Formation of 2-Methylaminopyridine-3-carbaldehyde and the Corresponding Methylimine by Ring-opening and Ring-closing Reactions of 3-Cyano-1-methylpyridinium Iodide in N-Sodium Hydroxide

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Steam distillation of a solution of 3-cyano-1-methylpyridinium iodide in N-sodium hydroxide yields a mixture of 2-methylaminopyridine-3-carbaldehyde (I) and the corresponding methylimine (II). The formation of the former most probably proceeds *via* ring opening of the pseudo-base to give 2-formyl-5-methylaminopenta-2,4-dienenitrile (III) (or a tautomer). Ring closure of this intermediate should give 1,2-dihydro-2-imino-1-methylpyridine-3-carbaldehyde (IV), which under the reaction conditions would undergo the Dimroth rearrangement. Methylamine is also a reaction product, and could be formed by hydrolysis either of the intermediate (III) or of 2-methylaminomethylene-5-oxopent-3-enenitrile, the latter being formed by an initial attack at the 6-position. The methylimine (II) could be formed by the reaction of compound (I) with methylamine. Assignment of structure (I) is based on n.m.r. spectrometry and the fact that a Cannizzaro reaction yields an alcohol and a carboxylic acid, the latter giving 2-methylaminopyridine on decarboxylation. Further, the reaction of compound (I) with methyl iodide yields 3-formyl-1-methyl-2-methylaminopyridinium iodide, which on treatment with sodium hydroxide is converted into 1,2-dihydro-1-methyl-2-methyliminopyridine-3-carbaldehyde. Bromination and nitrosation of compound (I) yield 5-bromo-2-methylaminopyridine-3-carbaldehyde and 2-methyl(nitroso)-aminopyridine-3-carbaldehyde, respectively.

We have previously reported [1] that the u.v. spectrum of 3-cyano-1-methylpyridinium iodide in 0·1N-sodium hydroxide at 25° is markedly different from that of a solution in water, and concluded that some rapid reaction occurs in alkaline solution. The change in the spectrum with time at various sodium hydroxide concentrations indicated that several reactions were involved. Comparison of the u.v. spectrum of the reaction mixture with the spectra of the corresponding amide, carboxylic acid, and hydroxy-compound in alkaline solution showed that none of these compounds is the main product.

Preliminary experiments showed that some products could be either extracted or steam distilled from the reaction mixture, and the aim of the present work was to isolate these compounds and determine their structure. For isolation, steam distillation was found most suitable, and subsequent extraction and distillation yielded a yellow liquid, b.p. 55°/0·3 mm. G.l.c. of this gave two main peaks, their relative heights varying from 2 : 1 to 1 : 1, depending on the reaction conditions. Combined g.l.c. and mass spectrometry of the mixture indicated that the components had molecular weights of 136 [compound (I)] and 149 [compound (II)], respectively. The compounds were not readily separable by fractionated distillation. Compound (II) could, however, be converted into compound (I) by acid hydrolysis, and analysis of the latter, in conjunction with the molecular weight, indicated the composition $C_7H_8N_2O$.

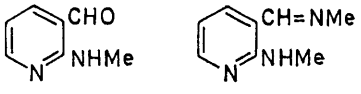
The ^{1}H n.m.r. spectrum of compound (I) shows an uncoupled aldehydic proton and the i.r. spectrum shows a carbonyl band at 1670 cm.$^{-1}$. The n.m.r. spectrum also shows a methyl doublet and a broad unresolved NH signal. The chemical shift of the former is consistent with a methylamino-group,[2] and this assignment is confirmed by the coalescence of the doublet into a singlet and the disappearance of the amino-proton signal on deuterium exchange. The remaining n.m.r. signals comprise three one-proton double doublets.

