A New Route to 3-Alkoxypyridine 1-Oxides

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Summary Dihydro-oxazines, prepared by the addition of enol ethers to 1-chlorobutane-2,3-dione 2-oxime, are converted into 3-alkoxypyridine 1-oxides by the action of alcoholic HCl.

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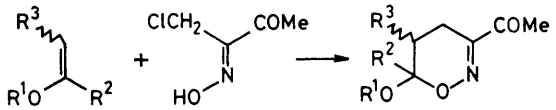
THERE are few useful methods for the preparation of pyridine 1-oxides other than the N-oxidation of pyridines.[1] We have found that 3-alkoxypyridine 1-oxides can be prepared in good yields by the acid-catalysed rearrangement of 3-acetyl-6-alkoxy-5,6-dihydro-4*H*-1,2-oxazines (**2**) in the presence of alcohols.

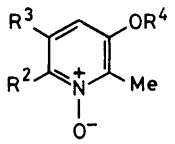
It was shown earlier that 1-chlorobutane-2,3-dione 2-oxime (**1**) reacts with nucleophilic olefins in the presence of sodium carbonate at room temperature to give 5,6-dihydro-4*H*-1,2-oxazines.[2] The chloro-oxime (**1**) reacted efficiently with enol ethers under these conditions to give the 6-alkoxy-derivatives (**2**) of the oxazines.‡ The oxazine (**2a**), when dissolved in aqueous methanol (1 : 9) which had been saturated with hydrogen chloride, was converted, during 3 h at room temperature, into the hydrochloride of 3-methoxy-2-methylpyridine 1-oxide (**3a**). After washing with base and crystallisation this gave the known[3] pyridine 1-oxide (**3a**) in 67% overall yield from the chloro-oxime (**1**). The structure of the product was confirmed by its deoxygenation with phosphorus trichloride to give 3-methoxy-2-methylpyridine which was found to be identical with an independently prepared specimen.[4]

Other pyridine 1-oxides (**3b**)—(**3d**) were prepared in the same way (Scheme 1); ethanolic hydrochloric acid gave compound (**3b**) from the oxazine (**2a**) and methanolic hydrochloric acid was used to convert the oxazines (**2b**) and (**2c**) into the pyridine 1-oxides (**3c**) and (**3d**), respectively.



(1) (2)

a; R^1 = Et, R^2 = R^3 = H
b; R^1 = Et, R^2 = H, R^3 = Me
c; R^1 = R^2 = Me, R^3 = H

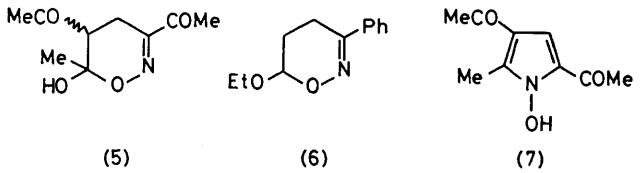


(3)

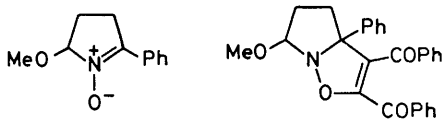
a; R^2 = R^3 = H, R^4 = Me (67%), m.p. 65 °C
b; R^2 = R^3 = H, R^4 = Et (70%), m.p. 85 °C
c; R^2 = H, R^3 = R^4 = Me (70%), m.p. 81 °C
d; R^2 = R^4 = Me, R^3 = H (42%), m.p. 84 °C

SCHEME 1

No long-lived intermediate could be detected when the conversion of the oxazine (**2a**) into the hydrochloride of compound (**3a**) was followed by u.v. spectroscopy. It seems likely, however, that the protonated nitrone (**4**) is an intermediate in the reaction. Circumstantial evidence to support this view is provided by the reactions of the oxazines (**5**) and (**6**) with methanolic HCl. Compound (**5**) gave 2,4-diacetyl-1-hydroxy-5-methylpyrrole (**7**) (62%), m.p. 104 °C, and the oxazine (**6**) gave the nitrone (**8**) in quantitative yield, this being characterised as its adduct (**9**) with dibenzoylacetylene, m.p. 122 °C. The nitrone (**8**) shows no tendency to aromatise to a hydroxypyrrole in acid, and this aromatisation appears to take place only if additional conjugative substituents are present [as in the pyrrole (**7**)]. There are a few earlier examples of the isolation of hydroxypyrroles in reactions of this type;[5,6] in one case, a nitrone was isolated as an intermediate and was subsequently converted into the hydroxypyrrole in acid.[6]



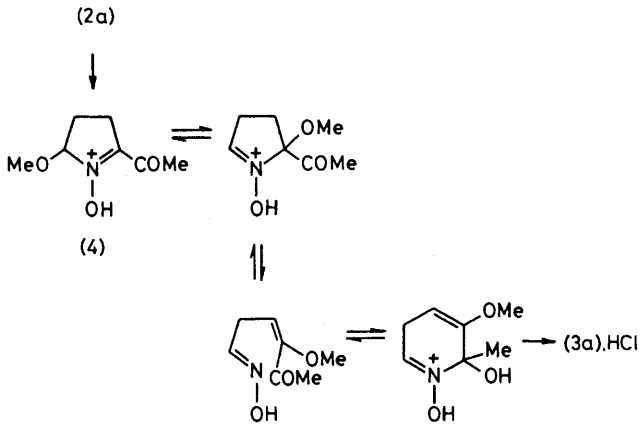
(5) (6) (7)



(8) (9)

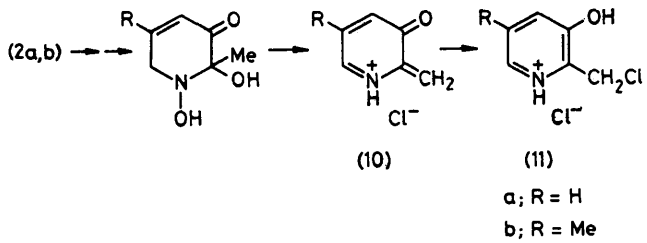
Scheme 2 shows a sequence by which compound (**3a**) might be formed: it is suggested that the nitrone (**4**), like compound (**8**), would not aromatise but instead could be cleaved to an acyclic oxime which could then re-cyclise by the attack of the nitrogen lone pair on the carbonyl of the acetyl group.

When an attempt was made to prepare 3-acetoxypyridine 1-oxides by carrying out the reaction of the oxazines in



SCHEME 2

‡ With a tenfold excess of enol ether the oxazines were formed quantitatively (n.m.r. spectroscopy); the crude oxazines were used directly for the next step. Analytical specimens were prepared by distillation. Satisfactory analytical data were obtained for these and other new compounds.



SCHEME 3

acetic acid saturated with HCl, a different type of product was isolated instead. The oxazines (**2a**) and (**2b**) gave the chloromethylpyridines (**11a**) and (**11b**), respectively, in high yields, the structure of compound (**11a**) being established by its hydrolysis to 3-hydroxy-2-hydroxymethylpyridine.[7] If traces of water are present to act as the nucleophile in place of the alcohol of Scheme 2, this could lead to the formation of the quinone methides (**10**) and thence to the pyridines (**11**) (Scheme 3).

(*Received, 22nd April* 1981; *Com.* 455.)

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