A Convenient Synthesis of Nicotinate Esters from 3-Cyanopyridones

John B. Paine III

Philip Morris U.S.A., Research Center, P. O. Box 26583,
Richmond, VA, 23261

Received July 28, 1986

A convenient synthesis of alkyl-substituted ethyl nicotinates **8** was devised, using 3-cyano-2(1*H*)-pyridones **4**. These were converted to the corresponding 2-bromo-3-cyanopyridines **5** with boiling phosphorus tribromide. The resulting **5** were smoothly debrominated to 3-cyanopyridines **6** with zinc dust in boiling ethanolic acetic acid. The nitrile function was hydrolyzed in boiling 6*N* hydrochloric acid, and the resulting nicotinic acid hydrochlorides **7** esterified with refluxing triethyl orthoformate, to give the ethyl nicotinates **8**. A modified formylation of 2-butanone led to the sodium salt of 2-methyl-3-oxobutanal (**3a**) of enhanced purity.

J. Heterocyclic Chem., **24**, 351 (1987).

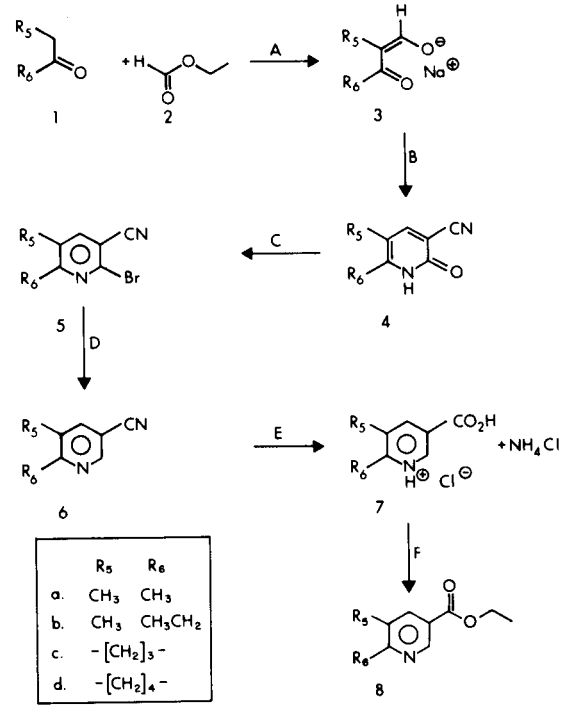
In the course of a program to prepare a series of analogs of nicotine [1], we required the preparation of a number of nicotinate esters, for use in the Hoffmann [2] procedure for the synthesis of myosmines. One of the more useful and convenient syntheses of the pyridine ring entails the reaction of β-ketoaldehydes or β-diketones with 2-cyanoacetamide to generate 3-cyano-2(1*H*)-pyridones with varying substituents at carbons 4, 5, and 6 [3]. β-Ketoaldehydes react specifically to give the 4-unsubstituted 3-cyanopyridones **4**.

The traditional conversion of 3-cyano-2(1*H*)-pyridones to nicotinonitriles has generally involved a deoxygenative chlorination with phosphorus pentachloride [4] or phosphorus oxychloride [4] to give a 2-chloro-3-cyanopyridine [5]. Procedures with phosphorus oxychloride often require the use of a sealed tube which both limits the size of a reaction and risks an explosion with a hazardous corrosive. Although phosphorus pentachloride can be employed at lower temperatures, we found it to effect a competing oxidative chlorination of 6-methyl or 6-methylene substituents (eq 1), and so a more satisfactory alternative was sought. Phenylphosphonic dichloride [6] (bp 258°) failed to react. A search suggested that the only commercially available simple phosphorus halide of suitable boiling-point was phosphorus tribromide (bp 175°, well within the range of the usual sealed tube reactions).

3-Cyano-2(1*H*)-pyridones **4** were indeed found to react with boiling phosphorus tribromide. Although dark reaction mixtures resulted, the product **5** was extracted efficiently into dichloromethane as the *free base* from the strongly acidic aqueous hydrolysis solution, *uncontaminated* by the deeply colored by-products. The resulting 2-bromo-3-pyridinecarbonitriles **5** could be obtained analytically pure by evaporation of solvent and Kugelrohr distillation. The reaction could be effected on a large scale (100+ g) in an open Erlenmeyer flask with a hotplate/magnetic stirrer. The ease of running the reaction excused the 50% yields usually obtained.

