Formation of 2-Acetylpyridines by the Base-catalysed Ring Opening of Dihydro-4*H*-furo[2,3-*e*]oxazines

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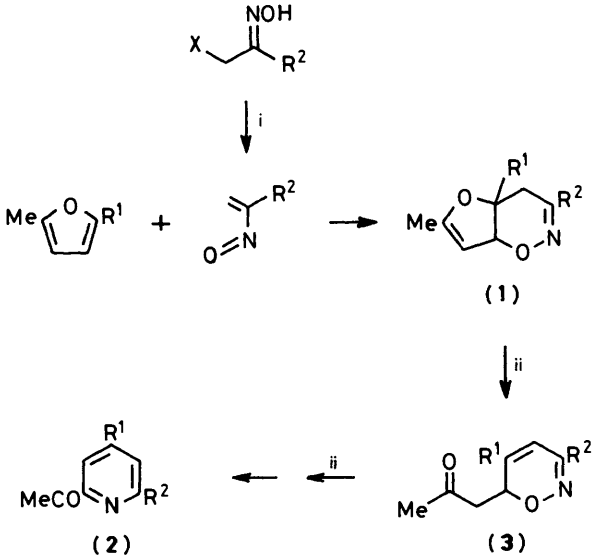
Furo-oxazines (**1**), which were formed by the addition of nitrosoalkenes to 2,5-dimethylfuran or 2-methylfuran, reacted with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to give 2-acetylpyridines (**2**). The reaction is postulated to involve an initial base-catalysed elimination to give the 6*H*-1,2-oxazines (**3**) which are then cleaved in a second base-catalysed elimination. In support of this proposal, the oxazine (**3a**) has been isolated and has been converted into the pyridine (**2a**) by reaction with DBU. A second intermediate, which has been detected spectroscropically, is formulated as the dihydropyridine (**7**). A deuterium labelled 6*H*-oxazine (**6**) has been prepared in order to elucidate the course of the reaction. An analogous furopyridazine (**9**) has been synthesized and its reaction with DBU has been investigated. Only the initial elimination reaction took place and the dihydropyridazine (**10**) was obtained as the reaction product.

Furo-oxazines having the general structure (**1**) are readily prepared by the cycloaddition of nitrosoalkenes to furans.[1,2] In this paper we describe more examples of this type of compound, formed from 2,5-dimethylfuran and 2-methylfuran, and their conversion into 2-acetylpyridines (**2**) by reaction with 1,8-diazabicylo[5.4.0]undec-7-ene (DBU). The original objective of the work was to convert the furo-oxazines (**1**) into 6*H*-oxazines (**3**) by base-catalysed elimination of the enolate anion. The 6*H*-oxazines (**3**) were indeed formed in this way, but under the reaction conditions they generally reacted further to give the pyridines (**2**), which were isolated in good yield (Scheme 1).



	R^1	R^2
a;	Me	CO_2Me
b;	Me	COMe
c;	Me	COEt
d;	Me	COPh
e;	Me	Ph
f;	H	CO_2Et

Scheme 1. *Reagents:* i, Na_2CO_3; ii, DBU

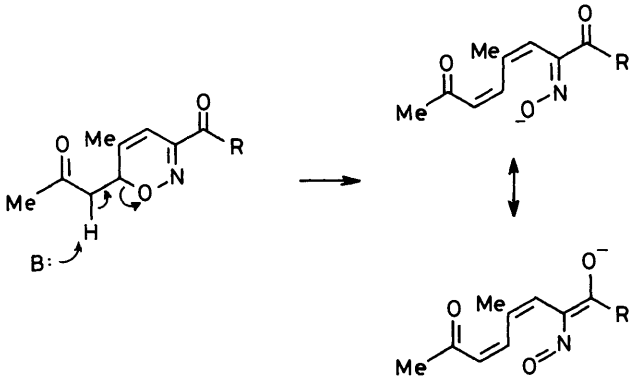
The furo-oxazine (**1a**) failed to react with triethylamine or with diazabicyclo[2.2.2]octane. With DBU, however, a reaction was observed and this was complete after a few hours at room temperature. The reaction was more rapid when 1 equiv. of base was used but it also went efficiently with a catalytic amount of base. The product was isolated in good yield as a crystalline solid and it was identified as the pyridine (**2a**). Similar reactions were carried out with the oxazines (**1b**)—(**1d**) and (**1f**), the corresponding pyridines (**2**) being isolated in each case. Only the 3-phenyloxazine (**1e**) reacted differently. This compound only reacted with DBU in boiling dichloromethane to give a product which was identified as the 6*H*-oxazine (**3e**). In concentrated solution the pyridine (**2e**) was also formed in low yield. The use of higher boiling solvents resulted in the formation of the pyridine of (**2e**), together with considerable amounts of tars. The pyridine (**2e**) was isolated in highest yield (26%) from a reaction carried out in benzene.

