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# The Action of Isoxazol-5-ones on Enamines

By **A. M. Knowles** and **Alexander Lawson,*** Department of Chemistry, Royal Free Hospital School of Medicine, 8 Hunter Street, London W.C.1

The reaction of enamines with isoxazol-5-ones unsubstituted at the 4-position takes place in a manner similar to that with oxazol-5-ones to give, in this case, the 4-alkenylisoxazol-5-olate salts of the appropriate amine. These salts are readily converted into the 4-alkylideneisoxazolones with hydrogen chloride. By using a mixture of ketone and base rather than the enamine, the same salts are obtained by a different mechanism.

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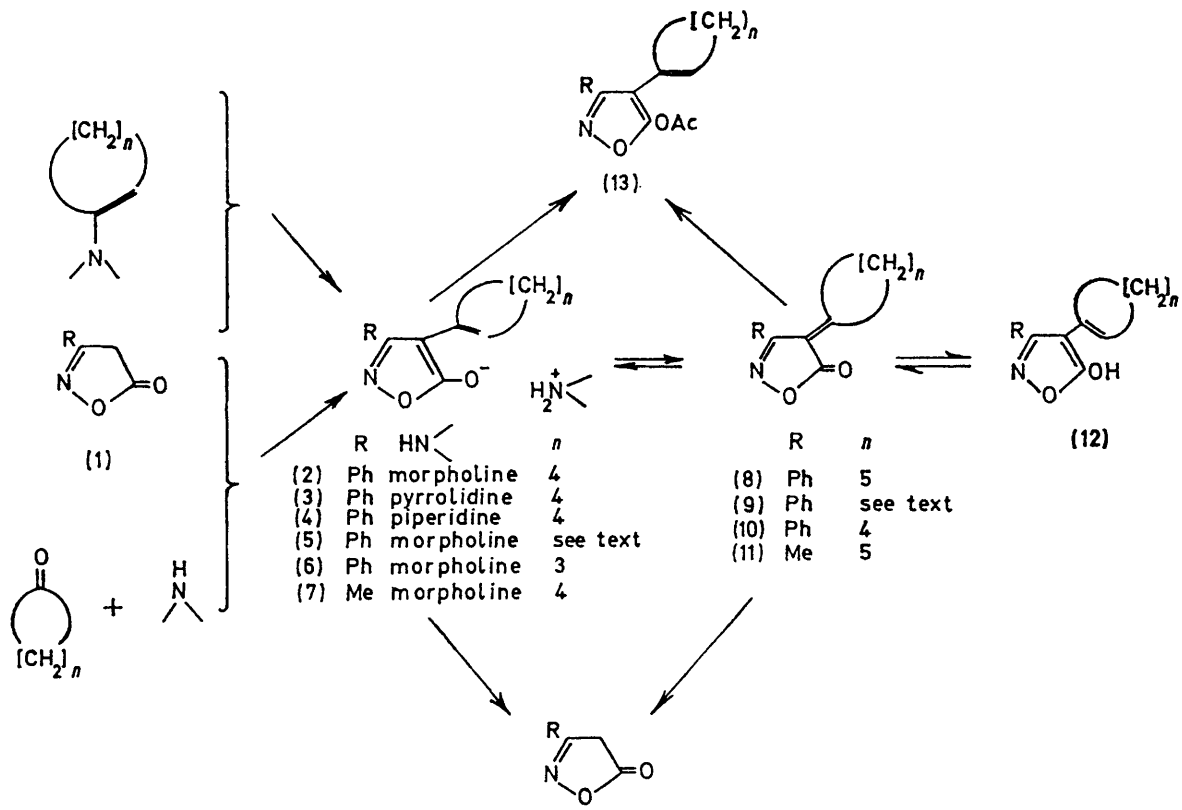
ISOXAZOL-5-ONES (1) (R = alkyl or aryl) unsubstituted in the 4-position are known to be highly reactive by virtue of their active methylene group. Thus they condense readily with aldehydes to give 4-alkylidene and -arylidene derivatives.[1-3] Condensation with ketones is reported [4] as being less ready and only a few examples are recorded. Schiff and Betti [5] described the isolation of 4-isopropylidene-3-methylisoxazol-5-one from the action of acetone on the oxime of ethyl acetoacetate, and Meyer [6] condensed 3-phenylisoxazol-5-one in boiling ethanol with benzil in the presence of piperidine to obtain 4-(benzoylbenzylidene)-3-phenylisoxazol-5-one. In subsequently reported condensations with ketones,[7] catalytic amounts of the base were used; sodium acetate–acetic acid has also been employed.[8] Ring closure has been effected with phosphoric acid [9] in reactions with ketoximes and β-keto-esters.