Since the hydrogenative dehalogenation of 2-halo-3-pyridinecarbonitriles can suffer losses due to reduction of either nitrile function or heterocyclic ring or both [5], we looked for alternative reagents for this step as well. We found that zinc dust in boiling acetic acid could dechlorinate the 2-chloro-3-pyridinecarbonitriles in good yield after several hours of reaction. The bromonitriles **5** prepared above proved even more reactive with zinc. The initial exothermic reaction could be completed by a brief reflux in ethanolic acetic acid. Yields of **6** exceeded 90% in several instances.

Published procedures [7] for the hydrolysis of 3-pyridinecarbonitriles **6** to nicotinic acids, and for the esterifi-

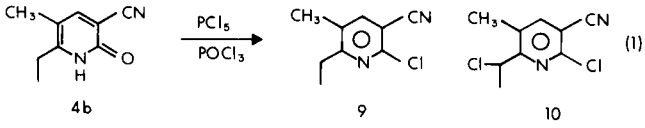


	R_5	R_6
a.	CH_3	CH_3
b.	CH_3	CH_3CH_2
c.	$-[CH_2]_3-$	
d.	$-[CH_2]_4-$	

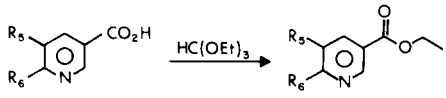
Reagents.

A. $NaOCH_3$, CH_3CH_2OH, $(CH_3CH_2)_2O$, 0° to room temperature. B. $NCCH_2CONH_2$, $[CH_2]_5NH$, CH_3CO_2H, H_2O, Reflux 4 hours. C. PBr_3, Reflux. D. Zn, CH_3CO_2H, CH_3CH_2OH, Reflux. E. 6*N* HCl, Reflux. F. $(CH_3CH_2O)_3CH$, Reflux.

cation of the latter, have generally required the prolonged action of sodium hydroxide or sulfuric acid, subsequent neutralization and the use of large volumes of solvent. Losses of product due to solubility were undoubtedly severe. We find that the nitrile function can be hydrolyzed smoothly in boiling 6*N* hydrochloric acid. Subsequent evaporation of the solvent allows the quantitative recovery of *crystalline* nicotinic acid hydrochloride (**7**) and ammonium chloride. Since this salt mixture could not be readily separated without loss of product, it was treated as such with excess boiling triethyl orthoformate [8]. By the use of sufficient reaction time (a vapor temperature of 146° being a *necessary* if not a sufficient indicator of reaction completion), esterification yields as high as 90% have been achieved. Reductions of yield generally appear to be due to insufficient reaction, rather than to side-reactions involving the alkyl-substituents: non-volatile by-products are minimal. "Free-base" nicotinic acids also esterify smoothly with triethyl orthoformate (eq 2). The apparently unsatisfactory results recorded [8] for nicotinic acid itself undoubtedly derived from the use of insufficient reagent or reaction time, since we found the parent substance to be *far less soluble* than its analogs, and therefore much slower to react.



4b 9 10 (1)



11 8 (2)

The workup entailed neutralization with a weak base (sodium acetate), hydrolytic destruction of excess orthoformate, and a Kugelrohr distillation to obtain pure product **8**.

Four series of compounds were carried through this sequence, derived respectively from the base-catalyzed formylation of 2-butanone (**1a**), 3-pentanone (**1b**), cyclopentanone (**1c**), and cyclohexanone (**1d**). The first of these ketones deserves comment. It has been established that **1a** reacts with base (sodium metal, sodium hydride, or sodium alkoxide) and ethyl formate somewhat unselectively, to give a mixture of the sodium salts of 2-methyl-3-oxobutanal (**3a**) and 3-oxopentanal [9]. The former product is apparently favored increasingly at lower reaction temperatures. Falk, Hofer, and Lehner [10] found that **3a** could be isolated from the crude mixture in significantly enhanced purity by recrystallization from methanol-ether-water.