The structure of the pyridines (**2**), which are all previously unreported, were supported by analytical and spectroscopic data. The 2,4,6-trisubstitution pattern of the pyridines (**2a**)—(**2e**) is evident from their ^{1}H n.m.r. spectra. The spectrum of the symmetrically substituted pyridine (**2b**) shows a singlet (2 H) for the hydrogens attached to C-3 and C-5 and a singlet (6 H) for the two methyl groups of the acetyl functions. The spectra of the pyridines (**2a**) and (**2e**) show separate signals for 3-H and 5-H. At 220 MHz these appear as broadened singlets. The spectrum of the pyridine (**2e**) was also recorded at 250 MHz with irradiation of the signal for the methyl group attached to C-4. The signals of the two aromatic hydrogens then appeared as sharp doublets (*J* 1.1 Hz). These signals thus show *meta* coupling and they are both also coupled to the methyl group at C-4. The structure (**2e**) is therefore distinguished from that of an isomer (**4**) which was recently isolated by Mackay and Watson from the pyrolysis of a 2:1 adduct of α-nitrosostyrene and 2,5-dimethylfuran.[3]

The 6*H*-oxazines (**3**) are intermediates in the conversion of the furo-oxazines (**1**) into the pyridines (**2**). Evidence to support this view is provided not only by the isolation of compound (**3e**) in the reaction of the furo-oxazine (**1e**) with DBU, but also by a more detailed study of the reactions of compound (**1a**). We found that the ester (**3a**) could be obtained from compound (**1a**) by an acid-catalysed rearrangement, using toluene-*p*-sulphonic acid as the catalyst. With aqueous HCl, the alcohol (**5a**) was

formed instead but this could then be converted into the ester (**3a**) by heating with toluene-*p*-sulphonic acid. Both compounds (**3a**) and (**5a**) were unstable and neither was fully characterised, although their n.m.r. spectra are completely consistent with the proposed structures. The 6*H*-oxazine (**3a**) could then be converted into the pyridine (**2a**) by reaction with DBU at room temperature. It was also possible to detect compound (**3a**) as an intermediate in the conversion of furo-oxazine (**1a**) into compound (**2a**) when the reaction was followed by n.m.r. By analogy it is reasonable that the 6*H*-oxazines (**3b**)—(**3d**) and (**3f**) are intermediates in the corresponding conversions, although they were not isolated or detected.

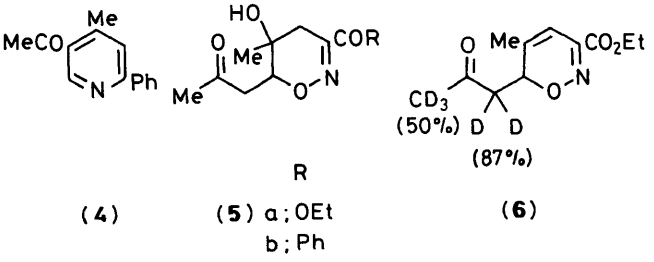
Compound (**3e**) is clearly much more resistant to base-catalysed ring cleavage than the other 6*H*-oxazines in this series. The 3-substituent may assist in the cleavage of the other 6*H*-oxazines by providing additional stabilisation to the leaving group (Scheme 2)



Scheme 2.

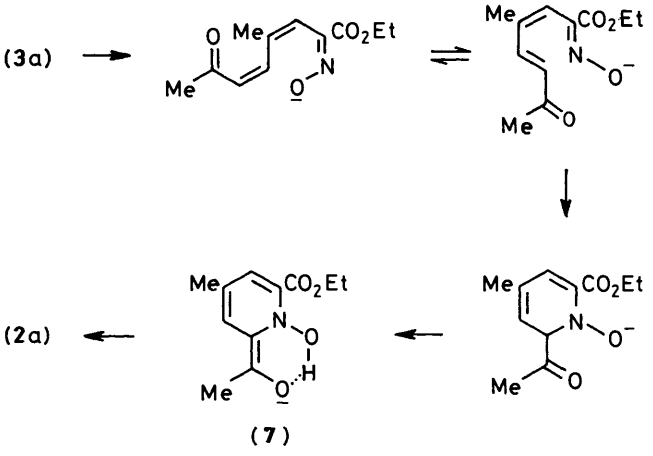
When the conversion of either the furo-oxazine (**1a**) or of the 6*H*-oxazine (**3a**) into the pyridine (**2a**) was followed by t.l.c., another intermediate could be detected. This substance appeared as a bright yellow spot on the t.l.c. plate but attempts to isolate it by rapid chromatography were unsuccessful: only the pyridine (**2a**) was obtained. The intermediate was also detectable by u.v. ($\lambda_{max.}$ 408 nm) and by n.m.r. When the reaction was followed by n.m.r., signals which were assignable to the intermediate were observed to appear and then disappear. By adjusting the concentrations of the substrate (**3a**) and the base, solutions were obtained in which the intermediate reached a maximum of about 70% of the mixture before being converted into the pyridine (**2a**), the only other signals in the spectrum being assignable to compounds (**2a**) and (**3a**). The intermediate showed two signals (each 1 H) at δ 6.00 and 6.28 which appeared at 220 MHz as broadened singlets, and two singlets (each 3 H) at δ 1.20 and 2.20. The positions of these signals were, to a small extent, dependent on the concentration of DBU: variations of up to 0.2 p.p.m. were noted, whereas the signals assigned to compounds (**2a**) and (**3a**) were unaffected by the concentration of the base.

