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REACTIVITY OF 3-CYANO-1-METHYLPYRIDINIUM IODIDE IN AQUEOUS AMMONIA OR AMINE SOLUTIONS

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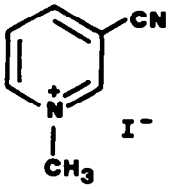
Abstract—Reaction of 3-cyano-1-methylpyridinium iodide (1) with aqueous methylamine or ethylamine yields 1-alkyl-3-alkyliminomethyl-2-imino-1,2-dihydropyridines 8. The related aldehydes 9 on alkaline treatment give 2-alkylamino-3-pyridinecarbaldehydes 10. Experimental evidence, including the related reactions of 1 with aqueous ammonia and diethylamine as well, suggest a general reaction sequence initiated by the attack of the nucleophile, followed by ring-opening, transamination and ring-closing steps.

We have previously reported[1] that the reaction between 3-cyano-1-methylpyridinium iodide (1) and aqueous NaOH (molar ratio 1:2) gives a mixture of the three isomeric 3-cyano-1-methyl-1,4-dihydropyridine (2), -1,6-dihydropyridine (3), and -1,2-dihydropyridine (4), and two isomeric 5-cyano-1-methyl-2-pyridone (5), and 3-cyano-1-methyl-2-pyridone (6), together with the ring-opened product 2-cyanoglutaconaldehyde sodium salt.



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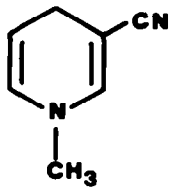

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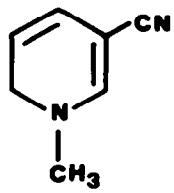

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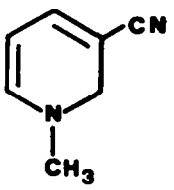

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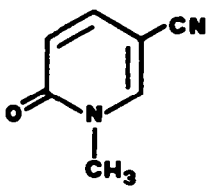

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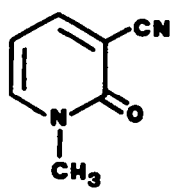

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We wish now to report studies on the reaction between 1 and aqueous solutions of ammonia or aliphatic amines. A number of papers appeared on the reactivity of pyridinium salts toward these nucleophiles. For example, it has been reported that N-alkoxypyridinium salts undergo ring-opening with aqueous solutions of secondary amines[2,3] as well as with liquid ammonia.[4] On the other hand, N-alkylpyridinium salts have been found to give stable addition products with aqueous secondary amines,[5] whereas reversible covalent amination occurs in the reaction with liquid ammonia.[4] We have found that in aqueous solution the reaction of 1 with diethylamine in the 1:3 molar ratio yields, in addition to the dihydropyridines 2–4 and pyridones 5 and 6, a product identified as 5-diethylamino-2-formyl-2,4-pentadienenenitrile (7).

$$(C_2H_5)_2N\text{–}CH\text{=}CH\text{–}CH\text{=}C(CHO)CN$$

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Reaction of 1 with methylamine under the same conditions yields as the major product a compound identified from its spectroscopic properties and from molecular weight determination (148, from mass spectrum) as 2-imino-1-methyl-3-methyliminomethyl-1,2-dihydropyridine (8a). Smaller amounts of the dihydropyridines 2–4 and pyridones 5 and 6 are also formed. The structure of 8a has been confirmed via an independent synthesis. In fact, 8a yields, by acid hydrolysis, the correspondent 1,2-dihydro-2-imino-1-methyl-3-pyridinecarbaldehyde (9a), that can be independently obtained from 2-amino-3-pyridinecarbaldehyde (12) according to the method described by Tschitschibabin *et al.*[6] (Scheme 1).

