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ACID CATALYSED REACTIONS OF ALCOHOLS IN ACETIC ANHYDRIDE

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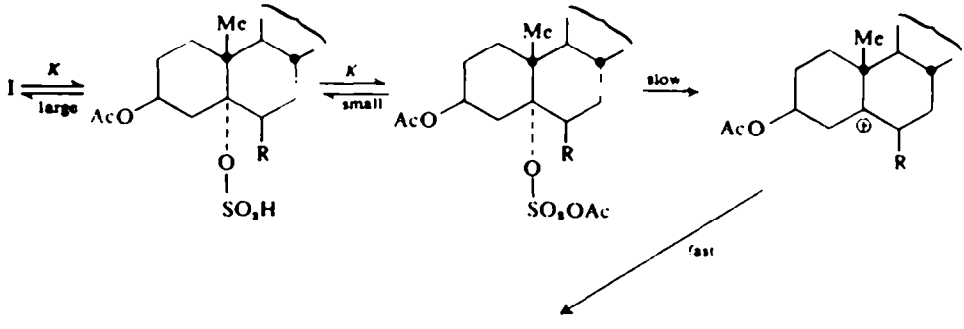
Abstract—Acetylation of cyclohexanol using sulphuric acid–acetic anhydride proceeds *via* attack of a cyclohexanol molecule on cyclohexyl acetyl sulphate. This result is discussed in relation to the reactions of cholestanol and 5α-hydroxy-steroids with sulphuric acid–acetic anhydride.

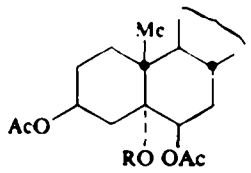
REACTION of 3β,6β-diacetoxycholestan-5α-ol (Ia) with acetic anhydride in the presence of acidic catalysts, hydrogen chloride,[1] toluene-*p*-sulphonic acid,[2] perchloric acid,[3] hydrofluoroboric acid[3] and sulphoacetic acid,[3] has been shown to convert the 5α-hydroxy compound into the corresponding 5α-acetate Ib. In contrast, the use of sulphuric acid[4] or potassium hydrogen sulphate[5] as the acidic catalyst for the reaction in acetic anhydride results in the isolation of the rearranged diacetate II as the major product. A kinetic study[6] of the reaction using sulphuric acid as the catalyst established the reaction path shown in Scheme 1.

SCHEME 1

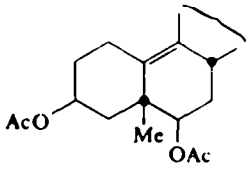


In addition to the rearranged material II, the Δ^4-unsaturated compounds III and the 5α-acetate were obtained. Formation of these products is consistent with intervention of an intermediate carbonium ion which may rearrange, or suffer proton loss,

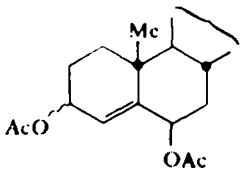
[1] Z. Hattori, *J. Pharm. Soc. Japan* **59**, 129 (1939); *Chem. Abstr.* 33, 8622 (1939).
[2] M. Davis and V. Petrow, *J. Chem. Soc.* 2536 (1949); A. T. Rowland and H. R. Nace, *J. Amer. Chem. Soc.* **82**, 2833 (1960).
[3] J. W. Blunt, M. P. Hartshorn, F. W. Jones and D. N. Kirk, *Tetrahedron Letters* 1399 (1964); J. W. Blunt, A. Fischer, M. P. Hartshorn, F. W. Jones, D. N. Kirk and S. W. Yoong, *Tetrahedron* **21**, 1567 (1965).
[4] T. Westphalen, *Chem. Ber.* **48**, 1064 (1915).
[5] V. Petrow, *J. Chem. Soc.* 998 (1939).
[6] J. W. Blunt, A. Fischer, M. P. Hartshorn, F. W. Jones, D. N. Kirk and S. W. Yoong, *Tetrahedron* **21**, 1567 (1965).



