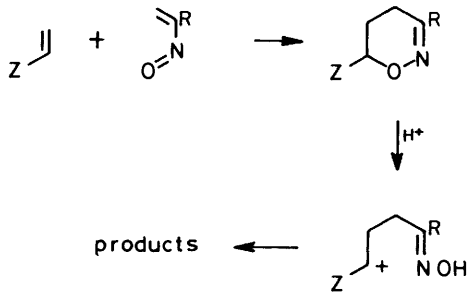
Acid-catalysed Rearrangement of 3-Acyl-6-alkoxy-5,6-dihydro-4*H*-1,2-oxazines: a Route to 3-Alkoxypyridine 1-Oxides[1]

Thomas L. Gilchrist,* George M. Iskander, and Ahmed K. Yagoub
The Robert Robinson Laboratories, University of Liverpool, P.O. Box 147, Liverpool L69 3BX

6-Alkoxy-5,6-dihydro-4*H*-1,2-oxazines (**2**) and (**5**) have been prepared by the reaction of chloro oximes (**1**) with enol ethers in the presence of sodium carbonate. The 3-phenyloxazine (**2**) rearranges to the nitrone (**3**) in methanolic HCl. In contrast, the 3-acyloxazines (**5a**—**e**) are converted into 3-alkoxypyridine 1-oxides (**7**) in aqueous alcoholic HCl. With HCl in acetic acid the oxazine (**5a**) is converted into 2-chloromethyl-3-hydroxypyridine hydrochloride (**10a**); analogous reactions take place with oxazines (**5b**) and (**5d**). Possible mechanisms for these reactions are discussed.

In earlier publications we have described the preparation and properties of 5,6-dihydro-4*H*-1,2-oxazines by the cycloaddition of transient nitroso alkenes to compounds containing carbon–carbon double bonds.[2,3] We have also shown that the dihydro-oxazines are susceptible to acid catalysed ring opening, by cleavage of the C-6 to oxygen bond, particularly when the substituents at C-6 can stabilise a positive charge (Scheme 1).[4] The products which result from this ring cleavage are highly dependent upon the nature of the substituents attached to the oxazine.

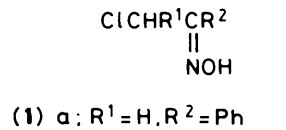


Scheme 1.

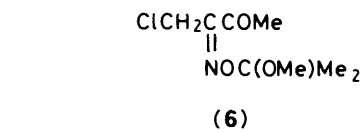
Simple enol ethers are excellent reaction partners for nitroso alkenes, and consequently 6-alkoxy-5,6-dihydro-4*H*-1,2-oxazines are easily prepared. We have made a series of such oxazines and have investigated their acid-catalysed rearrangement. Although the oxazines were purified by distillation or by layer chromatography, in many cases the crude reaction product, obtained directly from the appropriate chloro oxime (**1**) and enol ether in the presence of sodium carbonate, was sufficiently pure (by n.m.r.) for it to be used in the acid-catalysed reactions.† The 6-alkoxy substituents were expected to favour the acid-catalysed ring cleavage, and the original objective of the work was to use the reaction to produce 1-hydroxypyrroles. In the event, the reactions generally proved to be more complex.

6-Ethoxy-5,6-dihydro-3-phenyloxazine (**2**) reacted rapidly with methanolic HCl below room temperature to give a single product which was assigned the nitrone structure (**3**). The n.m.r. spectrum is consistent with this structure and the compound undergoes dipolar cycloaddition with dibenzoylacetylene to give an adduct (**4**). In this acid-catalysed rearrangement the cationic intermediate is intercepted by the nucleophilic nitrogen

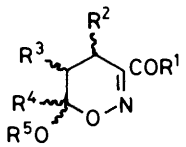
† In the reaction of 2-methoxypropene with the chloro oxime (**1b**) there was a minor product which was tentatively identified as the chloro oxime (**6**).



(**1**) a; R^1 = H, R^2 = Ph
b; R^1 = H, R^2 = COMe
c; R^1 = H, R^2 = COEt
d; R^1 = H, R^2 = COPh
e; R^1 = Me, R^2 = COMe

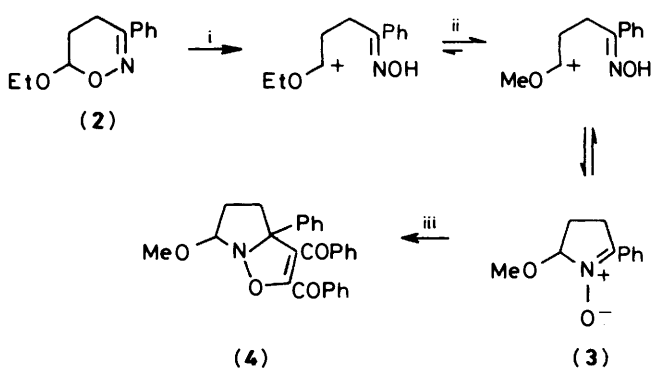


(**6**)