Pyridinium compounds are known to undergo ring opening in alkaline solution. The base attacks the 2- or the 6-position, and the products are derivatives of glutaconaldehyde.[3] By analogy, compound (I) could be 2-formyl-5-methylaminopenta-2,4-dienenitrile, (III), in agreement with the foregoing evidence. No nitrile band was observed in the i.r. spectrum of compound (I) or its derivatives, however. Further, the τ values for the methine protons of compound (I) and its derivatives are lower than expected for olefinic protons, and the coupling constants should also be higher.[4] The n.m.r. data are, however, in agreement with the structure of 2-methylaminopyridine-3-carbaldehyde,[5] and the following evidence supported this assignment. A Cannizzaro reaction of compound (I) gave an alcohol and a carboxylic acid, and the latter was readily decarboxylated to give 2-methylaminopyridine. The products of the Cannizzaro reaction are thus 2-methylamino-3-pyridylmethanol and 2-methylaminopyridine-3-carboxylic acid.

The i.r. spectrum of compound (I) shows a band at 3350 cm.$^{-1}$ assigned to the secondary methylamino-group. On nitrosation this band and the n.m.r. amino-proton signal disappear and the methyl signal becomes a singlet, indicating formation of a nitrosamine. Further, the aldehydic proton is now coupled with the proton corresponding to that in the 5-position of the pyridine ring. This is analogous to a corresponding β-coupling found for pyridine-3-carbaldehyde [6] and for some benzal-

[1] J. H. Blanch and O. T. Onsager, *J. Chem. Soc.*, 1965, 3729.
[2] D. H. Williams and I. Fleming, 'Spectroscopic Methods in Organic Chemistry,' McGraw-Hill, London, 1966, p. 126.
[3] E. Klingsberg, 'Pyridine and Its Derivatives,' Interscience, London, part I, 1960, p. 57; part II, 1961, p. 58.
[4] D. W. Mathieson, 'Nuclear Magnetic Resonance for Organic Chemists,' Academic Press, London, 1967, pp. 183 and 188.
[5] W. Brügel, *Ber. Bunsengesellschaft Phys. Chem.*, 1962, **66**, 159.
[6] V. J. Kowalewski and D. G. de Kowalewski, *J. Chem. Phys.*, 1962, **36**, 266.

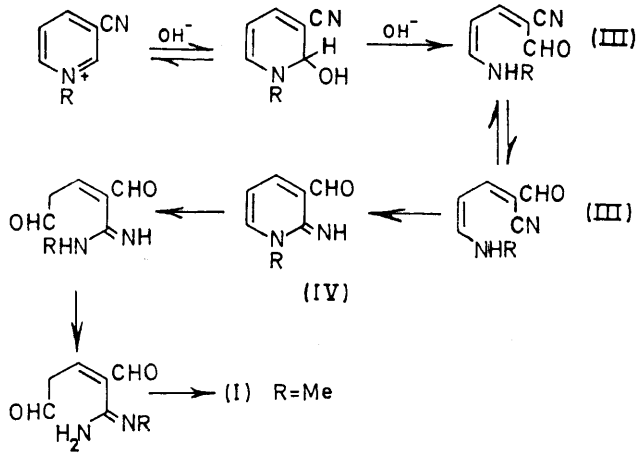
dehydes,[7] and indicates that the nitroso-derivative is 2-methyl(nitroso)aminopyridine-3-carbaldehyde. Consonant with the bromination of 2-aminopyridine in the 3- and 5-positions,[8] bromination of compound (I) gives 5-bromo-2-methylaminopyridine-3-carbaldehyde. Methylation of compound (I) with methyl iodide gives a product, the n.m.r. spectrum of which shows two individual methyl signals, in agreement with the occurrence of methylation at the 1-position. Treatment of the product with aqueous sodium hydroxide gives 1,2-dihydro-1-methyl-2-methyliminopyridine-3-carbaldehyde.



(I) (II)

The second reaction product (II) can also be obtained by treatment of compound (I) with methylamine, and is thus 2-methylamino-3-methyliminomethylpyridine, in agreement with its n.m.r. spectrum.[9]