The n.m.r. spectrum is inconsistent with an open-chain structure for the intermediate such as that shown in Scheme 2. In order to obtain further information about its structure, a deuteriated analogue (**6**) of the 6*H*-oxazine (**3a**) was prepared by acid-catalysed deuterium exchange of compound (**3a**). The product was shown by n.m.r. to be deuteriated only at the positions adjacent to the carbonyl group of the propanoyl substituent at C-6. The methylene group showed 87% incorporation of deuterium and the methyl group, 50% incorporation. The oxazine (**3a**) and its deuteriated analogue (**6**) were then allowed to react with DBU in tetrachloromethane, the concentrations of the two solutions and the reaction conditions being identical, and the reactions were followed by n.m.r.



(**4**) (**5**) a; OEt b; Ph (**6**)

The rate of reaction of compound (**6**) was appreciably slower (by a factor of about 3) than that of compound (**3a**). The intermediate which was generated from compound (**6**) showed evidence of deuterium incorporation only in the high field methyl signal and the acetylpyridine formed from this intermediate was deuteriated only in the acetyl group. The lack of coupling to the high field methyl group of the intermediate and its position (close to δ 1.2) suggest that it is attached to an enol or enolate anion. The u.v. and n.m.r. data are best accommodated by structure (**7**) for the species present in solution, the intermediate which is observed on t.l.c. being the corresponding protonated species. A possible reaction sequence is shown in Scheme 3.

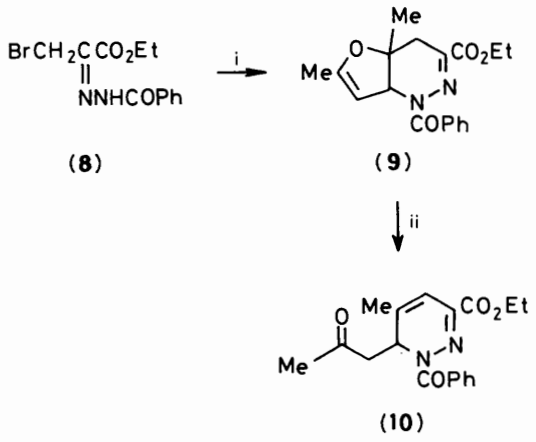


Scheme 3.

One attempt was made to carry out an analogous reaction starting from a furopyridazine. The benzoylhydrazone (**8**) of ethyl 3-bromo-2-oxopropanoate (ethyl bromopyruvate) was prepared and this compound was then dehydrobrominated by reaction with sodium carbonate in the presence of 2,5-dimethylfuran. The azoalkene cycloadduct, the furopyridazine (**9**), was isolated. This compound reacted with DBU at room temperature but the product was the pyridazine (**10**) (Scheme 4). Evidently the second base-catalysed elimination is more difficult than in the analogous oxazine (**3a**).

Experimental

M.p.s are uncorrected. I.r. spectra were recorded for KBr discs on a Perkin-Elmer 125 spectrophotometer. Unless indicated otherwise, n.m.r. spectra were recorded for solutions in $CDCl_3$



Scheme 4. *Reagents:* i, 2,5-dimethylfuran, Na_2CO_3; ii, DBU

on a Perkin-Elmer R34 spectrometer operating at 220 MHz. The 250 MHz spectra were recorded on a Bruker WM 250 machine. Mass spectra were recorded by electron impact at 70 eV, using a direct insertion probe. Medium pressure column chromatography[4] was carried out on S.O. t.l.c. silica gel (Whatman) as the stationary phase. Light petroleum refers to the fraction with b.p. 40—60 °C, and it was distilled before use.