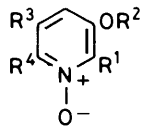
(**5**) a; R^1 = Me, R^2 = R^3 = R^4 = H, R^5 = Et
b; R^1 = R^5 = Et, R^2 = R^3 = R^4 = H
c; R^1 = Ph, R^2 = R^3 = R^4 = H, R^5 = Et
d; R^1 = R^3 = Me, R^2 = R^4 = H, R^5 = Et
e; R^1 = R^4 = R^5 = Me, R^2 = R^3 = H
f; R^1 = R^2 = R^3 = Me, R^4 = H, R^5 = Et
g; R^1 = Me, R^2 = R^4 = H, R^3, R^5 = $(CH_2)_2$
h; R^1 = Me, R^2 = R^4 = H, R^3, R^5 = $(CH_2)_3$

atom of the oxime function (Scheme 2). Compound (**3**) showed no tendency to aromatise to 1-hydroxy-2-phenylpyrrole. There are some literature examples of the synthesis of 1-hydroxypyrroles by related cyclisations of oximes,[5] but in these cases the products bear acyl groups or other conjugative substituents which apparently promote aromatisation.



(**2**) (**4**) (**3**)

Scheme 2. *Reagents*: i, HCl; ii, MeOH; iii, PhCOC≡CCOPh



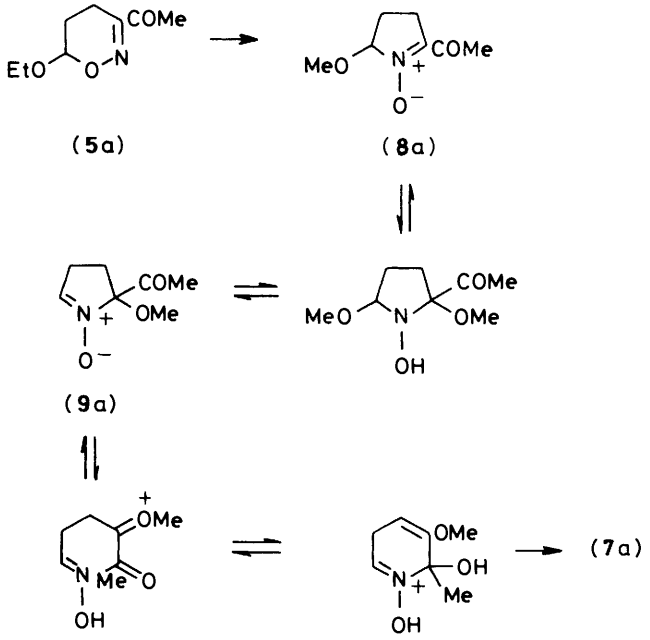
(7) a; $R^1 = R^2 = Me, R^3 = R^4 = H$
b; $R^1 = Me, R^2 = Et, R^3 = R^4 = H$
c; $R^1 = Et, R^2 = Me, R^3 = R^4 = H$
d; $R^1 = Ph, R^2 = Me, R^3 = R^4 = H$
e; $R^1 = R^2 = R^3 = Me, R^4 = H$
f; $R^1 = R^2 = R^4 = Me, R^3 = H$

On this basis we considered that 3-acyl-6-alkoxy-5,6-dihydro-oxazines might give 2-acyl-1-hydroxypyrroles rather than 2-acylnitrones when treated with acid. The oxazines (**5**) were prepared and were subjected to acid-catalysed cleavage under a variety of conditions. In a 9:1 mixture of methanol and water saturated with HCl the oxazine (**5a**) rapidly gave a new major product. This proved to be neither a nitrone nor a 1-hydroxypyrrole, but was identified as the known[6] 3-methoxy-2-methylpyridine 1-oxide (**7a**). This structural assignment was supported by the deoxygenation of the compound to 3-methoxy-2-methylpyridine, which was compared with a specimen prepared by an independent route.[7] When aqueous ethanol was used as the solvent in place of aqueous methanol the product was the analogous 3-ethoxy-2-methylpyridine 1-oxide (**7b**). Pyridine 1-oxides (**7c**—**f**) were similarly isolated in moderate to good yield from the reactions of the oxazines (**5b**—**e**), respectively, with HCl in aqueous methanol. These pyridine 1-oxides were obtained as crystalline solids after purification by sublimation. The n.m.r. spectra were consistent with the proposed structures but some were very hygroscopic and difficult to obtain analytically pure. These compounds were characterised as the picrates of the corresponding pyridines, which were obtained from the 1-oxides by reaction with phosphorus trichloride. The oxazine (**5f**) gave a mixture of products with HCl in aqueous methanol, of which the expected pyridine 1-oxide appeared to be a component (by n.m.r.) but the compound was not isolated in a pure state. The oxazines (**5g**) and (**5h**) derived from cyclic enol ethers gave mixtures in which the signals expected for the pyridine 1-oxides could not be detected by n.m.r.

