Synthesis of 3-Alkyl-2,6-dicyanopyridines by a Unique Rearrangement. Preparation of Fusaric Acid Analogs

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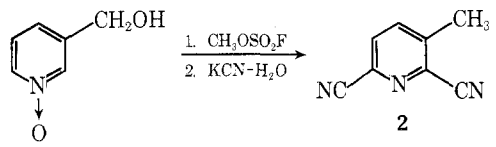
The reaction of 3-hydroxymethylpyridine 1-oxide with methyl fluorosulfonate and potassium cyanide produced a simple, direct synthesis of 2,6-dicyano-3-methylpyridine. The mechanism and scope of this reaction are discussed. Chemical transformations of 2,6-dicyano-3-methylpyridine produced 6-cyano-5-methylpicolinic acid and, by acid hydrolysis, methyl 6-cyano-5-methylpicolinate via an imino ester and dimethyl 3-methyl-2,6-pyridinedicarboxylate through a bis imino ester. In a similar fashion 3-α-hydroxy-*n*-butylpyridine 1-oxide gave 3-*n*-butyl-2,6-dicyanopyridine, which was converted to 6-cyano-5-*n*-butylpicolinic acid and 2,6-biscarbamyl-3-*n*-butylpyridine, analogs of fusaric acid.

The reaction of 1-alkoxypyridinium quaternary salts with cyanide ion to give α- and γ-cyanopyridine derivatives is a general reaction.[1,2] Thus far, there are no reports on the use of methyl fluorosulfonate[3] to generate such 1-alkoxypyridinium salts by alkylation of pyridine 1-oxides. Moreover, methyl fluorosulfonate is such a powerful alkylating agent that it will react with a variety of functional groups such as amides, nitriles, ethers, esters, etc.[4] The question then arises as to what reactions would occur when a pyridine 1-oxide bearing such a functional group is allowed to react with methyl fluorosulfonate and cyanide ion. We wish to report the novel reaction of 3-hydroxymethylpyridine 1-oxide (**1**)[5] with these reagents to form 2,6-dicyano-3-methylpyridine (**2**) and to comment on the scope of this reaction and its utilization for the synthesis of fusaric acid analogs.



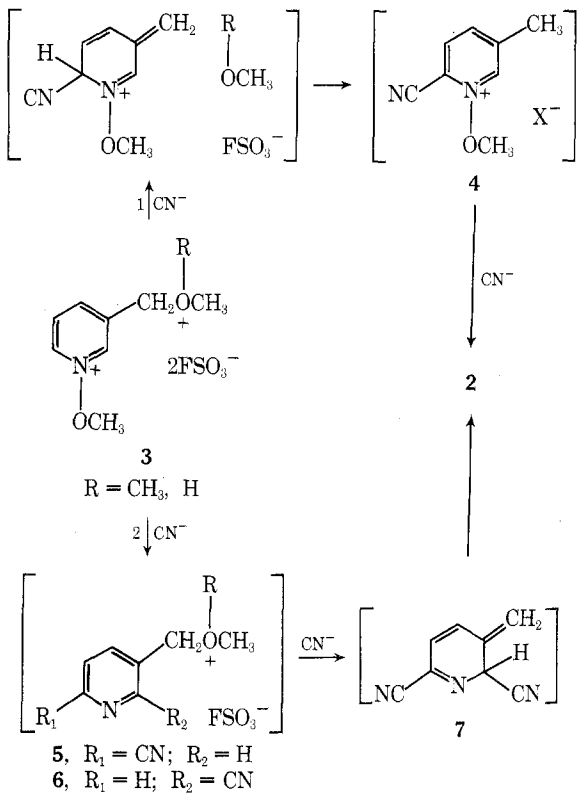
1 **2**

Treatment of **1** with 3 equiv of methyl fluorosulfonate under anhydrous conditions resulted in a mildly exothermic reaction, leaving a liquid product. Addition of an aqueous solution of potassium cyanide to this liquid resulted in a vigorously exothermic reaction. The product **2** was easily isolated, the yield being consistently in the 30–35% range. While the exothermic reaction upon the addition of potassium cyanide could be controlled on a small scale, this procedure was not feasible for the preparation of larger quantities of **2**. Thus, the product from the reaction of **1** and methyl fluorosulfonate was dissolved in a limited[6] amount of methylene chloride and added to a cooled mixture of an aqueous potassium cyanide solution and methylene chloride. The reaction was easily controlled and the yield of **2** remained the same as above.