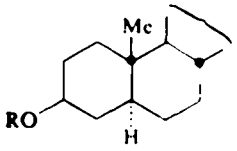
I a R, H
b R, Ac



II



III



IV a R, H
b R, Ac
c R, $CH_3C_6H_4$—SO_2—
d R, $AcOSO_2$—

or be captured by acetic acid and thus lead to acetylation *via* alkyl-oxygen fission. Conversion of the 5α-alcohol Ia into the corresponding acetate Ib, without concomitant formation of rearranged compound II and Δ^4-unsaturated compounds III, when other acids are used as catalysts, is indicative of acetylation *via* acyl-oxygen fission. It seems likely that this involves the same mechanism as that proposed[7] for acetylation of phenols, *viz.* rapid formation of the acetyl derivative of the catalysing acid followed by rate-determining reaction of this with the hydroxy compound. Sulphuric acid and acetic anhydride also react to form powerful acetylating species, acetyl hydrogen sulphate and diacetyl sulphate. The different reaction path which results from the use of sulphuric acid is a consequence of its apparently unique ability to react rapidly and completely with the alcohol to form an ester—the alkyl hydrogen sulphate. This not only removes the sulphuric acid or alcohol (whichever is not in excess), but also leads, on further reaction with acetic anhydride, to the formation of the very powerful leaving group acetyl sulphate. For the tertiary steroidal alcohols investigated[8] direct acetylation by acetyl hydrogen sulphate or by diacetyl sulphate cannot compete with carbonium ion formation. If the intermediate carbonium ion were made sufficiently less stable its rate of formation could conceivably become slow enough for direct acetylation to compete. When 3β-acetoxy-5α-hydroxycholestan-6-one was reacted with sulphuric acid and acetic anhydride the only product isolated was the 3β,5α-diacetoxycholestan-6-one.[8] Our previous studies with 6β substituted 3β-acetoxy-5α-hydroxycholestanes showed that the more electron-withdrawing the 6β substituent the greater the yield of rearrangement product and the lower the yield of acetate. We therefore attribute the absence of other than acetate product to the complete suppression of the carbonium ion forming reaction by the highly deactivating 6-oxo substituent. Direct acetylation, being less

[7] E. A. Jeffrey and D. P. N. Satchell, *J. Chem. Soc.* 1887 (1962).
[8] Y. Shealy and R. Dodson, *J. Org. Chem.* **16**, 1427 (1951).

sensitive to polar effects, is dominant here. Secondary carbonium ions are considerably less stable than tertiary. Accordingly we have investigated the mechanism of the reaction of secondary alcohols with sulphuric acid and acetic anhydride.

Reaction of cholestan-3β-ol (IVa) with sulphuric acid and acetic anhydride in acetic acid at 20° for 16 hr gave a crude product which was shown by physical constants and TLC to consist essentially of the 3β-acetate IVb. In contrast, the solvolysis of 3β-tosyloxycholestane (IVc) in acetic acid is reported[9] to yield Δ^2- and Δ^3-cholestenes as major products. The behaviour of cholestan-3β-ol (IVa) is more consistent with a direct O-acetylation than with solvolysis, involving alkyl-oxygen fission, of the 3β-acetylsulphate (IVd) formed *in situ*, where formation of olefins and/or the epimeric acetate might be expected. No such products were found.

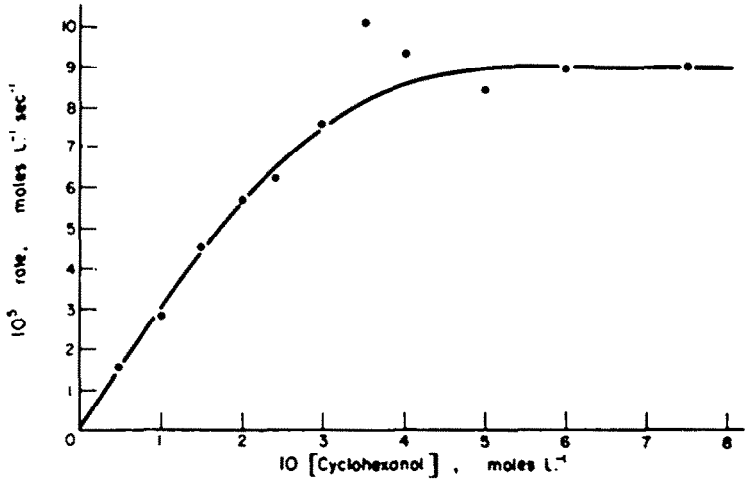


FIG. 1. Rate plot for reaction of cyclohexanol with 2×10^{-4}M H_2SO_4 and 2M Ac_2O.