A procedure was devised to take advantage of both features simultaneously. To aid in keeping the reaction mixture cold, sodium methoxide was employed as base instead of sodium metal, thereby avoiding the generation of the heat of solvation of sodium cation in the reaction mixture, evolved as sodium *metal* reacts. Although sodium methoxide proved essentially insoluble in diethyl ether, it dissolved readily in the presence of *two* equivalents of absolute *ethanol*. Such a solution could be cooled easily, and reacted smoothly with ketone/ethyl formate mixtures. The resulting reaction-mixture resembled Falk's recrystallization-solvent in its properties, and deposited the sodium salt of 2-methyl-3-oxobutanal (**3a**) greatly enriched in the desired component. A significant but harmless impurity proved to be *sodium formate*, recently reported as a by-product from the formylation of acetone [11]. Compound **3a** as obtained above was converted [12] to the cyanopyridone **4a** without further purification, and the latter obtained isomerically pure after a single crystallization from acetic acid.

EXPERIMENTAL

Phosphorus tribromide (Technical grade) was obtained from Aldrich and employed as such, as were most of the other reagents. Melting points (uncorrected) were obtained on a Thomas Micro Hot Stage. The nmr spectra were obtained in 5 mm tubes on a Varian XL-300 or XL-400 spectrometer, with tetramethylsilane or sodium 3-trimethylsilylpropionate as internal standards for deuteriochloroform or deuterium oxide, respectively. Mass spectra were obtained with a Finnegan 3300 GC/MS with INCOS Data System. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

2-Methyl-3-oxobutanal, Sodium Salt (**3a**) [10].

A stirred, ice-cooled solution of sodium methoxide (192.6 g, 3.566 moles, Aldrich) in absolute diethyl ether (2800 ml) and absolute ethanol (455 ml) was treated, dropwise, under nitrogen, with a mixture of 2-butanone (256.8 g, 3.561 moles) and ethyl formate (268.8 g, 3.629 moles). A dense crystalline product separated during the addition, which required 200 minutes. After standing overnight, the solids were filtered off, rinsed with absolute ether (250 ml) and dried in an evacuated desiccator over potassium hydroxide, yield 317.3 g (73% nominal); ^{1}H nmr (deuterium oxide, sodium 3-trimethylsilylpropionate = 0): [10] δ 1.59 (3H, s, 2-CH_3), 2.19 (3H, s, 4-CH_3), 8.98 (H, s, 1-H); deuterium hydroxide at 4.78, sodium formate [11] at 8.49; ^{13}C nmr (deuterium oxide, sodium 3-trimethylsilylpropionate = 0): δ 200.85 (3), 185.24 (1), 115.99 (2), 25.06 (4), 9.79 (2-CH_3), sodium formate at 173.78. Ratio of sodium 2-methyl-3-oxobutanal to sodium 3-oxopentanal: *circa* 5:1. The sodium formate content was around 15 mole %. The signals for sodium 3-oxopentanal were extremely broad and diffuse, perhaps due to *E,Z* isomerism, *etc.* This material was employed as such for the next step.

1,2-Dihydro-5,6-dimethyl-2-oxo-3-pyridinecarbonitrile (**4a**) [12].

A solution of 2-methyl-3-oxobutanal, sodium salt (**3a**) (168.0 g, 1.377 moles nominal), 2-cyanoacetamide (126.1 g, 1.500 moles), and piperidine acetate (97 ml) [prepared from glacial acetic acid (42 ml), water (100 ml) and piperidine (72 ml)] in water (1000 ml) was refluxed for 4 hours. Acetic acid (150 ml) was added to the hot solution, causing vigorous boiling and effervescence. The precipitated solids were filtered off, washed with water and dried, yield 100.8 g (49%). A parallel reaction from 152.1 g (1.247 moles) of **3a** gave 99.6 g (54%). The combined solids were recrystallized once from glacial acetic acid (900-1000 ml), recovery: 158.6 g (80%), mp 276.5-281.0° dec [Lit [12] 270-272° dec]. 3-Cyano-6-ethyl-2(1*H*)-pyridone was undetectable by nmr in the recrystallized material; ^{1}H nmr (deuteriochloroform-trifluoroacetic acid): δ 2.27 (3H, s, 5-CH_3),

