

## Nucleophilic Replacements in 4-Cyanopyridinium Salts

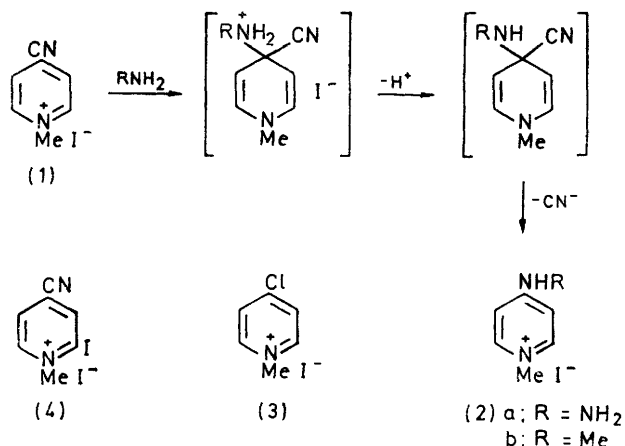
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The cyano-group in 1-alkyl-4-cyanopyridinium salts is readily replaced by hydrazine or aliphatic amines. The carbamoyl group does not have similar reactivity. Halogen exchange occurs during the quaternisation of 2-chloro-4-cyanopyridine with methyl iodide.

THE reaction of hydrazine with cyanopyridines in acid solution affords 3,6-dipyridyldihydropyridazines, from which 3,6-dipyridyltetrazines may be made by oxidation.<sup>1</sup> It was expected that similar reactions with quaternary salts of cyanopyridine would lead to diquaternary derivatives of the dipyridyltetrazines, but when this was tried with 4-cyanopyridine derivatives the reaction took a different course.

When a concentrated solution of 4-cyano-1-methylpyridinium iodide (1) in cold water was treated with hydrazine hydrate (2 equiv.) the yellow solution became deep blue, there was a brisk evolution of hydrogen cyanide, the colour rapidly changed through violet to deep red, and after a short time 4-hydrazino-1-methylpyridinium iodide (2a) crystallised out. This compound was identical with material made from 4-chloro-1-methylpyridinium iodide (3) and hydrazine.<sup>2</sup> The reaction of compound (1) with methylamine occurred with similar colour changes and evolution of hydrogen cyanide, and evaporation of the solution gave 1-methyl-4-methylaminopyridinium iodide (2b), which was also made from compound (3). Compound (3) and its precursor, 4-chloropyridine, are unstable, and the use of 4-cyanopyridine derivatives for these nucleophilic re-

placements offers the advantage of accessible and stable intermediates. It has the disadvantage that the products are coloured by traces of a red substance that



is very soluble in water or ethanol and is difficult to remove.

There was evidence of similar reactions with other aliphatic amines, *e.g.* piperidine and dodecylamine, but not with aniline, and also with other quaternary salts of 4-cyanopyridine, *e.g.* 4-cyano-1-dodecylpyridinium bro-

<sup>1</sup> F. Dallacker, *Monatsh.*, 1960, **91**, 294.

<sup>2</sup> B. D. Batts and E. Spinner, *Austral. J. Chem.*, 1969, **22**, 2611.

mide and 1,1'-hexamethylenebis-(4-cyanopyridinium) dibromide, but in many instances the physical properties of the products made purification insuperably difficult. A postulated reaction pathway is shown; a similar sequence of addition and elimination would explain the hydrolysis of 2-cyano-1-methylpyridinium iodide to 1-methyl-2-pyridone by sodium hydroxide,<sup>3</sup> but no colour changes or evolution of hydrogen cyanide were observed when the methiodides of 2- and 3-cyanopyridines were treated with hydrazine or methylamine.

The action of some other nucleophiles on 4-cyanopyridine methiodide was investigated briefly. No reaction was observed with sodium azide. With sodium thiophenolate in aqueous ethanol the colour change through violet to red was observed but no substitution occurred, and spontaneous evaporation of the solution gave a mixture of diphenyl disulphide and 4-carbamoyl-1-methylpyridinium iodide. The latter compound did not react with hydrazine or methylamine in a warm aqueous solution, but on prolonged heating at 90–100 °C hydrazine converted it into 4-carbazoyl-1-methylpyridinium iodide. The lability of the cyano-group is not shared by the carbamoyl group.