The structure of **2** was established from its NMR spectral data, which consisted of only a methyl absorption at δ 2.72 and two pyridine proton absorptions, H_4 and H_5, as an AB quartet with overlapping inner lines and a coupling constant of 9 Hz. Thus, a 2,3,4- or a 2,4,5-trisubstituted pyridine is ruled out on the basis of the coupling constants as well as chemical shifts of the pyridine protons.

The reaction to form **2** can be rationalized by assuming alkylation of the *N*-oxide to form a 1-methoxypyridinium salt and alkylation of the primary alcohol to form a methyl ether with liberation of fluorosulfonic acid. The ether moiety would in turn be either alkylated with methyl fluorosulfonate to form an oxonium ion or protonated with fluorosulfonic acid to give intermediate **3** (see Scheme I). The product **2** would then arise from two distinct reactions of

Scheme I



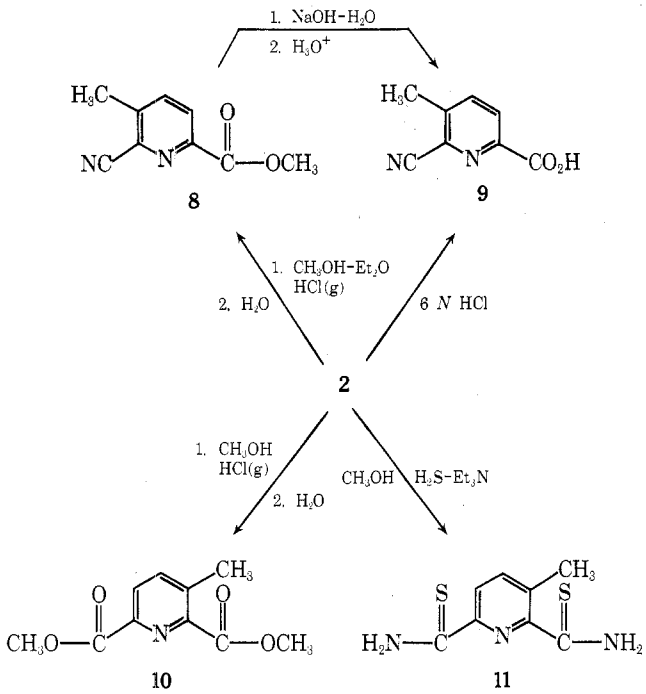
cyanide ion with **3**, namely, nuclear substitution with expulsion of dimethyl ether (or methanol) and nuclear substitution with expulsion of methoxide. The order in which these reactions occur is unknown but, for reasons to be discussed shortly, we favor pathway 1. Cyanide attack on **3** could occur at either the 2 or 6 position of the pyridine ring, expelling dimethyl ether or methanol. Aromatization would then give **4** or its equivalent for purposes of our argument, the 1-methoxy-2-cyano-3-methylpyridinium salt. A second ring attack by cyanide ion with expulsion of methoxide would give **2**. There is some evidence to support the driving forces operative in this mechanism. It has been shown that 1-alkoxypyridinium salts bearing a cyano,[7] methoxycarbonyl,[7] or keto[8] function in the 2 position direct cyanide ion exclusively to the 6 position. In pathway 2 nuclear substitution by cyanide ion would give either **5** or **6** with expulsion of methoxide. Further ring substitution by cyanide ion would give **7**, but the driving force in this

mechanism favoring ring over side-chain substitution is not obvious.

The yield of **2** is undoubtedly reduced by competing reactions which are possible under these alkaline conditions. Abstraction of a proton from the *N*-methoxyl would generate formaldehyde and a pyridine.[9,10] Dealkylation of an oxonium ion or neutralization of a protonated ether, as in **3**, would result in only monosubstitution of the pyridine ring by cyanide ion.

Some of the chemistry of 2,6-dicyano-3-methylpyridine (**2**) is depicted in Scheme II.

