779. *Heterocyclic Rearrangements. Part I. The Mechanism of a Ring Expansion*

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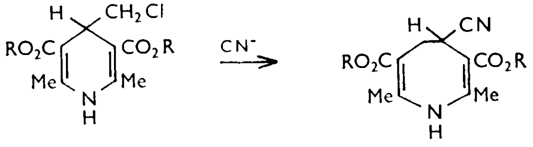
The kinetics of the ring expansion of the dihydropyridine (I) to the dihydroazepine (II) have been investigated. A mechanism is suggested in which the rate-determining step is the formation of the dihydropyridine anion (III) in a second-order general base-catalysed reaction. The subsequent fast steps involve rearrangement of the anion to the azepine (IV) followed by 1,4-addition of hydrogen cyanide.

We have recently described[1] the reaction of the dihydropyridine (I)[*] with cyanide ion which yields the dihydroazepine (II).[*] Whilst it is tempting to regard this rearrangement as a 1,2-shift proceeding *via* a carbonium ion, this mechanism seemed unlikely in view of the observation[1] that only basic nucleophiles bring about rearrangement to a dihydroazepine. A kinetic study of the reaction was therefore undertaken.



(I) (II)

Preliminary experiments were carried out to determine the stoicheiometry of the reaction and to establish whether or not it was an equilibrium. It was shown that 1 mole of cyanide ion was consumed per mole of reactant (I). Isolation of the product (II) in quantitative yield in buffered or unbuffered solution indicated that the reaction went to completion. The cyanodihydroazepine (II) was unaffected by excess of potassium chloride, confirming that the reaction was irreversible.

The kinetic experiments were carried out in 90% ethanol and the reaction was followed spectrophotometrically. Since both the starting material (I) and the product (II) absorb in essentially the same region, the instantaneous concentrations of the former during the kinetic run were obtained from a calibration curve.

Initial experiments using the chloro-compound (I) and potassium cyanide showed that the reaction was of first order with respect to each of the reactants. Whilst the rate constants were in good agreement in duplicate runs, they fluctuated widely over a series of experiments. In spite of careful control and precautions to exclude carbon dioxide rigorously from the reaction medium, consistent results could not be obtained.

The kinetics in buffered solution were next investigated. Potentiometric titration of 90% ethanolic potassium cyanide with 90% ethanolic hydrogen chloride showed that the " pH " remained constant to within 1 unit of " pH " (measured by a pH meter) over a range of 5—80% neutralisation, showing that buffering was effective within these limits. In the kinetic runs the concentration of the chloro-compound (I) was kept constant and the cyanide ion and acid concentrations were varied, the latter over a range of 7—30% neutralisation (Table 1). Another set of runs was carried out with a different concentration of the chloro-compound (I) (Table 2).

Since it can be assumed that the reaction

$$\mathrm{KCN + HCl \longrightarrow HCN + KCl} \qquad (1)$$

goes to completion, the initial effective cyanide ion concentration was taken as the excess of cyanide ion remaining after allowing for reaction with the acid.

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[*] R = Et unless otherwise stated.

[1] P. J. Brignell, E. Bullock, U. Eisner, B. Gregory, A. W. Johnson, and H. Williams, *J.*, **1963**, **4819**.

TABLE 1

$[\mathrm{RNH}] = 0{\cdot}0199 \pm 0{\cdot}0001\,\mathrm{M}$; $[\mathrm{CN}^-] = 0{\cdot}0596 \pm 0{\cdot}0003\,\mathrm{M}$

No.	1A	1B	2A	2B	3A	3B	4A	4B	5A	5B
1/[HCl]	250·6	250·6	214·6	215·5	183·5	182·8	150·8	151·3	83·1	83·1
10^3k	0·563	0·538	0·524	0·527	0·441	0·449	0·390	0·408	0·257	0·270

In this and the following Tables, A and B refer to duplicate experiments. A plot of these results, as in the Figure, gave a straight line with intercept $0{\cdot}105 \times 10^{-3}$ and slope $1{\cdot}83 \times 10^{-6}$.