Cyclohexanol was used as the substrate in kinetics studies. Reactions were followed by gas chromatographic analysis for cyclohexyl acetate and formation of the acetate was shown to be essentially quantitative. At constant sulphuric acid (2×10^{-4}M) and acetic anhydride (2M) concentrations a first-order dependence on alcohol concentration between 0·05 and 0·2M was found, followed by a transition to a zeroth-order dependence at higher concentrations (Fig. 1). At fixed cyclohexanol (0·1M) and anhydride (0·5M) concentrations a first-order dependence on sulphuric acid (10^{-4}–10^{-2}M) was observed (Fig. 2). With 0·1M alcohol and 10^{-3}M sulphuric acid a slightly greater than first-order dependence on acetic anhydride was found.

The kinetic results described above are consistent with acetylation of cyclohexanol by acetonium ion or a source of potential acetonium ion such as acetyl hydrogen sulphate. The results are not consistent with acetylation through acetolysis of an intermediate alkyl sulphate species either *via* direct displacement or *via* carbonium ion formation. Rate determining reaction of an intermediate alkyl sulphate species, e.g. fission of an alkyl–oxygen bond in acetyl cyclohexyl sulphate, would exhibit a first-order dependence on the component (alcohol or sulphuric acid) present in lesser amount and zeroth-order dependence on the other component. This is subject to the

[9] Cf. J. F. Biellmann and G. Ourisson, *Bull. Soc. Chim. Fr.* 341 (1962).

proviso that formation of the cyclohexyl sulphate is complete. Formation of the hydrogen sulphate of the tertiary steroidal alcohol Ia is complete and the equilibrium constant for formation of the less hindered cyclohexyl hydrogen sulphate should be even more favourable. While acetylation of cyclohexanol is indeed zeroth-order in alcohol above 0·2M it is, however, first-order in alcohol at concentrations greatly exceeding the sulphuric acid concentration. Rate-determining reaction of cyclohexyl hydrogen sulphate, or of any species derived from it by a fast equilibrium, is therefore rejected.

The observed first-order dependence on alcohol concentration does not, however, exclude a mechanism involving formation of an intermediate cyclohexyl hydrogen

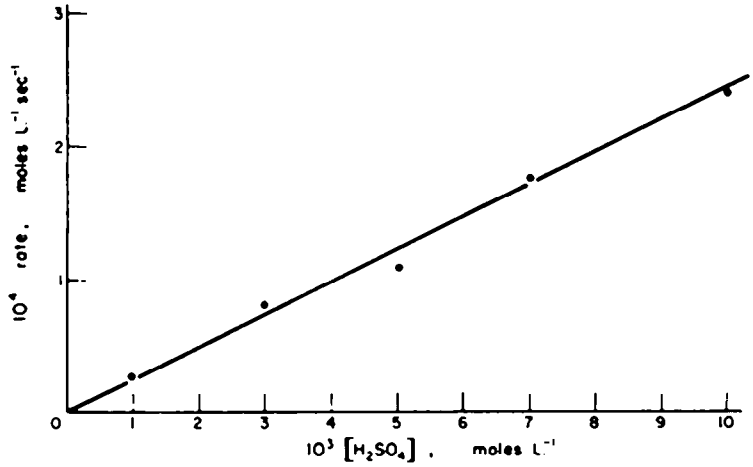


FIG. 2. Rate plot for reaction of 0·1M cyclohexanol with H_2SO_4 and 0·5M Ac_2O.