Scheme II

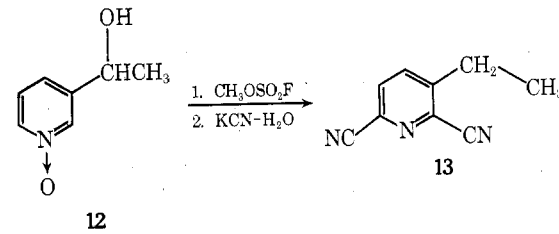


Treatment of **2** with 3 equiv of methanol in diethyl ether and saturation with anhydrous hydrogen chloride resulted in precipitation of an imino ester hydrochloride. Hydrolysis of this salt gave a solid, methyl 6-cyano-5-methylpicolinate (**8**), in 52% yield. The presence of the ester function affected the chemical shifts of the pyridine ring protons, which now appeared as two well-separated doublets at δ 7.93 and 8.27. Relative to **2** one of the ring protons experienced a slight downfield shift ($\Delta\delta$ 0.05) while the other proton showed a significantly greater downfield shift ($\Delta\delta$ 0.31), indicating that the methoxycarbonyl group was adjacent to this proton. Saponification of **8** gave the carboxylic acid **9**.

The methyl group in **2** conferred some protection upon the adjacent nitrile. After heating **2** with dilute hydrochloric acid and cooling, 6-cyano-5-methylpicolinic acid (**9**) spontaneously crystallized. Prolonged heating in acid, however, reduced the yield of **9**.

The bis imino ester dihydrochloride of **2** was formed by treating a methanolic solution of **2** with anhydrous hydrogen chloride. Hydrolysis gave the diester **10**, the NMR spectrum of which exhibited a methoxycarbonyl absorption (six protons) at δ 4.05. The chemical shifts of the two ring protons were again affected relative to **2** and appeared as two doublets at δ 7.82 and 8.19.

To determine the scope of this reaction, pyridine 1-oxides bearing secondary and tertiary alcohol functions in the 3 position were synthesized. 3-α-Hydroxyethylpyridine 1-oxide (**12**), prepared from 3-α-hydroxyethylpyridine[11] by oxidation with aqueous hydrogen peroxide in acetic acid, reacted with methyl fluorosulfonate and potassium cyanide and gave **13** in 30% yield. The NMR spectrum of **13** displayed the methyl and methylene absorptions at δ 1.45 and



3.09, respectively, and the ring proton absorptions as an AB quartet with overlapping inner lines.

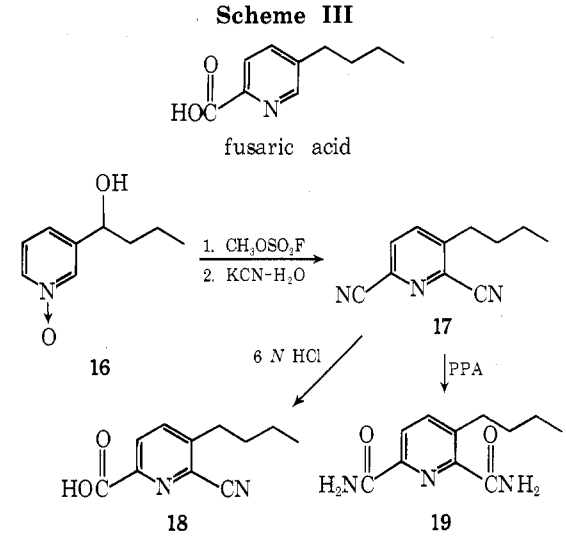
3-α-Hydroxyisopropylpyridine[12] was converted to its *N*-oxide **14** with aqueous hydrogen peroxide in acetic acid. TLC analysis of the crude product from the reaction of **14** with methyl fluorosulfonate and potassium cyanide on silica gel showed three major and three minor components. We did not pursue the identification of these components.

3-α-Hydroxybenzylpyridine[11] was oxidized with aqueous hydrogen peroxide to 3-α-hydroxybenzylpyridine 1-oxide (**15**). Reaction of **15** with methyl fluorosulfonate and potassium cyanide gave a dark, viscous oil but no identifiable products.

