The filtrate was freed of solvent by heating *in vacuo*. Vacuum distillation of the oily residue yielded 17.5 g. of unchanged indole (b.p. 90–110°/0.1–0.3 mm.) and 3.4 g. 3-indoleacetonitrile (0.021 mole; 14.5% yield at 6.5% conversion) (b.p. 160–180°/0.2 mm.). The nitrile was characterized as its 1,3,5-trinitrobenzene complex, m.p. 138–139.5°.

Carrying out the above procedure with alumina (6 g., Alcoa F-20) and potassium acetate (5 g., 0.05 mole) in place of the dipotassium phosphate produced 3-indoleacetic acid in 55% yield and 3,3′-diindolylmethane in 20% yield.

3-Indoleacetonitrile from 1-Acetyl-3-acetoxymethylindole.—1-Acetyl-3-acetoxymethylindole (4.6 g., 0.02 mole) and potassium cyanide (2.6 g., 0.04 mole) were placed in ethanol (30 ml.) and water (30 ml.) and the mixture refluxed gently for 4 hr. Most of the solvent was then removed by heating *in vacuo*, and the residue obtained extracted with ether (three 50-ml. portions). These extracts were combined, dried over anhydrous sodium carbonate, and the ether removed by gentle heating. The residue (2.4 g.) was vacuum distilled and yielded 1.2 g. (0.0076 mole, 38%) 3-indoleacetonitrile (b.p. 155–163°/0.10–0.15 mm.). The product was characterized as its 1,3,5-trinitrobenzene adduct, m.p. 138.5–139.5°.

Experiments in the Synthesis of Pyridinium Amidines and Imino Esters

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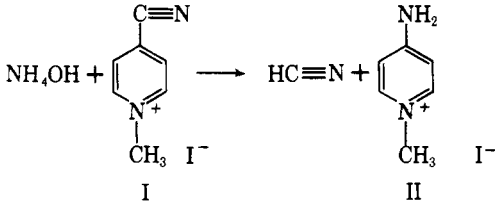
A comparison of the previously reported chemistry of formylpyridinium salts[1,2] and chloral[3] coupled with the ease of trichloroacetonitrile addition reactions[4,5] led us to investigate the possibility of forming pyridinium amidines and imino esters from 4-cyano-1-methylpyridinium iodide (I) with amines and alcohols.

The reaction of I with ethanol, either in the presence or absence of an equimolar quantity of hydrogen iodide led to a recovery of starting materials. Additionally, starting reagents were recovered in attempted reactions of I with aniline or 4-amino-1-methylpyridinium iodide (II). However, the reaction of I with ammonium hydroxide led to an over-all displacement of the cyano function and formation of II. This displacement reaction is analogous to the formation of methyl-4-pyridone from I with excess alkali.[6]

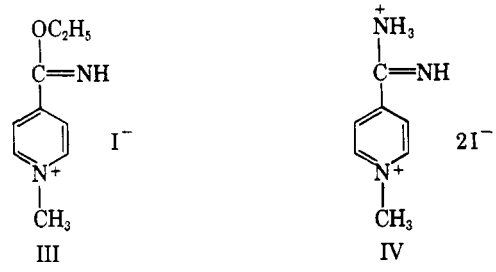


I II

The ammonolysis results using I led us to experiment under similar conditions with the corresponding carbamyl, carboxy, and carbomethoxy derivatives, as well as with isonicotinonitrile, and *p*-nitrobenzonitrile However, the formation of an amine was specific to I.

A blue color followed by red was noticed in the reaction of I with bases. Patton[6] also noticed the transient blue color, the nature of which he did not investigate further. It was reported previously that pyridinalchlorimine dimethyl sulfate gave a brilliant blue color with excess triethylamine.[7] Presumably 4-cyano-1-methylpyridinium methyl sulfate was formed by the elimination of hydrogen chloride, and further reaction of the cyano compound with base resulted in color. It was also found that addition of aqueous base to mixtures of 4-formyl-1-methylpyridinium iodide oximes with acetic anhydride gave a blue color, again through the probable formation of I.[8] The *anti* oxime produced color at a faster rate but quantitative data are not available. In all of these studies the chromogenic substance was present in low concentrations and could not be isolated. The blue color may be related to the formation of free radicals in the reduction of I by some reaction intermediate.[9]

Though no success was met in synthesizing amidines and imino ester derivatives from I, isonicotinimidic acid ethyl ester methiodide (III) and 4-amidino-1-methylpyridinium iodide hydroiodide (IV) were obtained through an alternate route involving methylation of the appropriate pyridine base.