sulphate by rate-determining sulphation of cyclohexanol. Such a mechanism is ruled out on the following grounds. Sulphation is a fast step in the carbonium ion-forming reaction of the alcohol Ia and this reaction is faster than acetylation of cyclohexanol under the same conditions. Since sulphation of cyclohexanol should be at least as fast as sulphation of the more hindered alcohol Ia, sulphation cannot be the rate limiting step in the acetylation of cyclohexanol. Unfortunately, it did not prove possible to compare the rates of reaction of cyclohexanol and hydroxysteroid Ia under the same conditions. The rate of disappearance of steroid Ia was $1{\cdot}5 \times 10^{-6}$ mole l^{-1} sec^{-1} when [Ia] = 0·01M, $[H_2SO_4]$ = 0·003M and $[Ac_2O]$ = 0·5M. Under the same conditions the rate of acetylation of cyclohexanol is calculated (Figs. 1, 2) to be $4{\cdot}6 \times 10^{-6}$ mole l^{-1} sec^{-1}. Because of the first-order dependence of the steroid reaction and the second-order dependence of the cyclohexanol reaction it is clear that, at lower concentrations of acid and alcohol, the steroid would react faster than cyclohexanol. This argument is reinforced when comparison is made with other 6β-substituted 3β-acetoxy-5α-hydroxycholestanes which react very much faster than the 6β-acetoxy compound Ia and hence cyclohexanol.

The kinetic results, therefore, are in agreement with the deduction based on the absence of any inversion or elimination product in the acetylation of cholestan-3β-ol: acetylation of secondary alcohols with sulphuric acid and acetic anhydride involves acyl-oxygen fission and not alkyl-oxygen fission. The kinetic results also imply that

the transition state for the reaction is obtained from the substrate alcohol, sulphuric acid *as it exists in the system* ("sulphuric acid") and acetic anhydride. A mechanism involving rate-determining attack by an acetylating species derived from "sulphuric acid" and acetic anhydride would seem appropriate. The acetylating species cannot be acetyl hydrogen sulphate or diacetyl sulphate since, in our system (containing excess alcohol) sulphuric acid exists as cyclohexyl hydrogen sulphate.* The acetylating species must therefore be acetyl cyclohexyl sulphate. The proposed mechanism is as follows.

$$ROH + H_2SO_4 + Ac_2O \underset{}{\overset{K_1(\text{large})}{\rightleftharpoons}} ROSO_2OH + 2AcOH \quad (1)$$

$$ROSO_2OH + Ac_2O \overset{K_2(\text{small})}{\rightleftharpoons} ROSO_2OAc + AcOH \quad (2)$$

$$ROSO_2OAc + ROH \xrightarrow{k_3(\text{slow})} ROSO_2OH + ROAc \quad (3)$$

The rate expression (k_3 rate-determining) is

$$\text{rate} = k_3[ROH][ROSO_2OAc]$$
$$= k_3K_2[ROH][ROSO_2OH][Ac_2O]/[AcOH]$$

This rate expression is in agreement with the observation of a first-order rate dependence on alcohol and sulphuric acid (added $[H_2SO_4] = [ROSO_2OH]$) and as predicted a linear dependence of the rate on the ratio $[Ac_2O]/[AcOH]$ is observed (Fig. 3). We

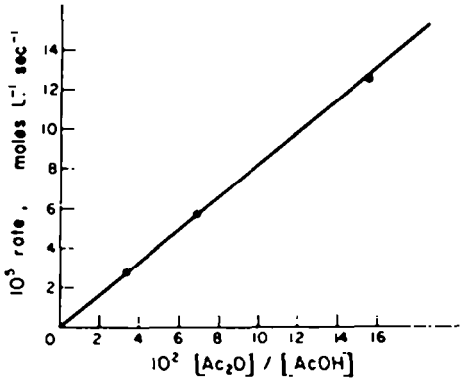


FIG. 3. Rate plot for reaction of 0·1M cyclohexanol with 10^{-3}M H_2SO_4 and Ac_2O.

attribute the zeroth-order dependence observed at high alcohol concentration to the fact that reaction (2), which is independent of alcohol concentration, is then slower than reaction (3), which is first-order in alcohol.