A consequence of the successful reaction of **12** with methyl fluorosulfonate and potassium cyanide was the synthesis of a number of analogs of fusaric acid (5-*n*-butylpicolinic acid), an antibiotic produced by the fungus *Fusarium oxysporum*. Fusaric acid is a potent noncompetitive inhibitor of dopamine-β-hydroxylase, both in vitro and in vivo.[13] 5-*n*-Butylpicolinamide was also reported to be an effective dopamine-β-hydroxylase inhibitor with hypotensive properties.[14]

3-α-Hydroxy-*n*-butylpyridine 1-oxide (**16**) was prepared by oxidation of 3-α-hydroxy-*n*-butylpyridine[15] with aqueous hydrogen peroxide in acetic acid. The product from the reaction of **16** with methyl fluorosulfonate and cyanide ion was obtained by distillation and 3-*n*-butyl-2,6-dicyanopyridine (**17**) was isolated as an oil by silica gel column chroma-

Scheme III



tography. In the NMR spectrum of **17** the pyridine ring protons appeared as an AB quartet with overlapping inner lines. Heating **17** with 6 *N* hydrochloric acid for 5 hr and cooling resulted in the spontaneous crystallization of **18**. The crystalline bisamide **19** was prepared by treating **17** with polyphosphoric acid at 120° and quenching with water.[16] These fusaric acid analogs are currently being evaluated for possible pharmacological properties.

Experimental Section

2,6-Dicyano-3-methylpyridine (2). A. In a dry one-neck, 100-ml, round-bottom flask protected with a $CaCl_2$ drying tube was placed 4.0 g (0.032 mol) of 3-hydroxymethylpyridine 1-oxide.[5] While this solid was stirred with a magnetic bar 10.72 g (0.094 mol) of methyl fluorosulfonate[3] was added in one portion, resulting in a mildly exothermic reaction, and the solution was stirred for 20 min. A solution of 10 g (0.154 mol) of KCN in 30 ml of water was added to the above solution in portions over a 5-min period, resulting in a very rigorous exothermic reaction which was moderated with a cold water bath. After stirring for several hours, the solution was extracted with CH_2Cl_2 and dried ($MgSO_4$) and the solvent was removed in vacuo to give an oil which was Kugelrohr distilled. After a small forerun was discarded, the product was collected at 115–120° (0.01–0.15 mm) as an oil which solidified to yield 1.7 g; TLC on silica gel with CH_2Cl_2 showed a major component (R_f 0.25) with some impurities at the origin. Recrystallization from 4 ml of EtOH gave, after drying, 1.5 g (32.7%): mp 78–80°, homogeneous by TLC; ir max (melt) 4.46 μ; NMR ($CDCl_3$) δ 2.72 (s, 3 H, 3-CH_3) and 7.75, 7.90, 7.93, and 8.07 (AB quartet, J = 9 Hz, 2 H, pyridine H_4, H_5, calcd[17] δ_{AB} 7.88 and 7.96).

Anal. Calcd for $C_8H_5N_3$: C, 67.12; H, 3.52; N, 29.36. Found: C, 66.94; H, 3.47; N, 29.48.

B. In a dry two-neck, 200-ml, round-bottom flask protected with a $CaCl_2$ drying tube and equipped with an addition funnel (equilibrating side arm) was placed 25 g (0.20 mol) of 3-hydroxymethylpyridine 1-oxide.[5] While this solid was stirred with a magnetic bar, 75.2 g (0.66 mol) of methyl fluorosulfonate was added in portions from the addition funnel. After completion of the addition, the product was stirred for 1 hr at ambient temperature. This liquid was dissolved in 50 ml of CH_2Cl_2[6] and transferred to a dry addition funnel (without equilibrating side arm), protected with a $CaCl_2$ drying tube. This addition funnel was attached to a three-neck, 1-l., round-bottom flask equipped with a condenser and mechanical stirrer with a Teflon paddle. The flask was charged with 65 g (1.0 mol) of KCN, 100 ml of water, and 100 ml of CH_2Cl_2 and cooled in ice. The solution from the addition funnel was then added portionwise with stirring. After stirring overnight at room temperature the contents of the flask were diluted with 100 ml of water and 100 ml of CH_2Cl_2 and filtered through Celite. The organic phase was separated, the aqueous phase was again extracted with CH_2Cl_2, and the combined organic extract was dried ($MgSO_4$). Removal of solvent in vacuo left a dark oil which was Kugelrohr distilled at 125–135° (0.1–0.4 mm). The resulting oil solidified to yield 15.11 g of a brown solid; TLC analysis on silica gel with CH_2Cl_2 showed a major component with R_f 0.25 along with some material at the origin. Recrystallization from 5 ml of EtOH gave 12.0 g which by TLC still indicated a slight impurity at the origin. A second recrystallization from 10 ml of EtOH gave, after drying, 10.2 g (35.66%), mp 77–79°, homogeneous by TLC (conditions cited).

