On the Base Catalysed Ring Opening of 3-Unsubstituted Isoxazoles. Derivatives of 4- and 5-Phenylisoxazole

By **Angela De Munno,* Vincenzo Bertini,** and **Francesco Lucchesini,** Istituto di Chimica Organica della Facoltà di Scienze M.F.N., Via Risorgimento 35, 56100 Pisa, Italy and Dipartimento di Chimica dell'Università della Calabria, 87030 Arcavacata di Rende, Cosenza, Italy

The kinetics of the base-induced decomposition of 4- and 5-phenylisoxazole and their *p*-bromo- and *p*-nitrophenyl derivatives, and 3-deuterio-5-phenylisoxazole, to the corresponding cyanoenolate anions have been studied. The mechanism of reaction has been established as a one-stage concerted abstraction of the proton in position 3 and scission of the N–O bond. 4-Phenylisoxazole, previously synthesized by laborious methods, has been prepared by a simpler procedure.

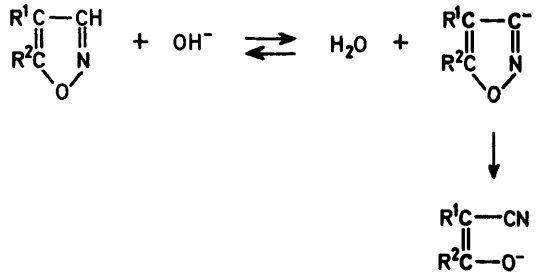
PREVIOUS kinetic studies [1-3] of the irreversible transformation of 3-unsubstituted isoxazoles into cyanoenolate anions catalysed by base provided information on the mechanism of the reaction. The order of reaction is one in both base and heterocyclic substrate. The u.v. spectra of reaction mixtures showed sharp isosbestic points indicating a transformation of reactants into products without formation of an intermediate. The substituent effect was consistent with negatively charged transition state, *i.e.* electron-withdrawing groups accelerated the reaction. A primary deuterium isotope effect

[1] V. Bertini, A. De Munno, and P. Pino, *Chimica e Industria*, 1966, **48**, 491.

[2] V. Bertini, A. De Munno, and P. Pino, *Gazzetta*, 1967, **97**, 185.

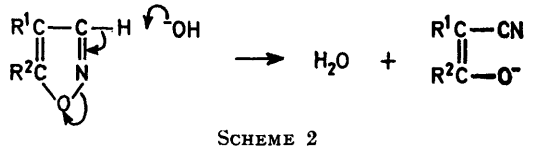
[3] V. Bertini, A. De Munno, and P. Pino, *Gazzetta*, 1967, **97**, 173.

was detected. The results were interpreted by assuming that the nucleophile attacks the hydrogen atom in position 3 and that the scission of the carbon–hydrogen bond is rate determining. However two mechanisms, *E*1cB and *E*2,[4] were consistent with the findings. In an *E*1cB mechanism abstraction of a proton yields a



SCHEME 1

cyclic carbanion (acid–base equilibrium) which in a second step isomerizes, isomerization being much faster than reprotonation (Scheme 1). In an *E*2 mechanism abstraction of the proton and cleavage of the ring are concerted (Scheme 2). In any case incipient bond



SCHEME 2

formation, in the transition state, between hydroxide ion and the hydrogen of the isoxazole ring generates a partial negative charge on the organic substrate which could be placed on C-3 or on oxygen depending on the mechanism. We report here a comparison of the relative effectiveness of 4- and 5-substituents in stabilizing the transition state which provides evidence of which of the two mechanisms is operating.

EXPERIMENTAL

M.p.s were determined on a Kofler apparatus and are uncorrected. I.r. spectra were recorded on a Perkin-Elmer 225 spectrophotometer. N.m.r. spectra were determined with a JEOL 100 MHz instrument using Me_4Si as internal standard. U.v. spectra and kinetic measurements were carried out with a Hilger–Watts Uvispek H 700 spectrophotometer fitted with a water thermostatted cell block (±0.1 °C). Isosbestic points were recorded on a Unicam SP 800 u.v. spectrophotometer.