4a,7a-*Dihydro*-4H-*furo*[2,3-e]-1,2-*oxazines*. *General Procedure*.—A solution of the appropriate halogeno oxime (20 mmol) and 2-methylfuran or 2,5-dimethylfuran (100 mmol) in dichloromethane (25 ml) was stirred with anhydrous sodium carbonate (11 g) for 24 h. The reaction mixture was filtered through Celite and the solvent was evaporated from the filtrate. The residue, when a solid, was recrystallised from the solvents indicated. The following compounds were prepared by this method:

(a) Ethyl 3-bromo-2-hydroxyiminopropanoate[2] and 2,5-dimethylfuran gave *ethyl* 4a,7a-*dihydro*-4a,6-*dimethyl*-4H-*furo*[2,3-e]-1,2-*oxazine*-3-*carboxylate* (**1a**) (82%), m.p. 85—87 °C (from ether–hexane) (Found: C, 58.4; H, 6.7; N, 6.4. $C_{11}H_{15}NO_4$ requires C, 58.7; H, 6.7; N, 6.2%); $\nu_{max.}$ 1 720 cm^{-1} (CO); δ 1.35 (3 H, t), 1.43 (3 H, 4a-Me), 1.77 (3 H, 6-Me), 2.23 and 2.91 (2 H, J_{AB} 15.4 Hz, 4-H), 4.25 (2 H, q), 4.66 (1 H, br, 7a-H), and 4.73 (1 H, br, 7-H); *m/z* 225 (M^+), 208 and 96 (base); *m** (225—208) 192.3.

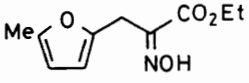
(b) 4-Chloro-3-hydroxyiminobutan-2-one[5] and 2,5-dimethylfuran gave 3-acetyl-4a,7a-dihydro-4a,6-dimethyl-4*H*-furo[2,3-*e*]-1,2-oxazine (**1b**) (63%), m.p. 33—35 °C (lit.,[2] 32—35 °C).

(c) 1-Chloro-2-hydroxyiminopentan-3-one[5] and 2,5-dimethylfuran gave 4a,7a-dihydro-4a,6-dimethyl-3-propionyl-4*H*-furo[2,3-*e*]-1,2-oxazine (**1c**) (60%) as an oil which rapidly deteriorated in air. Satisfactory analytical data were not obtained; δ 1.16 (3 H, t), 1.52 (3 H, 4a-Me), 1.76 (3 H, 6-Me), 2.13 and 3.08 (2 H, J_{AB} 14.4 Hz, 4-H), 2.92 (2 H, q), 4.76 (1 H, 7a-H), and 4.90 (1 H, br, 7-H), *m/z* 209 (M^+).

(d) 3-Chloro-2-hydroxyimino-1-phenylpropan-1-one[5] and 2,5-dimethylfuran gave 3-benzoyl-4a,7a-dihydro-4a,6-dimethyl-4*H*-furo[2,3-*e*]-1,2-oxazine (**1d**) (68%), m.p. 84—86 °C (from hexane). This compound proved to be heat- and acid-sensitive and it was not fully characterised (Found: N, 5.4. $C_{15}H_{15}NO_3$ requires N, 5.4%); $\nu_{max.}$ (liq. paraffin) 1 670 cm^{-1} (CO); δ 1.46 (3 H, 4a-Me), 1.74 (3 H, 6-Me), 2.24 and 2.96 (2 H, J_{AB} 14.4 Hz, 4-H), 4.60—4.80 (2 H, m, 7- and 7a-H), 7.18—7.54 (3 H, m), and 7.90—8.14 (2 H, m). On attempted purification by chromatography on silica the substance was converted into 3-*benzoyl*-5,6-*dihydro*-5-*methyl*-6-(2-*oxopropyl*)-4H,1,2-*oxazin*-5-*ol* (**5b**), an oil (Found: C, 65.7; H, 6.2; N, 5.2. $C_{15}H_{17}NO_4$ requires C, 65.4; H, 6.2; N, 5.1%); δ 1.29 (3 H), 2.25 (3 H), 2.55 and 2.78 (2 H, J_{AB} 18.0 Hz), 3.91 (2 H, d, *J* 6.0 Hz), 4.32 (1 H, t, *J* 6.0 Hz), 7.46—7.50 (3 H, m), and 8.00—8.10 (2 H, m).

(e) Phenacyl chloride oxime[6] and 2,5-dimethylfuran gave 4a,7a-dihydro-4a,6-dimethyl-3-phenyl-4*H*-furo[2,3-*e*]-1,2-oxazine (**1e**) (64%), m.p. 62—64 °C (from dichloromethane–hexane) (lit.,[1] 62—64 °C).