6-Cyano-5-methylpicolinic Acid (9). A. 2,6-Dicyano-3-methylpyridine (**2**, 1.0 g, 0.007 mol) was treated with 6 ml of 6 N HCl, heated in an oil bath at 115° for 5 hr, and left at room temperature overnight. The resulting solid was collected by filtration and dried to yield 0.79 g (69.6%), mp 190–193°. This material was recrystallized from 10 ml of n-BuOH and dried to yield 0.63 g, mp 192–194°, ir max (Nujol) 5.86 μ (s).

Anal. Calcd for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 58.99; H, 3.72; N, 17.13.

B. Methyl 6-cyano-5-methylpicolinate (**8**, 0.65 g, 0.0037 mol) was dissolved in 5 ml of MeOH, treated with 0.18 g (0.0045 mol) of NaOH in 4 ml of water, and stirred overnight at room temperature. The MeOH was removed in vacuo using a Büchi evaporator and a water bath at room temperature. The residue, upon treatment with 0.4 ml of concentrated HCl, gave a precipitate which was collected and dried to yield 0.33 g, mp 192.5–193°. The infrared spectrum was entirely superimposable with that of the acid above.

Methyl 6-Cyano-5-methylpicolinate (8). In a dry three-neck, 100-ml, round-bottom flask equipped with a condenser ($CaCl_2$ drying tube) and gas inlet tube was placed 4.3 g (0.030 mol) of **2**, 2.37 g (0.075 mol) of MeOH, and 50 ml of Et_2O. The solution was cooled in ice and treated with HCl(g) for 30 min, causing a yellow solid to separate. The heterogeneous solution was stirred at room temperature overnight and the solid was collected and dried to yield 6.9 g of the imino ester hydrochloride, mp 75–76° dec. Of this material 4.4 g (0.021 mol) was dissolved in 6 ml of water and heated on a steam bath. After 2 min a solid separated and after 10 min the solution was cooled and the solid was collected, washed with water, and dried to yield 1.90 g (51.4%): mp 108–109°; ir max (Nujol) 4.49 (w) and 5.75 μ (s); TLC analysis on silica gel with diethyl ether showed a single component. Recrystallization of 0.40 g from a minimum of n-BuOH gave, after drying, the analytical specimen of 0.30 g: mp 107–108.5°; ir max (Nujol) 4.48 (w) and 5.75 μ (s); NMR ($CDCl_3$) δ 2.80 (s, 3 H, 5-CH_3), 4.15 (s, 3 H, -CO_2CH_3), 7.85, 7.99, 8.22, and 8.35 (AB quartet, J_{AB} = 8 Hz, 2 H, pyridine H_3 and H_4, calcd[17] δ_{AB} 7.93 and 8.27).

Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.04; H, 4.58; N, 15.78.

Dimethyl 3-Methyl-2,6-pyridinedicarboxylate (10). A dry, three-neck, 100-ml, round-bottom flask equipped with a condenser ($CaCl_2$ drying tube) and gas inlet tube was charged with 5.8 g (0.040 mol) of **2** and 60 ml of MeOH and then cooled in ice and saturated with HCl(g) for 1 hr. The stoppered flask was refrigerated overnight and the MeOH was removed in vacuo. Trituration of the residue with Et_2O gave 9.4 g (theory 9.14 g) of a solid which was dissolved in 20 ml of water and warmed on a steam bath. After 2 min an oil separated. The cooled solution was treated with $NaHCO_3$, diluted with water, extracted with Et_2O, and dried ($MgSO_4$). Removal of solvent in vacuo gave an oil which solidified to yield 5.1 g: mp 67–71.5°; ir max (Nujol) 5.82 μ; TLC on silica gel with Et_2O showed a major component and a small amount of less mobile material. Of the above material, 4.0 g was recrystallized from 16 ml of n-BuOH to yield, after drying, 3.1 g: mp 75–77°; TLC analysis now showed a single component; ir max (Nujol) 5.82 μ (s); NMR ($CDCl_3$) δ 2.66 (s, 3 H, 3-CH_3), 4.05 (s, 6 H, O=C-OCH_3), 7.74, 7.89, 8.15, 8.27 (2 H, pyridine H_4, H_5, AB quartet with J = 8 Hz, calcd[17] δ_{AB} 7.82 and 8.19).