Kinetic Measurements.—Rates were followed at the absorption maximum of the cyanoenolate anion; for 5-*p*-nitrophenylisoxazole measures were carried out also at the absorption maximum of the isoxazole giving the same results. All the substances studied, both isoxazoles and cyanoenolates, were found to obey Beer's law at the wavelengths employed. For a kinetic run, the required volume, to obtain a final concentration of 0.05—0.15N, of freshly prepared carbonate-free potassium hydroxide solution was introduced into a 25 ml stoppered volumetric flask, CO_2-free distilled water was added, the solution was thermostatted at the desired temperature for *ca.* 1 h, 1 ml of a methanol solution of isoxazole reagent of suitable concentration was added, and the mixture was made up to the mark with prethermostatted water, shaken, and rapidly transferred to the cell of the spectrophotometer. The decomposition of each isoxazole was examined for at least three different concentrations of potassium hydroxide. After preliminary experiments performed by adding KCl to the reacting solution, which showed that concentrations of the salt lower than 0.3N had no appreciable effect on the rate of the reaction as expected for a process in which an ion interacts with a neutral molecule, no precautions were taken to maintain constant ionic strength. The absorbance was taken at least up to 60% conversion, then irregularly up to seven half-lives or more. In each case, save for 4-phenyl-, 4-*p*-bromophenyl-, and 4-*p*-nitrophenyl-isoxazole, the absorbance reached a constant 'infinity' value. For the three 4-arylisoxazoles mentioned, owing to the instability of the corresponding cyanoenolates, the absorbance *versus* time plot showed a maximum. Taking the interpolated value of $A_{max.}$ as the lower limit of the absorbance at infinite time, the value of A_∞ for each compound was deduced, using the molar extinction coefficient, from the u.v. spectrum of the anhydrous potassium cyanoenolate salt measured in the same solvent at 15—20 °C at which cyanoenolate decomposition is slow enough to be disregarded. In each case the calculated A_∞ value was slightly higher than the interpolated $A_{max.}$. Pseudo-first-order rate constants were determined by a least-squares treatment of a plot of log $(A_\infty - A_t)$ *versus* time, which always afforded good ranging of the experimental points. Second-order rate constants (Table 1) were determined by dividing pseudo-first-order constants by the molar concentration of hydroxide ion. Each mixture prepared for kinetic measurements was also examined by an automatic u.v. spectrophotometer by recording the spectrum from time to time up to *ca.* 60% conversion: in each case a sharp isosbestic point was observed.

4-Phenylisoxazole.—From 3-NN-dimethylamino-2-phenylprop-2-enal. (a) *In water.* A mixture of the aldehyde (2.216 g, 12.65 mmol),[5a] hydroxylamine hydrochloride (1.184 g, 17.04 mmol), water (10 ml), and concentratred hydrochloric acid (0.3 ml) was refluxed for 1 h, then cooled in an ice-bath. Brownish crystals of 4-phenylisoxazole (1.751 g, 12.06 mmol) were collected and dried overnight on P_2O_5. The product upon decolourization with carbon and crystallization from n-pentane yielded crystals, m.p. 46—47 °C (lit.,[6] 46 °C).

(b) *In acetic acid.* A mixture of the above aldehyde (2.602 g, 14.85 mmol), hydroxylamine hydrochloride (1.10 g, 15.83 mmol), glacial acetic acid (12.5 ml), and concentrated sulphuric acid (0.2 ml) was refluxed for 2 h, diluted with five times its volume of water, and cooled in an ice-bath. The product (1.58 g, 10.88 mmol) was filtered and treated as described under method (a).

From sodium salt of phenylmalonaldehyde. A solution of the salt (1.536 g, 9.03 mmol) [5b] in water (10 ml) was added during 45 min to a solution of hydroxylamine hydrochloride (0.912 g, 13.12 mmol) in water (5 ml) and 2N-hydrochloric acid (4 ml) and heated at 85 °C on a water-bath. After addition, heating was continued for 1 h with stirring, then the mixture was allowed to crystallize by cooling. The product (1.271 g, 8.76 mmol) was filtered and treated as described above.

[4] F. G. Bordwell, *Accounts Chem. Res.*, 1972, **5**, 374; D. J. McLennan, *Quart. Rev.*, 1967, **21**, 490.

[5] (*a*) Z. Arnold, *Coll. Czech. Chem. Comm.*, 1961, **26**, 3051; (*b*) Z. Arnold and F. Sorm, *Chem. listy*, 1957, **51**, 1082.

[6] V. Bertini, A. De Munno, V. Dell'Amico, and P. Pino, *Gazzetta*, 1967, **97**, 1604.

From phenylmalonaldehyde. The sodium salt of phenylmalonaldehyde (6.48 g, 38.09 mmol) [5b] and ethanol (30 ml) were heated at the reflux temperature and a 3.32N solution of hydrogen chloride in ethanol (11.5 ml) was added. After precipitation of sodium chloride, hydroxylamine hydrochloride (2.80 g, 40.29 mmol) was added and refluxed for 2 h. The reddish solution, added after cooling with a double volume of water, yielded an oil that soon solidified Crystals of the product (4.08 g, 28.11 mmol) were collected and treated as described above.