2.55 (3H, s, 6-CH_3), 8.05 (H, s, 4-H), 12.54 (2H, broad rise); ^{13}C nmr (10% w/w trifluoroacetic acid-deuteriochloroform): (deuteriochloroform at 77.30, trifluoroacetic acid at 114.97 & 161.49) δ 162.70 (2), 151.67 (4), 150.96 (6), 118.58 (5), 114.36 (CN), 100.16 (3), 18.22 (6-CH_3), 16.19 (5-CH_3); ms: m/z (relative intensity) 149 (7), 148 (100) (M^+), 147 (13), 133 (5), 120 (24), 119 (80), 105 (24), 78 (16), 52 (19), 51 (19), 42 (32), 39 (11).

2-Bromo-5,6-dimethyl-3-pyridinecarbonitrile (**5a**).

3-Cyano-5,6-dimethyl-2(1*H*)-pyridone (**4a**) (44.6 g, 0.301 mole) was added in portions to magnetically stirred, boiling phosphorus tribromide (122.8 g, 0.453 mole) in a 500 ml Erlenmeyer flask (Hood!). Further phosphorus tribromide (62.7 g, 0.232 mole) was used to rinse it in. Gentle boiling was maintained until the solids had dissolved, and gas evolution had abated (90 minutes). Dark tars separated over the course of the reaction. The cooled reaction mixture was suspended in dichloromethane (500 ml), and added cautiously to ice and water (1000 ml). After the violent reaction was over, the resulting pale organic phase was isolated from the dark orange-brown aqueous solution, filtered through Celite/sintered glass to remove tars, and evaporated *in vacuo*. The dichloromethane was recycled to extract the aqueous phase a second time, as before. The combined residues (36.2 and 2.4 g respectively) were distilled (Kugelrohr); yield 34.6 g (55%) as snow-white dense granules, mp 106.0-110.5°, with recrystallization at 109.5°. The solids were analyzed as such; ^1H nmr (deuteriochloroform): δ 2.32 (3H, s, 5-CH_3), 2.57 (3H, s, 6-CH_3), 7.65 (H, s, 4-H); ^{13}C nmr (deuteriochloroform at 77.10): δ 163.12 (6), 142.48 (4), 139.51 (2), 131.48 (5), 116.11 (CN), 110.99 (3), 22.91 (6-CH_3), 18.31 (5-CH_3); ms: m/z (relative intensity) 213 (4), 212 (56) [M^+, ^{81}Br], 210 (54) [M^+, ^{79}Br], 132 (11), 131 (100), 130 (17), 129 (10), 104 (75), 103 (18), 90 (15), 78 (11), 77 (45), 76 (16), 64 (12), 63 (14), 52 (13), 51 (22), 50 (12), 39 (33), 38 (12).

Anal. Calcd. for $C_8H_7BrN_2$: C, 45.53; H, 3.34; N, 13.27; Br, 37.86. Found: C, 45.24; H, 3.54; N, 13.37; Br, 37.91.

5,6-Dimethyl-3-pyridinecarbonitrile (**6a**).

2-Bromo-5,6-dimethyl-3-pyridinecarbonitrile (**5a**) (34.0 g, 0.161 mole) was dissolved from the Kugelrohr bulb by refluxing ethanol (150 ml), into a 500 ml standard taper 24/40 heavy-wall Erlenmeyer flask. The magnetically stirred solution was diluted with glacial acetic acid (52 ml), and treated, starting at 58°, with portions of zinc dust (45 g, 0.69 g-atom). The exothermic reaction warmed the mixture to 80°. Acetic acid (50 ml) was added, following the zinc, and the mixture was refluxed for 45 minutes. When tlc (dichloromethane-silica gel) confirmed the disappearance of **5a**, the solution was filtered and the zinc residue rinsed with ethanol. The filtrates were concentrated *in vacuo*. The residue was extracted with dichloromethane-water. The organic phase was isolated, washed with 1:1 ammonium hydroxide-water (100 ml), and concentrated *in vacuo*. The residue was twice distilled (Kugelrohr), yield 19.6 g (92%). A sample was recrystallized for analysis from ethyl acetate-hexane, mp 73.5-74.5°; ^1H nmr (deuteriochloroform): δ 2.37 (3H, s, 5-CH_3), 2.58 (3H, s, 6-CH_3), 7.68 (H, br, s, 4-H), 8.57 (H, br, s, 2-H); ^{13}C nmr (deuteriochloroform): δ 162.18 (6), 149.17 (2), 139.30 (4), 132.34 (5), 117.04 (CN), 107.20 (3), 23.10 (6-CH_3), 18.92 (5-CH_3); ms: m/z (relative intensity) 133 (9), 132 (100) (M^+), 131 (67), 117 (25), 105 (18), 104 (26), 91 (28), 90 (12), 78 (10), 77 (12), 64 (22), 63 (23), 52 (14), 51 (18), 42 (15), 39 (37), 38 (12).

