 cm^{-1}.

Reactions of 5α-hydroxy-6-substituted compounds with sulphuric acid–acetic acid–acetic anhydride

(a) *6β-Fluoro*-(Ib). To a solution of steroid (1 g) in acetic acid (50 ml) and acetic anhydride (18 ml) at 25° was added H_2SO_4 (0·75 g) in acetic acid (5 ml). Isolation after 1 hr by means of ether–benzene (1:1) gave a gum (991 mg) which solidified spontaneously. Adsorption on deactivated alumina (50 g) in light petroleum and elution with the same solvent gave first a gum (23 mg), ν_{max} 1735, 1240 cm^{-1}. Continued elution with light petroleum gave the rearranged material (IIb; 776 mg) while crystallized from MeOH as needles, m.p. 92·5–93°, $[\alpha]_D$ +95° (*c*, 1·05); Lit.[15] value m.p. 92·5–93°, $[\alpha]_D$ +93·3°.

Further elution with graded solvents up to ether gave only minor traces of steroidal material.

(b) *6β-Chloro*-(Ic). To a solution of steroid (2 g) in acetic acid (110 ml) and acetic anhydride (5·5 ml) at 25° was added H_2SO_4 (0·2 g) in acetic acid (2 ml). Isolation after 1·5 hr by means of ether–benzene (1:1) gave a gum (2·152 g) which solidified spontaneously. Adsorption on deactivated alumina (85 g) in light petroleum and elution with the same solvent gave the rearranged material (IIc; 1·391 g) which crystallized from MeOH as needles, m.p. 138–140°, $[\alpha]_D$ +131° (*c*, 1·01); Lit.[15] value, m.p. 139–141°, $[\alpha]_D$ +132°.

Further elution with the same solvent gave a gum (179 mg) ν_{max} 1735 and 1240 cm^{-1}. Elution with light petroleum–benzene (2:1) gave a further gum (92 mg), ν_{max} 1733 and 1245 cm^{-1}. Thin-layer chromatography revealed the presence of at least six components in these materials. Finally elution with ether gave 4β-acetoxycholest-5-en-3β-ol (175 mg) which crystallized from pentane as needles, m.p. 164–165°, $[\alpha]_D$ −87·5 (*c*, 1·0), ν_{max} 3450, 1740, 1260 and 1230 cm^{-1}; Lit.[20] value, m.p. 164–165°, $[\alpha]_D$ −89°.

(c) *6β-Acetoxy*-(Ia). H_2SO_4 (0·05 g) in acetic acid (5 ml) was added to a solution of steroid (2·026 g) in acetic acid (80 ml) and acetic anhydride (20 ml) at 25°. Isolation by means of ether–benzene (1:1) after 1·5 hr gave a gum (2·040 g) which solidified spontaneously and was adsorbed onto deactivated alumina (110 g) in light petroleum. Elution with light petroleum–benzene (20:1) gave IIa (1·296 g), m.p. 125–127°; Lit[2] value m.p. 128°.

Elution with light petroleum–benzene (20:1 and 10:1) gave a gum (37 mg), $[\alpha]_D$ +42° (*c*, 1·1) which was assigned as a mixture (1:1) of Ia and 3β,6β-diacetoxycholest-4-ene by specific rotations and IR data.

Elution with light petroleum–benzene (5:1) gave 3β,6β-diacetoxycholest-4-ene (262 mg) which crystallized from MeOH as needles, m.p. 130–131°, $[\alpha]_D$ −7° (*c*, 0·98), ν_{max} 1740, 1240–1227 and 1016 cm^{-1}; Lit.[21] value m.p. 136°, $[\alpha]_D$ −13°.

Further elution with light petroleum–benzene (5:1) gave a gum (20 mg). Elution with light petroleum–benzene (2:1) gave 3α,6β-diacetoxycholest-4-ene (106 mg) which crystallized from MeOH as needles, m.p. 102–102·5°, $[\alpha]_D$ +136° (*c*, 0·55) ν_{max} 1735, 1657, 1235 and 1015 cm^{-1}; Lit.[22] value, m.p. 102·5–103·5°, $[\alpha]_D$ +117°.