Bromination of 4-Phenylisoxazole.—4-Phenylisoxazole (0.167 g, 1.15 mmol) was treated at room temperature with bromine (0.17 ml, 3.32 mmol) and left at room temperature for 2.5 h with occasional stirring. The mixture, after removal of the excess of bromine at the water-pump, was refluxed with n-hexane until evolution of hydrogen bromide ceased. The solution, after removal of a part of the solvent, yielded 4-p-*bromophenylisoxazole* (0.253 g, 1.13 mmol), which was further purified by sublimation, m.p. 113 °C, $\nu_{max.}$ (KBr) 1 880, 1 760, 1 580, 1 482, and 810 (*p*-substituted phenyl) cm^{-1} (isoxazole ring), $\delta(CCl_4)$ 7.40 (4 H, q, ArH), 8.40 (1 H, s, isoxazole 3-H), and 8.60 (1 H, s, isoxazole 5-H); $\lambda_{max.}$ [96 : 4 (v/v) water–methanol] 247 nm (log ε 4.25) (Found: C, 48.05; H, 2.55; N, 6.1. C_9H_6BrNO requires C, 48.25; H, 2.7; N, 6.25%).

3-*Deuterio-5-phenylisoxazole*.—A sample of 4.84N-deuteriosulphuric acid (4.75 ml) in heavy water and a 3.65N solution of sodium fulminate (6 ml) in heavy water were simultaneously added over 40 min with vigorous stirring to a solution of phenylacetylene (2.10 g, 20.56 mmol) in anhydrous tetrahydrofuran (3 ml) in such a manner to keep the mixture slightly acid. The mixture, treated with water (*ca.* 100 ml), yielded by distillation, in different fractions, unchanged phenylacetylene and 3-deuterio-5-phenylisoxazole; a tarry residue remained. The recovery of the distilled products was carried out by extraction with n-pentane, drying (Na_2SO_4), removal of the solvent, and distillation at reduced pressure, giving 3-deuterio-5-phenylisoxazole (0.120 g, 0.82 mmol). N.m.r. analysis showed an isotopic purity >91%.

Potassium Cyanoenolate Salts.—An anhydrous ether or methanol solution of a phenylisoxazole derivative was treated under nitrogen with the stoicheiometric amount of potassium methoxide in methanol–ether solution. More ether was added to induce precipitation. The solid potassium cyanoenolate salt after filtering and washing with anhydrous ether was obtained in nearly quantitative yield.

4-Phenylisoxazole yielded crystals of the potassium salt of cyano(phenyl)acetaldehyde, $\lambda_{max.}$ [0.1N-KOH in 96 : 4 (v/v) water–methanol] 254 (log ε 3.92) and 285 nm (4.17). A sample of the salt upon acidification yielded cyano(phenyl)-acetaldehyde.[7] A sample of the salt, heated at 50 °C for 5 h with aqueous 1N-KOH produced ammonia and formic and phenylacetic acid.

4-*p*-Nitrophenylisoxazole [6] yielded red, air stable crystals of the *potassium salt* of *cyano*-(p-*nitrophenyl*)*acetaldehyde*, which were recrystallized from methanol–ether, $\lambda_{max.}$ [0.1N-KOH in 96 : 4 (v/v) water–methanol] 231 (log ε 4.00), 256 (3.95), and 411 nm (4.21) (Found: C, 47.55; H, 2.5; N, 12.05. $C_9H_5KN_2O_3$ requires C, 47.35; H, 2.2; N, 12.25%).

5-*p*-Nitrophenylisoxazole [8] yielded yellow-green crystals of the *potassium salt* of p-*nitrobenzoylacetonitrile* which were recrystallized from anhydrous methanol–ether, $\lambda_{max.}$ [0.1N-KOH in 96 : 4 (v/v) water–methanol] 258 (log ε 4.19) and 358 nm (3.81) (Found: C, 47.55; H, 2.25; N, 12.35. $C_9H_5KN_2O_3$ requires C, 47.35; H, 2.2; N, 12.25%). The yellow-green crystals, by exposure to the air or by crystallization from not anhydrous solvent, yielded red crystals of the hydrated *salt*,[9] stable by prolonged heating at 120 °C (Found C, 41.05; H, 3.65; N, 10.45. $C_9H_5KN_2O_3,2H_2O$ requires C, 40.9; H, 3.45; N, 10.6%). The u.v. spectrum was superimposable on that of the yellow-green product with the assumption of hydration.

