Tetrahedron. Vol. 25, pp. 5915 to 5919. Pergamon Press 1969. Printed in Great Britain

ACETYLATION OF SUBSTITUTED BENZYL ALCOHOLS WITH ACETIC ANHYDRIDE CATALYSED BY SULPHURIC ACID

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(*Received in the UK* 10 *August* 1969; *Accepted for publication* 21 *August* 1969)

Abstract—Kinetic and mass spectrometric evidence show that *p*-anisyl alcohol is acetylated *via* a carbonium ion intermediate. Other, less activated, benzyl alcohols are acetylated via a mechanism which does not involve C—O fission in the alcohol.

THE tertiary steroidal alcohol, 3β,6β-diacetoxycholestan-5α-ol, reacts with sulphuric acid and acetic anhydride to form products which include the rearranged 3β,6β-diacetoxy-5β-methyl-19-norcholest-9-ene, *via* an intermediate carbonium ion.[1,2] Other substituted cholestan-5α-ols react similarly,[2,3] the mechanism involving the following steps

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

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

$$ROSO_2OAc \overset{k_3}{\rightarrow} R^+ + {}^-OSO_2OAc \quad (3)$$

$$R^+ \overset{k_4}{\rightarrow} \text{products} \quad (4)$$

When the potential carbonium ion is sufficiently destabilized an alternative reaction intervenes. The alkyl acetyl sulphate is intercepted by a second molecule of alcohol which is acetylated by the alkyl acetyl sulphate before the latter can undergo fission ($k_5[ROH] > k_3$):

$$ROSO_2OAc + ROH \overset{k_5}{\rightarrow} ROSO_2OH + ROAc \quad (5)$$

This alternative mechanism operates in the cases of cholestan-3β-ol and of cyclohexanol.[4] Here the potential carbonium ions are secondary and would be formed only slowly; reaction (5) supersedes reaction (3). The alternative mechanism also appears to operate in the case of 3β-acetoxy-5α-hydroxy-cholestan-6-one, where the potential tertiary carbonium ion is heavily destabilized by the adjacent CO group. The stability of the benzyl carbonium ion is comparable to that of a secondary alkyl carbonium ion.[5] Benzyl alcohol was therefore expected to react by the second (non-carbonium ion-forming) mechanism.

The rate of acetylation of benzyl alcohol (rate of increase of the concentration of benzyl acetate) in acetic anhydride-acetic acid mixtures catalysed by sulphuric acid exhibited a first order dependence on sulphuric acid concentration from 0·2 to 2 mmol dm^{-3}, on alcohol from 0·06 to 0·3 mol dm^{-3} and on the ratio $[Ac_2O]/[AcOH]$

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from $[Ac_2O] = 0{\cdot}4$ to 2 mol dm^{-3}. The plot for dependence of rate on alcohol concentration exhibited a slight curvature towards a lower than first order dependence in the region from 0·3 to 0·5 mol dm^{-3} and this behaviour was more marked in the case of 4-nitrobenzyl alcohol where the first order behaviour was exhibited up to 0·2 mol dm^{-3}; above this concentration the rate appeared to be constant. Accordingly we limited our study of other alcohols to concentrations not greater than this. *p*-Anisyl alcohol was so much more reactive than benzyl alcohol that its kinetics could not be studied under the standard conditions ($[H_2SO_4] = 0{\cdot}2$ mmol dm^{-3}, Ac_2O: AcOH = 20:80 by vol.) and instead we compared its rate with that of benzyl alcohol at [alcohol] = 0·1 mol dm^{-3}, $[H_2SO_4] = 0{\cdot}2$ mmol dm^{-3} and Ac_2O:AcOH = 2:98 by vol. *p*-Anisyl alcohol appeared to exhibit a zeroth order dependence on the alcohol concentration as the rates at 0·1 and 0·2 mol dm^{-3} were closely similar. *p*-Methylbenzyl alcohol exhibited a mixed zeroth and first order dependence; the plot of rate versus alcohol concentration had a significant positive intercept. With the exception of the *p*-anisyl alcohol, pseudo first order rate constants were derived from plots of rate against [alcohol] which were linear and, apart from the case of *p*-methylbenzyl alcohol, passed through the origin. Rate constants and relative rates are shown in Table 1.

The rate of acetylation of *p*-anisyl alcohol appears to be abnormally large compared to the other rates shown in Table 1. This is more clearly revealed by a correlation of log k_{rel} against σ°. In the correlation the results for all the alcohols except *p*-anisyl were used. The slope of the line (ρ) = +0·1, intercept = 0·035, standard deviation = 0·06 and standard deviation of the slope = 0·06. Whereas the maximum deviation of the log k_{rel} values for any of the other alcohols from this line is 0·086, that for *p*-anisyl alcohol is 0·91, fifteen times the standard deviation.