[19] W. C. J. Ross, *J. Chem. Soc.* 737 (1946).
[20] V. Petrow, O. Rosenheim and W. W. Starling, *J. Chem. Soc.* 135 (1943).
[21] V. Petrow, O. Rosenheim and W. W. Starling, *J. Chem. Soc.* 677 (1938).
[22] Y. Urushibara and K. Mori, *Bull. Chem. Soc., Japan* 31, 1068 (1958).

Elution with light petroleum–benzene (1:1) gave a gum (34 mg). Benzene–ether (50:1) eluted IIIa (106 mg) which crystallized from MeOH as needles, m.p. 148–149°. Finally elution with ether gave a further gum (48 mg).

(d) 6β-*Methoxy*-(Id). H_2SO_4 (0·18 g) in acetic acid (2 ml) was added to a solution of the steroid (3 g) in acetic acid (80 ml) and acetic anhydride (20 ml) at 25°. Isolation by means of ether–benzene (1:1) after 1·5 min gave a gum (2·74 g) which was adsorbed on deactivated alumina (150 g). Elution with light petroleum–benzene (10:1) gave the *rearranged product* (IId; 1·02 g) which crystallized from MeOH as needles, m.p. 69–71°, $[\alpha]_D$ +100° (*c*, 0·82) ν_{max} 1734, 1240, 1101 and 1019 cm^{-1}. (Found: C, 78·4; H, 11·0. $C_{30}H_{50}O_3$ requires: C, 78·55; H, 11·0%.) Elution with light petroleum–benzene (4:1) gave the 3β,5α-*diacetate* (IIIb; 1·313 g) which crystallized from MeOH as prisms, m.p. 90–92°, $[\alpha]_D$ −18° (*c*, 0·61) ν_{max} 1735, 1241, 1095, 1035 and 1020 cm^{-1}. (Found: C, 74·2; H, 10·7. $C_{33}H_{54}O_5$ requires: C, 74·1; H, 10·5%.)

Light petroleum–benzene (1:1) gave 3β,6β-diacetoxycholest-4-ene (200 mg) which crystallized from MeOH as needles, m.p. 130–131°, $[\alpha]_D$ −8° (*c*, 1·01).

Finally elution with ether gave a gum (81 mg).

(e) 6β-*Bromo*-(Ie). To a solution of the steroid (2·236 g) in acetic acid (164 ml) and acetic anhydride (47 ml) was added H_2SO_4 (0·2 g) in acetic acid (23 ml) and the resulting solution kept at 25° for 45 min. The crude product (2·2 g) isolated by means of ether–benzene (1:1) was adsorbed on deactivated alumina (110 g). Elution with light petroleum–benzene (33:1) gave IIe (490 mg) which crystallized from MeOH as needles, m.p. 139–140°, $[\alpha]_D$ +135° (*c*, 1·10); Lit.[15] value m.p. 140–142°, $[\alpha]_D$ +133°.

Elution with light petroleum–benzene (20:1) gave a gum (84 mg). Light petroleum–benzene (20:3) gave the 3β,5α-*diacetate* (IIIc; 608 mg) which crystallized from MeOH as needles, m.p. 158–160°, $[\alpha]_D$ −16° (*c*, 0·50) ν_{max} 1735, 1234, 1033 and 1014 cm^{-1}. (Found: C, 65·5; H, 9·2; Br, 14·15. $C_{31}H_{51}BrO_4$ requires: C, 65·6; H, 9·1; Br, 14·1%.)

Elution with light petroleum–benzene (1:1) gave 3β,6β-diacetoxycholest-4-ene (107 mg), m.p. 130–131°, $[\alpha]_D$ −7° (*c*, 0·90). Further elution with light petroleum–benzene (1:1) gave a gum (10 mg) identified by IR spectra as a mixture of 3β,6β- and 3α,6β-diacetoxycholest-4-enes. Finally light petroleum–benzene (1:1) eluted 3α,6β-diacetoxycholest-4-ene (71 mg) which crystallized from MeOH as needles, m.p. 102–103°, $[\alpha]_D$ +135° (*c*, 0·75).

