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INCREASED RATE OF O-METHYLATION AS A RESULT OF INTRAMOLECULAR HYDROGEN BONDING

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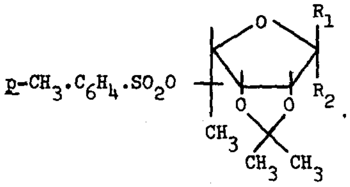
Although hydrogen bonds have been suggested as important factors influencing both reaction rate and reaction pattern (1), the only example of their influence on alkylation is the work of Gol'dfarb and Kondakova on the α-aminonicotines (2). The present work shows that the hydroxyl group in 2,3-O-isopropylidene-5-O-tosyl-β-L-rhamnofuranose, I, is methylated faster than that in the anomer II, a result which would not be anticipated on steric grounds.



I R_1 = H, R_2 = OH

II R_1 = OH, R_2 = H

III R_1 = H, R_2 = OCH$_3$

IV R_1 = OCH$_3$, R_2 = H

A freshly prepared solution of II (3) in methyl iodide shows two peaks for the methyl groups of the isopropylidene residue, at 8.78 τ and 8.92 τ. As mutarotation proceeds, a new peak appears at 8.70 τ, attributable to one of these methyl groups in the β-isomer. The ratio I:II at equilibrium was 1:4.3 (from n.m.r. spectra). The ratio was also calculated from the equilibrium rotation ($[\alpha]_D$ + 28.5°) to be 1:4.2, after the specific rotation of I had been estimated from a knowledge of the specific rotations of II, III and IV in methyl iodide solution. Angyal has suggested that I may be stabilised in non-hydroxylic solvents by intramolecular hydrogen bonding from OH-1 to O-2 (4). Confirmation of this suggestion was obtained from the infrared spectrum in dilute solution (< 0.005 M) in carbon tetrachloride, of the mixture of I and II obtained on removal of the solvent from a fully mutarotated solution made from II in methyl iodide. Two absorptions (3608 cm^{-1}-free OH, and 3535 cm^{-1}-bonded OH) were observed, whereas a freshly prepared solution of II exhibited only one absorption (3608 cm^{-1}). The measured extinction coefficients suggested I to be almost completely in the hydrogen bonded form.

Treatment of II in excess methyl iodide with silver oxide for 48 hours yielded, as the sole products, III* (m.p. 61-63°; $[\alpha]_D + 100^\circ$ in MeOH) and IV (3) (α-configuration at C-1 confirmed by $J_{1,2} < 2\text{Hz}$) (4,5), which were readily separated by t.l.c. The rotation of the unseparated mixture gave the ratio III:IV as 1:1.4, and n.m.r. gave 1:1.38.**

A consideration of the reactant and product ratios shows that I reacts considerably faster than II. If the rate of equilibration between I and II is fast compared to the rate of methylation, the ratio of the pseudo first order rate constants $k_1:k_2$ may be calculated as 3.0:1 from equation (1) where $K_e = \frac{II}{I}$ at equilibrium.

$$\begin{tikzcd} I \arrow[r, shift left, "K_e"] \arrow[d, "k_1"'] & II \arrow[l, shift left] \arrow[d, "k_2"] \\ III & IV \end{tikzcd} \qquad \frac{III}{IV} = \frac{k_1}{k_2 K_e} \qquad \ldots\ldots (1)$$

That these rate requirements are met is suggested by the fact that although mutarotation of II is slow in methyl iodide (e.g. $[\alpha]_D + 20.8^\circ \rightarrow + 22.0^\circ$ in 2 hr.) it was complete in 10 minutes when silver oxide was present to the extent of only one twentieth the quantity used in the actual methylation.

The methylation probably involves nucleophilic attack by the oxygen atom of the unionised hydroxyl group, on methyl iodide, aided by electrophilic attack of silver ion on the halogen atom. Participation of the hydroxyl group in a hydrogen bond would be expected to enhance the nucleophilicity of the oxygen leading to the increased reaction rate observed for I.

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* Compound III gave a satisfactory elemental analysis.

** III and IV were not interconverted under the reaction conditions.