

## A New Route to 3-Alkoxyppyridine 1-Oxides

By THOMAS L. GILCHRIST, GEORGE M. ISKANDER,<sup>†</sup> and AHMED K. YAGOUR<sup>†</sup>

(*The Robert Robinson Laboratories, University of Liverpool, P.O. Box 147, Liverpool L69 3BX*)

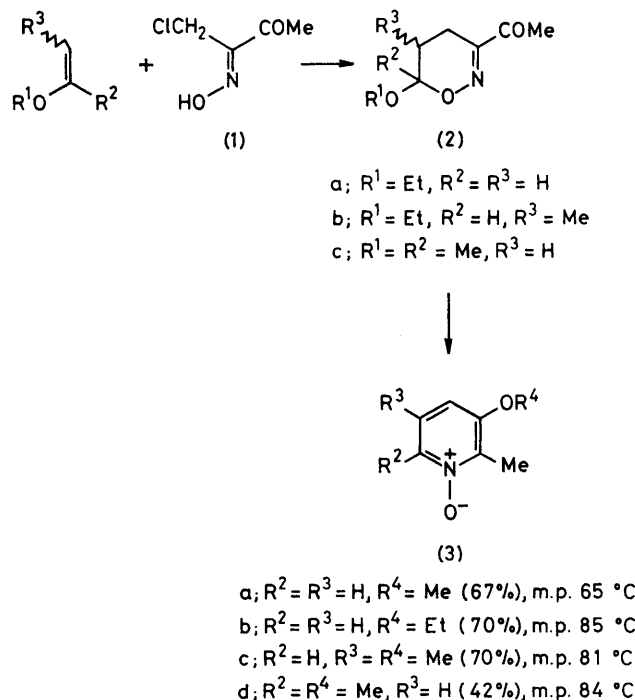
**Summary** Dihydro-oxazines, prepared by the addition of enol ethers to 1-chlorobutane-2,3-dione 2-oxime, are converted into 3-alkoxyppyridine 1-oxides by the action of alcoholic HCl.

<sup>†</sup> On leave from the University of Khartoum, Sudan.

THERE are few useful methods for the preparation of pyridine 1-oxides other than the N-oxidation of pyridines.<sup>1</sup> We have found that 3-alkoxy-pyridine 1-oxides can be prepared in good yields by the acid-catalysed rearrangement of 3-acetyl-6-alkoxy-5,6-dihydro-4H-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-4H-1,2-oxazines.<sup>2</sup> The chloro-oxime (1) reacted efficiently with enol ethers under these conditions to give the 6-alkoxy-derivatives (2) of the oxazines.<sup>†</sup> 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<sup>3</sup> 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.<sup>4</sup>

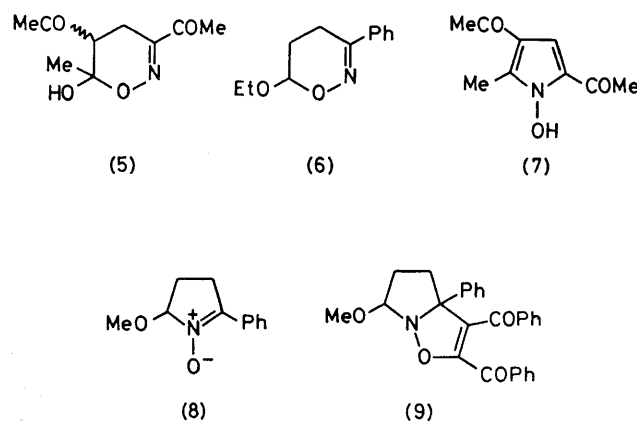
Other pyridine 1-oxides (3b)–(3d) were prepared in the same way (Scheme 1); ethanolic hydrochloric acid gave compound (3b) from the oxazine (2a) and methanolic hydrochloric acid was used to convert the oxazines (2b) and (2c) into the pyridine 1-oxides (3c) and (3d), respectively.



SCHEME 1

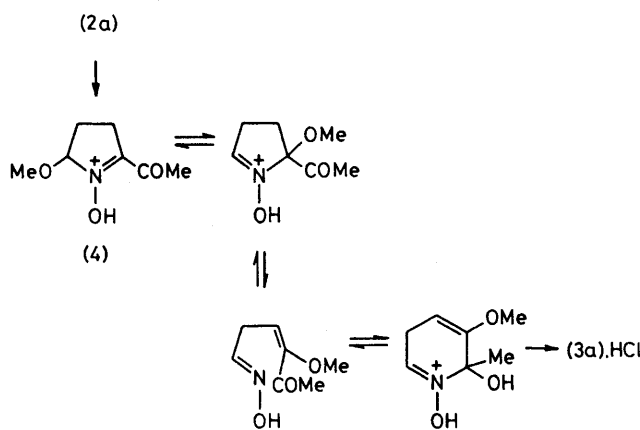
No long-lived intermediate could be detected when the conversion of the oxazine (2a) into the hydrochloride of compound (3a) was followed by u.v. spectroscopy. It seems

likely, however, that the protonated nitron (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 nitron (8) in quantitative yield, this being characterised as its adduct (9) with dibenzoylacetylene, m.p. 122 °C. The nitron (8) shows no tendency to aromatisate 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;<sup>5,6</sup> in one case, a nitron was isolated as an intermediate and was subsequently converted into the hydroxypyrrole in acid.<sup>6</sup>



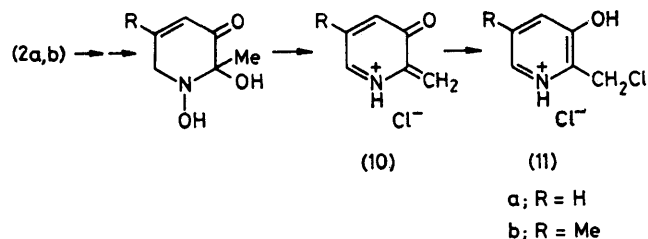
Scheme 2 shows a sequence by which compound (3a) might be formed: it is suggested that the nitron (4), like compound (8), would not aromatisate but instead could be cleaved to an acyclic oxime which could then re-cyclise by the attack of the nitrogen lone pair on the carbonyl of the acetyl group.

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



SCHEME 2

<sup>†</sup> 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

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<sup>1</sup> R. A. Abramovitch and E. M. Smith, in 'Heterocyclic Compounds,' ed. R. A. Abramovitch, Wiley, New York, 1974, vol. 14, Supplement, Part 2, p. 1.

<sup>2</sup> T. L. Gilchrist and T. G. Roberts, *J. Chem. Soc., Chem. Commun.*, 1978, 847.

<sup>3</sup> Y. Mizuno, T. Endo, and T. Nakamura, *J. Org. Chem.*, 1975, **40**, 1391.

<sup>4</sup> A. L. Logothetis, *J. Org. Chem.*, 1964, **29**, 1834.

<sup>5</sup> V. Sprio and G. C. Vaccaro, *Ann. Chim. (Rome)*, 1959, **49**, 2075; V. Sprio and P. Madonia, *ibid.*, 1960, **50**, 1627; V. Sprio and J. Fabra, *ibid.*, p. 1635.

<sup>6</sup> R. Ramasseul and A. Rassat, *Bull. Soc. Chim. Fr.*, 1970, 4330.

<sup>7</sup> L. R. Melby, *J. Am. Chem. Soc.*, 1975, **97**, 4044.

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.<sup>7</sup> 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).