Anal. Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.32; N, 6.70. Found: C, 57.15; H, 5.32; N, 6.69.

2,6-Bisthiocarbamyl-3-methylpyridine (11). Compound **2**, (3.4 g, 0.024 mol) was dissolved in 25 ml of MeOH and treated with 1 ml of triethylamine. This solution was saturated with H_2S for 20 min and then stirred overnight at room temperature. During this time a yellow solid separated, redissolved, and separated again. The solvent was removed in vacuo and the residue was dissolved in 100 ml of EtOH, concentrated to 50 ml where a solid started to separate, and left at room temperature. The resulting solid was collected and dried to give 3.0 g but had a strong odor of H_2S. This material was recrystallized from 75 ml of EtOH to give 2.1 g after drying in vacuo over refluxing water: mp 194–198° dec; ir max (Nujol) 3.05 (s), 3.15 (s), 6.20 μ (s).

Anal. Calcd for $C_8H_9N_3S_2$: C, 45.50; H, 4.30; N, 19.90; S, 30.31. Found: C, 45.45; H, 4.57; N, 19.82; S, 30.70.

3-α-Hydroxyethylpyridine 1-Oxide (12). 3-α-Hydroxyethylpyridine[11] (84 g, 0.68 mol) in 200 ml of glacial AcOH was treated with 50 ml of 35% aqueous H_2O_2 and heated at 70° in an oil bath for 3 hr. An additional 34 ml of H_2O_2 was added and heating was continued overnight. Excess solvent was removed in vacuo and the residue was treated with $CHCl_3$ and excess solid K_2CO_3. After stirring, the $CHCl_3$ was decanted and the residual salts were again extracted with $CHCl_3$. The combined organic extract was dried with $MgSO_4$ and concentrated in vacuo to give an oil which crystallized upon trituration with Et_2O. This solid was dried in vacuo to yield 88 g (93%), mp 108–110°. The analytical sample was obtained by dissolving 3.0 g in 10 ml of EtOH and treating this solution with 75 ml of Et_2O to yield 2.9 g after drying, mp 108–110°.

Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.61; H, 6.51; N, 9.99.

2,6-Dicyano-3-ethylpyridine (13). A dry one-neck, 100-ml, round-bottom flask with a $CaCl_2$ drying tube was charged with 5.0 g (0.036 mol) of **12** and 14.25 g (0.125 mol) of methyl fluorosulfonate was added in one portion, resulting in a mildly exothermic reaction. This solution was stirred with a magnetic bar for 30 min, dissolved in 20 ml of CH_2Cl_2, and transferred to an addition funnel (without a side arm) which was protected with a $CaCl_2$ drying tube. This addition funnel was attached to a three-neck, 100-ml, round-bottom flask equipped with a condenser and stirring bar. A solution of 16.5 g (0.254 mol) of KCN in 25 ml of water was placed in the flask, which was cooled with cold water. The solution from the addition funnel was then added over 5 min, resulting in a mildly exothermic reaction. Stirring was continued for 3 hr and the solution was extracted with additional methylene chloride and dried with $MgSO_4$. Removal of solvent in vacuo and Kugelrohr distillation of the residue up to 140° (0.25 mm) gave an oil which partially solidified on scratching; TLC on silica gel with CH_2Cl_2 showed a major component and two minor, less mobile impurities near the origin. This solid was dissolved with warming in 2 ml of n-BuOH and crystallization was induced, after cooling, by scratching. After

standing at room temperature for 10 min and refrigeration for 15 min, the solid was collected and dried in a drying pistol in vacuo without heating to yield 1.70 g (30.1%): mp 40.5–42°; homogeneous by TLC; ir max (Nujol) 4.46 μ (m); NMR ($CDCl_3$) δ 1.45 (t, 3 H, CH_2CH_3), 3.09 (q, 2 H, CH_2CH_3), 7.87, 8.01, 8.05, and 8.18 (AB quartet, J = 8.1 Hz, 2 H, pyridine H_4H_5, calcd[17] δ_{AB} 7.97 and 8.08).