The formation of the 3-alkoxypyridine 1-oxides can be rationalised if it is assumed that the reaction initially follows the same route as that of the oxazine (**2**). By analogy, the nitrone (**8a**) should be formed from the oxazine (**5a**) in aqueous methanol (Scheme 3). Nitrone (**8a**) should be much more susceptible to nucleophilic attack by the solvent than is compound (**3**). Thus, an isomeric nitrone (**9a**) could be formed which, after C–N bond cleavage and recyclisation onto the carbon atom of the carbonyl group, could lead to the observed product.

The overall reaction, from chloro oximes to pyridine 1-oxides, is simple to carry out and provides a useful method of preparation of these 1-oxides. Most pyridine 1-oxides are prepared by *N*-oxidation of the pyridines, although there are a few methods of limited scope, with some analogy to this one, in which open chain oximes are the precursors.[8]

In an attempt to obtain 3-acetoxypyridine 1-oxides, we also investigated the reaction of the oxazines (**5**) with HCl in acetic acid. The oxazine (**5a**) again gave a single product in high yield, but this proved to be the hydrochloride of 2-chloromethyl-3-hydroxypyridine, (**10a**). In an analogous reaction, the oxazine (**5d**) gave the pyridine hydrochloride (**10b**). The oxazine (**5b**) underwent the same type of reaction but the product was

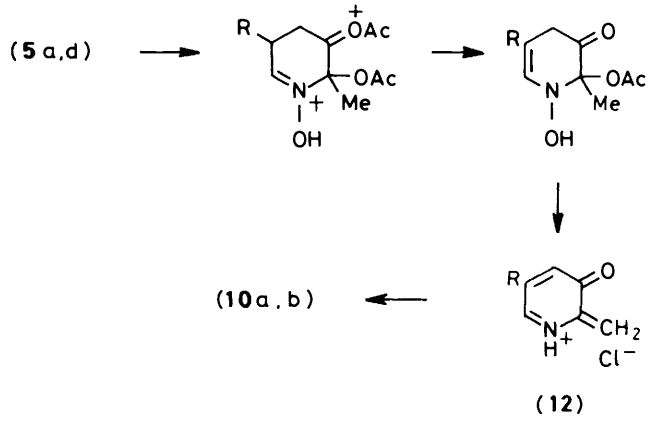


Scheme 3.

(10) a; R = H
b; R = Me

(11)

hydrolysed during the isolation procedure to give a compound tentatively identified, by n.m.r., as the alcohol (**11**); this was not further characterised. The reaction was not investigated with the other oxazines (**5c**) and (**5e**—**h**).



Scheme 4.

The unexpected substitution of the 2-methyl group of the pyridines probably takes place before the fully unsaturated ring system has been formed; from the known[9] method of preparation and properties of 3-hydroxy-2-methylpyridine 1-oxide, for example, it seems very unlikely that it could be an intermediate in the conversion of the oxazine (**5a**) into

compound (**10a**). A route by which the reaction might take place is shown in Scheme 4. The key difference between this sequence and that (Scheme 3) leading to the pyridine 1-oxides is suggested to be the role of the 3-substituent on the pyridine ring. Here it is a 3-oxo group, which allows elimination to involve the 2-methyl group with the generation of a transient enone, (**12**).

Experimental

I.r. spectra were recorded for KBr discs on a Perkin-Elmer 125 spectrophotometer. ^{1}H N.m.r. spectra were recorded using a Perkin-Elmer R34 spectrometer operating at 220 MHz, and with deuteriochloroform as the solvent, except where otherwise indicated. Mass spectra were recorded on an A.E.I. MS12 instrument at 70 eV using a direct insertion probe. Silica for layer chromatography was Kieselgel PF_{254} (Merck). Ether refers to diethyl ether.

The chloro oximes (**1b**), (**1d**), and (**1e**) were prepared by the methods described previously.[2,10] The chloro oxime (**1c**) was prepared by a method due to Dr. J. R. Moxey, as follows:

1-Chloropentane-2,3-dione 2-Oxime (**1c**).—Pent-1-en-3-one (5.0 g, 60 mmol) was dissolved in ether (20 cm^3) and the solution was cooled to −23 °C and stirred while nitrosyl chloride (4.42 g, 68 mmol) was passed in. The solution was stirred for 3 h, warmed to room temperature, and the solvent removed to leave the *chloro oxime* (**1c**) (8.55 g, 96%), m.p. 65—67 °C (from carbon tetrachloride) (Found: C, 40.2; H, 5.4; Cl, 23.5; N, 9.3. $C_5H_9ClNO_2$ requires C, 40.1; H, 5.35; Cl, 23.75; N, 9.4%); δ 1.15 (3 H, t), 2.83 (2 H, q), 4.37 (2 H), and 8.88 (1 H).