The Scheme represents a possible mechanism for the formation of compound (I), involving two ring-opening and two ring-closing reactions. The first ring-opening reaction is assumed to proceed *via* the pseudo-base to give a derivative (III) of glutaconaldehyde. Since this intermediate was not isolated, its tautomeric form could not be established. We assume, however, that the aldehyde, enol, and enolate are in equilibrium, and that the structure is not rigidly locked in *cis*- or *trans*-forms. The first ring closing reaction, which follows, corresponds to the reaction of *o*-aminocinnamonitrile with alkali, yielding 2-aminoquinoline,[10] which occurs under similar conditions. The subsequent Dimroth rearrangement[11] involves formal migration of an alkyl group from an endocyclic to an exocyclic nitrogen atom in the α-position. 1,2-Dihydro-2-imino-1-methyl-5-nitropyridine is similarly converted into 2-methylamino-5-nitropyridine by boiling for 15 min. in N-sodium hydroxide,[12] and the 5-nitro-group is expected to have an electron-withdrawing influence similar to that of a 3-formyl group. The possibility of compound (I) being 1,2-dihydro-2-imino-



SCHEME

TABLE

^{1}H N.m.r. spectra of some pyridine derivatives in carbon tetrachloride [τ values; internal standard Me_4Si; J in Hz (calc. by first-order analysis)]

	τ_3	τ_4	τ_5	τ_6	$J_{4,5}$ ($J_{3,4}$)	$J_{4,6}$ ($J_{3,5}$)	$J_{5,6}$ ($J_{3,6}$)	
2-Methylaminopyridine-3-carbaldehyde		2·34(dd)	3·46(dd)	1·73(dd)	7·5	2·0	4·8	τ (Me) 6·95 * (J 5·0); τ (NH) 1·7br †; τ (CHO) 0·25(s)
2-Methylamino-3-methyl-iminomethylpyridine		2·78(dd)	3·60(dd)	1·92(dd)	7·5	1·9	4·8	τ (NH*Me*) 6·96*(d, J 5·0); τ (NH) 1·0br †; τ (C*H*:NMe) 1·92(q, J 1·5); τ (CH:N*Me*) 6·62(d, J 1·5)
5-Bromo-2-methylamino-pyridine-3-carbaldehyde		2·29(d)		1·72(d)		2·6		τ (Me) 6·95*(d, J 5·0); τ (NH) 1·75br †; τ (CHO) 0·28(s)
2-Methyl(nitroso)amino-pyridine-3-carbaldehyde		1·64(dd)	2·59(ddd)	1·31(dd)	8·0	2·0	4·9	τ (Me) 6·40(s); τ (CHO) 0·12(d, J 0·7)
2-Methylamino-3-pyridyl-methanol (in $CDCl_3$)		2·83(dd)	3·55(dd)	2·03(dd)	7·4	2·0	5·4	τ (Me) 7·05(s); τ (CH_2·OH) 5·47(s); τ 4·7br †; τ 5·8br †
2-Methylaminopyridine-3-carboxylic acid [in $(CD_3)_2SO$]		1·94(dd)	3·42(dd)	1·72(dd)	7·6	2·0	4·8	τ (Me) 7·03(s)
2-Methylaminopyridine	3·76(m)	2·70(ddd)	3·58(ddd)	2·02(ddd)	7·4 (8·6)	2·0 (1·0)	5·2 (1·0)	τ (Me) 7·16*(d, J 4·0); τ (NH) 4·7br †
1,2-Dihydro-2-imino-1-methylpyridine	3·83(ddd)	3·34(ddd)	4·45(ddd)	3·03(ddd)	6·4 (9·7)	1·9 (1·6)	7·2 (0·8)	τ (Me) 6·73(s); τ (:NH) 4·39(s)
3-Formyl-1-methyl-2-methylaminopyridinium iodide [in $(CD_3)_2SO$]		1·2—1·5(m)	2·8(t)	1·2—1·5(m)	*ca.* 7·0	?	*ca.* 7·0	τ (NH*Me*) 6·80; τ (N+Me) 5·95(s); τ (CHO) −0·12(s); τ (N*H*Me) 1·2—1·5
1,2-Dihydro-1-methyl-2-methyliminopyridine-3-carbaldehyde		2·72(dd)	4·36(t)	2·46(dd)	6·8	2·0	7·0	τ (:NMe) 6·97(s); τ (NMe) 6·59(s); τ (CHO) 0·30(s)

* Coalesces into a singlet on deuterium exchange. † Disappears on deuterium exchange.

[7] V. J. Kowalewski and D. G. de Kowalewski, *J. Chem. Phys.*, 1962, **37**, 1009.