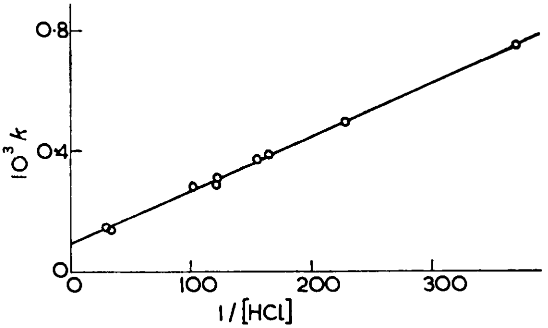
TABLE 2

$[\mathrm{RNH}] = 0{\cdot}0265 \pm 0{\cdot}0001\,\mathrm{M}$

No.	6	7	8	9	10	11	12	13	14
$[\mathrm{CN}^-]$	0·0365	0·0746	0·0741	0·1100	0·1096	0·0959	0·0960	0·0692	0·0778
1/[HCl]	373·1	229·9	160·5	126·3	124·1	104·3	104·1	37·7	36·0
10^3k	0·745	0·494	0·372	0·311	0·295	0·286	0·281	0·157	0·157

These results are shown graphically in the Figure, with intercept $0{\cdot}100 \times 10^{-3}$ and slope $1{\cdot}75 \times 10^{-6}$.

It was found that the second-order rate constants varied inversely as the initial acid concentration (see the Figure).



The rate of the reaction is therefore given by the expression

$$\text{Rate} = C[\mathrm{RNH}][\mathrm{CN}^-] + M[\mathrm{RNH}][\mathrm{CN}^-]/[\mathrm{HCl}] \qquad (2)$$

where [RNH] is the concentration of the chloro-compound (I) and C and M the intercept and slope of the straight line in the Figure.

Substituting [HCN] for [HCl] (from equation 1) and writing [HCN] as

$$[\mathrm{HCN}] = K_{\mathrm{h}}[\mathrm{CN}^-]/[\mathrm{OH}^-] \qquad (3)$$

where K_{h} is the hydrolysis constant of potassium cyanide, we may rewrite equation (2) as

$$\text{Rate} = C[\mathrm{RNH}][\mathrm{CN}^-] + (M/K_{\mathrm{h}})[\mathrm{RNH}][\mathrm{OH}^-]. \qquad (4)$$

This is the equation for general-base catalysis,[2] indicating catalysis by cyanide and by hydroxyl ions. The equilibrium constant for the reaction

$$\mathrm{OEt}^- + \mathrm{H_2O} \rightleftharpoons \mathrm{EtOH} + \mathrm{OH}^-$$

in 87·4% aqueous ethanol [3] is ~1 and the basicities of hydroxide and ethoxide ion are of the same order of magnitude,[4] hence presumably both the above species are involved in the catalysis. However, for the sake of simplicity the catalyst will be referred to as hydroxyl ion.

The rate constant for the reaction with hydroxyl ion can be calculated to be 0·130 l.

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[2] *E.g.*, E. S. Gould, " Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Wilson, New York, 1959, p. 189.

[3] E. F. Caldin and G. Long, *J.*, 1954, 3737.

[4] M. L. Bender and W. A. Glasson, *J. Amer. Chem. Soc.*, 1959, **81**, 1950.

mole^{-1} sec.$^{-1}$ by using the values of $M = 1{\cdot}81 \times 10^{-6}$ (mean of the slopes derived from plotting the results in Tables 1 and 2 as in the Figure) and $K_h = 1{\cdot}40 \times 10^{-5}$ (from the equation $K_h = K_w/K_a$, literature data [5,6] being used for K_w and K_a, respectively). This figure is necessarily approximate since the value for K_h applies only to aqueous solutions. Niether K_h nor K_w has been reported for cyanide in 90% ethanol. However, data are available [7] for the K_a value of acetic acid in various water–ethanol mixtures as well as the relevant autoprotolysis constants K_s. By using these figures the hydrolysis constant for acetate in 90% ethanol can be calculated. This differs from the K_h in aqueous solution by less than 40%. If it is assumed that replacement of water by 90% ethanol has a similar small effect on the hydrolysis constant of cyanide, the use of the above approximate value of K_h is justified.

In order to confirm the validity of the above rate equation, the kinetics of the reaction of the chloro-compound (I) with hydroxyl ion were investigated. Although this reaction yielded complex mixtures so that it was not possible to use a calibration curve as in the reaction with cyanide ion, the instantaneous concentration of the chloro-compound (I) during kinetic runs was determined by means of infinity readings. The order of the reaction was confirmed by the differential method of analysis.[8] The observed second-order rate constant (mean of five experiments, see Table 3) was 0·151 l. mole^{-1} sec.$^{-1}$, in excellent agreement with the calculated value. This is no doubt somewhat fortuitous in view of the approximate value of K_h and the different ionic strengths in the two series of experiments. (The ionic strengths differ by a factor of 40—100 since the runs had to be carried out at different concentrations in order to obtain measurable rates. However, since the reaction does not involve creation or destruction of charge, variations in ionic strength would be expected to have a small effect.)