6-Ethoxy-5,6-dihydro-3-phenyl-4H-1,2-oxazine (**2**).—α-Chloroacetophenone oxime (**1a**) (3.3 g, 21 mmol) was dissolved in a mixture of dichloromethane (30 cm^3) and ethoxyethene (20 cm^3) and the solution was stirred with sodium carbonate (5 g) at 20 °C for 24 h. The reaction mixture was filtered and the filtrate was evaporated to dryness. Crystallisation gave the *oxazine* (**2**) (4.0 g, 91%), m.p. 33 °C (from ether–hexane) (Found: C, 70.1; H, 7.4; N, 6.9. $C_{12}H_{15}NO_2$ requires C, 70.2; H, 7.4; N, 6.8%); $\nu_{max.}$ 1 100, 1 020, and 890 cm^{-1}; δ 1.18 (3 H, t), 1.90—2.20 (2 H, m, 5-H), 2.47 (1 H, ddd, *J* 17.7, 7.0, and 2.3 Hz, 4-H), 2.68 (1 H, ddd, *J* 17.7, 11.9, and 7.8 Hz, 4-H), 3.52—3.70 (1 H, m), 3.77—3.95 (1 H, m), 5.14 (1 H, t, *J ca.* 2 Hz, 6-H), 7.30—7.45 (3 H, m), and 7.63—7.75 (2 H, m); *m/z* 205 (M^+), 186, 159, and 142.

3,4-Dihydro-2-methoxy-5-phenyl-2H-pyrrole 1-Oxide (**3**) *and its Adduct* (**4**) *with Dibenzoylacetylene.*—The oxazine (**2**) (0.70 g, 3.4 mmol) was dissolved in methanol (50 cm^3) and hydrogen chloride was passed into the solution at 0 °C. The solution was kept at 0—5 °C for 2 h and the solvent was removed to give a violet solid. Crystallisation gave the colourless *pyrrole 1-oxide* (**3**) (0.46 g, 70%), m.p. 128—130 °C (from dichloromethane–ether) (Found: C, 68.5; H, 6.85; N, 7.3. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.3%); $\nu_{max.}$ 1 550, 1 270, 1 205 ($\overset{+}{N}$–$\overset{-}{O}$), 1 125, 955, and 760 cm^{-1}; δ 1.93—2.10 (1 H, m, 3-H), 2.30—2.49 (1 H, m, 3-H), 2.85—3.22 (2 H, m, 4-H), 3.84 (3 H), 5.13 (1 H, t, 2-H), 7.39—7.46 (3 H, m), and 8.30—8.38 (2 H, m); *m/z* 191 (M^+) and 174.

The pyrrole 1-oxide (0.50 g, 2.6 mmol) and dibenzoylacetylene (0.60 g, 2.6 mmol) were dissolved in dichloromethane (30 cm^3) and the solution was kept at room temperature for 3 days. Layer chromatography [silica; ethyl acetate–hexane (1:1)] gave 2,3-*dibenzoyl-6-methoxy-3a-phenyl-3a,4,5,6-tetrahydropyrrolo*[1,2-b]*isoxazole* (**4**) (0.64 g, 58%), m.p. 119—122 °C (from hexane) (Found: C, 76.4; H, 5.2; N, 3.3. $C_{27}H_{23}NO_4$ requires C, 76.2; H, 5.4; N, 3.3%); $\nu_{max.}$ 1 665 and 1 635 cm^{-1}; δ 2.00—2.40 (2 H, m, 4-H), 2.45—2.70 (1 H, m, 5-H), 3.40—3.60 (1 H, m, 5-H), 3.50 (3 H), 4.80—4.90 (1 H, m, 6-H), and 6.95—7.68 (15 H, m); *m/z* 425 (M^+).

3-Acyl-6-alkoxy-5,6-dihydro-4H-1,2-oxazines (**5**). *General Procedure.*—The chloro oxime (**1**) (10 mmol) and the appropriate enol ether (100 mmol) were dissolved in dichloromethane (30 cm^3) and the solution was stirred with sodium carbonate (20 mmol) for 12 h at room temperature. The reaction mixture was filtered and the filtrate was evaporated to leave the crude dihydro-oxazine, which was sufficiently pure (by n.m.r.) for further reactions. Analytical specimens of each of the oxazines were obtained by the methods indicated. The following were characterised:

(*a*) *3-Acetyl-6-ethoxy-5,6-dihydro-4H-1,2-oxazine* (**5a**). The characterisation of this compound has been recorded previously.[2]

(*b*) *6-Ethoxy-5,6-dihydro-3-propanoyl-4H-1,2-oxazine* (**5b**). The chloro oxime (**1c**) and ethoxyethene gave, by distillation, the *oxazine* (**5b**) as a mobile oil, b.p. 52—53 °C at 0.02 mmHg (Found: C, 58.2; H, 8.0; N, 7.5. $C_9H_{15}NO_3$ requires C, 58.4; H, 8.1; N, 7.6%); $\nu_{max.}$(film) 1 690 cm^{-1} (CO); δ 1.07 (3 H, t), 1.16 (3 H, t), 1.65—1.83 (1 H, m, 5-H), 1.90—2.07 (1 H, m, 5-H), 2.15—2.35 (1 H, ddd, 4-H), 2.37—2.53 (1 H, ddd, 4-H), 2.83 (2 H, q), 3.55—3.72 (1 H, m), 3.75—3.92 (1 H, m), and 5.15 (1 H, t, *J* 2 Hz, 6-H).

