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THE PRODUCTS AND KINETICS OF HYDROLYSIS OF CYANOPYRIDINIUM IONS

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Abstract—The hydrolysis of 1-methyl-2-cyano, 4-cyano-, and 3-cyanopyridinium ions by aqueous base has been studied. The kinetics of the reaction of the 2- and 4-cyano derivatives were measured by polarographic analysis of cyanide ion formation, and the rate of reaction of the 3-cyano ion was followed spectroscopically at 3500 Å. The 2- and 4-cyano ions yielded the corresponding pyridones and carbamidopyridinium ions, while the 3-cyano ion formed 3-carbamidopyridinium ion and 4-cyano-5-methyl-amino-2, 4-pentadienal. The ratios of the products varied in each case with pH. The ratio of carbamidopyridinium ion formation rates for the three isomers was 50:5·7:1 (2-:4-:3-) with a second-order rate constant for the 3-isomer of 0·28 l mol^{-1}sec^{-1}. The rate ratio for attack on the pyridinium ring was >1100:43:1 (2-:4-:3-) with a rate constant for the 2-isomer of ~76 l mol^{-1} sec^{-1} at 25°.

A mechanistic scheme to rationalize the results is presented. Hydroxide ion attack directly on the cyano group leads to the carbamidopyridinium ion, while hydroxide ion addition to the ring reversibly forms the cyanohydrin (or hydroxy addition product in the case of the 3-isomer) which is in equilibrium with the corresponding anion. Both the addition product and its anion decompose to give the products, either the pyridone or the dienal.

THE lability of 1-alkyl-2- and 4-cyanopyridinium ions was discovered through the detection of hydrogen cyanide evolution during recrystallization of the iodide salts[4] and independently by Ellin in a study of the reaction of 1-methyl-2-aldoximinopyridinium iodide (2-PAM) with base.[5] The formation of 1-methyl-2-cyanopyridinium iodide in the metabolism of 2-PAM has been observed[6,7] but subsequent production of cyanide ion does not seem to be sufficiently rapid to account for the toxicity of 2-PAM.[8]

Many substituted pyridinium ions are susceptible to nucleophilic replacement reactions. Attempts to prepare 1-methyl-2-bromo- or 2-chloropyridinium iodide lead to 1-methyl-2-iodopyridinium iodide[9] under the usual quaternization conditions; however, reaction temperatures below 0° permit the preparation of 1-methyl-2-

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[1] Alfred P. Sloan Fellow 1960–1964.

[2] Abstracted in part from the Ph.D. Thesis of J.W.P. submitted to the faculty of the University of Wisconsin, June 1961.

[3] Support from the National Institutes of Health under Grant E-1608, from the Ohio Oil Company for a fellowship and from the Wisconsin Alumni Research Foundation is gratefully acknowledged.

[4] It should be noted that substantial numbers of chemists are completely unable to detect HCN by odor. Cf. footnote 21, E. M. Kosower, J. A. Skorcz, Jr. and W. M. Schwartz, Jr., J. W. Patton, *J. Amer. Chem. Soc.* **82,** 2188 (1960).

[5] R. I. Ellin, *J. Amer. Chem. Soc.* **80,** 6588 (1958).

[6] I. Enander, A. Sundwall and B. Sorbo, *Biochem. Pharmacol.* **7,** 232 (1961).

[7] J. L. Way, School of Medicine, Marquette University, personal communication.

[8] I. Enander, A. Sundwall and B. Sorbo, *Biochem. Pharmacol.* **7,** 226 (1961).

[9] H. L. Bradlow and C. A. Vanderwerf, *J. Org. Chem.* **16,** 1143 (1951).

chloropyridinium iodide.[10] The N-(4-pyridyl)-4-chloropyridinium ion is hydrolyzed very rapidly by water to the corresponding pyridone[11] and 1-methyl-2-iodopyridinium ion readily yields 1-methyl-2-pyridone with acid or base.[9] Both 1,2,6-trimethyl-4-methylmercapto- and 4-methoxpyridinium iodides form the 4-methylamino derivative upon treatment with methylamine.[12] Replacement reactions of 2- and 4-halopyridines are catalyzed by acid.[13]

The only kinetic studies of replacement reactions on substituted pyridinium ions were carried out by Liveris and Miller.[10] Rate ratios at 50° for the reaction of 1-methyl-2-,4-, and 3-chloropyridinium ions with *p*-nitrophenoxide in methanol were found to be $50 \times 10^6 : 2 \times 10^6 : 1$.

The reaction of hydroxide ion with 1-methoxypyridinium ion has recently been studied by Eisenthal and Katritsky.[14] Ring-opening to a glutacondialdehyde derivative occurred in a reaction which was approximately second-order in hydroxide ion and first-order in the pyridinium ion.

We report in this paper data on the products and kinetics of hydrolysis of cyanopyridinium ions.

RESULTS

Products. The reaction of 1-methyl-2-cyano- and 1-methyl-4-cyanopyridinium ions with hydroxide ion leads to 1-methyl-2- and 4-carbamidopyridinium ions and 1-methyl-2- and 4-pyridones. (Eqs. 1 and 2) Hydroxide ion and the 1-methyl-3-cyanopyridinium ion react to give 1-methyl-3-carbamidopyridinium ion and a substantial amount of at least one other product, 4-cyano-5-methylamino-2, 4-pentadienal (I). (Eq. 3) It was possible to carry out the hydrolysis reactions so that little or no betaine could be detected in any of the hydrolysis mixtures.[15]

The 2- and 4-cyanopyridinium salts were reacted with base and separation of products was accomplished by cation-exchange column after removal of cyanide ion as silver cyanide and neutralization. Elution of the column with water yielded the 1-methyl-2- (or 4-) pyridone; the use of dilute barium perchlorate solution as eluant provided solutions of 1-methyl-2- (or 4-) carbamidopyridinium perchlorate. In typical experiments, 99·1% of the material from the 2-cyano- ion hydrolysis could be accounted for as 81·9% 2-pyridone and 17·2% 2-carbamido ion. Recovery of material from the 4-cyano ion in a similar experiment was 97·6% with 54·0% 4-pyridone and 43·6% 4-carbamido ion.