Anal. Calcd. for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.88; H, 6.18; N, 21.13.

Ethyl 5,6-Dimethyl-3-pyridinecarboxylate (**8a**) [1].

5,6-Dimethyl-3-pyridinecarbonitrile (**6a**) (13.4 g, 0.101 mole) was rinsed into a 500 ml flask with dichloromethane. Concentrated hydrochloric acid (100 ml) and water (100 ml) were added, and the mixture was heated. After the dichloromethane distilled off, the remainder was refluxed for 8 hours. The solvent was removed on a rotary evaporator, and the residue chased with glacial acetic acid followed by toluene. The resulting residue, a mixture of ammonium chloride and 5-carboxy-2,3-dimethylpyridinium chloride (**7a**) was refluxed with ethanol (25 ml, 100%) and triethyl orthoformate (100 ml initially, 104 ml was added later, in two portions). Low boilers were removed periodically. Reflux was continued until the vapor temperature remained above 146° (4.5 hours), and the solids had dissolved.

The reaction mixture was treated with anhydrous sodium acetate (8.4 g, 0.1 mole) in water (25 ml). The mixture was concentrated on a rotary evaporator. The residue was partitioned between dichloromethane and water. The organic phase was concentrated *in vacuo* and distilled (Kugelrohr), the undecomposed triethyl orthoformate and the crude product being collected separately. The product was warmed in aqueous ethanol for 20 minutes to complete the destruction of any remaining orthoformate. The solvent was removed *in vacuo* and the residue redistilled (Kugelrohr), yield 14.2 g (78%); ^1H nmr [1] (deuteriochloroform): δ 1.41 (3H, t, J = 7 Hz, CH_3CH_2O), 2.33 (3H, s, 5-CH_3), 2.55 (3H, s, 6-CH_3), 4.39 (2H, q, J = 7 Hz, CH_3CH_2O), 7.99 (H, d, J = 1.5 Hz, 4-H), 8.93 (H, d, J = 1.5 Hz, 2-H); ^{13}C nmr (deuteriochloroform at 77.40): δ 165.59 (C=O), 161.75 (6), 147.63 (2), 137.71 (4), 131.31 (5), 124.14 (3), 61.11 (OCH_2CH_3), 22.76 (6-CH_3), 19.01 (5-CH_3), 14.32 (CH_3CH_2O); ms: m/z (relative intensity) 180 (4), 179 (40) [M^+], 178 (3.5), 151 (66), 135 (14), 134 (100), 133 (10), 107 (10), 106 (60), 79 (25), 77 (23), 65 (16), 63 (12), 53 (22), 52 (14), 51 (19), 45 (11), 42 (25), 39 (82), 38 (18).

2-Methyl-3-oxopentanal, Sodium Salt (**3b**).

A solution of 3-pentanone (**1b**) (303.0 g, 3.518 moles) and ethyl formate (**2**) (272.8 g, 3.682 moles) was added over 2 hours to a stirred solution of sodium methoxide (189.8 g. 3.514 moles) in ethanol (413 ml, 100%, 2 equivalents) and absolute diethyl ether (1400 ml). The mixture refluxed spontaneously. After standing overnight, the mixture was filtered. The solids (hygroscopic) were rinsed with ether, and dried in a vacuum desiccator over potassium hydroxide, yield 262.2 g (55%); ^1H nmr (deuterium oxide, sodium 3-trimethylsilylpropionate = 0): δ 1.11 (3H, t, J = 7.7 Hz, 5-CH_3), 1.58 (3H, s, 2-CH_3), 2.54 (2H, q, J = 7.7 Hz, 4-CH_2), 9.00 (H, s, 1-CH), (deuterium hydroxide at 4.80); ^{13}C nmr (deuterium oxide, sodium 3-trimethylsilylpropionate = 0): δ 205.79 (3), 184.89 (1), 114.69 (2), 31.67 (4), 15.17 (5), 9.87 (2-CH_3).