(*c*) *3-Benzoyl-6-ethoxy-5,6-dihydro-4H-1,2-oxazine* (**5c**). The chloro oxime (**1d**) and ethoxyethene gave, by distillation, the *oxazine* (**5c**), b.p. 70 °C at 0.01 mmHg (Found: C, 66.5; H, 6.35; N, 6.0. $C_{13}H_{15}NO_3$ requires C, 66.9; H, 6.5; N, 6.0%); δ 1.18 (3 H, t), 1.75—1.95 (1 H, m, 5-H), 2.00—2.16 (1 H, m, 5-H), 2.38—2.70 (2 H, m, 4-H), 3.57—3.73 (1 H, m), 3.80—3.96 (1 H, m), 5.20 (1 H, t, *J* 2 Hz, 6-H), 7.35—7.60 (3 H, m), and 7.95—8.05 (2 H, m).

(*d*) *3-Acetyl-6-ethoxy-5,6-dihydro-5-methyl-4H-1,2-oxazine* (**5d**). The chloro oxime (**1b**) and 1-ethoxypropene [as a mixture of *E*- and *Z*- isomers] gave, by distillation, the *oxazine* (**5d**) as a mixture of *cis*- and *trans*- isomers in a 1:1 ratio, b.p. 70 °C at 0.02 mmHg (Found: C, 58.2; H, 8.2; N, 7.8. $C_9H_{15}NO_3$ requires C, 58.4; H, 8.2; N, 7.6%); $\nu_{max.}$(film) 1 695 cm^{-1} (CO); δ 1.37 and 1.52 (together 3 H, each d, *J* 7.2 Hz, 5-Me), 1.60—1.72 (together 3 H, 2 × t), 1.80—2.00 (1 H, m, 5-H), 2.05—2.20 (1 H, m, 4-H), 2.32—2.45 (1 H, m, 4-H), 2.38 (3 H, 3-Me), 3.50—3.70 (1 H, m), 3.76—3.93 (1 H, m), 4.80 (d, *J* 2 Hz), and 4.96 (d, *J ca.* 1 Hz) (together, 1 H, 6-H).

(*e*) *3-Acetyl-5,6-dihydro-6-methoxy-6-methyl-4H-1,2-oxazine* (**5e**). The chloro oxime (**1b**) and 2-methoxypropene gave, by distillation, the oxazine (**5e**), b.p. 67 °C at 0.02 mmHg. The oxazine was not obtained analytically pure: g.l.c. showed two components in the ratio 9:1. The minor component was tentatively identified as the oxime (**6**); δ [for the oxazine (**5d**)] 1.51 (3 H, 6-Me), 1.50—1.71 (1 H, m, 5-H), 1.98—2.15 (1 H, ddd, 5-H), 2.20—2.55 (2 H, m, 4-H), 2.41 (3 H, 3-Me), and 3.27 (3 H, 6-OMe); [for the oxime (**6**)] 1.59 (6 H), 2.45 (3 H), 3.31 (3 H), and 4.33 (2 H).

(*f*) *3-Acetyl-6-ethoxy-5,6-dihydro-4,5-dimethyl-4H-1,2-oxazine* (**5f**). The chloro oxime (**1e**) and 1-ethoxypropene gave, by distillation, the *oxazine* (**5f**) as a mixture of isomers, b.p. 70 °C at 0.02 mmHg (Found: C, 60.6; H, 8.6; N, 7.0. $C_{10}H_{17}NO_3$ requires C, 60.3; H, 8.6; N, 7.0%); $\nu_{max.}$(film) 1 698 cm^{-1} (CO); δ 0.8—1.35 (9 H, m, 4-Me, 5-Me, and OCH_2Me), 1.85—2.02 (1 H, m, 5-H), 2.31—2.46 (4 H, m, 3-Me and 4-H), 3.47—3.70 (1 H, m), 3.80—3.98 (1 H, m), and 4.83—4.98 (together, 1 H, 4 × d, 6-H).

(*g*) *3-Acetyl-4a,5,6,7a-tetrahydro-4H-furo*[3,2-e]*-1,2-oxazine* (**5g**). The chloro oxime (**1b**) and 2,3-dihydrofuran gave, by layer chromatography (silica), the oxazine (**5g**); $\nu_{max.}$ 1 690 cm^{-1} (CO); δ 1.49—1.69 (1 H, m, 5-H), 2.10—2.27 (1 H, m, 5-H), 2.41 (3 H, 3-Me), 2.43—2.55 (1 H, m, 4a-H), 2.65—2.75 (2 H, m, 4-H), 3.92—4.18 (2 H, m, 6-H), and 5.46 (1 H, d, *J* 5 Hz, 7a-H). The compound was characterised as its 2,4-*dinitrophenylhydrazone*,

m.p. 178—182 °C (from ethanol) (Found: C, 48.25; H, 4.5; N, 20.0. $C_{14}H_{15}N_5O_6$ requires C, 48.1; H, 4.3; N, 20.05%).