Hydrolysis of the 3-cyanopyridinium ion and use of the cation-exchange column after neutralization yielded a water eluate with absorption maxima at 2640 Å and 3470 Å. The NMR spectrum (after replacement of the water with deuterium oxide) (Fig. 1) suggested formulation of the product as the dienal (I) (Table 1). A parallel hydrolysis and separation led to 86·6% of the 3-carbamidopyridinium perchlorate. The estimated yield of the dienal is ca. 6%; its structure is supported by the isolation of 1-methyl-5-cyano-2-pyridone by a different workup.

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[9] H. L. Bradlow and C. A. Vanderwerf, *J. Org. Chem.* **16**, 1143 (1951).

[10] M. Liveris and J. Miller, *Austral. J. Chem.* **11**, 297 (1958).

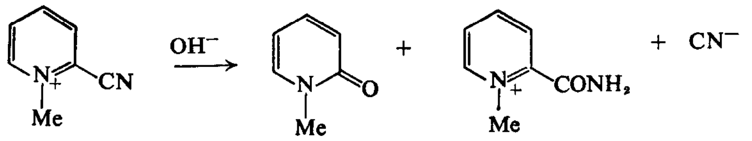
[11] J. P. Wibaut and F. W. Brockman, *Rec. Trav. Chim.* **78**, 593 (1959).

[12] L. C. King and F. J. Ozog, *J. Org. Chem.* **20**, 448 (1955).

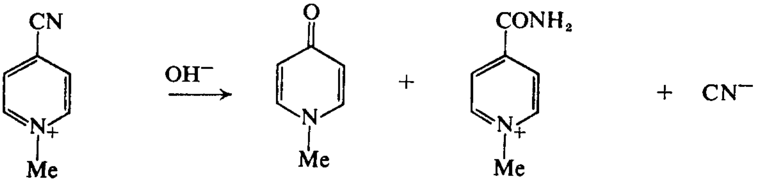
[13] C. K. Banks, *J. Amer. Chem. Soc.* **66**, 1127 (1944).

[14] R. Eisenthal and A. R. Katritsky, *Tetrahedron* **21**, 2205 (1965).

[15] E. M. Kosower and J. W. Patton, *J. Org. Chem.* **26**, 1318 (1961).



(1)



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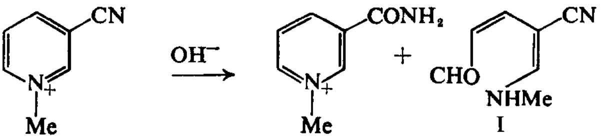

(3)

A useful comparison of the UV absorption curves for the isomeric 1-methylcyanopyridinium perchlorates is shown in Fig. 2. The differences between the isomers are striking and can probably be utilized in identification.[16]

Kinetics. Although spectrophotometric measurements of the rate of hydrolysis of the 1-methyl-4-cyanopyridinium ion in basic solution should have been convenient, constants obtained by the method of King[17] were not accurately reproducible due to a small variability in by-product formation. A polarographic method was therefore devised to measure the hydrolysis rates of the 2- and 4-cyano ions. Current measurements were made at $-0{\cdot}05$ V, a potential at which neither hydroxide ion nor oxygen interfered and a flowing junction was used to prevent contamination of the calomel reference electrode. Pseudo-first-order constants were obtained from runs in buffered solutions, and converted to second-order constants by dividing by the base concentration. Data on the kinetics of the hydrolysis of the 2- and 4-cyano ions are listed in Tables 2 and 3, respectively.

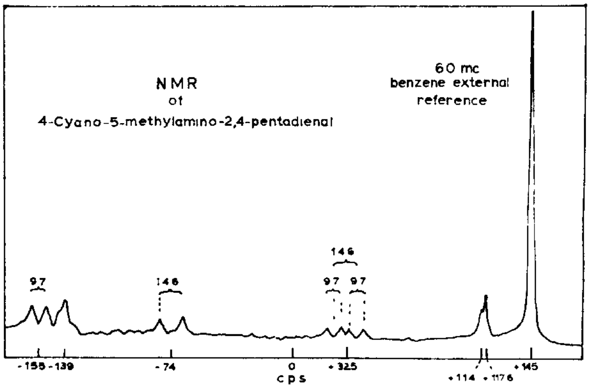

FIG. 1. The NMR spectrum of 5-methylamino-4-cyano-2, 4-pentadienal

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[16] The similarity in the UV absorption spectra of 1-methyl-3-cyanopyridinium perchlorate and 1-methyl-3, 5-dicyanopyridinium perchlorate was very helpful in confirming the presence of the latter. Miss M. Fischer, unpublished results.

[17] E. L. King, *J. Amer. Chem. Soc.* **74**, 563 (1952).

The hydrolysis of the 3-cyano ion could only be followed spectrophotometrically at 3500 Å. Table 4 summarizes our data for this reaction, and lists second-order constants obtained by dividing the pseudo-first-order constants by the hydroxide ion concentration.

Variation of product composition with pH. It was found that the ratio of pyridone to amide derived from the hydrolysis of 2- and 4-cyanopyridinium ions varied with the pH of the buffer used for the reaction. The yield of pyridone under a given set of conditions was determined by titration of the amount of cyanide ion formed. (Eqs 1 and 2) The ratio of 1-methyl-2-pyridone to 1-methyl-2-carbamidopyridinium ion varied from 2·6 at pH 8·99 to 5·40 at pH 11·06. The ratio of 1-methyl-4-pyridone to 1-methyl-4-carbamidopyridinium ion was 0·114 at pH 10·30 and 1·92 at pH 13·0. It is probable that product composition also changed with pH in the case of the 1-methyl-3-cyanopyridinium ion since the optical densities at the infinite time varied from 0·298 at pH 11·02 to 2·298 at pH 12·02 for solutions of similar initial pyridinium ion concentration.