6-Ethyl-1,2-dihydro-5-methyl-2-oxo-3-pyridinecarbonitrile (**4b**) [13].

Prepared using Mariella's [12] conditions, from the sodium salt of 2-methyl-3-oxopentanal (**3b**) and cyanoacetamide in yields of 53 to 59%. The product was recrystallized from aqueous acetic acid in 81% recovery (first crop), mp 226-229° (lit [13] 230-231°); ^1H nmr (10% w/w trifluoroacetic acid-deuteriochloroform): δ 1.32 (3H, t, J = 7.7 Hz, 6-CH_3CH_2), 2.23 (3H, s, 5-CH_3), 2.77 (2H, q, J = 7.7 Hz, 6-CH_3CH_2), 7.89 (H, s, 4-H), 12.06 (2H, broad rise, OH & NH); ^{13}C nmr (10% w/w trifluoroacetic acid-deuteriochloroform): (deuteriochloroform at 77.36, trifluoroacetic acid at 115.03 and 161.45) δ 162.82 (2), 155.70 (6), 152.12 (4), 117.05 (5), 114.71 (CN), 100.55 (3), 25.38 (6-CH_3CH_2), 15.75 (5-CH_3), 12.23 (6-CH_3CH_2); ms: m/z (relative intensity) 163 (6), 162 (55) [M^+], 161 (100), 147 (10), 143 (4), 135 (5), 134 (13), 119 (11), 116 (6), 106 (7), 92 (4), 79 (6), 78 (10), 77 (5), 65 (4), 52 (9), 51 (9), 43 (4), 41 (5), 39 (5).

2-Bromo-6-ethyl-5-methyl-3-pyridinecarbonitrile (**5b**).

Prepared similarly to the 5,6-dimethyl analog (**5a**), in 57 to 64% yield, mp 70.0-71.2° (from aqueous ethanol); ^1H nmr (deuteriochloroform): δ 1.29 (3H, t, J = 7.4 Hz, 6-CH_3CH_2), 2.38 (3H, s, 5-CH_3), 2.86 (2H, q, J = 7.6 Hz, 6-CH_3CH_2), 7.69 (H, s, 4-H); ^{13}C nmr (deuteriochloroform at 77.37): δ 167.40 (6), 142.89 (4), 139.63 (2), 130.99 (5), 116.11 (CN), 110.61 (3), 28.73 (6-CH_3CH_2), 17.78 (5-CH_3), 11.97 (6-CH_3CH_2); ms: m/z (relative intensity) 226 (46) [M^+, ^{81}Br], 225 (76), 224 (66) [M^+, ^{79}Br], 223 (100), 211 (4), 209 (4), 198 (19), 196 (16), 143 (12), 142 (11), 129 (10), 117 (19), 116 (50), 103 (7), 102 (8), 92 (9), 91 (16), 90 (16), 89 (10), 77 (11), 76 (17), 75 (11), 65 (12), 64 (18), 63 (25), 62 (14), 52 (22), 51 (33), 50 (24), 41 (26), 40 (17), 39 (100), 38 (34), 37 (17).

Anal. Calcd. for $C_9H_9BrN_2$: C, 48.03; H, 4.03; N, 12.45; Br, 35.50. Found: C, 48.34; H, 4.06; N, 12.34; Br 35.19.

6-Ethyl-5-methyl-3-pyridinecarbonitrile (**6b**).