(*h*) 3-*Acetyl*-4a,6,7,8a-*tetrahydro*-4H,5H-*pyrano*[3,2-e]-1,2-*oxazine* (**5h**). The chloro oxime (**1b**) and 3,4-dihydro-2*H*-pyran gave, by distillation, the *oxazine* (**5h**), b.p. 85 °C at 0.02 mmHg (Found: C, 58.6; H, 7.2; N, 7.7. $C_9H_{13}NO_3$ requires C, 59.0; H, 7.15; N, 7.65%); $\nu_{max.}$(film) 1 690 cm^{-1} (CO); δ 1.45—1.80 (4 H, m, 5-H and 6-H), 2.03—2.20 (1 H, m, 4a-H), 2.40—2.52 (5 H, m, 3-Me and 4-H), 3.68—3.80 (1 H, m, 7-H), 3.95—4.06 (1 H, m, 7-H), and 5.22 (1 H, d, *J* 2.5 Hz, 8a-H).

Pyridines by Acid-catalysed Rearrangement of Oxazines.—(*a*) 3-*Methoxy*-2-*methylpyridine* 1-*oxide* (**7a**) *and* 3-*methoxy*-2-*methylpyridine*. The oxazine (**5a**) (0.20 g, 1.2 mmol) was dissolved in 10% aqueous methanol (10 cm^3) which had previously been saturated with hydrogen chloride, and the solution was allowed to stand at room temperature for 2 h. The solvent was removed and the crystalline residue was washed with aqueous sodium hydroxide (1M) and extracted with dichloromethane to give the pyridine 1-oxide (**7a**) (0.10 g, 67%), m.p. 65 °C (sublimed at 0.02 mmHg) (lit.,[6] 64—66 °C); δ 2.73 (3 H), 4.10 (3 H), 7.75—7.88 (2 H, m, 4-H and 5-H), and 8.68 (1 H, dd, *J* 6.1 and 1.9 Hz, 6-H); *m/z* 139 (M^+) and 123.

The 1-oxide (**7a**) (0.26 g, 1.9 mmol) and phosphorus trichloride (0.5 g, 4 mmol) in dichloromethane (10 cm^3) gave, after 12 h at 20 °C, 3-methoxy-2-methylpyridine (0.18 g, 80%), b.p. 60 °C at 0.02 mmHg; δ 2.45 (3 H), 3.77 (3 H), 7.01—7.09 (2 H, 2 × dd, 4-H and 5-H), and 8.05 (1 H, dd, 6-H). The compound was identical with a specimen prepared from 2-acetylfuran and ammonia followed by *O*-methylation with dimethyl sulphate.[7]

(*b*) 3-*Ethoxy*-2-*methylpyridine* 1-*oxide* (**7b**). 10% Aqueous ethanol was saturated with hydrogen chloride at 0 °C. To this solution (10 cm^3) was added the oxazine (**5a**) (0.66 g, 3.8 mmol). After 3 h the solvent was removed and to the residual crystalline hydrochloride was added an excess of aqueous sodium hydroxide (1M). Extraction with dichloromethane gave the *pyridine* 1-*oxide* (**7b**) (0.47 g, 80%), m.p. 84 °C (sublimed at 0.02 mmHg) (Found: C, 62.6; H, 6.9; N, 9.2. $C_8H_{11}\overset{+}{N}\overset{-}{O}_2$ requires C, 62.7; H, 7.2; N, 9.1%); $\nu_{max.}$ 1 470, 1 380, 1 280 (N–O), 1 090, and 820 cm^{-1}; δ 1.53 (3 H, t), 2.73 (3 H), 4.29 (2 H, q), 7.65—7.80 (2 H, m, 4-H and 5-H), and 8.65 (1 H, dd, *J* 6.5 and 2.6 Hz, 6-H); *m/z* 153 (M^+) and 137.

(*c*) 2-*Ethyl*-3-*methoxypyridine* 1-*oxide* (**7c**) and 2-*ethyl*-3-*methoxypyridine*. A solution of the oxazine (**5b**) (0.92 g, 5.0 mmol) in 10% aqueous methanol (20 cm^3) previously saturated with hydrogen chloride was kept at 20 °C for 3 h. The solvent was evaporated off and dichloromethane (50 cm^3) was added. The organic phase was washed with aqueous sodium carbonate and water, dried, and evaporated to give the 1-oxide (**7c**) (0.62 g, 81%), m.p. 60 °C after sublimation at 0.05 mmHg. The compound is hygroscopic and a satisfactory analysis was not obtained; δ 1.15 (3 H, t), 3.00 (2 H, q), 3.84 (3 H), 6.78 (1 H, dd, *J ca.* 8 and 1 Hz, 4-H), 7.02 (1 H, dd, *J ca.* 8 and 6 Hz, 5-H), and 7.94 (1 H, dd, *J ca.* 6 and 1 Hz, 6-H).