In summary, reaction of the tertiary steroidal alcohol Ia and of cyclohexanol, with sulphuric acid and acetic anhydride, follow the same initial paths—complete formation of the alkyl hydrogen sulphate and equilibrium conversion of a fraction of this into the acetyl alkyl sulphate. The acetyl t-alkyl sulphate undergoes ionization to the tertiary carbonium ion but the acetyl sec-alkyl sulphate, being less reactive in ionization, is intercepted by a second molecule of alcohol which it acetylates.

* Rate-determining acetylation by either acetyl hydrogen sulphate or diacetyl sulphate leads to a zeroth-order rate dependence on cyclohexanol.

EXPERIMENTAL AND RESULTS

Reaction of cholestan-3β-ol with H_2SO_4–AcOH–Ac_2O. A soln of the steroid (700 mg) and H_2SO_4 (180 mg) in AcOH–Ac_2O (4:1; 25 ml) was kept at 20° for 16 hr. Isolation by means of pentane gave crude IVb (537 mg), m.p. 100–102°, (one spot by TLC). Crystallization from MeOH gave a sample m.p. 107–109° (Lit. m.p. 108–109°).

Kinetics. Cyclohexanol was dried over molecular sieves (4A) and fractionated through a spinning band column. AcOH ("AnalaR") was dried by azeotropic distillation with benzene.[10] Ac_2O ("AnalaR") was refluxed over Mg turnings and fractionally distilled.[11] H_2SO_4 was "AnalaR" grade.

A soln (35 ml) of H_2SO_4 and Ac_2O in AcOH was prepared and placed in a thermostatted bath (30·0°). A soln (15 ml) of cyclohexanol in AcOH was also prepared and after temp equilibrium had been attained (15 min) the two solns were mixed. At suitable time intervals 5 ml samples were withdrawn and added to a mixture of 10 ml 0·880 ammonia, 20 ml water and 15 g ice to which a suitable volume of a soln of mesitylene (employed as an internal standard) in MeOH (2% v.v.) had been added. The mixture was extracted (X3) with CH_2Cl_2 (25 ml), the combined extracts dried and the solvent removed by vacuum distillation and the residual liquid injected into a gas chromatograph (N carrier, 15% silicone oil on Chromosorb P column, 125°, gas density detector).

Pseudo first-order rate constants (k) were evaluated from linear plots of log ($a - x$) against time, where a was the initial concentration of alcohol and x the measured concentration of acetate. Initial reaction rates were obtained from the product ka and these are given in the Table below.

RATE DATA FOR REACTION OF CYCLOHEXANOL WITH SULPHURIC ACID AND ACETIC ANHYDRIDE IN ACETIC ACID

[Cyclohexanol]	10^4[H_2SO_4]	[Ac_2O]	10^6 Rate mole l^{-1} sec^{-1}
0·1	1	0·53	0·23
0·1	10	0·53	2·83
0·1	30	0·53	8·18
0·1	50	0·53	10·9
0·1	70	0·53	17·6
0·1	100	0·53	24·2
0·05	2	2·12	1·59
0·1	2	2·12	2·85
0·15	2	2·12	4·55
0·2	2	2·12	5·73
0·24	2	2·12	6·26
0·3	2	2·12	7·60
0·35	2	2·12	10·12
0·4	2	2·12	9·35
0·5	2	2·12	8·45
0·6	2	2·12	8·99
0·75	2	2·12	9·07
1	2	2·12	6·99
0·1	10	0·53	2·83
0·1	10	1·06	5·64
0·1	10	2·12	12·6
0·4	2	1·06	3·12
0·4	2	1·59	6·68
0·4	2	2·12	9·35
0·4	10	2·12	47·0

[10] D. P. N. Satchell, *J. Chem. Soc.* 3911 (1956).
[11] D. P. N. Satchell, *J. Chem. Soc.* 1752 (1960).