Elution with ether–benzene mixtures (100:1 and 10:1) gave gums (37 mg and 300 mg respectively) shown by thin-layer chromatography to be complex mixtures. Finally elution with ether gave a solid (132 mg) identical with the material isolated from the 6β-chloro reaction b (above), m.p. 159–162°, ν_{max} 3450, 1740, 1710, 1260 and 1230 cm^{-1}.

(f) 6β-*Iodo*(If). H_2SO_4 (0·09 g) in acetic acid (10 ml) was added to a suspension of the steroid (1·17 g) in acetic acid (70 ml) and acetic anhydride (20 ml). The steroid dissolved in 1 min, with liberation of I_2. The crude material (964 mg), isolated after 10 min by means of ether–benzene (1:1), was adsorbed on deactivated alumina (40 g). Titration of the aqueous solutions from the extraction with $Na_2S_2O_3$ indicated that ca. 30% of the initial I_2 had been liberated as molecular I_2.

Elution with light petroleum–benzene (50:1) gave cholesteryl acetate (143 mg), m.p. 113·5–114°, $[\alpha]_D$ −42° (*c*, 0·95). Light petroleum–benzene (10:1) afforded the 3β,5α-*diacetate* (IIId; 440 mg) which crystallized from pentane as needles, m.p. 102–109° (dec), $[\alpha]_D$ −36° (*c*, 1·06) ν_{max} 1731, 1232, 1034 and 1014 cm^{-1}. (Found: C, 60·0; H, 8·3; I, 20·3. $C_{31}H_{51}IO_4$ requires: C, 60·5; H, 8·35; I, 20·6%.) Light petroleum–benzene (5:1) gave unstable solids (100 mg) which decomposed, liberating I_2 in 6 hr.

Elution with light petroleum–benzene (3:2) gave the 3β,6β-diacetoxycholest-4-ene (116 mg) which crystallized from MeOH as needles, m.p. 130–131°, $[\alpha]_D$ −5° (*c*, 0·78). Finally, elution with light petroleum–benzene (1:1) and benzene gave 3α,6β-diacetoxycholest-4-ene (75 mg), needles from MeOH, m.p. 102–103°, $[\alpha]_D$ +136° (*c*, 0·57).

(g) 6β-*Trifluoroacetoxy*(Ig). H_2SO_4 (0·01 ml) in acetic acid (5 ml) was added to the steroid (376 mg) in acetic acid (20 ml) and acetic anhydride (10 ml). After 17 hr the solution was poured into water, and the product was extracted into $CHCl_3$. The crude product, a gum, ν_{max} 1781 ($CF_3CO.O$-) and 1736 cm^{-1} (AcO), was adsorbed onto deactivated alumina. Elution with light petroleum–benzene mixtures gave only gums (106 mg) showing AcO absorption in the IR. Benzene eluted the 3-monoacetate of "Westphalen's diol," (257 mg) m.p. 169–170° (needles from hexane),

$[\alpha]_D$ +103° (lit.[23] m.p. 169–170°, $[\alpha]_D$ +108°). Acetylation using acetic anhydride–pyridine gave the known diacetate (IIa).

3β,5α-Diacetoxy-6β-bromocholestane (IIIc)

A solution of Ie (100 mg) in acetic acid (5 ml) and acetic anhydride (2 ml) containing $HClO_4$ (0·1 ml; 65%) was kept at 20° for 15 min Isolation by means of benzene–ether (1:1) gave the diacetate, m.p. and m.m.p. 158–160°, $[\alpha]_D$ −16° (*c*, 0·75).

3β,5α-Diacetoxy-6β-iodocholestane (IIId)

Prepared by the above procedure to give the diacetate as needles, m.p. and m.m.p. 103–108° (dec), $[\alpha]_D$ −35° (*c*, 1·03).

KINETICS AND RESULTS

Acetic acid ("AnalaR") was dried by azeotropic distillation with benzene.[24] Acetic anhydride (Riedel de Haën reagent grade) was refluxed over Mg turnings and fractionally distilled.[25] H_2SO_4 was "AnalaR" grade.

Kinetics. Equal volumes (2 ml) of acetic acid solutions of hydroxy compound (I), H_2SO_4 and acetic anhydride, all at 25°, were mixed and the reaction mixture rapidly transferred into a 2 cm optical cell of a recording polarimeter (ETL-NPL Automatic Polarimeter type 143A, Bendix Electronics Ltd.). The optical unit was maintained at 25·0 ± 0·2° by means of an air thermostat. The optical rotation at 546 mμ (Mercury green) was recorded continuously.