The kinetic dependences observed for benzyl alcohol closely parallel those observed for cyclohexanol and imply that the same mechanism (reactions 1, 2 and 5) operates for benzyl alcohol as for cyclohexanol. This is further confirmed by the low ρ value. Direct acetylation of the alcohol involves attack on an atom (oxygen) at which the polar effect of the substituent is attenuated by the interposed methylene group. Moreover, the reaction involves rate-determining acetylation by a benzyl acetyl sulphate and any substituent effect which makes the alcohol acetylated more reactive (more nucleophilic) will have the opposite effect on the acetylating species, so that the net substituent effect is reduced further. Indeed, if the positive value of ρ were significant it would imply that the substituent effect in the acetylating species is the more important one and that *p*-anisyl alcohol should be less reactive than benzyl alcohol.

The large rate enhancement observed for *p*-anisyl alcohol is indicative of a mechanistic change and is consistent with the anisyl alcohol being acetylated *via* carbonium ion formation from the anisyl acetyl sulphate. The *p*-anisyl carbonium ion is the most stable of the carbonium ions which might be formed from the substituted benzyl alcohols studied and hence the *p*-anisyl alcohol is the most likely to react by carbonium ion formation. It is also consistent that the rate of acetylation of *p*-anisyl alcohol appears to be independent of the alcohol concentration, as it should be, and that *p*-methylbenzyl alcohol appears to react in part by a mechanism involving zeroth order dependence on alcohol. The *p*-methylbenzyl carbonium is the second most stable carbonoum ion of those which might be formed from the alcohols studied.

The conclusion from the kinetic results is that benzyl alcohol reacts by a mechanism involving acyl-oxygen and not alkyl-oxygen bond fission, i.e. direct acetylation, whereas *p*-anisyl alcohol is acetylated by a mechanism involving C—O bond-fission in the alcohol. In order to verify this we carried out the reaction in acetic acid–acetic anhydride enriched in ^{18}O. We also investigated the reaction with cholestanol for which we have presented arguments[4] to show that it is acetylated by the direct acetylation mechanism, reactions (1), (2) and (5). It was not possible to measure directly the extent of enrichment of the ^{18}O enriched acetic anhydride–acetic acid mixture because we could not detect the molecular ion of acetic anhydride in the mass spectrum of the mixture. However, accepting the conclusion from our previous work that cholestanol incorporates only one O atom from the solvent, we could calculate the degree of enrichment of the solvent from the intensity ratio of the M + 2 and M peaks and also from that of the M + 2 and M + 1 peaks, in the mass spectrum of the enriched cholestanyl acetate. By using this calculated value for the solvent enrichment and the measured intensity ratios of the M + 2 and M, and M + 2 and M + 1 peaks in the spectrum of benzyl acetate we calculated the number of solvent oxygen atoms incorporated into the product acetate. The mean value is 1·05. Similarly, *p*-anisyl acetate incorporates 1·93 oxygen atoms from the solvent. These figures are not significantly different from 1·0 and 2·0 respectively and the essential mechanistic difference in the acetylation of benzyl and anisyl alcohols, which was suggested by the kinetics results, is clearly demonstrated.

TABLE 1. FIRST ORDER RATE CONSTANTS AND RELATIVE RATES OF ACETYLATION OF X-BENZYL ALCOHOLS BY ACETIC ANHYDRIDE (2·12 mol dm^{-3}) IN ACETIC ACID CATALYSED BY SULPHURIC ACID (0·2 mmol dm^{-3}) AT 25°C.

X	3-Cl	4-Cl	3-Br	4-Br	3-Me	4-Me	3-NO_2	4-NO_2	H	3-OMe	4-OMe
k/ksec^{-1}	1·06	1·17	1·02	0·98	1·01	0·77	1·30	0·96	0·89	1·19	0·72*
$k_{rel.}$	1·19	1·31	1·15	1·10	1·13	0·86	1·46	1·08	1·00	1·34	8·6*

* [alcohol] = 0·1 mol dm^{-3}, [Ac_2O] = 0·21 mol dm^{-3}.

TABLE 2. INTENSITY RATIOS FOR M, M + 1, AND M + 2 PEAKS.

Ratio	Calc.	Found normal solvent	Found enriched solvent
	Cholestanyl Acetate $C_{29}H_{50}O_2$		
P_{M+1}/P_M	0·32	0·30	0·32
P_{M+2}/P_M	0·054	0·051	0·084
P_{M+2}/P_{M+1}	0·169	0·169	0·27
	Benzyl Acetate, $C_9H_{10}O_2$		
P_{M+1}/P_M	0·100	0·097	0·101
P_{M+2}/P_M	0·0084	0·0077	0·045
P_{M+2}/P_{M+1}	0·085	0·080	0·44
	p-Anisyl Acetate, $C_{10}H_{12}O_3$		
P_{M+1}/P_M	0·111	0·111	0·114
P_{M+2}/P_M	0·012	0·011	0·079
P_{M+2}/P_{M+1}	0·104	0·102	0·69