We have previously reported [10] on the action of enamines with 2-phenyloxazol-5(4*H*)-one to give the corresponding alkylidenehippuramides. This work has now been extended to include isoxazol-5-ones, which have been found to react rapidly at room temperature with enamines to give in high yield the 3-aryl- or -alkyl-4-




SCHEME 1

[1] A. Meyer, *Compt. rend.*, 1912, **155**, 841; *Ann. chim. Phys.*, 1914, **1**, 252.
[2] A. Wahl and C. Silberzweig, *Bull. Soc. chim. France*, 1913, **13**, 236.
[3] A. Wahl and J. Rolland, *Ann. Chim.* (*France*), 1928, **10**, 5.
[4] A. Quilico, in 'The Chemistry of Heterocyclic Compounds: Five- and Six-membered Compounds with Nitrogen and Oxygen,' ed. A. Weissberger, Interscience, New York–London, 1962, p. 128.
[5] R. Schiff and M. Betti, *Ber.*, 1897, **30**, 1337; *Gazzetta*, 1897, **27**, II, 212.
[6] A. Meyer, *Bull. Soc. chim. France*, 1913, **13**, 1000.
[7] L. G. S. Brooker and F. L. White, U.S.P. 2,882,159/1959.
[8] L. G. S. Brooker and D. W. Heseltine, U.S.P. 2,856,404/1958.
[9] J. T. Braunholtz and P. F. H. Freeman, B.P. 1,074,803/1967.
[10] A. M. Knowles, A. Lawson, G. V. Boyd, and R. A. Newberry, *J. Chem. Soc.* (*C*), 1971, 598.

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alk-1-enylisoxazol-5-olate salts of the basic portion of the enamine. Thus 3-phenylisoxazol-5-one (1; R = Ph) with 1-morpholinocyclohexene gave morpholinium 4-(cyclohex-1-enyl)-3-phenylisoxazol-5-olate (2). This reaction is a general one and has been carried out with a variety of enamines (Scheme 1).

Evidence for the structure of these salts (2)—(7) was provided by their reaction with anhydrous hydrogen chloride to give the 4-alkylideneisoxazol-5-ones (8)—(11) and by their reaction with hot aqueous hydrochloric acid to give the original isoxazolone (1), the ketone, and the base. Their i.r. spectra showed absorptions between 3000 and 2500 $cm^{-1}$ due to $\overset{+}{N}H_2$ [11] and their n.m.r. spectra showed resonances between $\tau$ 4·2 and 4·3 due to the vinylic proton and between −0·2 and 0·4 due to the $>\overset{+}{N}H_2$ protons. These resonances disappeared when the salts were converted into the 4-alkylideneisoxazol-5-ones. The structures of the cycloalkylideneisoxazolones (8)—(11) were confirmed by their reaction with aqueous hydrochloric acid to give the original isoxazolone (1) and the ketone, and by their n.m.r. spectra, no resonance due to unsubstituted methylene protons being observed.

The ease with which the 4-cycloalkylideneisoxazolone (8) is converted back into the parent salt (2) suggests that the proton on the carbon atom α to the double bond in the 4-substituent is labile, making easy the rearrangement to the enol form (12; R = Ph, $n = 4$). Further confirmation of this is provided by the ease with which the acetyl derivative (13; R = Ph, $n = 4$) is formed. Likewise, the parent salt is readily converted into (13). The acidity of the α-proton has been suggested [12] by the observed solubility of 4-isopropylideneisoxazol-5-one in alkali.