TABLE 3

$[\text{RNH}] = 5{\cdot}946\ (\pm 0{\cdot}120) \times 10^{-4}\text{M}$

No.	15A	15B	16	17	18	
$10^4[\text{OH}^-]$	39·0	39·0	31·22	23·41	15·61	Mean
k	0·149	0·145	0·159	0·149	0·152	0·151

The observed rate equation suggests that the rate-determining step in the reaction is the removal of the NH proton by base, *i.e.*,

$$\text{RNH} \xrightarrow[\text{slow}]{\text{base}} \text{RN}^- \xrightarrow{\text{fast}} \text{products}$$

Independent evidence for this hypothesis is derived from the fact that the *N*-methyl derivative of (I) [9] is recovered unchanged in 67% yield on prolonged treatment with excess of aqueous alcoholic alkali under conditions where rearrangement of the chloro-compound (I) is very rapid. Reaction of the *N*-methyl derivative of (I) with cyanide ion is slow and gives a product which is neither a dihydropyridine nor a dihydroazepine, the structure of which will be reported in a forthcoming publication. Also the chloro-compound (I) is recovered unchanged on treatment with the powerfully nucleophilic, non-basic, iodide ion in alcohol or dry acetone; however, in boiling acetonitrile, under conditions favouring S_N2 reactions, the chlorine in (I) is replaced by iodine without rearrangement. The product is a typical dihydropyridine, the structure of which is confirmed by elemental analysis and spectral characteristics (see Experimental section).

[5] S. Glasstone, " A Text-book of Physical Chemistry," Van Nostrand, 1946, p. 992.

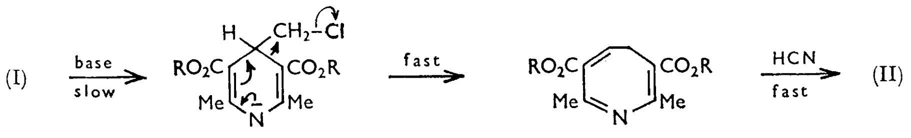
[6] " Handbook of Chemistry and Physics," Chemical Rubber Publishing Co., 41st edn., p. 1744.

[7] E. Grunwald and B. J. Berkowitz, *J. Amer. Chem. Soc.*, 1951, **73**, 4939; B. Gutbezahl and E. Grunwald, *ibid.*, 1953, **75**, 565.

[8] S. W. Benson, " The Foundations of Chemical Kinetics," McGraw-Hill, 1960, p. 83.

[9] E. Benary, *Ber.*, 1911, **44**, 489.

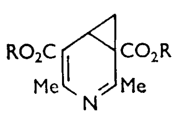
The subsequent stages of the rearrangement are postulated as follows:



(III) (IV)

Rapid rearrangement of the anion (III) to the azepine (IV) followed by rapid 1,4-addition of hydrogen cyanide would yield the dihydroazepine (II). Alternatively, the azacaradiene (V) could be the reaction intermediate.

In order to test this hypothesis we attempted to prepare the intermediates (IV) or (V) from the anion (III). Treatment of the chloro-compound (I) with methylsulphinyl carbanion [10] in dimethyl sulphoxide produced the typical yellow colour of a dihydropyridine anion ($\lambda_{max.}$ 425 mμ; the visible spectra of related dihydropyridine anions are recorded in a forthcoming publication). The colour slowly faded but only intractable mixtures were produced on working up. Similar results were obtained when the anion (III) was generated from sodium hydride in dimethoxyethane.



(V)

The preparation of the azepine (IV; R = Me) has recently been reported.[11] A sample of (IV; R = Me), kindly supplied by Professor A. W. Johnson, on treatment with potassium cyanide in aqueous ethanol was rapidly converted into the dihydroazepine (II; R = Me) in 85% yield. Under conditions simulating the kinetic runs [concentration of (IV; R = Me), 0·0456M; fourfold excess of potassium cyanide] reaction was essentially complete in 3 minutes; under comparable conditions rearrangement of the chloro-compound (I) is complete after 12 hours. With a low (10^{-4}M) concentration of (IV; R = Me), consistent with its role as a steady-state intermediate, and a cyanide-ion concentration equal to that used in the kinetic runs, reaction was instantaneous. These experiments are consistent with the intermediate formation of (IV) during the rearrangement, although the formation of (V) cannot be definitely excluded.