The UV spectra of 8a and 9a recorded in CCl_4 solution display absorption maxima at 400 and 425 nm respectively. It should be pointed out that a remarkable

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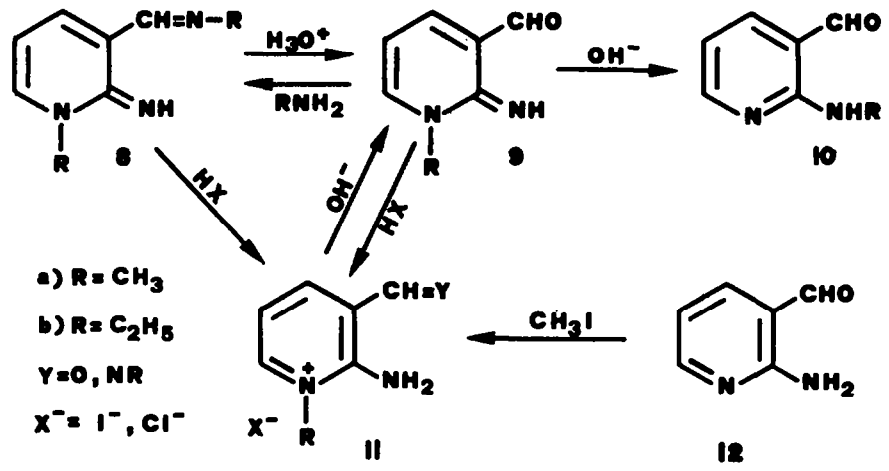


Scheme 1.

ipsochromic effect is observed in polar solvent. Thus, the UV spectra of **8a** and **9a** in aqueous solution exhibit maxima at 326 and 336 nm respectively. Since the UV spectra of the salts **11a**, whose heteroaromatic structure has been proved (Experimental), recorded either in $CHCl_3$ or in H_2O display maxima around 330 nm, it appears that **8a** and **9a** are likely to exist predominantly in the corresponding heteroaromatic cations structures of type **11**, when highly diluted in strongly polar solvents.

The formation of dihydropyridines and pyridones from the reaction between **1** and methylamine is affected by the molar ratio of the reagents. In fact, when a large excess of the amine is used, the only product recovered from the aqueous reaction medium by organic solvent extraction is the imino derivative **8a**. Under such conditions, the reaction between **1** and ethylamine as well yields practically one product, identified as 1-ethyl-3-ethyliminomethyl-2-imino-1,2-dihydropyridine (**8b**), whose acid hydrolysis yields the correspondent 1,2-dihydro-1-ethyl-2-imino-3-pyridinecarbaldehyde (**9b**). Both **9a** and **9b** on treatment with aqueous NaOH rearrange to the correspondent 2-alkylamino-3-pyridinecarbaldehydes **10**. The compound **10a** has been previously obtained[7] by steam distillation of a mixture of **1** and N NaOH, and its formation from **1** has been rationalized with a sequence of ring-opening and ring-closing steps, involving as key intermediate **9a**, that however had not been isolated. The availability of **9a** has allowed us to verify its actual conversion into **10a** on treatment with aqueous NaOH, which strongly supports the proposed mechanism.[7]

Finally, the reaction of **1** with a large excess of aqueous ammonia yields the aminoaldehyde **12**[8] and the 3-cyanopyridine (**13**) as major products, in addition to smaller amounts of the dihydropyridines **2–4** and pyridones **5** and **6**.

As already suggested,[1] the formation of dihydropyridines and pyridones in equimolar amounts can be explained with the attack of hydroxide ion on the α positions of the pyridinium cation, followed by a redox process between the hydroxydihydropyridines thus formed and the pyridinium cation.