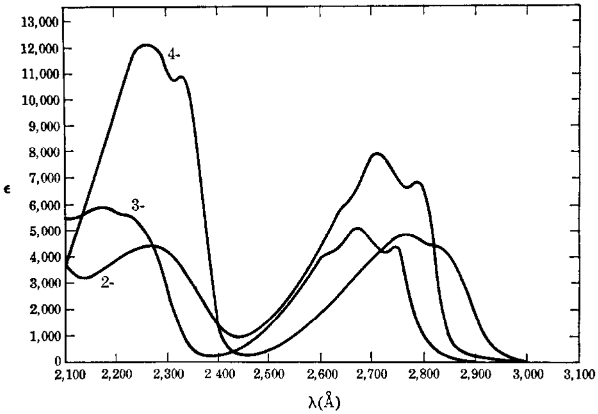

FIG. 2. The UV absorption spectra of 1-methyl-2-, 3-, and 4-cyanopyridinium perchlorates in water (*Reprinted by permission of the McGraw-Hill Book Co., Inc. from E. M. Kosower, "Molecular Biochemistry" Copyright* 1962).

DISCUSSION

There are three important facts to be learned from our experimental results. First, cyanopyridinium ions are highly reactive towards base; second, the rates of reaction are quite sensitive to the position of the cyano- group on the pyridinium ring. Third, hydrolysis of all three 1-methyl cyanopyridinium ions leads to at least two products, and the ratio of these products is dependent on pH.

The most likely mechanistic scheme is formulated in Eq. 19, and a kinetic scheme for this mechanism is developed below. The primary basis for the mechanism is the variation in product ratio over a wide range of pH. An upward trend in observed second-order rate constants is predicted by the kinetic scheme, and *this is observed* for the 1-methyl-4-cyanopyridinium ion (Table 3). It is not possible to be certain that the change in optical density at infinite time for the 1-methyl-3-cyanopyridinium ion reflects a change in product ratio over any given pH range since it is conceivable that other absorbing species may have changed in spectroscopic properties over this pH range. Kinetic measurements were made for the 1-methyl-2-cyanopyridinium ion

TABLE 1. NMR ASSIGNMENTS FOR 4-CYANO-5-METHYLAMINO-2, 4-PENTADIENAL

Band centered at ca.[a]	Assignment
0·94 τ	1-H, aldehyde proton (J_{12}9·7 c/s)
1·20 τ	5-H superimposed over broad N–H[b]
2·29 τ	3-H split by 2-H (J_{32}14·6 c/s)
4·06 τ	2-H split by 3-H (J_{23}14·6 c/s) split by aldehyde H (J_{21}9·7 c/s)
5·49 τ	water?
5·94 τ	CH_3

[a] Spectrum measured in D_2O with benzene capillary reference and converted to approximate τ-values by the addition of 3·52.

[b] Positions of N–H protons are very sensitive to molecular environment: τ_{NH} in acetone 2,4-dinitrophenylhydrazone occurs at $-0·95$ and in *o*-chloracetylaminobenzyl cyanide at $+1·68$ (Spectra 233 and 248 in Varian NMR Spectra Catalog, 1962).

TABLE 2. RATES OF REACTION OF HYDROXIDE ION WITH 1-METHYL-2-CYANOPYRIDINIUM ION

pH	Temp	$t_{1/2}$ sec	k_{obs}, l mol^{-1} sec^{-1}[a,b]	μ[c]
10·95	10·3°	183 ± 1	14·1 ± 0·7	0·049
10·80	10·3°	260 ± 1	14·0 ± 0·7	0·048
10·72	10·3°	320 ± 1	13·6 ± 0·6	0·048
10·52	25·2°	45·8 ± 2·2	45·6 ± 2·2	0·043
10·02	25·2°	126 ± 1	52·4 ± 2·4	0·036
9·70	25·2°	250 ± 1	55·4 ± 2·5	0·031
9·21	25·2°	799 ± 21	53·5 ± 2·8	0·026
8·99	25·2°	1375 ± 9	51·6 ± 2·4	0·025
9·07	39·1°	143 ± 1	143 ± 6·6	0·025
8·79	39·1°	254 ± 1	153 ± 7·1	0·025
8·48	39·1°	526 ± 3	151 ± 6·9	0·025

[a] apparent second-order constant

[b] polarographic, 3 sec drop time

[c] ionic strength

over the pH range (at 25°) 8·99 to 10·52. The change in product ratio was observed (Table 7) over the range 9·70 to 11·06 for the same ion. An upward drift was expected. It was not observed, a result for which two reasons can be advanced: (1) the change in product ratio is smaller than that for the 4-isomer (2) the experimental method may be less accurate than we have supposed at its limits for our particular technique (Experimental). Further work using a stopped-flow apparatus would certainly be desirable. The chemistry of the cyanopyridinium ions resembles that of 1-methoxypyridinium ion as reported by Eisenthal and Katritsky.[14]

Mechanistic and kinetic scheme. The symbols used in the schemes are P, cyanopyridinium ion, O, hydroxide ion, A, carbamido-pyridinium ion, N, pyridone, D, cyanide ion, H, cyanohydrin or other addition product, H$^-$, anion of H, L, pentadienal.