Anal. Calcd for $C_9H_7N_3$: C, 68.77; H, 4.49; N, 26.74. Found: C, 68.74; H, 4.60; N, 26.61.

3-α-Hydroxyisopropylpyridine 1-Oxide (14). A solution of 41.0 g (0.30 mol) of 3-α-hydroxyisopropylpyridine[12] in 80 ml of glacial AcOH was treated with 25 ml of 35% aqueous H_2O_2 and warmed at 70° in an oil bath for 3 hr. An additional 15 ml of H_2O_2 was added and heating was continued overnight. The solvent was removed in vacuo and the residue was stirred with $CHCl_3$ and excess solid K_2CO_3. The $CHCl_3$ was decanted and three extractions of the residual salts followed. The combined $CHCl_3$ extract was dried ($MgSO_4$) and concentrated in vacuo to yield an oil which crystallized upon trituration with Et_2O. The solid was collected, washed with Et_2O, and dried in vacuo to yield 44.1 g (96.1%), mp 90–94°. An analytical specimen was obtained by dissolving 4.0 g in 10 ml of EtOH and adding Et_2O gradually until an oil started to separate. Crystallization was induced by scratching, and more Et_2O was added. The solid was collected and dried to yield 3.2 g, mp 93.5–95°.

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.62; H, 7.37; N, 9.11.

3-α-Hydroxybenzylpyridine 1-Oxide (15). A solution of 87.0 g (0.47 ml) of 3-α-hydroxybenzylpyridine[11] in 200 ml of glacial AcOH was treated with 50 ml of 35% aqueous H_2O_2 and heated at 70° for 3 hr. Another 37 ml of H_2O_2 was added and heating was continued overnight. The solvent was removed in vacuo and the residue was treated with aqueous K_2CO_3 solution and extracted twice with $CHCl_3$ which was then dried ($MgSO_4$). Removal of solvent in vacuo gave an oil and trituration with Et_2O gave a solid which was dried to yield 87.1 g (92.1%), mp 102–105°. The analytical specimen was obtained by treating a solution of 4.0 g in 10 ml of EtOH with 75 ml of Et_2O. The resulting solid was collected and dried in vacuo to yield 2.5 g, mp 105–106°.

Anal. Calcd for $C_{12}H_{11}NO_2$: C, 71.62; H, 5.51; N, 6.96. Found: C, 71.60; H, 5.50; N, 6.87.

3-α-Hydroxy-n-butylpyridine 1-Oxide (16). A solution of 113.9 g (0.75 mol) of 3-α-hydroxy-n-butylpyridine[15] in 225 ml of glacial AcOH was treated with 70 ml of 35% aqueous H_2O_2 and warmed at 70° in an oil bath for 3 hr. An additional 45 ml of H_2O_2 was added and heating was continued overnight. Solvent was removed in vacuo and the residue was treated with excess solid K_2CO_3, diluted with water, extracted twice with $CHCl_3$, and dried ($MgSO_4$). Concentration in vacuo gave an oil which crystallized upon trituration with Et_2O to yield after drying in vacuo 121.6 g (97.1%), mp 98–102°. The analytical specimen was obtained by dissolving 3.0 g in 10 ml of EtOH and adding 100 ml of Et_2O to yield a flocculent precipitate. This solid was dried in vacuo to yield 2.2 g, mp 107–108°.

Anal. Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.59; H, 7.82; N, 8.46.