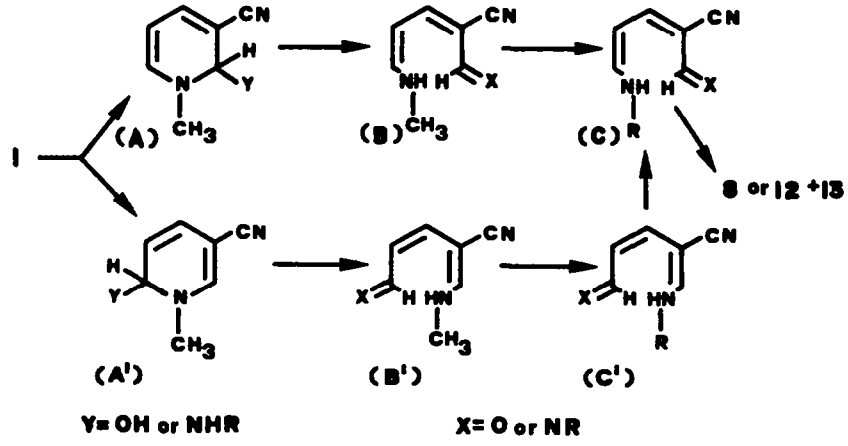
Concerning the formation of the products **8**, **12** and **13**, while the available evidence do not allow a detailed reaction sequence to be established, it appears nevertheless that the four following fundamental steps must be necessarily involved (Scheme 2).

(i) Attack of the OH^- ion or of the amine to the C-2 or C-6 of the pyridinium cation. In this connection, it can be usefully pointed out that Zoltewicz *et al.*[4] have demonstrated the addition of ammonia to both positions 2 and 6 of the cation **1**.

(ii) Ring-opening of the dihydropyridine adducts (A) or (A').

(iii) Transamination of the ring-opened intermediates (B) or (B').

(iv) Ring-closing.



Scheme 2.

Formation of 7 provides experimental evidence of the ring-opening step, and its conversion into 8a on treatment with aqueous methylamine shows that under present reaction conditions transamination can occur, and the transamination product can undergo recyclization. Furthermore, the simultaneous formation of 12 and 13 from the reaction of 1 with ammonia supports the suggested scheme, and can be traced to the double ring-closing capability, peculiar of 5-amino-2-formyl-2,4-pentadienenitrile (C, R=H, X=O), where the primary amino group can attack either the aldehyde group, leading to 13, or the nitrile group, yielding 12.

EXPERIMENTAL

The m.ps were taken upon a Tottoli apparatus, and are uncorrected. The UV spectra were recorded on a Perkin–Elmer 402 spectrophotometer and the IR spectra, as Nujol mulls or liquid films, on a Perkin–Elmer 177 grating spectrophotometer. The ^{1}H NMR spectra were recorded on a Varian EM-390 spectrometer, and the chemical shifts are reported as δ units. The *m/e* values were measured with a Hewlett–Packard 5980 A low resolution mass spectrometer. Column chromatography was carried out on Merck silica gel 70–230 mesh using, unless otherwise stated, a mixture of EtOAc MeOH 9:1 as eluent. All new compounds gave elemental analyses (C, H, N) within ±0.3% of the theoretical values.

Reaction between 1 *and diethylamine.* 1 (3.1 g, 12.6 mmol) was added to a soln of diethylamine (3.9 ml, 37.8 mmol) in H_2O (50 ml). The mixture was stirred 2 hr at room temp., extracted with CH_2Cl_2 (4 × 10 ml), the organic layer was separated, dried (Na_2SO_4), and evaporated under vacuum. Column chromatography of the residue (0.75 g, 150 g SiO_2) gave three main fractions: (i) a mixture of the three isomeric dihydropyridines 2–4 (0.17 g); (ii) (5) (0.13 g); (iii) a mixture, further resolved by crystallization from 2-propanol, of 6 (0.06 g) and 7 (0.17 g), 7, m.p. 68–69° (2-propanol); UV max (95° EtOH) 390 nm; IR $\bar{\nu}$ 2205, 1650 (sh), 1610 cm^{-1}; NMR ($CHCl_3$) δ 9.10 (s, 1, CHO), 7.50 (d, 1, H-5, $J_{4,5}$ = 12 Hz), 7.30 (d, 1, H-3, $J_{3,4}$ = 12 Hz), 5.74 (t, 1, H-4), 3.47 (q, 2, CH_2–N), 3.44 (q, 2, CH_2–N), 1.32 (t, 3, CH_3), and 1.28 ppm (t, 3, CH_3). Mol wt: Calc.: 178.23, Found: 178 (from mass spectrum).