The 1-oxide (**7c**) (0.32 g, 2.1 mmol) and phosphorus trichloride (0.825 g, 6 mmol) in dichloromethane gave 2-ethyl-3-methoxypyridine (0.22 g, 77%) as an oil; δ 1.23 (3 H, t), 2.83 (2 H, q), 3.80 (3 H), 7.08—7.13 (2 H, m, 4-H and 5-H), and 8.10—8.16 (1 H, m, 6-H); *picrate*, m.p. 126—128 °C (from ethanol) (Found: C, 45.8; H, 4.0; N, 15.3. $C_{14}H_{14}N_4O_8$ requires C, 45.9; H, 3.85; N, 15.3%); δ 1.30 (3 H, t), 3.20 (2 H, q), 4.05 (3 H), 7.65—7.82 (2 H, m), 8.30—8.36 (1 H, m), and 8.87 (2 H).

(*d*) 3-*Methoxy*-2-*phenylpyridine* 1-*oxide* (**7d**). A solution of the oxazine (**5c**) (0.50 g, 2.1 mmol) in 10% aqueous methanol (25 cm^3) saturated with hydrogen chloride was kept at 20 °C for 21 h. The solvent was removed and the residue was taken up in dichloromethane (40 cm^3). The organic solution was washed with aqueous sodium carbonate and water, dried, and the solvent evaporated to leave a viscous oil (0.40 g). Layer chromatography [silica; ethyl acetate–ethanol (9:1)] gave (at R_F 0.16) the 1-*oxide* (**7d**) (0.124 g, 30%), m.p. 157—159 °C (after sublimation at 0.05 mmHg) (Found: C, 71.5; H, 5.5; N, 7.2. $C_{12}H_{11}NO_2$ requires C, 71.6; H, 5.5; N, 7.0%); δ 3.73 (3 H), 6.87 (1 H, d, *J* 9.5 Hz, 4-H), 7.12 (1 H, dd, 5-H), 7.35—7.52 (5 H, m), and 8.01 (1 H, d, *J* 6 Hz, 6-H).

(*e*) 3-*Methoxy*-2,5-*dimethylpyridine* 1-*oxide* (**7e**). A solution of the oxazine (**5d**) (0.22 g, 1.2 mmol) in 10% aqueous methanol (10 cm^3) saturated with hydrogen chloride was kept at 20 °C for 15 h. The solvent was removed; the residue was then taken up in dichloromethane (40 cm^3) and the organic solution washed with aqueous sodium hydroxide and water. The organic phase was dried and evaporated and the residue was sublimed to give the 1-oxide (**7e**) (0.14 g, 70%) as a hygroscopic solid, m.p. 78—81 °C, for which a satisfactory analysis was not obtained; $\nu_{max.}$ 1 585, 1 310, 1 120, and 820 cm^{-1}; δ 2.24 (3 H), 2.38 (3 H), 3.84 (3 H), 6.63 (1 H, 4-H), and 7.82 (1 H, 6-H); *m/z* 153 (M^+) and 137. The compound was characterised by deoxygenation with phosphorus trichloride and conversion of the crude product into 3-*methoxy*-2,5-*dimethylpyridinium picrate*, m.p. 179—184 °C (from ethanol) (Found: C, 46.2; H, 4.1; N, 15.0. $C_{14}H_{14}N_4O_8$ requires C, 45.9; H, 3.85; N, 15.3%).

(*f*) 3-*Methoxy*-2,6-*dimethylpyridine* 1-*oxide* (**7f**). A solution of the crude oxazine (**5e**) (1.00 g, 0.58 mmol) in 10% aqueous methanol (25 cm^3) saturated with hydrogen chloride was kept at 20 °C for 24 h. The solvent was evaporated and the residue was dissolved in dichloromethane (50 cm^3). The solution was washed with aqueous sodium carbonate and water, dried, and evaporated to leave an oil (0.61 g). Layer chromatography [silica; ethyl acetate–ethanol (9:1)] gave (at R_F 0.3) the 1-*oxide* (**7f**) (0.38 g, 42%), m.p. 56 °C (after sublimation at 0.01 mmHg) (Found: C, 62.9; H, 7.4; N, 9.15. $C_8H_{11}NO_2$ requires C, 62.7; H, 7.2; N, 9.1%); δ 2.43 (6 H), 3.82 (3 H), 6.74 (1 H, d, *J* 8 Hz), and 7.03 (1 H, d, *J* 8 Hz).