The chart record for those runs in which the concentration of steroid was less than that of the H_2SO_4 exhibited the exponential decay typical of a first order reaction (Fig. 1). When recorder readings for these runs, which were followed to more than 90% reaction, were plotted by the Guggenheim[26] method excellent linear plots were obtained. The first order rate constant (k') derived from the slope of each plot led to a calculated half-life in good agreement with that evaluated directly from the recorder chart. Initial rates were calculated from the product k'[steroid I] and showed excellent agreement (±5%) with rates derived directly from the initial slope of the chart record.

When the initial steroid concentration was greater than the concentration of H_2SO_4 the chart record departed from the first order exponential decay. At high values of the $[I]:[H_2SO_4]$ ratio the chart record approximated to an initial zeroth order plot followed by an exponential decay (Fig. 1). It is to be noted that the rate in the course of a run fell off markedly only when the steroid (I) concentration approached that of the H_2SO_4. For these runs the initial rate was derived from the initial slope of the recorder plot. The required total rotation change in the course of the reaction was obtained as follows. For the set of runs which $[I] < [H_2SO_4]$ the total rotation change was calculated from the Guggenheim plot. Addition of the initial rotation, obtained by extrapolation of the recorder plot, to the total change in rotation gave the final rotation (at $t = \infty$). Thus, the mean final specific rotation for reaction of Ia was +71°. This value was in accord with all terminal measured values of the rotation and was therefore assumed to be the final specific rotation for all runs in which Ia was the substrate. Subtraction from the final rotation of the (extrapolated) value of the initial rotation then gave the total change in rotation for the run under study.

[23] H. Aebli, C. A. Grob, and E. Schumacher, *Helv. Chim. Acta* **41**, 774 (1958).
[24] D. P. N. Satchell, *J. Chem. Soc.* 3911 (1956).
[25] D. P. N. Satchell, *J. Chem. Soc.* 1752 (1960).
[26] E. Guggenheim, *Phil. Mag.* **2**, 538 (1926).

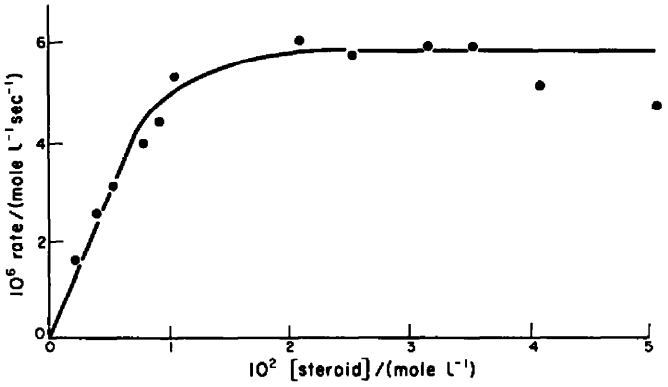


FIG. 3. Rate plot for reaction of 3β,6β-diacetoxycholestan-5α-ol with 0·01 M H_2SO_4 and 0·5 M Ac_2O.

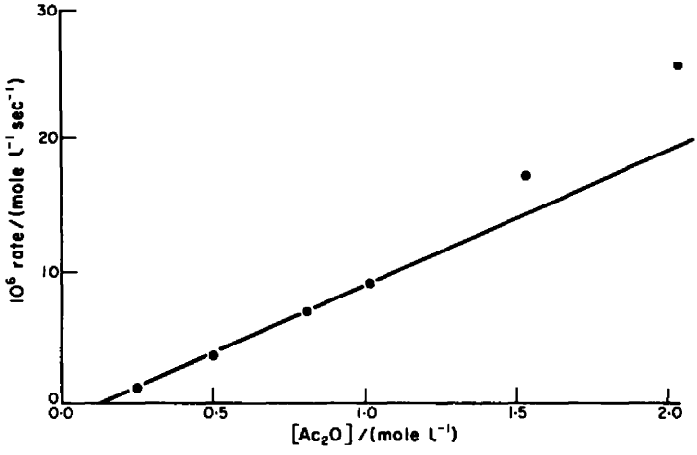


FIG. 4. Reaction of 0·01 M 3β,6β-diacetoxycholestan-5α-ol with 0·05 M H_2SO_4 and Ac_2O.