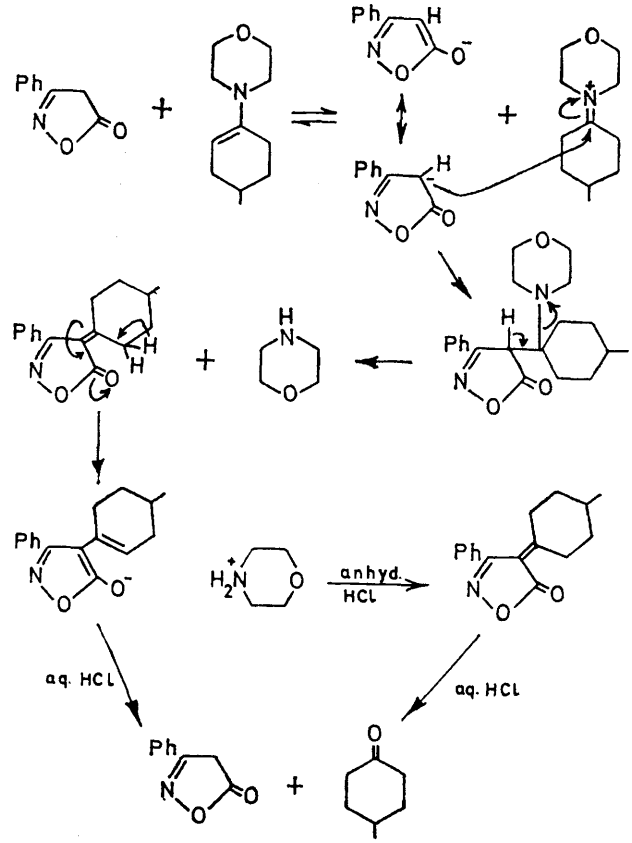
When ketones containing a hydrogen atom α to the keto-group (in contrast to benzil) are employed under the conditions used by Meyer,[6] the isoxazololate salts are again obtained.

There seems little doubt that there are two different mechanisms operating, depending on whether the ketone–base mixture or the enamine is used. In the former case the most probable mechanism is a base-catalysed condensation of the ketone with the active methylene group of the isoxazolone followed by salt formation; the latter case proceeds *via* an iminium ion intermediate as shown in Scheme 2.

Evidence for the existence of two distinct mechanisms was provided by measuring the rate of formation of the product in the two cases by u.v. spectroscopy. The u.v. spectrum of morpholinium 4-(cyclohex-1-enyl)-3-phenylisoxazol-5-olate (2) in chloroform showed two peaks: $\lambda_{max.}$ 261 (ε 8400) and 287 nm (ε 5530). The concentration of this product in the reaction mixture was estimated by measuring the absorption at 300 nm (ε 5020) in order to minimise interference from the absorption due to unchanged 3-phenylisoxazol-5-one [$\lambda_{max.}$ ($CHCl_3$) 263·5 nm (ε 13,930)] (see Figure).

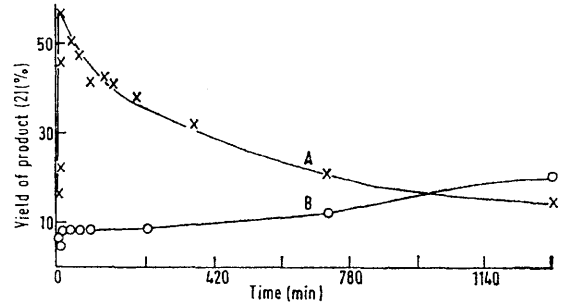
[11] R. A. Heacock and L. Marion, *Canad. J. Chem.*, 1956, **34**, 1782.

In another experiment the reaction mixture was worked-up after a set time and the yield determined by




SCHEME 2

weighing the product. With 3-phenylisoxazol-5-one and 1-morpholinocyclohexene the yield was 86% after 1 min, compared with 28% after 1 h when a mixture of ketone and base was used.




Formation of morpholinium 4-(cyclohex-1-enyl)-3-phenylisoxazol-5-olate from 3-phenylisoxazol-5-one; measurement of optical density at 300 nm: A, from 1-morpholinocyclohexene; B, from cyclohexanone and morpholine

Evidence that the enamine reaction proceeded *via* an iminium ion intermediate (Scheme 2) was provided by the hydrolysis of 4-(4-methylcyclohexylidene)-3-phenylisoxazol-5-one with aqueous hydrochloric acid to give the

[12] N. V. Kromov and A. E. Porai-Koshits, *J. Gen. Chem.* (*U.S.S.R.*), 1947, **17**, 1816 (*Chem. Abs.*, 1948, **42**, 4169).

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original 4-methylcyclohexanone, so indicating that nucleophilic attack by the anion of the isoxazolone took place at the α-carbon atom of the iminium ion of the enamine.[10]

## EXPERIMENTAL

Light petroleum refers to the fraction boiling in the range 40—60° unless otherwise stated. I.r. spectra were determined for potassium bromide discs; n.m.r. spectra were measured at 60 MHz. All solvents were dried: dichloromethane and ethanol with molecular sieve pellets (Grade 3A) and ether with sodium metal.