EXPERIMENTAL

Alcohols. Benzyl alcohol, b.p. 104–106°/20 mm and 3-chloro-benzyl alcohol, b.p. 135–137°/20 mm, were purified commercial products. 4-Methyl-benzyl alcohol, m.p. 58·5–59·5°, was obtained by hydrolysis of 4-methylbenzyl bromide. The other benzyl alcohols including 4-chloro-, m.p. 70·5–71°, 4-bromo-, m.p. 76·5–77·5°, 3-nitro, m.p. 25–27°, 4-nitro-, m.p. 93–94°, and 4-methoxybenzyl alcohol, m.p. 25–26°, were obtained by reduction of the corresponding aldehyde with sodium borohydride.

Kinetics. The procedure described previously[4] was followed with the modification that the product acetate was determined by infrared analysis rather than by gas chromatography. At suitable time intervals samples (3 ml) of the reaction mixture were withdrawn and added to a mixture of 0·880 ammonia (10 ml), water (20 ml), and ice (15 g). The mixture was extracted (X3) with CCl_4 and the combined extracts were dried (Na_2SO_4) and made up to 100 ml. The extent of reaction in each sample was evaluated by measurement of the decadic absorbance of the soln at the max in the region 1740–1720 cm^{-1} using a Perkin Elmer model 421 spectrophotometer with 5 mm path length cell. The reference was a similar cell containing CCl_4. A base height correction was made by subtracting from the absorbance at the max the absorbance at the min in the region 1800–1780 cm^{-1}. The extent of reaction (ξ) was given by the ratio (net absorbance at time t): (net absorbance after ten half-lives). Pseudo first-order rate constants (k) were evaluated from linear plots of log $(1 - \xi)$ against time.

Tracer experiments. Water (1 ml) of nominal 60% enrichment in ^{18}O (Yeda) was heated on a steam bath with Ac_2O (10·2 ml) for 7 hr. The mixture was diluted with AcOH to form a soln of Ac_2O–AcOH (20:80 by vol.) and 4% enriched in ^{18}O. The NMR spectrum of the soln was identical to that of a similar soln of Ac_2O–AcOH prepared by mixing Ac_2O and AcOH in the appropriate proportions. The alcohol (130 mg) was acetylated by treatment with H_2SO_4 (1 mmol dm^{-3}) in the enriched Ac_2O–AcOH soln (5 ml) for 6 half-lives. The soln was then added to a mixture of ice and ammonia and the acetate extracted with ether. The ethereal extract was washed with $NaHCO_3$aq, dried (Na_2SO_4) and the solvent removed under vacuum. The mass spectrum of the residual acetate was determined on an A.E.I. MS9 spectrometer and the region in the vicinity of the molecular ion repetitively scanned 10 times. Peak height ratios shown in Table 2 are mean values based on the 10 individual measurements. The experiment was repeated for each alcohol using solvent of natural oxygen isotopic abundance. Excellent agreement was obtained between the peak height ratios determined for the esters prepared in the medium of natural oxygen isotopic abundance and the values tabulated by Beynon and calculated from natural isotopic abundance ratios.[6] The relationships between the peak height ratios, the number of O atoms (n) introduced into the ester $C_wH_yO_z$ from the enriched source and the ratio (r) of $^{18}O/^{16}O$ in the enriched source are[7]

$$\frac{P_{M+2}}{P_M} = nr + 2{\cdot}00 \times 10^{-3}(z - n) + 0{\cdot}584 \times 10^{-4}\, w(w - 1)$$

$$\frac{P_{M+2}}{P_{M+1}} = \frac{nr + 2{\cdot}00 \times 10^{-3}(z - n) + 0{\cdot}584 \times 10^{-4}\, w(w - 1)}{1{\cdot}08 \times 10^{-2}\, w + 1{\cdot}6 \times 10^{-4}\, y}$$

For cholestanyl acetate ($C_{29}H_{50}O_2$) $n = 1$; hence $r = 0{\cdot}035$ from the first equation and 0·038 from the second. The mean value of the enrichment was 3·8%, in satisfactory agreement with the nominal value of 4%. Using the mean value of r, 0·0365, and applying this to the two equations using the data for benzyl acetate, $n = 1{\cdot}06$ and $n = 1{\cdot}03$, hence benzyl acetate like cholestanyl acetate acquires one oxygen from the solvent. For *p*-anisyl acetate $n = 1{\cdot}96$ and 1·89, the mean is 1·93. Both acetate oxygen atoms in *p*-anisyl acetate are derived from the solvent. For *p*-anisyl acetate no oxygen exchange occurred with the solvent (control experiment) under the reaction conditions.

Acknowledgement—We thank the Research Committee of the New Zealand University Grants Committee for grants, and a Research Fellowship to one of us (MJH).

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