TABLE 3. RATES OF REACTION OF HYDROXIDE ION WITH 1-METHYL-4-CYANOPYRIDINIUM ION

pH	Temp	$t_{1/2}$, sec	k_{obs}, l mol^{-1} sec^{-1} [a,b]	μ[e]
12·32	10·3°	221 ± 1	0·497 ± 0·023	0·20
12·07	10·3°	412 ± 3	0·474 ± 0·022	0·20
11·90	10·3°	631 ± 25	0·458 ± 0·028	0·20
11·88	25·2°	36·8 ± 0·6	2·46 ± 0·12	0·20
11·86[c]	25·2°	41·3 ± 0·3	2·32 ± 0·11	0·20
11·70	25·2°	72·8 ± 0·8	1·90 ± 0·09	0·20
11·46[c]	25·2°	139 ± 1·6	1·73 ± 0·08	0·20
11·07	25·2°	335 ± 3	1·76 ± 0·08	0·20
10·88	25·2°	559 ± 3	1·64 ± 0·08	0·069
10·86[d]	25·2°	510 ± 3	1·89 ± 0·08	0·0345
10·76	25·2°	721 ± 2	1·67 ± 0·08	0·20
10·52	25·2°	1100 ± 18	1·90 ± 0·09	0·061
10·58	39·1°	119 ± 1	5·31 ± 0·25	0·065
10·33	39·1°	212 ± 1	5·28 ± 0·24	0·059
9·98	39·1°	483 ± 1	5·22 ± 0·24	0·049

[a] apparent second-order constant
[b] polarographic, 3 sec drop time
[c] polarographic 1·5 sec drop time
[d] buffer of run at pH 10·88 diluted by a factor of two
[e] ionic strength

From Eq. 19 we may write

$$\mathrm{P} + \mathrm{O} \xrightarrow{k_1} \mathrm{A} \tag{4}$$

$$\mathrm{P} + \mathrm{O} \underset{k_{-2}}{\overset{k_2}{\rightleftarrows}} \mathrm{H} \tag{5}$$

$$\mathrm{H} + \mathrm{O} \overset{K_3}{\rightleftarrows} \mathrm{H}^- \tag{6}$$

$$\mathrm{H} \xrightarrow{k_4} \mathrm{N} + \mathrm{D} \tag{7}$$

$$\mathrm{H}^- \xrightarrow{k_5} \mathrm{N} + \mathrm{D} \tag{8}$$

$$\mathrm{H} \xrightarrow{k_4'} \mathrm{L} \tag{9}$$

$$\mathrm{H}^- \xrightarrow{k_5'} \mathrm{L} \tag{10}$$

From these reactions, the following rate equations apply:

$$\mathrm{dA/dt} = k_1\mathrm{PO} \tag{11}$$

$$\mathrm{dN/dt} = k_4\mathrm{H} + k_5\mathrm{H}^- \tag{12}$$

Assuming that total cyanohydrin ($\mathrm{H} + \mathrm{H}^-$) is small and that the steady state treatment may be derived with $\mathrm{dH_{total}/dt} = 0$, then

$$\mathrm{dN/dA} = \frac{k_2}{k_1}\left(\frac{k_4 + k_5K_3\mathrm{O}}{k_{-2} + k_4 + k_5K_3\mathrm{O}}\right) \tag{13}$$

Eq. (13) reduces to

$$\mathrm{dN/dA} = k_2/k_1 \text{ at high O} \tag{14}$$

and

$$\mathrm{dN/dA} = \frac{k_2}{k_1}\left(\frac{k_4}{k_{-2} + k_4}\right) \text{ at low O} \tag{15}$$

Also

$$-\mathrm{dP/dt} = \mathrm{dN/dt} + \mathrm{dA/Dt} = \left[k_2\left(\frac{k_4 + k_5K_3\mathrm{O}}{k_2 + k_4 + k_5K_3\mathrm{O}}\right) + k_1\right]\mathrm{PO} \tag{16}$$

At high O

$$-\mathrm{dP/dt} = (k_1 + k_2)\,\mathrm{PO}$$

and, at low O,

$$-\mathrm{dP/dt} = \left[k_2\left(\frac{k_4}{k_2 + k_4}\right) + k_1\right]\mathrm{PO} \tag{18}$$

Corresponding equations apply to the formation of L, with k_4' and k_5'. The suggested mechanism is illustrated in Eq. 19.

The kinetic scheme permits an estimation of certain of the individual rate constants as outlined in Table 5. Reaction rates of hydroxide ion with the nitrile group vary in the order 2- $\gg$ 4- $>$ 3-, the ratios of k_1 for the three ions being 50:5·7:1. The ratios for rates of hydroxide ion attack on the ring (at the position carrying the cyano group for the 2- and 4-ions and at the 6-position for the 3-cyano ion) are $>$1100:43:1.

TABLE 4. RATES OF REACTION OF HYDROXIDE ION WITH 1-METHYL-3-CYANOPYRIDINIUM ION

pH	Temp	$t_{1/2}$, sec	k_{obs}, l mol^{-1} sec^{-1} [a,b]	μ [c]
12·32	10·3°	1470 ± 11	0·0748 ± 0·0035	0·20
12·14	10·3°	2420 ± 22	0·0687 ± 0·0033	0·20
12·02	25·0°	256 ± 1	0·258 ± 0·012	0·20
11·88	25·0°	339 ± 1	0·269 ± 0·012	0·20
11·68	25·0°	479 ± 2	0·302 ± 0·014	0·20
11·02	25·0°	2240 ± 15	0·296 ± 0·014	0·070
11·71	39·1°	63·8 ± 0·4	0·734 ± 0·034	0·20
11·51	39·1°	109 ± 1	0·685 ± 0·032	0·20
11·43	39·1°	121 ± 1	0·739 ± 0·034	0·20

[a] apparent second-order constant
[b] spectroscopic, 3500 Å
[c] ionic strength

The hydrolysis rate of 2-cyanopyridine has been reported as 7 × 10^{-4} l mol^{-1} sec^{-1} at 25°.[18] Thus, quaternization increases the rate of nitrile hydrolysis by a factor of ca. 2 × 10^4.