4-*p*-Bromophenylisoxazole yielded crystals of the potassium salt of *p*-bromophenyl(cyano)acetaldehyde, $\lambda_{max.}$ [0.1N-KOH in 96 : 4 (v/v) water–methanol] 258 (shoulder) (log ε 3.97) and 292 nm (4.28). A sample of the salt was transformed into crystals of *p*-bromophenyl(cyano)acetaldehyde [10] by careful addition to an aqueous solution of 1N-hydrochloric acid. The aldehyde, after crystallization from ethanol–water, had m.p. 166 °C (lit.,[10] 164—166 °C). A sample (0.147 g, 0.56 mmol) of the salt heated at 50 °C for 5 h with aqueous 1N-KOH solution yielded *p*-bromophenylacetic acid (0.080 g, 0.37 mmol),[11] ammonia, and formic acid.

RESULTS AND DISCUSSION

General Remarks on the Preparation of Compounds.—As the kinetics of decomposition of isoxazole derivatives were taken by measuring from time to time the absorbance of the cyanoenolate produced by the reaction, both isoxazoles and the corresponding potassium cyanoenolate salts were prepared and their u.v. spectra determined.

The synthesis of 4-phenylisoxazole (1), previously carried out by rather laborious procedures,[7,12] was re-examined with the result of making this compound easily obtainable from phenylacetic acid and *NN*-dimethylformamide. These two reagents, according to Arnold,[5] were transformed into 3-*NN*-dimethylamino-2-phenylprop-2-enal (2), or the sodium salt of phenylmalondialdehyde (3), or phenylmalondialdehyde (4) (Scheme 3). Product (1) was obtained independently from each of (2)—(4) by cyclization with hydroxylamine hydrochloride, in 95, 97, and 74% yield respectively. The preparation from compound (2) in aqueous hydrochloric acid solution, which affords virtually pure (1) in 62% overall yield from phenylacetic acid is recommended for preparative purposes.

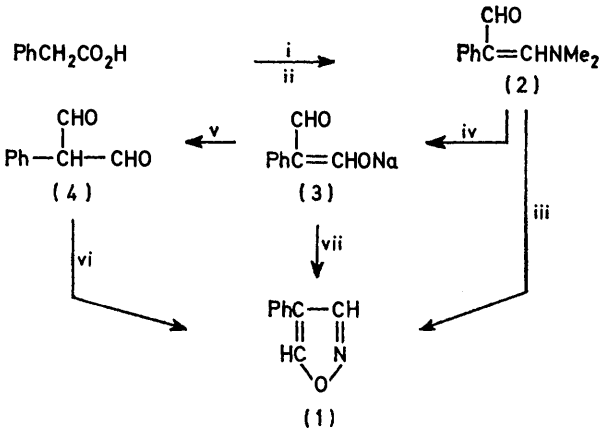
The synthesis of 4-*p*-bromophenylisoxazole was carried out as part of a study of the bromination of compound (1). The method used is desirable in that no trace of the *ortho*-isomer was found, and very pure *para*-isomer was obtained in high yield.

The alkaline decomposition of the 4-arylisoxazoles examined, by analogy with that found for other isoxazoles,[1] yielded cyanoenolates which, under the conditions of the reaction, underwent further transformation (Scheme 4). These reactions are slow enough, relative

[7] P. Pino and R. Ercoli, *Rend. Ist. Lomb. Sci. e Lett., Classe Sci.*, 1955, **88**, 378.
[8] N. K. Kochetkov and E. D. Khomutova, *Zhur. obshchei Khim.*, 1958, **28**, 359.
[9] S. Cusmano and G. C. Vaccaro, *Gazzetta*, 1948, **78**, 768.
[10] D. J. Brown and T. C. Lee, *J. Chem. Soc.* (*C*), 1970, 214.
[11] L. R. Cerecedo and C. P. Sherwin, *J. Biol. Chem.*, 1924, **62**, 217.
[12] H. Rupe and E. Knup, *Helv. Chim. Acta*, 1927, **10**, 299.

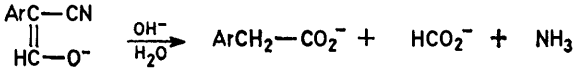
to the decomposition of the isoxazole derivatives, to be disregarded.