When 2-chloro-4-cyanopyridine was treated with 1 equiv. of methyl iodide in acetonitrile it was converted into 4-cyano-2-iodo-1-methylpyridinium iodide (4), none of the 2-chloro-methiodide being formed. This resembles the ready substitution of chlorine by iodine in the reactions of methyl iodide with 4-chloroquinoline<sup>4</sup> and with 2-amino-4-chloro-6-methylpyrimidine.<sup>5</sup> The solubility of compound (4) and of 4-cyano-1-methylquinolinium iodide in cold water was too low to permit reaction with hydrazine or amines under the conditions used with compound (1), but colour changes with these reagents suggested that similar substitutions should occur.

## EXPERIMENTAL

**1,1'-Hexamethylenebis-(4-cyanopyridinium) Dibromide.**—4-Cyanopyridine (14.4 g), 1,6-dibromohexane (16.9 g), and acetonitrile (50 ml) were heated under reflux for 9 h and allowed to cool slowly. The *quaternary salt* (8.3 g) was filtered off and crystallised from ethanol as pale yellow prisms, m.p. 265° (decomp.) (Found: C, 47.4; H, 4.6; N, 12.5. C<sub>18</sub>H<sub>20</sub>Br<sub>2</sub>N<sub>4</sub> requires C, 47.8; H, 4.4; N, 12.4%),  $\tau$  (D<sub>2</sub>O) 1.7–1.8 (4 H, m), 2.4–2.5 (4 H, m), 6.2 (4 H, t), and 8.8–9.6 (8 H, m). Prolonged heating of the mother liquor gave more quaternary salt (16 g).

**4-Cyano-1-dodecylpyridinium bromide**, prepared similarly, crystallised from acetonitrile as microcrystals, m.p. 201–203° (Found: C, 61.4; H, 8.3; N, 8.1. C<sub>18</sub>H<sub>29</sub>BrN<sub>2</sub> requires C, 61.2; H, 8.2; N, 7.9%),  $\tau$  [(CD<sub>3</sub>)<sub>2</sub>SO] 0.35–0.45 (2 H, m), 1.1–1.2 (2 H, m), 5.2 (2 H, m), and 8.7–9.1 (23 H, m).

**4-Cyano-2-iodo-1-methylpyridinium Iodide.**—2-Chloro-4-cyanopyridine (6.2 g), acetonitrile (35 ml), and methyl

iodide (6.5 g) were boiled under reflux for 6 h and allowed to cool. The product (0.7 g) was filtered off and the filtrate was evaporated to give almost pure 2-chloro-4-cyanopyridine. A better conversion was achieved by heating in acetonitrile with an excess of methyl iodide. The *quaternary salt* crystallised from water in orange-brown prisms, m.p. 206–207° (Found: C, 23.0; H, 1.5; N, 7.5. C<sub>7</sub>H<sub>6</sub>I<sub>2</sub>N<sub>2</sub> requires C, 22.6; H, 1.6; N, 7.5%).

**4-Hydrazino-1-methylpyridinium Iodide.**—4-Cyanopyridine methiodide (10 g) was dissolved in cold water (12 ml) and hydrazine hydrate (4 g) was added. The solution became blue and then red, with evolution of hydrogen cyanide [detected by benzidine-copper(II) acetate]. Dark red crystals of the crude product (5.2 g) were filtered off after 4 h and were freed from the coloured impurity by repeated crystallisation from methanol (carbon). The pure quaternary salt, m.p. 206–207°, was identical with a sample made from 4-chloro-1-methylpyridinium iodide [lit.,<sup>3</sup> m.p. 184° (decomp.)] (Found: C, 28.8; H, 4.2; N, 17.0. Calc. for C<sub>6</sub>H<sub>10</sub>IN<sub>3</sub>: C, 28.7; H, 4.0; N, 16.7%).