[8] A. E. Chichibabin and A. W. Kirssanow, *Ber.*, 1928, **61**, 1236.

[9] K. A. W. Parry, P. J. Robinson, P. J. Sainsbury, and Miss M. J. Waller, *J. Chem. Soc.* (*B*), 1970, 700.

[10] R. Pschorr, *Ber.*, 1898, **31**, 1289.

[11] K. Schofield, 'Hetero-Aromatic Nitrogen Compounds: Pyrroles and Pyridines,' Butterworth, London, 1967, p. 269.

[12] J. Goerdeler and W. Roth, *Chem. Ber.*, 1963, **96**, 534.

1-methylpyridine-3-carbaldehyde (IV), is excluded by comparison of its n.m.r. spectrum with that of 1,2-dihydro-2-imino-1-methylpyridine.[13]

To explain the formation of the Schiff base (II) it is necessary to assume that methylamine is formed in a side reaction. Methylamine cannot be formed from compound (I), as the latter is relatively stable towards alkali, and only undergoes the Cannizzaro reaction under more vigorous conditions. Methylamine could be formed either by hydrolysis of the intermediate (III), or by attack of base at the 6-position of the 3-cyano-1-methylpyridinium iodide in a side reaction, forming 2-methylaminomethylene-5-oxopent-3-enenitrile, hydrolysis of which would give methylamine. A remarkable increase in the yields of compounds (I) and (II) effected by initial addition of methylamine hydrochloride to the reaction mixture may be caused by suppression or reversal of these reactions. We have shown that compound (II) can be formed by treatment of compound (I) with methylamine. It is, however, possible that compound (II) is formed by ring closure and rearrangement of 2-methylaminomethylene-5-methyliminopent-3-enenitrile. The product accompanying the methylamine formation was not isolated or identified. It is presumably 2-cyanoglutaconaldehyde or a derivative (glutaconaldehyde is known to be unstable [3]).

EXPERIMENTAL

Analyses were performed by Alfred Bernhardt, 5251 Elbach, West Germany, I.r. spectra were taken for liquid films or for potassium bromide discs with a Perkin-Elmer Infracord 337. U.v. spectra were measured for aqueous or ethanolic (95%) solutions with a Perkin-Elmer 137UV spectrophotometer. ^{1}H N.m.r. spectra were, unless otherwise stated, taken for solutions in carbon tetrachloride with tetramethylsilane as internal standard. G.l.c. was carried out with a Hewlett–Packard 5750 chromatograph with flame detector. Mass spectra were recorded with a Varian CH-7 spectrometer connected to a Varian 1400 gas chromatograph, or with an A.E.I./G.E.C. MS-902 spectrometer.

2-Methylaminopyridine-3-carbaldehyde (I).—A solution of 3-cyano-1-methylpyridinium iodide (25·0 g.) in N-sodium hydroxide (300 ml.) was distilled. The volume was kept approximately constant by addition of water. The distillate (300 ml.) was acidified with 2N-hydrochloric acid (45 ml.), and the solution was kept at 80° for 1 hr. The pH of the cooled solution was adjusted to 6·5 with 2N-sodium hydroxide, and the solution was extracted with chloroform (4 × 40 ml.). The chloroform solution was extracted with N-hydrochloric acid (3 × 50 ml.), and the aqueous extract was kept at 80° for 15 min. Its pH was adjusted to 6·5 with 2N-sodium hydroxide, and the chloroform extraction was repeated. The chloroform solution was dried (Na_2SO_4) and fractionated to give a yellow liquid (2·8 g., 20%), b.p. 55°/0·3 mm., which slowly solidified at 0° (m.p. 19°).

A similar experiment involving initial addition of methylamine hydrochloride (25·0 g.) to the reaction mixture and use of 2N-sodium hydroxide gave a higher yield of *product* (8·4 g., 60%) (Found: C, 61·9; H, 6·05; N, 20·5; O, 11·9. $C_7H_8N_2O$ requires C, 61·75; H, 5·9; N, 20·6; O, 11·75%), pK (25°; thermodynamic), 4·46 (by titration of an aqueous 0·01M-solution with 0·1N-hydrochloric acid [14]); d_4^{20} 1·159, n_D^{20} 1·616, $\lambda_{max.}$ (0·1N-HCl) 261 (ε 8300) and 345 nm. (6400), $\lambda_{max.}$ (0·1N-NaOH) 265 (ε 6500) and 371 nm. (6800), $\nu_{max.}$ 3350 (NH) and 1670 cm.$^{-1}$ (C=O).