Activation parameters calculated from data at three temperatures are listed in Table 6.

Whatever the precise mechanistic description of the reactions of cyanopyridinium ions, it should be quite clear that the electrostatic factor controls the position of

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[18] E. Laviron, *C. R. Acad. Sci., Paris* **250**, 3671 (1960).

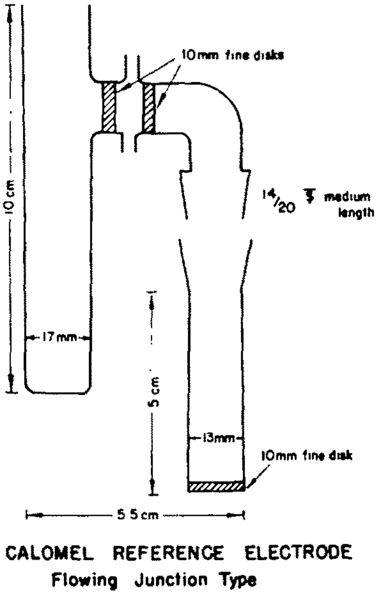


FIG. 3. Flowing junction reference electrode.

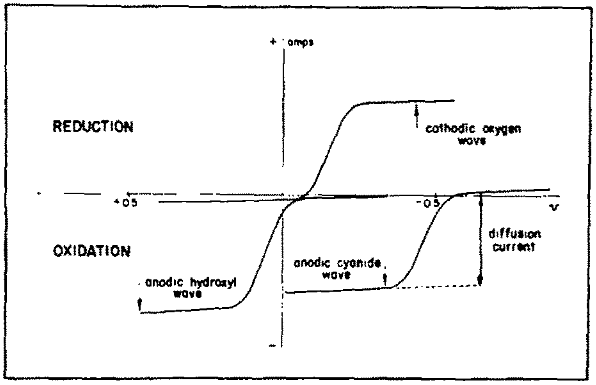


FIG. 4. Polarograms of cyanide ion, oxygen and hydroxide ion.

TABLE 5. SUMMARY OF KINETIC CONSTANTS AT 25°

Pyridinium Ion	k_3/k_1	$k_4/k_3 + k_4$	k_3, l mol^{-1} sec^{-1}	k_1, l mol^{-1} sec^{-1}
2-Cyano	5·40	0·49[a]	~76[b]	~14[c]
3-Cyano	<0·25[d]	small	<0·07	0·28[e]
4-Cyano	1·92	very small[f]	~3·0[g]	~1·6[g]

[a] From a comparison of product ratios (N/A) at high and low pH (Compare Eqs. 14 and 15).

[b] 5·4 times k_1, which contributes about 0·25 of the product at pH 9·70.

[c] 0·25 times the observed rate at pH 9·70, based on the amount of 2-carbamidopyridinium ion formed.

[d] An estimate relying on the maximum of 3-carbamidopyridinium ion formed in any hydrolysis experiment.

[e] Slightly less than the rate observed at pH 11·02 in order to allow for attack on the ring.

[f] The yield of pyridone is undetectable at pH 9·20 by UV spectroscopy.

[g] Based on the observed rate at pH 10·76 at which the yield of pyridone is small.

attack on pyridinium ions. The rates of decarboxylation of 1-methylpyridine carboxylic acid betaines exhibit a pattern similar to that observed for attack of hydroxide ion on the pyridinium ring.[19]

TABLE 6. ACTIVATION PARAMETERS FOR HYDROLYSIS REACTIONS[a,b]

1-Methylpyridinium Ion	ΔH*, kcal/mole	ΔS*, cal/mol-deg
2-Cyano	13·8 ± 0·3	−4·6 ± 0·9
3-Cyano	13·5 ± 0·8	−15·9 ± 2·6
4-Cyano	14·3 ± 0·4	−9·6 ± 1·2

[a] Hydroxide ion at unit activity, 25°.

[b] The change, if any, in the ratios of products with temp was not investigated.