*Morpholinium* 4-(*Cyclohex*-1-*enyl*)-3-*phenylisoxazol*-5-*olate* (2).—(*a*) A solution of 3-phenylisoxazol-5-one [13] (4·0 g) in dichloromethane (50 ml) was stirred at room temp. with 1-morpholinocyclohexene [14] (4·1 g). After 1 min the solvent was removed and the resulting oil triturated with ether. The product, recrystallised from ethanol–light petroleum, was the *isoxazololate salt* (2) (7·0 g, 86%), m.p. 137—140°, $\nu_{max.}$ 2940, 2870, 2730, 2670, 2490, and 1620 $cm^{-1}$, τ ($CDCl_3$) −0·20 (s, $\overset{+}{N}H_2$), 2·30—2·70 (m, Ph), 4·31 (m, vinylic H), 6·10—6·40 and 6·80—7·10 (m, 8H from morpholinium), and 7·50—8·50 (m, 8H from cyclohexenyl) (Found: C, 69·6; H, 7·1; N, 8·4. $C_{19}H_{24}N_2O_3$ requires C, 69·5; H, 7·3; N, 8·5%).

(*b*) A solution of 3-phenylisoxazol-5-one (4·8 g) in dichloromethane (50 ml) was stirred with cyclohexanone (2·9 g) and morpholine (2·6 g) at room temp. After 1 h the solvent was removed and the resulting oil triturated with ether. Recrystallisation from ethanol–light petroleum gave the isoxazololate salt (2) (2·7 g, 28%).

(*c*) 3-Phenylisoxazol-5-one (5·0 g) in ethanol (50 ml) was refluxed for 30 min with cyclohexanone (3·0 g) and morpholine (2·7 g). The solvent was removed and the resulting oil triturated with ether. Recrystallisation from ethanol–light petroleum gave the isoxazololate salt (2) (9·0 g, 89%).

(*d*) A solution of 4-cyclohexylidene-3-phenylisoxazol-5-one (8) (2·0 g) in dichloromethane (25 ml) was treated with morpholine (0·8 g) at room temp. After 1 h the solvent was removed and the resulting oil triturated with ether. Recrystallisation from ethanol–light petroleum gave the isoxazololate salt (2) (2·5 g, 92%).

4-*Cyclohexylidene*-3-*phenylisoxazol*-5-*one* (8).—Into a solution of the morpholinium salt (2) (3·3 g) in dichloromethane (30 ml) and ether (20 ml) anhydrous hydrogen chloride was bubbled for 10 min. The morpholine hydrochloride was filtered off and the solvent removed. The resulting oil was dissolved in ether (20 ml), light petroleum was added, and the solution was cooled in solid carbon dioxide–acetone. The *product* (1·5 g, 73%) had m.p. 68—69°, $\nu_{max.}$ 1730 and 1625 $cm^{-1}$, τ ($CDCl_3$) 2·50—2·60 (m, Ph) and 6·60—7·65 (m, 10H from cyclohexylidene) (Found: C, 74·6; H, 6·1; N, 5·6. $C_{15}H_{15}NO_2$ requires C, 74·8; H, 6·2; N, 5·8%).

5-*Acetoxy*-4-(*cyclohex*-1-*enyl*)-3-*phenylisoxazole* (13).—(*a*) A solution of the morpholinium salt (2) (1·64 g) in pyridine (5 ml) was treated with acetic anhydride (5·1 g). After 1 h at room temp. the solution was poured into ice–water containing 10N-hydrochloric acid (5 ml). The oil rapidly crystallised to give the *isoxazole* (1·0 g, 70%), m.p. 120—121° (from ethanol), $\nu_{max.}$ 1754, 1720, 1700, and 1610 $cm^{-1}$, τ ($CDCl_3$) 2·57—2·8 (m, Ph), 9·96 (m, vinylic H), 7·68 (s, Me), and 7·8—8·65 (m, 8H from cyclohexenyl) (Found: C, 72·1; H, 5·5; N, 5·0. $C_{17}H_{17}NO_3$ requires C, 72·5; H, 5·3; N, 5·0%).

(*b*) Likewise a solution of the alkylideneisoxazolone (8) (0·5 g) in pyridine (2·0 ml), treated with acetic anhydride (2·0 g), gave the isoxazole (13) (0·3 g, 51%).