2-*Chloromethyl*-3-*hydroxypyridine Hydrochloride* (**10a**).—The oxazine (**5a**) (0.60 g, 3.5 mmol) was dissolved in acetic acid (20 cm^3) which had previously been saturated with hydrogen chloride. The solution was kept at 20 °C for 24 h. The solvent was then removed and a crystalline residue of the hydrochloride (**10a**) (0.63 g, 100%) remained. Recrystallisation gave an analytical specimen of the *pyridine hydrochloride* (**10a**), m.p. 160 °C (decomp.) (from acetic acid) (Found: C, 40.2; H, 3.9; N, 7.5. $C_6H_7Cl_2NO$ requires C, 40.0; H, 3.9; N, 7.8%); $\nu_{max.}$ 3 000—2 500 (NH), 1 560, 1 475, 1 310, and 790 cm^{-1}; δ[$(CD_3)_2SO$] 4.99 (2 H), 7.85 (1 H, dd, *J* 8.3 and 5.5 Hz, 5-H), 8.16 (1 H, dd, *J* 8.3 and 1.1 Hz, 4-H), and 8.37 (1 H, dd, *J* 5.5 and 1.1 Hz, 6-H); *m/z* 145/143 (M^+) and 108.

The hydrochloride (0.14 g, 0.78 mmol) was dissolved in water (2 cm^3) and the solution was evaporated to dryness on a steam-bath. Layer chromatography [silica; ethyl acetate–hexane–ethanol (9:9:2)] gave 3-hydroxy-2-hydroxymethylpyridine (0.04 g, 41%), m.p. 141—142 °C (from ethanol) (lit.,[11] 137—141 °C); δ(CF_3CO_2H) 5.30 (2 H), 7.80—7.90 (1 H, m, 5-H), 8.07 1 H, dd, *J* 8 and 1 Hz, 4-H), and 8.31 (1 H, dd, *J* 5 and 1 Hz, 6-H).

2-*Chloromethyl*-3-*hydroxy*-5-*methylpyridine Hydrochloride* (**10b**).—The oxazine (**5d**) (0.90 g, 4.9 mmol) was dissolved in acetic acid (30 cm^3) and hydrogen chloride was passed into the solution at below 10 °C. The solution was then kept at 20 °C for 24 h. The solvent was then removed and the residue washed with dichloromethane and then crystallised to give the *pyridine hydrochloride* (**10b**) (0.71 g, 75%), m.p. 140 °C (decomp.) (from acetic acid) (Found: C, 43.5; H, 4.7; N, 7.3. $C_7H_9Cl_2NO$ requires C, 43.3; H, 4.6; N, 7.2%); $\nu_{max.}$ 3 000—2 500 (NH), 1 580, 1 470, 1 380, 1 175, and 875 cm^{-1}; δ[$(CD_3)_2SO$] 2.40 (3 H), 4.97 (2 H), 7.97 (1 H, 4-H), and 8.28 (1 H, 6-H); *m/z* 159/157 (M^+) and 122.

Reaction of the Oxazine (**5b**) *With Hydrogen Chloride in Acetic Acid.*—The oxazine (**5b**) (0.52 g, 3.1 mmol) was dissolved in acetic acid (10 cm^3) which had been saturated with hydrogen chloride, and the solution was kept at 20 °C for 24 h. The solvent was removed to leave a viscous oil. This was dissolved in water (20 cm^3), the solution washed with dichloromethane, and evaporated to leave a brown solid (0.19 g). Purification was effected by dissolution of the solid in the minimum of ethanol and reprecipitation by the addition of ethyl acetate. This gave colourless crystals, m.p. 176—180 °C; δ(CD_3OD) 1.52 (3 H, d, *J* 7 Hz), 5.11 (2 H, br), 5.30 (1 H, q, *J* 7 Hz), 7.75—7.90 (1 H, m), 7.92—8.02 (1 H, m), and 8.19—8.30 (1 H, m); *m*/*z* 139. On the basis of these data the compound was assigned the structure 3-hydroxy-2-(1-hydroxypropyl)pyridinium chloride (**11**).

Acknowledgements

This work was carried out while G. M. I. and A. K. Y. were on leave from the University of Khartoum, Sudan. We thank the British Council for support.

References

1 Preliminary communication, T. L. Gilchrist, G. M. Iskander, and A. K. Yagoub, *J. Chem. Soc., Chem. Commun.*, 1981, 696.
2 T. L. Gilchrist and T. G. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1983, 1283.
3 R. Faragher and T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, 1979, 249; D. E. Davies, T. L. Gilchrist, and T. G. Roberts, *ibid.*, 1983, 1275.
4 R. Faragher and T. L. Gilchrist, *J. Chem. Soc., Perkin Trans. 1*, 1979, 258.
5 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.
6 Y. Mizuno, T. Endo, and T. Nakamura, *J. Org. Chem.*, 1975, **40**, 1391.
7 A. L. Logothetis, *J. Org. Chem.*, 1964, **29**, 1834.
8 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.
9 K. Undheim, V. Nordal, and L. Borka, *Acta Chem. Scand.*, 1969, **23**, 2075; K. M. Dyumaev, L. D. Smirnov, R. E. Lokhov, and B. E. Zaitsev, *Izv. Akad. Nauk SSSR*, 1970, 2599.
10 K. A. Ogloblin and A. A. Potekhin, *J. Gen. Chem. USSR*, 1974, **34**, 2710.
11 L. R. Melby, *J. Am. Chem. Soc.*, 1975, **97**, 4044.

Received 31*st May* 1985; *Paper* 5/921