Determination of Methylamine Produced in the Reaction of 3-Cyano-1-methylpyridinium Iodide with Sodium Hydroxide.—3-Cyano-1-methylpyridinium iodide (1·0 g., 0·00406 mole) was dissolved in N-sodium hydroxide (20 ml.), and 10 ml. of aqueous solution was distilled from the reaction mixture into 0·1N-hydrochloric acid (50 ml.). The distillate was adjusted to pH 6·5 with 0·1N-sodium hydroxide, and was extracted with chloroform (4 × 25 ml.). The aqueous layer was made alkaline with 10N-sodium hydroxide (5 ml.), and the base was distilled into 0·1N-hydrochloric acid (40 ml.). Titration with 0·1N-sodium hydroxide revealed the presence of methylamine hydrochloride (0·0252 mole, 62%), identified by comparing the i.r. spectrum of the residue after evaporation with that of an authentic sample.

2-Methylamino-3-methyliminomethylpyridine (II).—A solu- of 3-cyano-1-methylpyridinium iodide (25·0 g.) and methylamine hydrochloride (10·0 g.) in 2N-sodium hydroxide (300 ml.) was distilled. The volume was kept approximately constant by addition of water. The distillate (500 ml.) was extracted with chloroform and the extract was evaporated. 30% Methylamine in ethanol (20 ml.) was added to the residue and the mixture was left overnight at room temperature. After evaporation of the ethanol and the excess of methylamine the residue was fractionated to give a pale yellow liquid (7·7 g., 51%), b.p. 63°/0·3 mm.

Compound (II) was also prepared as follows. A solution of compound (I) (5·0 g.) in 30% methylamine in ethanol was left overnight at room temperature. After evaporation of the ethanol and the excess of methylamine the residue was fractionated, yielding *compound* (II) (4·1 g., 89%) (Found: C, 64·6; H, 7·4; N, 28·3. $C_8H_{11}N_3$ requires C, 64·4; H, 7·45; N, 28·15%), d_4^{20} 1·060, n_D^{20} 1·608, $\lambda_{max.}$ (EtOH) 267 (ε 7400) and 348 nm. (7700), $\nu_{max.}$ 3240 cm.$^{-1}$ (NH).

5-Bromo-2-methylaminopyridine-3-carbaldehyde.—A solution of bromine (0·75 g.) in ether (20 ml.) was slowly added to a solution of 2-methylaminopyridine-3-carbaldehyde (0·5 g.) in ether (15 ml.). A yellow precipitate formed immediately, and the suspension was evaporated to dryness. The residue (1·2 g.) was suspended in water, and the pH of the solution was adjusted to 8 with 2N-sodium hydroxide. The suspension was extracted with ether and the extract was evaporated to dryness. Recrystallization from light petroleum (b.p. 80—100°) gave yellow *needles* (0·7 g., 89%), m.p. 99·5° (Found: C, 39·1; H, 3·3; Br, 37·1; N, 12·9. $C_7H_7BrN_2O$ requires C, 39·1; H, 3·3; Br, 37·15; N, 13·05%), $\lambda_{max.}$ (EtOH) 273 (ε 10,600) and 388 nm. (5800); $\nu_{max.}$ 3350 (NH) and 1660 cm.$^{-1}$ (C=O).

2-Methyl(nitroso)aminopyridine-3-carbaldehyde.—To a solution of 2-methylaminopyridine-3-carbaldehyde (1·0 g.) and sodium nitrite (2·0 g.) in water, 2N-hydrochloric acid (8 ml.) was slowly added at room temperature. A precipitate formed slowly, and after 20 min. the suspension was extracted with ether. The extract was evaporated to dryness. Recrystallization from light petroleum (b.p. 80—100°) gave the *nitrosamine* as light yellow flat needles (0·9 g., 75%), m.p. 82° (Found: C, 51·1; H, 4·4; N, 25·3. C_7H_7-

[13] A. E. Chichibabin, R. A. Konowalowa, and A. A. Konowalowa, *Ber.*, 1921, **54**, 814.