(f) Ethyl 3-bromo-2-hydroxyiminopropanoate and 2-methylfuran gave ethyl 4a,7-dihydro-6-methyl-4*H*-furo[2,3-*e*]-1,2-oxazine-3-carboxylate (**1f**) (50%) as an oil; $\nu_{max.}$ 1 720 cm^{-1} (CO); δ 1.30 (3 H, t), 1.74 (3 H, 6-Me), 2.57 (1 H, dd, *J* 15.3 and 4.3 Hz, 4-H), 2.91 (1 H, dd, *J* 15.3 and 6.0 Hz, 4-H), 4.28 (2 H, q), 4.80 (1 H, 7-H), 5.13 (2 H, br, 4a- and 7a-H); δ(C_6D_6) 1.05 (3 H, t), 1.51 (3 H, 6-Me), 2.35 (1 H, dd, 4-H), 2.92 (1 H, dd, 4-H), 4.10 (2 H, q), 4.70 (1 H, 7-H), 4.72—4.83 (1 H, m, 4a-H), and 4.98 (1 H, d, *J* 7.2 Hz, 7a-H). The compound was contaminated with *ca.* 5% of its rearrangement product, ethyl 2-hydroxyimimo-3-(5-methyl-2-furyl)propanoate (**11**). When a solution of the oxazine in dichloromethane was kept at 0 °C for 18 h, it isomerised



(11)

completely to the furan (**11**) (Found: *m/z* 211.0849. $C_{10}H_{13}NO_4$ requires *m/z* 211.0845); δ 1.28 (3 H, t), 2.18 (3 H), 3.92 (2 H), 4.28 (2 H, q), 5.81 (1 H, d, *J* 1.7 Hz, 3-H of furan), 5.92 (1 H, d, *J* 1.7 Hz, 4-H of furan), and 10.5 (1 H, OH).

Ethyl 6-*Acetyl*-4-*methylpyridine*-2-*carboxylate* (**2a**).—A solution of DBU (0.003 g, 0.2 mmol) in ether (5 ml) was added to the oxazine (**1a**) (0.42 g, 8.0 mmol) in dry ether (10 ml). The reaction mixture was stirred for 16 h at room temp. under N_2. Medium pressure chromatography gave (with ether–light petroleum, 3:2) the *pyridine* (**2a**) (0.35 g, 84%), m.p. 82—82.5 °C (from hexane) (Found: C, 63.7; H, 6.4; N, 6.75. $C_{11}H_{13}NO_3$ requires C, 63.75; H, 6.3; N, 6.8%); $\nu_{max.}$ 1 725 and 1 705 cm^{-1} (CO); δ 1.41 (3 H, t), 2.47 (3 H, 4-Me), 2.73 (3 H, COMe), 4.46 (2 H, q), 7.98 (1 H, 3-H), and 8.08 (1 H, 5-H).

2,6-*Diacetyl*-4-*methylpyridine* (**2b**).—The oxazine (**1b**) (0.81 g, 4.15 mmol) and DBU (0.68 g, 4.5 mmol) were dissolved in dichloromethane (40 ml) and the solution was kept at room temp. for 16 h. Medium pressure chromatography gave (with ether–light petroleum, 1:1) the *pyridine* (**2b**) (0.60 g, 83%), m.p. 100.5—102 °C (from hexane) (Found: C, 68.1; H, 6.4; N, 7.9. $C_{10}H_{11}NO_2$ requires C, 67.8; H, 6.3; N, 7.9%); $\nu_{max.}$ 1 705 cm^{-1} (CO); δ 2.47 (3 H, 4-Me), 2.75 (6 H, 2 × COMe), and 8.05 (2 H, 3- and 5-H).

2-*Acetyl*-4-*methyl*-6-*propionylpyridine* (**2c**).—A solution of the oxazine (**1c**) (1.0 g, 4.8 mmol) and DBU (0.72 g, 4.8 mmol) in dichloromethane (35 ml) was kept at room temp. for 24 h. Column chromatography (silica) gave (with dichloromethane) the *pyridine* (**2c**) (0.39 g, 42%), m.p. 75—77 °C (from dichloromethane) (Found: C, 68.85; H, 6.9; N, 7.4. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.3%); $\nu_{max.}$ 1 700 cm^{-1} (CO); δ 1.24 (3 H, t, *J* 7.2 Hz), 2.48 (3 H, 4-Me), 2.76 (3 H, COMe), 3.29 (2 H, q. *J* 7.2 Hz), and 8.04 (2 H, 3- and 5-H).

2-*Acetyl*-6-*benzoyl*-4-*methylpyridine* (**2d**).—A solution of the oxazine (**1d**) (1.50 g, 5.8 mmol) and DBU (0.78 g, 5.8 mmol) in dichloromethane (60 ml) was kept at room temp. for 24 h. Column chromatography (silica) gave (with dichloromethane) the *pyridine* (**2d**) (0.96 g, 69%), m.p. 75—77 °C (from hexane)

(Found: C, 75.3; H, 5.6; N, 5.95. $C_{15}H_{13}NO_2$ requires C, 75.3; H, 5.5; N, 5.9%); $\nu_{max.}$ 1 700 and 1 660 cm^{-1} (CO); δ 2.51 (3 H, 4-Me), 2.64 (3 H, COMe), 7.47—7.59 (3 H, m), and 8.03—8.21 (4 H, m).