Reaction between 1 *and methylamine.* 1 (3.1 g, 12.6 mmol) was added to a soln of 35% aqueous methylamine (3.7 ml, 37.8 mmol) in H_2O (46.5 ml).

The mixture was stirred 2 hr at room temp., extracted with CH_2Cl_2 (4 × 25 ml), the organic layer was separated, dried (Na_2SO_4), and evaporated under vacuum. The residue (0.98 g) was worked up as follows: (i) 0.48 g was resolved by column chromatography (100 g SiO_2) obtaining three main fractions: a mixture of 2–4 (0.05 g), 5 (0.04 g), and 6 (0.02 g); (ii) 0.5 g of the residue was added to N HCl (25 ml), and extracted with CH_2Cl_2 (4 × 25 ml); the aqueous layer was separated, made alkaline with solid Na_2CO_3, and extracted with CH_2Cl_2 (4 × 25 ml), the organic layer separated, dried (Na_2SO_4), and evaporated under vacuum. The residue solidified on freezing, and was further purified by crystallization from light petroleum ether to give 8a (0.30 g). 8a, m.p. 55–56°, UV max (CCl_4) 400 nm; (H_2O) 225, 253, 326 nm; IR $\bar{\nu}$ 3250, 1650, 1615, 1560, 1535 cm^{-1}; NMR (CCl_4) δ 0.09 (br s, 1, NH, disappeared on deuteration), 8.02 (d, 1, –CH=N, J = 1.1 Hz), 7.06 (dd, 1, H-6, $J_{6,4}$ = 1.2 Hz, $J_{6,5}$ = 6.6 Hz), 6.82 (dd, 1, H-4, $J_{4,5}$ = 6.9 Hz), 5.58 (dd, 1, H-5), 3.47 (d, 3, =N–CH_3, J = 1.1 Hz), and 3.41 ppm (s, 3, N–CH_3). Mol wt: Calc. 149.19, Found 149 (from mass spectrum). By bubbling gaseous HI into a soln of 8a in Et_2O, 11a (Y=NR, X$^-$ = I$^-$) was formed, mp 203–204° (2-propanol); UV max ($CHCl_3$) 263, 335 nm; (H_2O) 226, 255, 326 nm; IR $\bar{\nu}$ 3260, 3100, 1670, 1630, 1610, 1595 cm^{-1}; NMR (D_2O) δ 8.57 (d, 1, –CH=N, J = 1.3 Hz), 8.27–7.97 (group of signals, 2, H-4 + H-6), 7.08 (t, 1, H-5, J = 7.2 Hz), 3.89 (s, N–CH_3), and 3.55 ppm (d, 3, =N–CH_3, J = 1.3 Hz). In the NMR spectrum recorded in DMSO-d_6 solution a broad signal centered at δ 9.8 ppm attributable to the amine group is present.

The reaction was also carried out using a large excess of methylamine. 1 (3.1 g, 12.6 mmol) was added to a 35% aqueous soln of methylamine (92.6 ml, 945 mmol). The mixture was stirred 2 hr at room temp., extracted with CH_2Cl_2 (4 × 25 ml), the organic layer separated, dried (Na_2SO_4), and evaporated under vacuum to give essentially pure 8a (1.9 g).

