Phosphorylated Derivatives of Hydroxy- and Methoxy-pyridines

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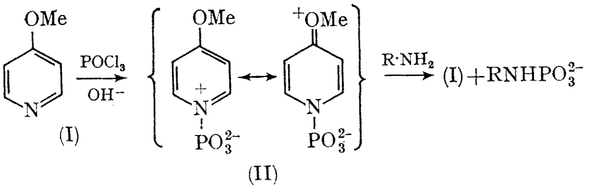
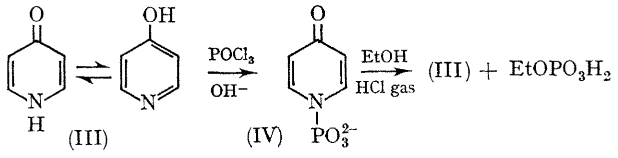
CHANLEY and Feageson,[1] and Jencks and Gilchrist[2] have found evidence for *N*-phosphoryl pyridinium type intermediates during the reaction of phosphoramidate, $H_3\overset{+}{N}PO_3{}^{2-}$, with pyridines without substituents on the 2 and 6 positions. The rate of formation of these intermediates, which were not isolated, was proportional to the pKa of the amine.[2]

Previously we have shown[3] that γ-picoline reacts with $POCl_3$ in aqueous alkali to give the unstable *N*-phosphoryl γ-picolinium ion, which is a phosphorylating agent for amines.

By varying the nature of the substituent in the pyridine nucleus we have been able to improve the yield of phosphorylated amine. 4-Methoxypyridine (pKa 6·55), which is more basic than γ-picoline (pKa 6·02) reacts with $POCl_3$ at pH 11 and 0° to give phosphorylated derivative (II) which is more stable to hydrolysis. Consequently the yield of the aminolysis product is better (for example a 60% yield of *N*-phosphoryl ethanolamine is obtained, compared with only 40% using picoline). This stabilisation can be interpreted in terms of a partial delocalisation of the positive charge.



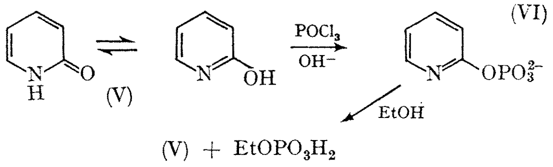
In the case of 4-hydroxypyridine (III), the loss of a proton can complete this stabilisation. Thus *N*-phosphoryl 4-pyridone (IV), prepared in the same conditions as (II), is very stable in a basic or neutral aqueous medium, even in the presence of an amine. It is hydrolysed rapidly in aqueous acid, and with a large excess of an ethanolic solution of hydrogen chloride, monoethyl dihydrogen phosphate is obtained.



(IV) can be isolated as the barium salt by adding $BaCl_2$ and precipitation with ethanol, or as the lithium salt after cation exchange on Dowex 50 W.

The spectral data for the lithium salt of (IV) ($C_5H_{14}NO_4PLi_2,2H_2O$) are: ν_{max} (Nujol) 1660 cm.$^{-1}$ (s, C=O), λ_{max} (H_2O) 262 nm., δ (D_2O) 6·5 (m, 2H, H-3 and H-5) 8·1 (m, 2H, H-2 and H-6) p.p.m.

2-Hydroxypyridine (V) behaves differently under the same conditions to give the *O*-phosphoryl derivative (VI). Kampe[4] has shown that (V) in the presence of $POCl_3$ or $ArOP(O)Cl_2$ in benzene gives triesters of which one hydroxypyridine group can be hydrolysed. Steric hindrance of attack on nitrogen, which does not occur for the *p*-hydroxy



case, or a fast migration of the phosphoryl group from the nitrogen to the oxygen could explain these *O*-phosphorylations. In contrast to (IV) the phosphate (VI) is rapidly hydrolysed in a neutral medium at pH 6·8 ($t_{\frac{1}{2}}$ at 20° $\simeq$ 20 min.). A quantitative yield of monoethyl dihydrogen phosphate can be obtained either by heating an ethanolic suspension of (VI), or by passing hydrogen chloride.

The spectral data for the cyclohexylammonium salt of (VI) ($C_{17}H_{32}N_3O_4P,2H_2O$), prepared by cation exchange from the barium salt, are: λ_{max} (H_2O) 263 nm., δ (D_2O) 7 to 8·5 (m, ArH). There is no carbonyl band between 1660 and 1670 cm.$^{-1}$.

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