III IV

It was interesting to find that whereas 2,2,2-trichloroacetamidine is unstable at room temperature and trimerizes spontaneously to give a mixture of triazines,[10] IV is stable both in the solid state and in refluxing ethanol. This may indicate a decrease in the nucleophilic character and basic strength of the imino group of IV relative to the same function in 2,2,2-trichloroacetamidine, thus leading to an inhibition of the trimerization reaction.

Reaction of the imino ester III with ammonium hydroxide gave a complicated mixture of products. Chromatographic separation followed by infrared analysis indicated II and 4-carbamyl-1-methylpyridinium iodide as two of the components. Since under similar ammonolysis conditions 4-carbomethoxy-1-methylpyridinium iodide did not give the 4-amino derivative the intermediate formation of I would be deduced logically.

The general results of this investigation indicate that the strongest electrophilic site in I exists on the ring

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carbon at the 4-position. Therefore, trichloroacetonitrile chemistry based on the low electronic density on the carbon in the nitrile may not be used as a basis on which to predict the reactions of I.

It was reported that the higher the electronic density on a carbon atom carrying a nitrile function, the greater is the intensity of the infrared absorption resulting from vibration of the nitrile bond.[11a] There are many exceptions to this generality[11b] but the correlation is sometimes true in a closely related class of compounds and perhaps is valid in a comparison of isonicotinonitrile and its methiodide (I). Whereas isonicotinonitrile exhibited characteristic nitrile absorption, no absorption appeared in the same spectral region of I. This further reflects the strong electrophilic character of the 4-position ring carbon of I.

Experimental[12]

4-Cyano-1-methylpyridinium iodide (I) was obtained as bright orange needles, m.p. 200–202° dec., reported,[13] 197–198.5°. Infrared absorption maxima in potassium bromide using a Perkin–Elmer Infracord, μ (s, strong; m, medium; w, weak) 3.75 w, 3.25 s, 6.10 m, 6.85 m, 6.95 m shoulder, 7.5 w, 7.8 m shoulder, 7.9 s, 8.18 w, 8.31 w, 8.5 m, 8.7 w, 9.5 w, 11.66 s, 11.89 w, 13.98 w.

Anal. Calcd. for $C_7H_7IN_2$: C, 34.2; H, 2.9; I, 51.6. Found: C, 34.4; H, 3.0; I, 51.6.

4-Amino-1-methylpyridinium Iodide (II).—To 1.8 g. (0.0193 mole) of 4-aminopyridine in 20 ml. of acetone was added 3.0 ml. of methyl iodide. Within 5 min. a crystalline solid precipitated. The mixture was allowed to stand overnight, then filtered to give 3.0 g. (65%) of a colorless solid, m.p. 179–82°.

Anal. Calcd. for $C_6H_9IN_2$: C, 30.5; H, 3.8; I, 53.8. Found: C, 30.2; H, 3.9; I, 53.0.

Ammonolysis of 4-Cyano-1-methylpyridinium Iodide.—A solution of 2.5 g. of 4-cyano-1-methylpyridinium iodide in 12 ml. of concentrated ammonium hydroxide was heated overnight at 70° in a 200-ml. capped bottle. The reaction mixture was added to a 3 ft. × 5/8 in. column of Woelm basic aluminum oxide prepared using *n*-butyl alcohol. The chromatogram was developed using methanol. The main band was purple; remaining colored zones were red and orange-brown. The purple zone was collected, ether was added to precipitate 1.0 g. of a purple solid, m.p. 185–189°, whose infrared absorption spectrum corresponded exactly to that of an authentic sample of 4-amino-1-methylpyridinium iodide. It was found later that repeated treatment with charcoal in methanol will remove the color.