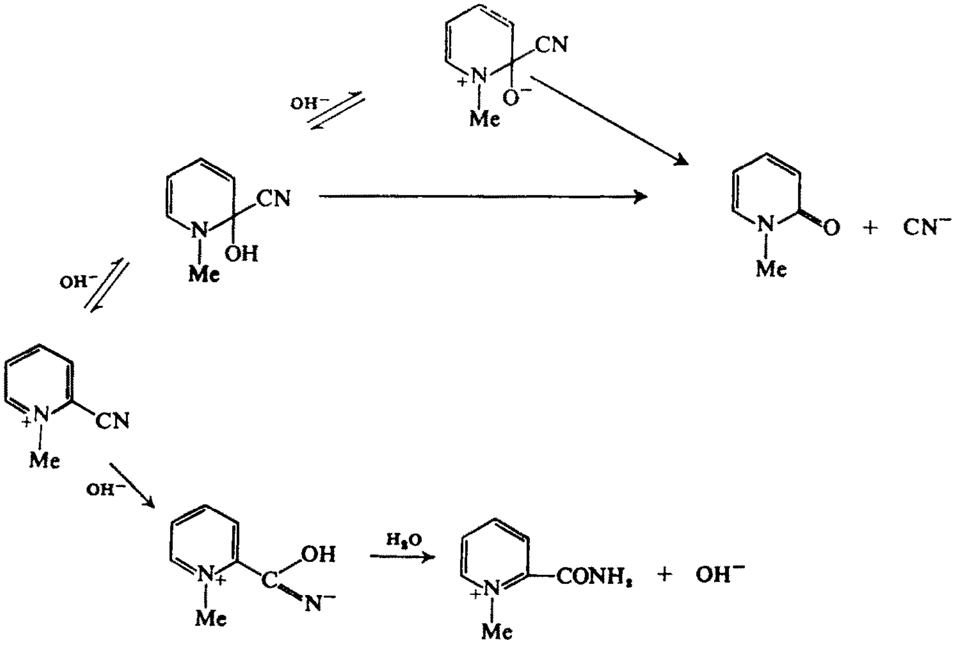
EXPERIMENTAL

Materials

1-*Methyl-2-cyanopyridinium iodide*, m.p. 175–176° (vac., dec)[4], *perchlorate*, from reaction of aqueous silver perchlorate with aqueous pyridinium iodide followed by filtration, passage through IR-45 resin in the perchlorate form, evaporation of solution almost to dryness, filtration with the aid of t-butyl alcohol, and an ether wash. The ion-exchange resin was prepared by treatment of IR-45 resin (200 ml, Rohm and Haas) with 4 M perchloric acid (100 ml) behind a safety shield, followed by water washing until no longer acid to congo red indicator, m.p. 158–160°. (Found: C, 38·72; H, 3·26. Calc. for $C_7H_7N_2ClO_4$: C, 38·46; H, 3·23%).

1-*Methyl-3-cyanopyridinium iodide*, yellow prisms from EtOH, m.p. 200–201° (dec)[19a] (reported 194·5–196·1°)[9]. (Found: C, 34·21; H, 2·72; Eq. wt. 246·2. Calc. for $C_7H_7N_2I$: C, 34·16; H, 2·87% Eq. wt. 246·1).

Perchlorate, as above, m.p. 135–137°. (Found: C, 38·15; H, 3·01. Calc. for $C_7H_7N_2ClO_4$: C, 38·46; H, 3·23%).



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[19] P. Haake and J. Mantecon, *J. Amer. Chem. Soc.* **86**, 5230 (1964).

[19a] All m.ps are uncorrected and were taken by placing the sample in the bath ca. 10° below the m.p.

1-*Methyl-4-cyanopyridinium iodide*, orange crystals from acetone-water (20:1), m.p. 198·5–199·5° (dec).[10]

Perchlorate, as above, m.p. 134·5–136°. (Found: C, 38·30; H, 3·47. Calc. for $C_7H_7N_2ClO_4$: C, 38·46; H, 3·23%).

1-*Methyl-2-carbamidopyridinium iodide*, from picolinamide, m.p. 106–107° and MeI, light yellow crystals from EtOH, m.p. 158·5–161°. (Found: C, 31·92; H, 3·33; Eq. wt. 264·4. Calc. for $C_7H_9N_2OI$: C, 31·83; H, 3·44% Eq. wt. 264·1).

Perchlorate, as above, m.p. 118–119·5°. (Found: C, 35·54; H, 3·90. Calc. for $C_7H_9N_2ClO_5$: C, 35·53; H, 3·83%).

1-*Methyl-3-carbamidopyridinium perchlorate* and 1-*methyl-4-carbamidopyridinium perchlorate* have been previously reported.[11] UV maxima (absorption coefficients) for the pyridinium perchlorates were measured in water: 1-methyl-2-cyano, 2260 Å (4460), 2710 Å (7950), 2790 Å (6820); 1-methyl-3-cyano, 2180 Å (5850), 2675 Å (4060), 2750 Å (3350); 1-methyl-4-cyano, 2260 Å (12100), 2332 Å (10900), 2775 Å (4825); 1-methyl-2-carbamido, 2660 Å (6080); 1-methyl-3-carbamido, 2648 Å (4430); 1-methyl-4-carbamido, 2190 Å (8100), 2650 Å (4950).

1-*Methyl-4-pyridone*, from chelidonic acid (Aldrich Chem. Co.), resublimed colorless hygroscopic crystals, m.p. 94·5–96·5° (vac), reported[22] 89°. The non-hygroscopic *hydrochloride* was prepared from the pyridone and dry HCl in ether–$CHCl_3$, white needles from isopropyl alcohol, m.p. 186–188°. (Found: C, 49·47; H, 5·65; Eq. wt. 145·2. Calc. for C_6H_8NClO: C, 49·49; H, 5·50% Eq. wt. 145·6). λ_{max} 2610 Å (ε 17400) in water.

1-*Methyl-2-pyridone*, air-sensitive liquid prepared by the method of Prill and McElvain.[23] The hydrochloride was recrystallized from MeOH, m.p. 168–170° (reported[9] 167–168°). λ_{max} 2255 Å (ε 6540), 2972 Å (ε 5750) in water.

Products

Hydrolysis of 1-*methyl-2-cyanopyridinium ion.* 0·1013M NaOH (60 ml), was pipetted into a solution of 1-methyl-2-cyanopyridinium perchlorate (621·7 mg, 2·844 mmoles) in 400 ml water and the whole allowed to stand 5 min. The solution was titrated to the dicyanoargentate endpoint with silver perchlorate (11·90 ml, 0·09768 M), using a Sargent-Malmstadt automatic titrator with carbon and palladium-rhodium electrodes. The solution was titrated to neutrality with perchloric acid (0·5511 M, 2·37 ml) and then to the AgCN end point with silver perchlorate (11·85 ml, 0·09768 M). The yields of 1-methyl-2-pyridone indicated at each end point were, respectively, 81·74%, 83·90% and 81·57%.

The solution was filtered through a sintered glass funnel, then passed through a 1 × 13 cm column of IR-120 ion-exchange resin in the sodium form. The column was eluted with water. UV spectra of the eluate fractions showed the presence of 1-methyl-2-pyridone (2·328 mmoles) or 81·86%. No sign of betaine was observed. (Betaine has an UV spectrum different from that of the pyridone and is produced by further hydrolysis of the carbamidopyridinium ion.) The first 500 ml of eluate, containing 2·117 mmoles of pyridone, was evaporated to dryness under red. press., the last traces of water being removed by boiling with benzene. The benzene was replaced with $CHCl_3$. An IR spectrum of the solution was identical to that of authentic 1-methyl-2-pyridone. Dry HCl yielded the pyridone hydrochloride (265 mg, 86% of that expected), m.p. 167–170°, no depression on mixed m.p. with authentic hydrochloride.