**1-Methyl-4-methylaminopyridinium Iodide.**—(a) Cyanopyridine methiodide (2.5 g) in water (5 ml) was treated with aqueous 33% methylamine (2.5 ml). The colour changed through violet to red, with evolution of hydrogen cyanide, and the solution was allowed to evaporate at room temperature until crystallisation began. The *product* (1.2 g) was filtered off and the filtrate was treated with acetone to precipitate a further 0.5 g. Crystallisation from ethanol (carbon) gave needles, m.p. 226° (Found: C, 33.6; H, 4.9; N, 11.5; I, 51.2. C<sub>7</sub>H<sub>11</sub>IN<sub>2</sub> requires C, 33.6; H, 4.4; N, 11.2; I, 50.8%),  $\tau$  (D<sub>2</sub>O) 1.9–2.0 (2 H, m), 3.05–3.2 (2 H, m), 6.02 (3 H, s), and 7.0 (3 H, s); *picrate*, m.p. 187–188° (Found: C, 44.4; H, 3.5; N, 20.2. C<sub>13</sub>H<sub>13</sub>N<sub>5</sub>O<sub>7</sub> requires C, 44.4; H, 3.7; N, 19.9%).

(b) 4-Chloro-1-methylpyridinium iodide (2.4 g) was treated cautiously with ethanolic methylamine (20 ml; ca. 33%) cooled in ice, and the mixture was then boiled under reflux until the solid dissolved. The product (0.65 g) crystallised on cooling and after crystallisation from ethanol was identical with the material from method (a), m.p. and mixed m.p. 225–226°. Addition of sodium hydroxide solution to a concentrated aqueous solution of the iodide caused precipitation of the iodide, m.p. 225–226°, and not of the free base.

The following were prepared similarly from quaternary salts of 4-cyanopyridine: **4-dodecylamino-1-methylpyridinium iodide**, m.p. 122–124° (Found: C, 53.6; H, 8.3; N, 7.3; I, 30.2. C<sub>18</sub>H<sub>33</sub>IN<sub>2</sub> requires C, 53.5; H, 8.2; N, 6.9; I, 31.4%), which crystallised as a hydrate, m.p. 94–96°, from water; **1,1'-hexamethylenebis-(4-methylaminopyridinium) dibromide**, m.p. 214–216° (Found: C, 44.8; H, 6.0; N, 11.6. C<sub>18</sub>H<sub>28</sub>Br<sub>2</sub>N<sub>4</sub>·H<sub>2</sub>O requires C, 45.2; H, 6.3; N, 11.7%).

**4-Carbamoyl-1-methylpyridinium Iodide.**—Sodium thiophenolate (1.3 g) in aqueous 35% ethanol (30 ml) was added to 4-cyano-1-methylpyridinium iodide (4.8 g) in water (10 ml). The solution was allowed to evaporate in an open beaker to ca. 10 ml. The solid was filtered off, extracted into hot water (leaving diphenyl disulphide), treated with carbon, and recovered by cooling in ice. The amide formed plates, m.p. 264–267°, identical with a sample made from isonicotinamide and methyl iodide in

<sup>3</sup> R. I. Ellin, *J. Amer. Chem. Soc.*, 1958, **80**, 6588.

<sup>4</sup> W. Brydówna, *Roczniki Chem.*, 1932, **12**, 89 (*Chem. Abs.*, 1933, **27**, 298).

<sup>5</sup> A. D. Ainley, F. H. S. Curd, W. Hepworth, A. G. Murray, and C. H. Vasey, *J. Chem. Soc.*, 1953, 59.

methanol (lit.,<sup>6</sup> m.p. 255°) (Found: C, 31.7; H, 3.6; N, 10.8. Calc. for C<sub>7</sub>H<sub>8</sub>IN<sub>2</sub>O: C, 31.8; H, 3.4; N, 10.6%).

*Reaction of 4-Carbamoyl-1-methylpyridinium Iodide with Hydrazine.*—4-Carbamoyl-1-methylpyridinium iodide (2.64 g) in water (10 ml) and hydrazine hydrate (0.5 g) was heated

at 95—100 °C for 1 h and the solution was then evaporated to small bulk and cooled. 4-Carbazoyl-1-methylpyridinium iodide crystallised out; m.p. 212—214°, not depressed in admixture with a sample made from ethyl isonicotinate by reaction with methyl iodide and then with hydrazine.

<sup>6</sup> P. Karrer, F. W. Kahut, R. Epstein, W. Jaffé, and T. Ishii, *Helv. Chim. Acta*, 1938, **21**, 223.

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