Isonicotinimidic acid ethyl ester dihydrochloride was obtained as colorless crystalline solid, m.p. 240–250° dec.; reported,[14] 252–253°. A potentiometric titration of this crude material indicated the presence of equivalent amounts of a strong and weak acids, approximate pK_a values, 3.3 and 9.0.

Isonicotinimidic Acid Ethyl Ester.—Crude isonicotinimidic acid ethyl ester dihydrochloride (60 g.) was added to 1.0 l. of 10% potassium carbonate at 0°. The cold solution was extracted with three 160-ml. portions of ethyl ether. The etherates were combined, dried over potassium carbonate, and evaporated on a rotating evaporator to give 28 g. of a colorless liquid, b.p. 67° (0.28 mm.).

Anal. Calcd. for $C_8H_{10}N_2O$: C, 64.0; H, 6.7; N, 18.7. Found: C, 64.4; H, 6.8; N, 18.3.

Isonicotinimidic Acid Ethyl Ester Methiodide.—A solution of isonicotinimidic acid ethyl ester (6.5 g., 0.043 mole), methyl iodide, (6.0 g., 0.043 mole), and 25 ml. of acetone was allowed to stand at room temperature for 3 hr., then filtered to give 5.6 g. of a yellow crystalline solid. The product was recrystallized from absolute ethanol to give 4.4 g. (35.1%) of yellow needles, m.p. 193–194° dec.

Anal. Calcd. for $C_9H_{13}IN_2O$: C, 37.1; H, 4.5; I, 43.4. Found: C, 37.1; H, 4.5; I, 43.6.

Isonicotinamidine Hydrochloride Hydrate.—The method described by Gardner, Wenis, and Lee[15] was followed in that 3.5 g. (0.023 mole) of isonicotinimidic acid ethyl ester, 15 ml. of ethanol, 5 ml. of water, and 1.2 g. of ammonium chloride were combined and allowed to reflux for 4 hr. The solution was cooled to room temperature and filtered to give 2.6 g. (56%) of a colorless crystalline solid, m.p. 246–248°; reported,[15] 242–243°; reported,[16] 230–232°.

Anal. Calcd. for $C_6H_8N_3Cl \cdot 2\ 1/2\ H_2O$: C, 35.7; H, 6.5; neut. equiv., 202. Found: C, 35.7; H, 6.2; neut. equiv., 200; pK_a 9.9.

4-Amidino-1-methylpyridinium Iodide Hydroiodide.—A methanolic solution (10 ml.) of isonicotinamidine hydrochloride (0.5 g., 0.0025 mole) and methyl iodide (2 g.) was refluxed for 18 hr. Ether was added to precipitate 0.7 g. (72%) of an orange solid decomposing over 206°. The conversion of a chloride salt to the corresponding iodide by the addition of methyl iodide was noted previously.[17]

Anal. Calcd. for $C_7H_{11}I_2N_3$: C, 21.5; H, 2.8; neut. equiv., 391. Found: C, 21.7; H, 2.9; neut. equiv., 394; pK_a 8.5.

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(12) All melting points are uncorrected. The pK_a values were determined at room temperature (25–27°) from potentiometric titration data, assuming pK_a to be the pH of half neutralization. In each case approximately 100 mg. of compound dissolved in 10 ml. of water was titrated with 0.1 *N* sodium hydroxide or hydrogen chloride.

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Vincaminyl Alcohol and Vincamine Nitrite

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Plat, Manh, Le Men, Janot, Budzikiewicz, Wilson, Durham, and Djerassi have recently reported the conversion of vincamine into eburnamonine by means of lithium aluminum hydride.[1]

In the course of our investigations of the structures of vincamine and other alkaloids of *Vinca minor*, prior to the publication of the structure of vincamine by Trojanek, *et al.*,[2] we also studied the reduction of vincamine by lithium aluminum hydride. By means of lithium aluminum hydride vincamine was reduced to an amino alcohol which we have named vincaminyl alcohol. Reduction of the carbomethoxy group in vincamine[3] to a primary alcoholic group was quite evident from the anal-

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