*Hydrolysis of the Isoxazololate Salt* (2).—To a solution of the morpholinium salt (2) (2·0 g) in hot water (30 ml) was added 3N-hydrochloric acid (5 ml). After warming for 30 min the insoluble tarry material was removed and the cooled filtrate gave 3-phenylisoxazol-5-one (0·9 g, 92%). Cyclohexanone, identified as its 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 155—156°, was present in the tarry material and in the filtrate. Hydrolysis of the alkylideneisoxazolone (8) (2·0 g) likewise gave 3-phenylisoxazol-5-one (0·9 g, 92%) and cyclohexanone.

*Pyrrolidinium* 4-(*cyclohex*-1-*enyl*)-3-*phenylisoxazol*-5-*olate* (3) (5·5 g, 44%), m.p. 142—144° (from ethanol), $\nu_{max.}$ 2920, 2840, 2770, 2610, 2480, and 1612 $cm^{-1}$, τ ($CDCl_3$) 0·2 (s, $\overset{+}{N}H_2$), 2·2—2·7 (m, Ph), 4·32 (m, vinylic H), 6·6—7·0 and 8·1—8·3 (m, 8H from pyrrolidine), and 7·8—8·6 (m, 8H from cyclohexenyl) (Found: C, 73·0; H, 7·8; N, 9·1. $C_{19}H_{24}N_2O_2$ requires C, 73·0; H, 7·7; N, 9·0%), was similarly prepared from 3-phenylisoxazol-5-one (6·5 g) and 1-pyrrolidinocyclohexene [14] (6·0 g) in dichloromethane (50 ml) at room temp. for 15 h.

Reaction of the 3-phenylisoxazol-5-one (3·0 g) with 1-piperidinocyclohexene [14] (3·0 g) in dichloromethane (30 ml) at room temp. for 1 h gave *piperidinium* 4-(*cyclohex*-1-*enyl*)-3-*phenylisoxazol*-5-*olate* (4) (5·6 g, 94·5%), m.p. 164—167° (from ethanol), $\nu_{max.}$ 2930, 2850, 2740, 2650, 2540, and 1610 $cm^{-1}$, τ ($CDCl_3$) 0·23 (s, $\overset{+}{N}H_2$), 2·2—2·7 (m, Ph), 4·27 (m, vinylic H), 6·8—7·1 and 7·7—8·0 (m, 10H from piperidine), and 8·0—8·6 (m, 8H from cyclohexenyl) (Found: C, 73·4; H, 7·6; N, 8·7. $C_{20}H_{26}N_2O_2$ requires C, 73·6; H, 8·0; N, 8·6%).

*Morpholinium* 4-(4-*methylcyclohex*-1-*enyl*)-3-*phenylisoxazol*-5-*olate* (5) (9·6 g, 92%), m.p. 136—138° (from ethanol), $\nu_{max.}$ 2950, 2870, 2720, 2660, 2500, and 1625 $cm^{-1}$, τ ($CDCl_3$) −0·4 (s, $\overset{+}{N}H_2$), 2·3—2·7 (m, Ph), 4·28 (m, vinylic H), 6·0—6·4 and 6·7—7·1 (m, 8H from morpholine), 7·6—8·6 (m, 7H from cyclohexenyl), and 9·0 (m, Me) (Found: C, 70·1; H, 7·3; N, 7·9. $C_{20}H_{26}N_2O_3$ requires C, 70·2; H, 7·6; N, 8·2%), was obtained from 4-methyl-1-morpholinocyclohexene [14] (5·5 g) and 3-phenylisoxazol-5-one (4·9 g) in dichloromethane (50 ml) at room temp. for 1 h, and in 44% yield from 4-methylcyclohexanone (2·3 g), morpholine (1·8 g), and 3-phenylisoxazol-5-one (3·2 g) in refluxing ethanol (30 ml) for 30 min.

4-(4-*Methylcyclohexylidene*)-3-*phenylisoxazol*-5-*one* (9) (3·0 g, 50%), m.p. 80—83° (from ether–light petroleum), $\nu_{max.}$ 1750 and 1620 $cm^{-1}$ (Found: C, 74·2; H, 6·6; N, 5·6. $C_{16}H_{17}NO_2$ requires C, 74·2; H, 6·6; N, 5·6%), was obtained by treating the isoxazol-5-olate (5) (8·0 g) in dichloromethane (50 ml) and ether (20 ml) with anhydrous hydrogen chloride as in the previous case. Hydrolysis of the morpholinate (5) with 3N-hydrochloric acid as before gave 3-phenylisoxazol-5-one and 4-methylcyclohexanone, identified as its 2,4-dinitrophenylhydrazone, m.p. and mixed m.p. 129—130°. Likewise, hydrolysis of the alkylideneisoxazolone (9) gave 3-phenylisoxazol-5-one and 4-methylcyclohexanone.