Hydrolysis of 8a *to* 1,2 - *dihydro* - 2 - *imino* - 1 - *methyl* - 3 - *pyridinecarbaldehyde* (9a). A soln of 8a (0.1 g) in 1.5 N HCl (5 ml) was evaporated to dryness at 50° under reduced pressure. From the residue by several crystallization from anhyd. EtOH was obtained a solid (0.06 g) identified as 11a (Y=O, X$^-$=Cl$^-$), UV max (95° EtOH) 225, 259, 323 nm; IR $\bar{\nu}$ 3330, 1680, 1615, 1590 cm^{-1}; NMR (D_2O) δ 10.03 (s, 1, CHO), 8.67 (dd, 1, H-6, $J_{6,4}$ = 1.1 Hz, $J_{6,5}$ = 7.5 Hz), 8.34 (dd, 1, H-4, $J_{4,5}$ = 7.5 Hz), 7.23 (t, 1, H-5), and 3.97 ppm (s, 3, N–CH_3). The above chloride (0.06 g) was dissolved in 0.4 N NaOH (5 ml) and the soln rapidly extracted with CH_2Cl_2 (4 × 5 ml), the organic layer separated, dried (Na_2SO_4), and evaporated under vacuum to give a solid (0.04 g) identified as the free base 9a, m.p. 110–111° (benzene); mol wt: Calc. 136.15, Found 136 (from mass spectrum); UV max (CCl_4) 425 nm; (H_2O) 223, 257, 336 nm; IR $\bar{\nu}$ 3310, 1680, 1630, 1560, 1530 cm^{-1}; NMR ($CDCl_3$) δ 9.67 (s, 1, CHO), 7.41 (d, 2, H-6 + H-4), 5.88 (t, 1, H-5, J = 7.5 Hz), and 3.52 ppm (s, 3, N–CH_3). A very broad signal in the region δ 7–9 ppm, which disappeared on deuteration, can be attributed to the imine proton.

Synthesis of 9a *from* 2-*amino*-3-*pyridinecarbaldehyde* (12). MeI (1.5 ml) was added to a soln of 12 (0.06 g) in AcOEt (2 ml). The mixture was stirred at room temp. for 20 hr, the ppt formed was collected by suction, washed with Et_2O, and crystallized from anhyd. EtOH to give 11a (Y=O, X$^-$=I$^-$; 0.07 g), m.p. 210–211°; UV max (95° EtOH) 230, 258, 325 nm; IR $\bar{\nu}$ 3335, 3160, 1685, 1655, 1605, 1595 cm^{-1}; NMR (D_2O) δ 10.00 (s, 1, CHO), 8.66 (dd, 1, H-6, $J_{6,4}$ = 1.5 Hz, $J_{6,5}$ = 7.5 Hz), 8.32 (dd, 1, H-4, $J_{4,5}$ = 7.5 Hz), 7.24 (t, 1, H-5) and 3.95 ppm (s, 3, N–CH_3). In the NMR spectrum recorded in DMSO-d_6 soln a singlet at δ 9.20 ppm, attributable to the amine group is present.

According to Ref. 6, the above iodide (0.03 g) was added to 0.5 N NaOH (1 ml), the yellow soln extracted with CH_2Cl_2, the organic layer separated, dried (Na_2SO_4) and evaporated under vacuum to give essentially pure 9a.

Rearrangement of 9a *to* 2-*methylamino*-3-*pyridinecarbaldehyde* (10a). 9a (0.04 g) was added to 1.2 N NaOH (1.5 ml), the organic layer separated, dried (Na_2SO_4) and evaporated under vacuum. The residue (0.03 g) was identified as essentially pure 10a, by comparison with an authentic sample.[7]

Reaction between 1 *and ethylamine.* 1 (3.1 g, 12.6 mmol) was added to a 33% aqueous soln of ethylamine (138 ml, 945 mmol). The mixture was stirred at room temp. for 2 hr, extracted with CH_2Cl_2 (4 × 35 ml), the organic layer separated, dried (Na_2SO_4), and evaporated under vacuum to give essentially pure 8b (2.0 g). An analytical sample of 8b was obtained by crystallization from light petroleum ether: m.p. 51–52°; UV max (CCl_4) 405 nm; (H_2O) 227, 256, 332 nm; IR $\bar{\nu}$ 3240, 1650, 1615, 1560, 1535 cm^{-1}; NMR (CCl_4) δ 9.25 (broad signal, 1, NH, disappeared on deuteration), 8.02 (s, 1, –CH=N), 7.02 (dd, 1, H-6, $J_{6,4}$ = 1.5 Hz, $J_{6,5}$ = 6.7 Hz), 6.77 (dd, 1, H-4, $J_{4,5}$ = 6.7 Hz), 5.55 (t, 1, H-5), 3.96 (q, 2, N–CH_2), 3.53 (q, 2, N–CH_2), 1.27 (t, 3, CH_3), and 1.25 ppm (t, 3, CH_3). Mol wt: Calc. 177.24. Found: 177 (from mass spectrum).