2-Acetyl-4-methyl-6-phenylpyridine (**2e**).—A solution of the oxazine (**1e**) (0.46 g, 2.0 mmol) in benzene (25 ml) was heated under reflux for 5 days, during which a black tarry precipitate appeared. The solvent was removed from the reaction mixture and the residue was subjected to medium pressure chromatography. This gave (with ether–light petroleum, 1:1) the *pyridine* (**2e**) (0.11 g, 26%), m.p. 40—41 °C (from pentane) (Found: C, 79.25; H, 6.1; N, 6.6. $C_{14}H_{13}NO$ requires C, 79.6; H, 6.2; N, 6.6%); $\nu_{max.}$ 1 705 cm^{-1} (CO); δ (250 MHz) 2.45 (3 H, 4-Me), 2.80 (3 H, COMe), 7.43—7.49 (3 H, m), 7.72 (1 H, br, 3-H), 7.79 (1 H,, br 5-H), and 8.06—8.10 (2 H, m). On decoupling the 4-Me signal, those at 7.72 and 7.79 sharpened to doublets ($J_{3,5}$ 1.1 Hz).

Ethyl 6-Acetylpyridine-2-carboxylate (**2f**).—The crude oxazine (**1f**) (0.42 g, 2.0 mmol) and DBU (0.30 g, 2.0 mmol) were dissolved in dichloromethane (15 ml) and the solution was kept at room temp. for 24 h. Column chromatography (silica) gave (with ether–light petroleum, 3:2) the *pyridine* (**1f**) (0.22 g, 58%), m.p. 49.5—50 °C after sublimation (Found: C, 62.0; H, 5.8; N, 7.05. $C_{10}H_{11}NO_3$ requires C, 62.2; H, 5.7; N, 7.25%); $\nu_{max.}$ 1 735 and 1 702 cm^{-1} (CO); δ 1.40 (3 H, t), 2.78 (3 H), 4.46 (2 H, q), 7.92—8.00 (1 H, m, 4-H), and 8.16—8.30 (2 H, m, 3- and 5-H).

Acid-catalysed Ring Opening of Oxazine (**1a**).—(a) *Reaction with* HCl. Conc. HCl (1 ml) was added to a solution of the oxazine (**1a**) (0.23 g, 1.0 mmol) in dichloromethane (10 ml) and the mixture was stirred vigorously for 2 h. The organic phase was then separated, washed with water (3 × 25 ml), and dried to give an oil (0.23 g, 96%) to which was assigned the structure ethyl 5,6-dihydro-5-hydroxy-5-methyl-6-(2-oxopropyl)-4*H*-1,2-oxazine-3-carboxylate (**5a**) (Found: *m/z* 226.1079 (M^+ − OH). $C_{11}H_{17}NO_5$ − OH requires *m/z* 226.1079); $\nu_{max.}$ 3 460 (OH) and 1 715 cm^{-1} (CO); δ 1.23 (3 H, 5-Me), 1.31 (3 H, t), 2.23 (3 H, CH_2COMe), 2.45 (1 H, d, *J* 18.0 Hz, 4-H), 2.60 (1 H, d, *J* 18.0 Hz, 4-H), 2.84 (2 H, d, *J* 5.1 Hz, CH_2COMe), 3.30 (1 H, br, OH), 4.20 (1 H, t, *J* 5.1 Hz, 6-H), and 4.25 (2 H, q). The substance decomposed when an attempt was made to form a 2,4-dinitrophenylhydrazone and it was not further characterised.

(b) *Reaction with toluene-p-sulphonic acid.* The oxazine (**1a**) (0.45 g, 2.0 mmol) and benzene (40 ml) containing toluene-*p*-sulphonic acid (40 mg) were heated under a Dean and Stark apparatus for 2 h. The solution was then cooled, washed with aqueous sodium hydrogen carbonate and water, and dried. Medium pressure chromatography gave (with ethyl acetate–light petroleum, 4:1) an oil (4.2 g, 93%) to which was assigned the structure ethyl 5-methyl-6-(2-oxopropyl)-6*H*-1,2-oxazine-3-carboxylate (**3a**); $\nu_{max.}$ 1 715 (CO) and 1 650 cm^{-1} (C=C); δ 1.39 (3 H, t), 1.95 (3 H, 5-Me), 2.25 (3 H, CH_2COMe), 2.50 (1 H, dd, *J* 16.6 and 3.95 Hz, CH_2COMe), 3.00 (1 H, dd, *J* 16.6 and 8.35 Hz, CH_2COMe), 4.40 (2 H, q), 5.18 (1 H, dd, *J* 8.35 and 3.95 Hz, 6-H), and 6.30 (1 H, 4-H). The substance failed to give a crystalline 2,4-dinitrophenylhydrazone and it was not further characterised. Under the same conditions as (b), the oxazinol (**5a**) was converted into the oxazine (**3a**) (96%).