[14] A. Albert and E. P. Serjant, ' Ionization Constants of Acids and Basis,' Chapman and Hall, London, 1962, ch. 3.

N_3O_2 requires C, 50·9; H, 4·25; N, 25·45%), $\lambda_{max.}$ (EtOH) 232 (ε 11,000) and 285 nm. (6400).

Cannizzaro Reaction of 2-Methylaminopyridine-3-carbaldehyde.—2-Methylaminopyridine-3-carbaldehyde (1·0 g.) in 10N-sodium hydroxide (10 ml.) was refluxed for 5 hr. under nitrogen. The cooled mixture solidified to a moist white mass which was suspended in water. The suspension was extracted with ether and the extract was evaporated to dryness. Recrystallization of the residue from light petroleum (b.p. 80—100°) yielded *2-methylamino-3-pyridylmethanol* as white needles (0·2 g., 39%), m.p. 104° (Found: C, 60·6; H, 7·1; N, 20·1. $C_7H_{10}N_2O$ requires C, 60·85; H, 7·3; N, 20·25%), $\lambda_{max.}$ (0·1N-HCl) 239 (ε 11,500) and 305 nm. (7800), $\lambda_{max.}$ (0·1N-NaOH) 244 (ε 9800) and 300 nm. (4100).

The aqueous solution from the ether extraction was adjusted to pH 4 with 5N-hydrochloric acid and evaporated to dryness. The residue was extracted with boiling acetone, the extract was reduced in volume and cooled, and *2-methylaminopyridine-3-carboxylic acid* separated as white crystals (0·3 g., 54%), m.p. 237°: (subl. and decomp.) (Found: C, 55·1; H, 5·2; N, 18·2. $C_7H_8N_2O_2$ requires C, 55·25; H, 5·3; N, 18·4%), $\lambda_{max.}$ (0·1N-HCl) 249 (ε 10,600) and 333 nm. (ε 6900), $\lambda_{max.}$ (0·1N-NaOH) 253 (ε 10,300) and 333 nm. (4400).

Decarboxylation of 2-Methylaminopyridine-3-carboxylic Acid.—The acid (70 mg.) was placed in a glass tube and heated at 240—250° for 30 min. A colourless liquid condensed in the colder part of the tube, and was identified as 2-methylaminopyridine by comparison of its i.r. spectrum with that of an authentic sample.[13]

3-Formyl-1-methyl-2-methylaminopyridinium Iodide.—2-Methylaminopyridine-3-carbaldehyde (I) (1·0 g.) and methyl iodide (10·0 g.) were heated at 105° for 1 week in a sealed tube. The excess of methyl iodide was evaporated off under reduced pressure and the residue was washed with acetone, dissolved in ethanol, and treated with active charcoal; crystallization gave yellow crystals of the *pyridinium iodide*, m.p. 167° (1·5 g., 73%) (Found: C, 34·7; H, 3·9; I, 45·5; N, 10·0. $C_8H_{11}IN_2O$ requires C, 34·55; H, 4·0; I, 45·65; N, 10·05%), $\lambda_{max.}$ (EtOH) 269 (ε 4600) and 326 nm. (4700).

1,2-Dihydro-1-methyl-2-methyliminopyridine-3-carbaldehyde.—3-Formyl-1-methyl-2-methylaminopyridinium iodide (1·5 g.) was dissolved in 0·5N-sodium hydroxide (50 ml.) and extracted with chloroform. The extract was evaporated to dryness. Recrystallization from light petroleum (b.p. 60—80°) gave the *imine* as red-orange needles, m.p. 73° (0·5 g., 62%) (Found: C, 64·0; H, 6·6; N, 18·8%; M^+, 150·0789. $C_8H_{10}N_2O$ requires C, 64·0; H, 6·7; N, 18·65%; *M*, 150·0793), $\lambda_{max.}$ (EtOH) 272 (ε 6000) and 412 nm. (4500).

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