EXPERIMENTAL

Stoicheiometry of the Reaction of Diethyl 4-*Chloromethyl*-1,4-*dihydro*-2,6-*lutidine*-3,5-*dicarboxylate with Potassium Cyanide.*—(a) *In unbuffered solution.* Potassium cyanide (0·278 g.) in water (5 ml.) was added to the chloro-compound (I; 0·432 g.) in ethanol (40 ml.), and the mixture was kept at room temperature for 3 days. The ethanol was removed under reduced pressure and the aqueous residue extracted with ether (5 × 50 ml.). The combined ethereal extracts were dried ($MgSO_4$) and evaporated under reduced pressure to yield the dihydroazepine (II; 0·398 g., 95%) which on crystallisation from aqueous ethanol had m. p. 108—109·5°.

(b) *In buffered solution.* The chloro-compound (I; 0·204 g.) and potassium cyanide (0·182 g.) in 90% ethanol (50 ml.) with ethanolic hydrogen chloride (4·1 ml.; 0·079N) were left at room temperature for 7 days. The bulk of the ethanol was removed under reduced pressure and the aqueous layer extracted with ether (4 × 25 ml.). The ethereal extracts were dried and evaporated to yield the cyano-compound (II; 0·196 g., 99%), m. p. 107—109·5°.

(c) *Determination of cyanide consumption.* To the chloro-compound (I; 0·303 g.) in ethanol (50 ml.) was added potassium cyanide (98·5% pure; 0·209 g.; a threefold excess) in water (5 ml.). The mixture was left at room temperature for 3·5 days, poured into water (100 ml.), and extracted with ether (5 × 50 ml.). The ethereal layer was washed with water (50 ml.) and these washings added to the aqueous layer which was titrated with standard silver nitrate solution. The titre was equivalent to 0·1270 g. of potassium cyanide (92% of that theoretically remaining after reaction).

Kinetics.—All absorbance measurements were made on a Unicam S.P. 500 instrument in

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[10] E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, 1962, **84**, 866.

[11] M. Anderson and A. W. Johnson, *Proc. Chem. Soc.*, 1964, 263.

0·2 cm. cells with a constant slit width (0·56 mm.) at 366 mμ unless otherwise stated. The wavelength calibration and absorbance of the instrument were checked before each run.

Materials.—The chloro-compound (I) [1] was crystallised from benzene to m. p. 136—137°. AnalaR potassium cyanide was dried at 120° for 10 hr. and kept in a desiccator. It was assayed at regular intervals. Ethanol was dried [12] and distilled.

Preliminary Experiments.—It was established that the chloro-compound (I) obeyed Beer's law and was stable at 25° in 90% ethanol for at least 96 hr. The quenching procedure used in the kinetic runs (see below) was effective provided the optical measurements were made immediately.

General Procedure.—(a) *Reaction with cyanide ion.* The chloro-compound (I) was dissolved in dry ethanol and treated with the requisite amount of ethanolic hydrogen chloride. The potassium cyanide was dissolved in 2·50 ml. of water and added to the solution which was then made up to 25 ml. with dry ethanol. After thorough mixing, 1 ml. portions of this solution were placed into a series of ground-glass stoppered tubes maintained at 25·4° ± 0·1°. After equilibrating for 15 min. the first portion (0·25—0·35 ml.) was measured out with a calibrated Agla syringe and diluted to 10 ml. and the absorbance read immediately. The results were calculated from the standard second-order equation (ref. 8, p. 18).

A typical run is shown in the following Table.

Initial [RNH] 0·0198M; [HCl] 0·00399M; 1/[HCl] 250·6; initial [CN$^-$] 0·0637M; initial effective [CN$^-$] 0·0597M

Instantaneous 10^2[RNH] = C_A	Instantaneous 10^2[CN$^-$] = C_B	$\log_{10}(C_A/C_B)$	t (sec.)
1·72	5·71	0·521	0
1·55	5·54	0·554	3720
1·40	5·39	0·585	7200
1·26	5·25	0·619	10,800
1·04	5·03	0·684	18,000
0·93	4·92	0·723	21,600

$k = 0{\cdot}538 \times 10^{-3}$

(b) *Reaction with hydroxyl ion.* The chloro-compound (I) in carbon dioxide free ethanol (prepared by treatment with a current of nitrogen) was treated with the requisite amount of aqueous AnalaR barium hydroxide solution and with sufficient carbon dioxide free water to bring the total water concentration to 10%. The solution was made up to 25 ml. with carbon dioxide free ethanol, well mixed, and placed in a 0·2-cm. silica cell maintained at 25° ± 0·5°. Absorbance readings were made at timed intervals and an infinity reading after 13—25 hr.

A typical run is shown in the following Table.