Hydrolysis of 8b *to* 1,2 - *dihydro* - 1 - *ethyl* - 2 - *imino* - 3 - *pyridinecarbaldehyde* 9b. A soln of 8b (0.2 g) in N HCl (20 ml) was concentrated to small volume (2 ml) at 50° under reduced pressure (20 Torr). The residual solution was diluted with H_2O (5 ml), made alkaline with solid Na_2CO_3, extracted with CH_2Cl_2 (4 × 5 ml), the organic layer separated, and evaporated under vacuum. The residue was again submitted to the same procedure. The new residue (0.15 g) was essentially pure 9b, mol wt: Calc. 150.18. Found: 150 (from mass spectrum); UV max (CCl_4) 426 nm; (H_2O) 220, 260, 338 nm; IR $\bar{\nu}$ 3300, 1670, 1620, 1560, 1530 cm^{-1}; NMR ($CDCl_3$) δ 9.66 (s, 1, CHO), 7.6–7.3 (group of signals, 2, H-6 + H-4), 5.93 (t, 1, H-5, J = 7.2 Hz), 4.05 (q, 2, N–CH_2), and 1.35 ppm (t, 3, CH_3). A very broad signal in the region 9.3–7.9 ppm, which disappears on deuteration, can be attributed to the immine proton. 9b picrate, m.p. 175–176° (dec) (H_2O).

Rearrangement of 9b *to* 2-*ethylamino*-3-*pyridinecarbaldehyde*

10b. A soln of **9b** (0.15 g) in 1.2 N NaOH (5 ml) was stirred at room temp. for 12 hr, extracted with CH_2Cl_2, the organic layer separated, dried (Na_2SO_4) and evaporated under vacuum to give **10b** (0.12 g), UV max (95° EtOH) 269, 372 nm; IR $\bar{\nu}$ 3350, 1670, 1610, 1590 cm^{-1}; NMR (CCl_4) δ 9.75 (s, 1, CHO), 8.6–8.1 (broad signal, 1, NH, disappeared on deuteration), 8.23 (dd, 1, H-6, $J_{6,4}$ = 2.2 Hz, $J_{6,5}$ = 4.9 Hz), 7.62 (dd, 1, H-4, $J_{4,5}$ = 7.5 Hz), 6.50 (dd, 1, H-5), 3.58 (m, 2, N–CH_2), and 1.26 ppm (t, 3, CH_3). Mol wt: Calc. 150.18. Found: 150 (from mass spectrum). **10b**·HCl, m.p. 193–194° (2-propanol).

Reaction between **1** *and ammonia.* **1** (3.1 g, 12.6 mmol) was added to a 32% aqueous soln of ammonia (56.7 ml, 945 mmol). The mixture was stirred at room temp. for 2 hr, extracted with CH_2Cl_2 (4 × 25 ml), the organic layer separated, dried (Na_2SO_4), and evaporated under vacuum to give a residue, which was resolved by column chromatography [SiO_2, using as eluent AcOEt–CH_2Cl_2 1:9 (600 ml), AcOEt–CH_2Cl_2 1:1 (100 ml), AcOEt–CH_2Cl_2 5:1 (100 ml), AcOEt, (100 ml), AcOEt–MeOH 9:1 (300 ml) in the stated order]. The major components sequentially eluted were (i) a mixture of the dihydropyridines **2–4**; (ii) the 3-cyanopyridine (**13**); (iii) the 2-amino-3-pyridinecarbaldehyde (**12**); (iv) the pyridone **5**, and (v) the pyridone **6**.

Reaction of **7** *with methylamine.* A soln of **7** (0.02 g) in 35% aqueous methylamine (1 ml) was stirred at room temp. for 2 hr, extracted with CH_2Cl_2 (4 × 2 ml), the organic layer separated, dried (Na_2SO_4) and evaporated under vacuum to give essentially pure **8a** (0.013 g).

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