[13] A. Hantzsch, *Ber.*, 1891, **24**, 495.
[14] G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, 1963, **85**, 207.

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*Morpholinium* 4-(*cyclopent*-1-*enyl*)-3-*phenylisoxazol*-5-*olate* (6) (12·5 g, 94%), m.p. 119—121° (from ethanol), $\nu_{max.}$ 2940, 2840, 2720, 2650, 2480, and 1615 cm$^{-1}$, $\tau$ ($CDCl_3$) 0·4 (s, $\overset{+}{N}H_2$), 2·5—2·7 (m, Ph), 4·25 (m, vinylic H), 6·1—6·4 and 6·8—7·1 (m, 8H from morpholine), and 7·5—8·5 (m, 6H from cyclopentenyl) (Found: C, 68·6; H, 6·8; N, 8·9. $C_{18}H_{22}N_2O_3$ requires C, 68·8; H, 7·0; N, 8·9%), was prepared from 1-morpholinocyclopentene [14] (6·5 g) and 3-phenylisoxazol-5-one (6·9 g) in dichloromethane (50 ml) at room temp. for 1 h.

4-Cyclopentylidene-3-phenylisoxazol-5-one (10) (1·2 g, 66·5%), m.p. 157—158° (from ether–light petroleum) (lit.,[7] 157—158°), $\nu_{max.}$ 1750 and 1645 cm$^{-1}$ (Found: C, 73·7; H, 5·8; N, 5·7. $C_{14}H_{13}NO_2$ requires C, 74·0; H, 5·7; N, 6·2%), was obtained from the isoxazol-5-olate (6) (2·5 g) in dichloromethane (20 ml) and ether (10 ml) saturated with anhydrous hydrogen chloride.

*Morpholinium* 4-(*cyclohex*-1-*enyl*)-3-*methylisoxazol*-5-*olate* (7) (3·0 g, 33%), m.p. 106—108° (from ethanol–light petroleum), $\nu_{max.}$ 2930, 2860, 2730, 2670, 2500, and 1610 cm$^{-1}$ (Found: C, 63·0; H, 8·1; N, 10·3. $C_{14}H_{22}N_2O_3$ requires C, 63·2; H, 8·3; N, 10·5%), was prepared from the oxime of acetoacetic ester [15] (49 g) and 1-morpholinocyclohexene (5·6 g) in dichloromethane (30 ml) at room temp. for 15 h.

4-*Cyclohexylidene*-3-*methylisoxazol*-5-*one* (11) (0·3 g, 30%), m.p. 56—58°, $\nu_{max.}$ 1745 and 1625 cm$^{-1}$ (Found: C, 67·1; H, 7·0; N, 7·6. $C_{10}H_{13}NO_2$ requires C, 67·0; H, 7·3; N, 7·8%), was isolated from the morpholinium salt (7) (1·5 g) in dichloromethane (20 ml) and ether (10 ml) saturated with anhydrous hydrogen chloride.

*Spectroscopic Experiment.*—(*a*) 3-Phenylisoxazol-5-one (0·805 g) and 1-morpholinocyclohexene (0·835 g) were dissolved in chloroform (100 ml) at room temp. (initial concentration of reactants 0·5 mol l$^{-1}$). After intervals of 2, 5, 15, 40, 60, 90, 120, 150, 180, 210, 360, and 1320 min, 1 ml portions of the solution were diluted with chloroform to 0·00125 mol l$^{-1}$, and their spectra were determined between 350 and 240 nm.

(*b*) Likewise, 3-phenylisoxazol-5-one (0·805 g), cyclohexanone (0·490 g), and morpholine (0·435 g) were dissolved in chloroform (100 ml) at room temp. (initial concentration of reactants 0·5 mol l$^{-1}$). As before, 1 ml portions of the solution were diluted with chloroform to 0·00125 mol l$^{-1}$, and their spectra determined.

[15] R. Schiff, *Ber.*, 1895, **28**, 2731.

[1/2402 *Received*, 15*th December*, 1971]