Elution of 1-methyl-2-carbamidopyridinium perchlorate from the column was accomplished with 0·01M barium perchlorate. UV spectroscopic analysis of the solution indicated the presence of 0·4899 mmole (17·23%). Total yield of products in eluate by UV was 99·09%). A portion of the eluate was evaporated to dryness under red. press. and dissolved in a small volume of warm acetone. Addition of an almost equal volume of ether and cooling in ice gave colorless plates of the pyridinium perchlorate, m.p. 114–118°. A second crop had m.p. 114–116°. Mixed m.p. with authentic 1-methyl-

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[10] E. M. Kosower, *J. Amer. Chem. Soc.* **80**, 3253 (1958).

[11] E. M. Kosower and S. W. Bauer, *J. Amer. Chem. Soc.* **82**, 2191 (1960).

[22] L. Haitinger and A. Lieben, *Monatsh.* **6**, 293, 309 (1885).

[23] E. A. Prill and S. M. McElvain, *Org. Syn. Coll.* Vol. II, p. 419, John Wiley and Sons, Inc., New York, 1943.

2-carbamidopyridinium perchlorate showed no depression and an IR spectrum was the same as that of the pure compound. Of the theoretically possible salt, 30 mg (26%) was isolated. Inorganic salts made high recoveries of pure material difficult.

Hydrolysis of 1-methyl-4-cyanopyridinium ion. 0·1013M NaOH (50 ml), was pipetted into a solution of 1-methyl-4-cyanopyridinium perchlorate (622·9 mg, 2·849 mmoles) in 450 ml water and allowed to stand for 10 min. Upon the addition of the base, the solution turned violet, gradually fading to a faint pink. Titration as described above gave 53·6%, 54·1% and 53·5% pyridone formation. Separation by ion-exchange column gave 54·0% pyridone (by UV) of which 94% could be isolated as the hydrochloride, m.p. 180–184° (mixed m.p., no depression) by evaporation of the eluate, extraction with $CHCl_3$ and treatment with dry HCl. Spectroscopic examination indicated 43·6% yield of 1-methyl-4-carbamidopyridinium perchlorate in the barium perchlorate eluate, of which 154 mg (62%) could be isolated by evaporation to dryness and crystallization from EtOH as colorless plates, m.p. 183·5–184°, with an IR spectrum identical to authentic material.

Hydrolysis of 1-methyl-3-cyanopyridinium ion. 0·0929M NaOH (50 ml), was added to a solution of 1-methyl-3-cyanopyridinium perchlorate (508·0 mg, 2·324 mmoles) and allowed to stand 10 min. The solution was titrated to pH 7 with HCl (9·37 ml, 0·476M), corresponding to 11·6% base consumption. The light yellow solution was passed through an ion-exchange column. The water eluate exhibited a UV maximum at 3470 Å and a less intense maximum at 2550 Å. Barium perchlorate elution and UV analysis indicated 86·6% 1-methyl-carbamidopyridinium perchlorate, and a 42% yield of the salt, m.p. 140–142° (mixed m.p., IR), was readily isolated from part of the eluate.

A parallel experiment with 3·115 g 1-methyl-3-cyanopyridinium perchlorate (14·25 mmoles) led to 10·0% base consumption. The light yellow solution was passed through a 2 × 18 cm IR-120 ion exchange resin column in the sodium form. Elution with 500 ml water gave a solution with an UV spectrum suggestive of a mixture. The solution was evaporated to dryness under red. press., the residue extracted 4 times with boiling benzene, and the residue redissolved in water. The UV spectrum was then relatively simple, λ_{max} 2640 Å (ε_{min} 2500) and 3470 Å (ε_{min} 12500). The water was removed under red. press. and replaced with D_2O. The NMR spectrum of this solution (Fig. 1) was in agreement with the structure, 4-cyano-5-methylamino-2, 4-pentadienal. IR spectra confirmed the presence of the nitrile group.

1-Methyl-5-cyano-2-pyridone. 0·616M KOH (2 ml), was added to a solution of 1-methyl-3-cyanopyridinium perchlorate (994 mg, 4·54 mmoles) in water and the solution allowed to stand 1 hr. The yellow solution was brought to neutrality by titration with perchloric acid and evaporated to dryness under red. press. The residue was extracted with $CHCl_3$ and the solution chromatographed on 4 g Florisil. The third 20 ml fraction ($CHCl_3$) was evaporated and the residue recrystallized from benzene–pet. ether (65–70°) to give a yellow solid, 12 mg, m.p. 154–159°. Sublimation under vacuum yielded a bright yellow solid, m.p. 157–159°. IR spectra showed both carbonyl and nitrile groups. (Found: C, 62·53; H, 4·49; N, 20·62. Calc. for $C_7H_6N_2O$: C, 62·68; H, 4·51; N, 20·89%). The structure was confirmed by hydrolysis of 0·4 mg pyridone in 25 ml 0·01M NaOH for 24 hr at 65°. The UV spectrum of the resulting solution was identical to that of 1-methyl-5-carbamido-2-pyridone (California Corporation for Biochemical Research) and quite different from those of the other two possible products, 1-methyl-3-carbamido-2-pyridone[24] and 1-methyl-4-carbamido-2-pyridone.[25]

Variation in product composition with pH. Only two products were found in the hydrolysis products of 1-methyl-2- and 4-cyanopyridinium ions. The amount of cyanide ion formed from these two reactants was equal to the amount of pyridone formed. The ratio of pyridone to amide was therefore determined by allowing the pyridinium ions to hydrolyse in alkaline buffers and titration with $AgNO_3$ using diphenylcarbazide as absorption indicator. No direct method existed for the 1-methyl-3-cyanopyridinium ion hydrolysis products except for assuming that light absorption at 3500 Å at infinite time in a rate run was a measure of the amount of pentadienal formed. The results are tabulated in Table 7.