The 6β-acetoxy-alcohol (Ia) was used as substrate in the majority of runs. Measurements on the 6β-chloro (Ic), 6β-fluoro (Ib), 6β-methoxy (Id) and 6β-trifluoroacetoxy (Ig) alcohols were confined to obtaining relative rates for the evaluation of substituent effects. Most runs were carried out with 0·002–0·05 M Ia, 0·001–0·2 M H_2SO_4, and 0·1–2·0 M Ac_2O.

Figure 2 is a plot of rate *vs* [H_2SO_4] for a series of runs in which [Ia] and [Ac_2O] are both constant. It is to be noted that the rate is strictly first order in H_2SO_4 when [H_2SO_4] < 0·01 M (the constant concentration of Ia) but when H_2SO_4 > 0·01 M the rate, although still dependent on [H_2SO_4], increases much more slowly. The initial slope of Fig. 2 is $5{\cdot}6 \times 10^{-4}$ sec^{-1} and the final slope $0{\cdot}55 \times 10^{-4}$ sec^{-1}. When the concentration of Ia is higher then the rate increases in a first order manner with increasing [H_2SO_4] up to a concentration equal to the new concentration of Ia.

Figure 3 depicts the relationship between rate and Ia when [H_2SO_4] and [Ac_2O] are held constant. Again a first order dependence is exhibited provided [Ia] < 0·01 M, the constant concentration of H_2SO_4. When [Ia] > 0·01 M the rate remains constant,

TABLE 2. RATE DATA FOR REACTION OF 3β-ACETOXY-6β-X-CHOLESTAN-5α-OL WITH SULPHURIC ACID AND ACETIC ANHYDRIDE IN ACETIC ACID

Run No.	X	10^3[I] mole l^{-1}	10^3[H_2SO_4] mole l^{-1}	[Ac_2O] mole l^{-1}	10^6 Rate mole l^{-1} sec^{-1}	Rate ratio	Rel. rate
108	CF_3CO_2-	3·0	5·0	3·5	1·37	0·051	1
109	AcO	3·1	5·0	3·5	26·6	1	—
49	F	10·1	50	0·50	1·14	0·10	2
51	AcO	10·1	50	0·50	11·3	1	20
106	Cl	3·1	5·0	0·51	7·6	4·4	88
105	AcO	3·1	5·0	0·51	1·71	1	—
71	MeO	5·7	0·25	0·50	15·7	75	6,600
70	Cl	5·2	0·25	0·50	0·206	1	—

or perhaps decreases slightly. The limiting rate is set by [H_2SO_4] since when this is raised the rate rises.

The effect of varied [Ac_2O] at constant [H_2SO_4] and [Ia] was also studied (Fig. 4). Up to [Ac_2O] = 1·0 M there appears to be a linear dependence of rate on concentration although the plot, unlike those of Fig. 3 and Fig. 4 does not pass through the origin. It is suggested that the failure to pass through the origin is a result of the presence of a small amount of water in the solvent which hydrolyses part of the added Ac_2O. The intercept is at [Ac_2O] = 0·13 M which would correspond to less than 0·25% water. Two comments may be made on the deviation of the points at [Ac_2O] = 1·5 M and 2 M from the linear relationship. First, at such concentrations the solvent properties of the medium may well be affected and second, these points represent very fast rates, subject to greater than usual error.

Table 2 shows rate data for various 6β-derivatives (I). Alternation of the 6β-substituent had such a marked effect on the rate that it was not possible to make the comparative rate measurements under the same set of conditions. It was possible to compare rates for the chloro (Ic), fluoro (Ib) and trifluoroacetoxy (Ig) compounds directly with that for the acetoxy compound (Ia) although each comparison was performed under a different set of conditions. The rates of acetoxy (Ia) and methoxy (Id) alcohols were, however, too different for direct comparison to be made and the methoxy compound (Id) was compared directly with the chloro (Ic) and thus related to the acetoxy compound (Ia).

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