Reaction of the Oxazine (**3a**) *with* DBU.—The oxazine (**3a**) (0.42 g, 2.0 mmol) was dissolved in dichloromethane (20 ml) and DBU (0.30 g, 2.0 mmol) was added. After 16 h the solvent was removed. Medium pressure chromatography of the residue gave (with ether–light petroleum, 3:2) ethyl 6-acetyl-4-methylpyridine-2-carboxylate (**2a**) (0.36 g, 88%), which was identical with the specimen isolated from the reaction for the furo-oxazine (**1a**) with DBU.

The reaction of compound (**3a**) was monitored by t.l.c. (ether–light petroleum, 3:2) which showed the formation of the pyridine (R_F 0.06) and also an intense yellow spot (R_F 0.5) which disappeared as the reaction proceeded. The formation and disappearance of the yellow intermediate was also monitored by u.v. At intervals during the course of the reaction, 0.5 ml aliquots were removed and were diluted with dichloromethane (10 ml). The maximum of the starting oxazine (**3a**) ($\lambda_{max.}$ 296 nm) was replaced by that of the yellow intermediate ($\lambda_{max.}$ 408 nm), then by that of the pyridine (**2a**) ($\lambda_{max.}$ 273 nm).

5-Methyl-6-(2-oxopropyl)-3-phenyl-6H-1,2-oxazine (**3e**).—(a) A solution of the oxazine (**1e**) (0.46 g, 2.0 mmol) and DBU (0.30 g, 2.0 mmol) in dichloromethane (20 ml) was heated under reflux for 3 days. Column chromatography (silica) gave (with ether–light petroleum, 2:3) the oxazine (**3e**) (0.33 g, 71%) as a yellow oil, b.p. 70 °C/0.1 mmHg; $\nu_{max.}$ 1 715 (CO) and 1 660 cm^{-1} (C=C); δ 1.83 (3 H, 5-Me); 2.10 (3 H, CH_2COMe), 2.43 (1 H, dd, *J* 16.7 and 3.8 Hz, CH_2COMe), 2.89 (1 H, dd, *J* 16.7 and 8.4 Hz, CH_2COMe), 4.95 (1 H, dd, *J* 8.4 and 3.8 Hz, 6-H), 6.11 (1 H, 4-H), 7.30—7.40 (3 H, m), and 7.61—7.72 (2 H, m); *semicarbazone*, m.p. 185—186 °C (from ethanol) (Found: C, 63.1; H, 6.3; N, 19.8. $C_{15}H_{18}N_4O_2$ requires C, 62.9; H, 6.3; N, 19.6%).

(b) A solution of the oxazine (**1e**) (1.15 g, 5.0 mmol) and DBU (0.75 g, 5.0 mmol) in dichloromethane (25 ml) was heated under reflux for 3 days. Medium pressure chromatography gave (with ether–light petroleum, 2:3) 2-acetyl-4-methyl-6-phenylpyridine (**2e**) (0.15 g, 14%) and the oxazine (**3**) (0.72 g, 63%).

Ethyl 5-Methyl-6-([1′,1′,3′,3′,3′-$^2H_5$]-2′-oxopropyl)-6H,1,2-oxazine-3-carboxylate (**6**).—Phosphorus pentachloride (1.0 g, 5 mmol) was added to D_2O (2 ml) at 0 °C. A portion of the resulting solution (1 ml) was added to the oxazine (**3a**) (0.15 g, 0.6 mmol) in dry tetrahydrofuran (2 ml). The mixture was stirred under N_2 for 16 h. Hexane (2 ml) was added and the organic and aqueous layers were separated. The aqueous layer was washed with ether (2 × 5 ml) and the combined organic solutions were dried and evaporated to leave the oxazine (**6**) as an oil. N.m.r. showed 50% incorporation of deuterium at C-1′ and 87% incorporation at C-3′.

Conversion of the 6H-*Oxazine* (**3a**) *into the Pyridine* (**2a**): *Monitoring of the Reaction by N.m.r.*—(a) A solution containing equimolar quantities of the oxazine (**3a**) and DBU in tetrachloromethane containing tetramethylsilane as an internal reference was kept at 25 °C in the probe of the n.m.r. spectrometer, and the course of the reaction was monitored by recording the spectrum at 5—10 min intervals. Signals due to the intermediate, which is assigned structure (**7**), were observed at δ 1.35 (3 H, Me of enolate), 1.42 (3 H, t), 2.14 (3 H, 4-Me), 4.35 (2 H, q), 6.08 (1 H, 5-H), and 6.28 (1 H, 3-H). These signals were replaced by those of the pyridine (**2a**) as the reaction proceeded.