Kinetic measurements

Polarographic. Buffer solutions were used both to maintain the pH and to provide a supporting electrolyte. The phosphate buffers were those of Britton and Welford[26] and the borax and carbonate

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[24] M. E. Pullman and S. P. Colowick, *J. Biol. Chem.* **206**, 121 (1954).

[25] M. L. Wu Chang and B. C. Johnson, *J. Biol. Chem.* **234**, 1917 (1959).

[26] H. T. S. Britton and G. Welford, *J. Chem. Soc.* 1848 (1937).

buffers those of Bates.[27] The hydroxide ion concentration was calculated from the pK_w values reported by Washburn[28] and the pH values measured with a Beckman Model G pH meter, with 0·0100M borax as an alkaline pH standard.[29] The pH values of the buffer solution could thus not be checked to better than ±0·02 pH units.

A Sargent Model XV recording polarograph was used for the measurements in its most sensitive setting, 0·003 μamps/mm. The polarographic cell used a flowing junction reference electrode (Fig. 3) and itself was made from a weighing bottle fitted with a Teflon lid having holes for the reference electrode, a stirrer, the dropping mercury electrode and for admission of the sample. The cell was thermostatted in a water bath. The drop time was held as 3 sec for almost all runs except for a few in which 1½ sec was utilized. It is not known whether those runs in which the half-life (40 sec) approached the usual drop time (3 sec) are based on a proper concentration gradient for cyanide ion. Shorter drop times than 3 sec are avoided because turbulence seems to interfere with the establishment of the concentration gradient of electroactive material.

The polarograph was set at −0·05 v *vs.* S.C.E. to avoid contributions to the diffusion current from O_2 or OH ion. Purging of the solution was not used to prevent the loss of HCN. Cyanide ion was therefore measured by the anodic wave produced through the reaction of Eq. 20.[30]

$$Hg + 2CN^- = Hg(CN)_2 + 2e^- \tag{20}$$

The polarograms relevant to our particular application are shown in Fig. 4. Stirring changed the characteristics of the system in an inconstant way during a run, and was therefore only used at the very beginning to ensure thorough mixing of the reagents.

TABLE 7. VARIATION IN PRODUCT COMPOSITION WITH pH

pH	2-Cyano N/A[a]	4-Cyano N/A[a]	3-Cyano D_∞[b]
7·00	2·18[c]		
8·99	2·66		
9·20	2·88	0·00[c]	
9·40	2·87		
9·70	3·03		
10·02	3·41		
10·30	4·10	0·114	
10·44	4·55		
10·76	5·10	0·224	
11·00		0·328	
11·02			0·298
11·06	5·40		
11·34		0·576	
11·68			1·400
11·72		1·04	
11·88			1·840
12·0	5·40	1·47	
12·02			2·298
12·30		1·75	
12·70		1·85	
13·0		1·92	
14·0		1·90	

[a] pyridone/amide ratio
[b] optical density at infinite time observed in rate run
[c] estimated by UV spectroscopy.

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[27] R. G. Bates and V. E. Bower, *Analyt. Chem.* **28,** 1322 (1956).

[28] E. W. Washburn, *International Critical Tables*, Vol. VI; p. 152 McGraw-Hill, New York (1929).

[29] G. G. Manov, N. J. De Lollis, P. W. Lindvall and S. F. Acree, *J. Res. Nat'l. Bur. Standards* **36,** 543 (1953).

[30] I. M. Kolthoff and C. S. Miller, *J. Amer. Chem. Soc.* **63,** 1405 (1941).

A solution of either 1-methyl-2-cyano or 1-methyl-4-cyano-pyridinium ion was prepared and 1 ml was pipetted into 35 ml alkaline buffer contained in the polarographic cell. The stirrer was turned on for a brief period to ensure mixing, and a record of the change in cyanide ion concentration with time was made. First order constants were obtained through the usual equation, Eq. 21, the error in k being taken as the standard deviation of the slope.

$$\log(\mathrm{CN}_{\infty} - \mathrm{CN}_t^-) = \log \mathrm{CN}_{\infty}^- - kt/2{\cdot}303 \tag{21}$$

The pseudo first-order constants were converted into apparent second-order constants and listed as k_{obs} in Tables 2 and 3.

Spectroscopic. Rate constants were calculated from Eq. 22

$$\log(\mathrm{D}_{\infty} - \mathrm{D}_t) = \log \mathrm{D}_{\infty} - kt/2{\cdot}303 \tag{22}$$

for which data were obtained by pipetting a solution of 1-methyl-3-cyanopyridinium ion into an alkaline buffer in a 10 cm cell and following the gain in optical density at 3500 Å. In order to verify that this procedure truly reflected the rate of hydrolysis of the cyano group, an experiment was carried out to determine the ratio of 1-methyl-3-cyanopyridinium ion to 1-methyl-3-carbamido-pyridinium ion after 1920 sec under conditions for which the expected half-life was 2240 sec. A rough measure of the ratio was available from the position of the maximum in the region of the pyridinium ion absorption: for ratios of 3-cyano ion to 3-carbamido ion, the maximum is given in parenthesis, 40/60 (2660), 50/50 (2669), 60/40 (2673), 70/30 (2677). The 3-cyano perchlorate was dissolved in buffer, the reaction mixture neutralized after 1920 sec, and the pyridinium ion products and reactants separated by ion-exchange chromatography. The maximum found was 2671, very close to that predicted for a mixture 55/45 in composition. No correction was made for the 1–2% ring-opened aldehyde formed at pH 11, at which the reaction was carried out, since its absorption in the region of the maximum is not appreciable under these conditions.