3-n-Butyl-2,6-dicyanopyridine (17). In a dry one-neck, 100-ml, round-bottom flask protected with a $CaCl_2$ drying tube was placed 16.7 g (0.10 mol) of **16** and 39.9 g (0.35 mol) of methyl fluorosulfonate, resulting in a mildly exothermic reaction. After being stirred at room temperature for 45 min, the viscous material was dissolved in 50 ml of CH_2Cl_2 and transferred to an addition funnel (without a side arm) and protected with a $CaCl_2$ drying tube. This addition funnel was attached to a three-neck, 500-ml, round-bottom flask containing a magnetic stirring bar and equipped with a condenser. The flask, charged with 32.5 g (0.50 mol) of KCN and 50 ml of water, was cooled with cold water and the CH_2Cl_2 solution was added to the cyanide solution over 30 min. The reaction mixture was diluted with 100 ml of water, stirred overnight at room temperature, and extracted with additional CH_2Cl_2. This extract was filtered through Celite, dried with $MgSO_4$, and concentrated in vacuo to give an oil. Kugelrohr distillation at 115–150° (0.06–0.45 mm) gave 9.5 g of a red oil which by TLC on silica gel with CH_2Cl_2 showed a major mobile component with some material at the origin. This oil was dissolved in 25 ml of C_6H_6 and applied to a column of silica gel (100 g) packed in C_6H_6 and 15-ml fractions were collected using a fraction collector. Elution with 525 ml of C_6H_6 and with 400 ml of 25% CH_2Cl_2–C_6H_6 gave 3.80 and 2.20 g, respectively, of an oil which was homogeneous by TLC. Elution with 250 ml of 50% C_6H_6–CH_2Cl_2 gave 0.55 g which on TLC showed some material on the origin in addition to a single mobile component. Elution with 500 ml of CH_2Cl_2 gave only a slight amount of material. The above homogeneous material, 6.0 g, (32.4%), was Kugelrohr distilled at 110° (0.04 mm) in quantitative yield: ir max (film) 4.44 μ; NMR ($CDCl_3$) δ 7.83, 7.98, 8.00, and 8.15 (AB quartet, J_{AB} = 9 Hz, 2 H, pyridine H_4H_5; calcd[17] δ_{AB} 7.95 and 8.04).

Anal. Calcd for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.50; H, 6.37; N, 22.73.

5-n-Butyl-6-cyanopicolinic Acid (18). Compound **17** (1.0 g, 0.0054 mol) was heated with 6 ml of 6 N HCl (aqueous) at 115° for 5 hr, cooled, and stirred at room temperature overnight to deposit 0.90 g (81.6%), mp 104–110°. This material was dissolved in 15 ml of C_6H_6, concentrated to 3 ml, and left at room temperature. The resulting solid was collected by filtration and dried in vacuo to yield 0.59 g (53.5%), mp 111–113°, ir max (Nujol) 5.87 μ (s).

Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.86; H, 5.98; N, 14.04.

2,6-Biscarbamyl-3-n-butylpyridine (19). Compound **17** (2.0 g, 0.08 mol) was mixed with 35 g of polyphosphoric acid in a one-neck flask equipped with a mechanical stirrer with a Teflon blade. The viscous solution was heated at 120° in an oil bath for 1.25 hr, cooled, and quenched with cold water. The resulting solid (2.0 g) was dissolved in 75 ml of hot EtOH and concentrated to 15 ml, where a solid started to separate. After standing overnight the solid was collected and dried in vacuo to yield 1.62 g (67.8%): mp 220–222°; ir max (Nujol) 2.96 (m), 3.15 (m), 5.94 (s), and 5.96 μ (sh, s).

Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.71; H, 6.83; N, 18.99. Found: C, 59.92; H, 6.95; N, 19.00.

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Registry No.—**1**, 6968-72-5; **2**, 55267-66-8; **8**, 55267-67-9; **8** HCl, 55267-68-0; **9**, 55267-69-1; **10**, 55267-70-4; **11**, 55267-71-5; **12**, 4319-52-2; **13**, 55267-72-6; **14**, 55267-73-7; **15**, 39585-76-7; **16**, 55267-74-8; **17**, 55267-75-9; **18**, 55267-76-0; **19**, 55267-77-1; methyl fluorosulfonate, 421-20-5; KCN, 151-50-8; 3-α-hydroxyethylpyridine, 4754-27-2; 3-α-hydroxyisopropylpyridine, 15031-77-3; 3-α-hydroxybenzylpyridine, 6270-47-9; 3-α-hydroxy-n-butylpyridine, 18085-85-3.

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