Kinetics of the Base-induced Decomposition of 3-Unsubstituted Isoxazoles.—Table 1 summarizes the rate constants for the reaction of seven isoxazole derivatives



SCHEME 3 Reagents: i, $POCl_3$–$HCONMe_2$; ii, K_2CO_3–H_2O; iii, a, NH_2OH,HCl–H_2O, b, NH_2OH,HCl–AcOH–H_2SO_4; iv, NaOH–H_2O–EtOH; v, HCl–Et_2O; vi, NH_2OH,HCl–EtOH; vii, NH_2OH,HCl–H_2O

with potassium hydroxide. The primary deuterium isotope effect for 5-phenylisoxazole ($k_H/k_D = 3.1$) is explicable in terms of an incomplete proton transfer from the isoxazole ring to the hydroxide ion. Comparing the rate constants of either 4- or 5-phenylisoxazole derivatives with those of the corresponding nitro- and bromo-compounds electron-withdrawing substituents



SCHEME 4

accelerate the reaction rate in agreement with a negative charge developing on the proton donor in the transition state as already deduced from the isotope effect. Moreover, from comparison of analogous derivatives, substituents in the 4-position are more effective in stabilizing the transition state than those in the 5-position. 4-

TABLE 1

Rate constants at 25 °C for the reaction of 3-unsubstituted isoxazoles with hydroxide ion in 96 : 4 (v/v) water–methanol

Isoxazole	k/l mol^{-1} s^{-1}
4-Phenyl-	1.06×10^{-2}
5-Phenyl-	5.63×10^{-4} *
3-Deuterio-5-phenyl-	1.79×10^{-4}
4-*p*-Bromophenyl-	1.81×10^{-2}
5-*p*-Bromophenyl-	7.39×10^{-4} *
4-*p*-Nitrophenyl-	8.20×10^{-2}
5-*p*-Nitrophenyl-	1.74×10^{-3}

* See ref. 2.

Phenylisoxazole reacts 19 times faster than 5-phenylisoxazole; the presence of a bromine atom in the *para*-position of the phenyl ring raises this ratio to 24, and the presence of a nitro-group further raises it to 47. The greater effectiveness of 4- rather than 5-substituents in stabilizing the transition state is further shown by the Hammett plot; the (4-substituted phenyl)isoxazoles give $\rho + 1.15$, while the 5-derivatives have $\rho + 0.51$.[2]

The activation parameters (Table 2) allow the observed effects on the reaction rate to be attributed to the electronic effects of the substituents rather than to other external factors, such as solvation. The energies of activation of 5-substituted isoxazoles are higher than those of the corresponding 4-derivatives, and the differences in barriers between analogously substituted isoxazoles increase on going from the phenyl to the *p*-bromophenyl to the *p*-nitrophenyl derivatives. On the other hand any control by the activation entropy of the reaction rate can be excluded; on going from 5- to 4-substituted isoxazoles the activation entropy decreases while at the same time the reaction rate increases. Differences in activation entropy between 5- and 4-substituted compounds increase on going from the

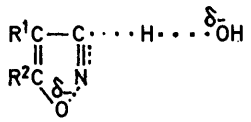
TABLE 2

Energy of activation and entropy of activation at 25 °C for the reaction of 3-unsubstituted isoxazoles with hydroxide ion in 96 : 4 (v/v) water–methanol

Isoxazole	E/kcal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}
4-Phenyl-	19.6 ± 0.2	−3.6
5-Phenyl- [2]	22.1 ± 0.1	−1.3
4-*p*-Bromophenyl-	19.0 ± 0.2	−4.6
5-*p*-Bromophenyl- [2]	22.0 ± 0.1	−0.9
4-*p*-Nitrophenyl-	17.0 ± 0.2	−8.5
5-*p*-Nitrophenyl-	20.5 ± 0.2	−4.3

phenyl to the *p*-bromophenyl to the *p*-nitrophenyl derivatives which may be accounted for by higher charge delocalization (which has an effect on the solvation) of the transition state of 4- with respect to 5-substituted isoxazoles. Nevertheless any deductions on this matter are hardly reliable owing to the fact that comparisons are being made among transition states with different degree of scission of the C–H bond and with different fraction of charge on the proton donor.

The results clearly do not agree with a transition state involving a negative charge localized on the 3-position and stabilized by inductive effects. They accord with a transition state with the character of a cyanoenol anion, *i.e.* with a partial negative charge on the oxygen of the isoxazole ring. A 4-aryl substituent, which is in alternate position to the oxygen atom, is favoured in stabilizing the transition state by conjugation. A transition state with the indicated charge delocalization, and with the 3-proton in an intermediate position between the donor and the nucleophile [structure (5)], is in accord with the concerted one-stage reaction shown in Scheme 2. This is in agreement with observations for the base-catalysed decomposition of benzisoxazoles.[13]



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[13] M. L. Casey, D. S. Kemp, K. G. Paul, and D. D. Cox, *J. Org. Chem.*, 1973, **38**, 2294.