Initial [RNH] 0·0006094M; initial [OH$^-$] 0·0039M; initial absorbance 0·710

Absorbance	$\log_{10}\left(\frac{\text{instantaneous [OH}^-]}{\text{instantaneous [RNH]}}\right)$	Time (sec.)	Absorbance	$\log_{10}\left(\frac{\text{instantaneous [OH}^-]}{\text{instantaneous [RNH]}}\right)$	Time (sec.)
0·537	0·921	0	0·318	1·146	1020
0·501	0·950	120	0·292	1·185	1200
0·448	0·996	300	0·278	1·208	1320
0·423	1·020	420	0·258	1·243	1500
0·390	1·056	600	0·245	1·267	1620
0·355	1·097	720	0·035		18 hr.
0·343	1·112	900			

$k = 0{\cdot}149$

Reaction of Diethyl 4-*Chloromethyl*-1,4-*dihydro*-1,2,6-*trimethylpyridine*-3,5-*dicarboxylate with Hydroxyl Ion.*—To diethyl 4-chloromethyl-1,4-dihydro-1,2,6-trimethylpyridine-3,5-dicarboxylate [9] [0·114 g.; $\lambda_{\text{max.}}$ 231, 254, and 340 mμ (ε 15,200, 9060, and 6570)] in ethanol (5 ml.) was added 2N-sodium hydroxide solution (2 ml.) and the mixture left at room temperature for 14 hr. The solution was poured into water (100 ml.) and filtered to yield the product (0·0769 g.; 67%), m. p. 88·5—89°, undepressed on admixture of starting material.

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[12] A. I. Vogel, "A Text-book of Practical Organic Chemistry," 3rd edn., Longmans, Green, 1956, p. 167.

Reaction of the Chloro-compound (I) *with Iodide Ion.*—The 4-chloromethyl-1,4-dihydropyridine (I; 0·635 g.) and sodium iodide (2 g.) in acetonitrile (15 ml.) were boiled for 4 hr. and kept at room temperature for 2 days. The solution was evaporated to dryness and the residue extracted several times with dry ether. Evaporation of the extracts yielded *diethyl* 1,4-*dihydro*-4-*iodomethyl*-2,6-*lutidine*-3,5-*dicarboxylate* (0·761 g.), which on crystallisation from ethyl acetate afforded crystals, m. p. 134—135° (Found: C, 42·7; H, 5·2; I, 32·0; N, 3·6. $C_{14}H_{20}O_4IN$ requires C, 42·8; H, 5·1; I, 32·3; N, 3·6%); $\nu_{max.}$ 3380w, 3280w, 2940, 2890, 1680s, 1610, 1460s, 1435, 1370, 1355, 1330, 1310, 1290, 1225, 1165, 1145, 1090, 1045, 1010, and 940 cm.$^{-1}$; $\lambda_{max.}$ (cyclohexane), 227 and 339 mμ; (ε 16,200, 5,840) [the corresponding chloromethyl derivative (I) has $\lambda_{max.}$ 227 and 339 mμ (ε 16,600 and 6,110) in cyclohexane. The dihydroiodomethylpyridine reacts with ethanol in dilute solution and hence its u.v. spectrum cannot be measured in this solvent.

Reaction of Cyanide Ion with Dimethyl 2,7-*Dimethyl*-4H-*azepine*-3,6-*dicarboxylate.*—Dimethyl 2,7-dimethyl-4*H*-azepine-3,6-dicarboxylate (0·170 g.; kindly supplied by Professor A. W. Johnson) in 90% aqueous ethanol (40 ml.) and potassium cyanide (0·5 g.) were left at room temperature for 15 min. The mixture was rapidly concentrated under reduced pressure and extracted with ether (5 × 25 ml.). The ethereal extracts were dried and evaporated to yield a white powder (0·163 g., 85%) which on crystallisation from methanol yielded *dimethyl* 4-*cyano*-4,5-*dihydro*-2,7-*dimethyazepine*-3,6-*dicarboxylate*, m. p. 183—185° [mixed m. p. 185—188° with an authentic sample (m. p. 186—187°), supplied by Professor A. W. Johnson].

The infrared spectra of the two samples were identical: $\nu_{max.}$ (Nujol), 3240m, 3220w, 1690s, 1640, 1620, 1520s, 1290, 1240, 1175, 1110, 1105, 1085, 1070, and 925 cm.$^{-1}$; (hexachlorobutadiene) 2900, 1440, 1365, and 1310 cm.$^{-1}$.

Identity was also confirmed by thin-layer chromatography on Kieselgel G, benzene–ethyl acetate (4 : 1) being used as eluent. Both samples had an R_F value of 0·4.

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