(b) A similar experiment in which 0.1 mol equiv. of DBU was used gave spectra with signals at δ 1.20 (3 H), 1.35 (3 H, t), 2.20 (3 H), 4.35 (2 H, q), 6.00 (1 H), and 6.28 (1 H).

(c) A solution of the oxazine (**3a**) (0.090 g, 0.4 mmol) and DBU (0.060 g, 0.4 mmol) in tetrachloromethane (2 ml) was monitored by n.m.r. as before. Proportions of starting material, intermediate, and product at different times were estimated from integrals of the methyl group signals. After 8 min the solution contained a mixture of the oxazine (**3a**) (8%), the intermediate (71%), and the pyridine (**2a**) (21%). After 30 min the solution contained the intermediate (14%) and the pyridine (86%). A solution of the deuteriated oxazine (**6**) containing the same concentrations of oxazine and DBU was monitored in the

same manner. After 7 min 75% of the starting oxazine was present; after 85 min the mixture contained the intermediate (14%) and the pyridine (86%).

Ethyl 2-Benzoylhydrazono-3-bromopropanoate (**8**).—Ethyl 3-bromo-2-oxopropanoate (4.51 g, 23 mmol) was added slowly to a stirred suspension of benzoylhydrazine (3.15 g, 23 mmol) in ether (30 ml). After 1 h the solvent was evaporated off and the residue was subjected to column chromatography (silica). Elution with dichloromethane gave a single major component. Crystallisation gave the *benzoylhydrazone* (**8**) (4.12 g, 57%), m.p. 96—100 °C (from ether–light petroleum) (Found: C, 45.7; H, 4.0; N, 9.1. $C_{12}H_{13}BrN_2O_3$ requires C, 46.0; H, 4.2; N, 8.95%); δ 1.42 (3 H, t), 4.40 (2 H), 4.40 (2 H, q), 7.48—7.60 (3 H, m), and 7.90—7.94 (2 H, m).

Ethyl 1-Benzoyl-4a,6-dimethyl-1,4,4a,7a-tetrahydrofuro[3,2-c]*pyridazine-3-carboxylate* (**9**).—Anhydrous sodium carbonate (3.5 g) was added to a solution of the hydrazone (**8**) (2.05 g, 6.55 mmol), and 2,5-dimethylfuran (0.63 g, 6.55 mmol) in dichloromethane (50 ml). The mixture was stirred for 18 h and the solid was then filtered off through Celite. The filtrate was evaporated to dryness. Column chromatography (silica) of the residue (with dichloromethane) gave the *pyridazine* (**9**) (1.34 g, 62%), m.p. 105—106 °C (from hexane) (Found: C, 65.8; H, 6.1; N, 8.7. $C_{18}H_{20}N_2O_4$ requires C, 65.8; H, 6.1; N, 8.5%); $\nu_{max.}$ 1 740 and 1 660 cm^{-1} (CO); δ 1.26 (3 H, t), 1.57 (3 J, 4a-Me), 1.70 (3 H, 6-Me), 2.21 and 3.44 (2 H, J_{AB} 16.0 Hz, 4-H), 4.25 (2 H, m), 5.02 (2 H, br, 7-and 7a-H), 7.28—7.48 (3 H, m), and 7.72—7.78 (2 H, m).

Ethyl 1-Benzoyl-1,6-dihydro-5-methyl-6-(2-oxopropyl)pyridazine-3-carboxylate (**10**).—A solution of the furopyridazine (**9**) (1.10 g, 3.35 mmol) and DBU (0.51 g, 3.35 mmol) in dichloromethane (30 ml) was kept at room temp. for 48 h. Column chromatography (silica) gave (with dichloromethane–ethyl acetate, 1:19) the *pyridazine* (**10**) (0.62 g, 58%), m.p. 108 °C (from ether–hexane) (Found: C, 65.6; H, 6.1; N, 8.7. $C_{18}H_{20}N_2O_4$ requires C, 65.8; H, 6.1; N, 8.5%); $\nu_{max.}$ 1 700 and 1 650 cm^{-1} (CO); δ 1.29 (3 H, t), 2.02 (3 H, 5-Me), 2.22 (3 H, $CH_2CO\mathit{Me}$), 2.73 (2 H, d, *J* 5.0 Hz, $C\mathit{H}_2COMe$), 4.28 (2 H, m), 5.61 (1 H, t, *J* 5.0 Hz, 6-H), 6.40 (1 H, 4-H), 7.38—7.48 (3 H, m), and 7.79—7.83 (2 H, m).

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