From the 2-bromopyridine (**5b**), zinc dust and ethanolic acetic acid as for **6a**, in yields of 90 to 96% mp 51.5-53.6°. ^{1}H nmr (deuteriochloroform): δ 1.31 (3H, t, J = 7.5 Hz, 6-C*H*$_3$CH$_2$), 2.39 (3H, s, 5-CH$_3$), 2.88 (2H, q, J = 7.5 Hz, 6-CH$_3$C*H*$_2$), 7.69 (H, bs, 4-H), 8.64 (H, bs, 2-H); ^{13}C nmr (deuteriochloroform at 77.48): δ 166.33 (6), 149.40 (2), 139.71 (4), 131.67 (5), 117.12 (CN), 107.05 (3), 28.87 (6-CH$_3$*C*H$_2$), 18.45 (5-CH$_3$), 12.07 (6-*C*H$_3$CH$_2$); ms: m/z (relative intensity) 147 (4), 146 (46) [M$^+$], 145 (100), 143 (5), 131 (7), 119 (6), 118 (24), 117 (15), 104 (4), 91 (7), 90 (5), 77 (6), 64 (10), 63 (12), 52 (8), 51 (10), 39 (30), 38 (11).

Anal. Calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16. Found: C, 73.87; H, 6.84; N, 19.10.

Ethyl 6-Ethyl-5-methyl-3-pyridinecarboxylate (**8b**).

From the nitrile **6b**, by sequential use of 6*N* hydrochloric acid and then triethyl orthoformate, as for **8a**, an oil was obtained, yield 90%. ^{1}H nmr (deuteriochloroform): δ 1.30 (3H, t, J = 7.5 Hz, 6-C*H*$_3$CH$_2$), 1.40 (3H, t, J = 7.1 Hz, C*H*$_3$CH$_2$O), 2.36 (3H, s, 5-CH$_3$), 2.86 (2H, q, J = 7.5 Hz, 6-CH$_3$C*H*$_2$), 4.39 (2H, q, J = 7.1 Hz, CH$_3$C*H*$_2$O), 8.00 (H, d, J = 1.8 Hz, 4-H), 8.98 (H, d, J = 1.8 Hz, 2-H); ^{13}C nmr (deuteriochloroform at 77.32): δ 166.14 (6), 165.70 (C=O), 147.95 (2), 138.11 (4), 130.53 (5), 123.91 (3), 61.07 (CH$_3$*C*H$_2$O), 28.81 (6-CH$_3$*C*H$_2$), 18.49 (5-CH$_3$), 14.33 (*C*H$_3$CH$_2$O), 12.44 (6-*C*H$_3$CH$_2$); ms: m/z (relative intensity) 194 (8), 193 (73) [M$^+$], 192 (47), 178 (2), 166 (5), 165 (43), 164 (100), 150 (5), 148 (23), 137 (25), 120 (19), 118 (8), 104 (4), 93 (5), 92 (8), 91 (10), 77 (11), 65 (17), 64 (4), 63 (5), 53 (7), 52 (4), 51 (5), 41 (6), 39 (18).

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.06; H, 8.06; N, 7.20.

2-(Hydroxymethylene)cyclopentanone, Sodium Salt (**3c**).

Prepared similarly to **3a**, in 75% yield; ^{13}C nmr (deuterium oxide, sodium 3-trimethylsilylpropionate = 0): δ 209.33 (1), 178.56 (CHO), 115.33 (2), 41.55 (5), 27.80 (3), 22.43 (4); sodium formate at 173.83.

2,5,6,7-Tetrahydro-2-oxo-1*H*-1-pyrindine-3-carbonitrile (**4c**) [14].

Prepared from the sodium salt of 2-formylcyclopentanone (**3c**) and 2-cyanoacetamide in 42% yield. The product as obtained was highly colored. Much of the color could be eliminated by Soxhlet extraction (dichloromethane) with activated charcoal. The minor impurities were destroyed in the ensuing reaction with phosphorus tribromide, mp 213-249.5° dec. A sample recrystallized from acetic acid had mp 243.5-247.0° dec; ^{1}H nmr (trifluoroacetic acid-deuteriochloroform): δ 2.31 (2H, quintet, J = 7.5 Hz, 6-CH$_2$), 2.94 (2H, t, J = 7.5 Hz, 5-CH$_2$), 3.11 (2H, t, J = 7.5 Hz, 7-CH$_2$), 8.06 (H, s, 4-H), 12.35 (2H, br s); ^{13}C nmr (*ca.* 20% w/w trifluoroacetic acid-deuteriochloroform) (deuteriochloroform at 77.43, trifluoroacetic acid at 115.00, 160.82): δ 163.90 (2), 159.67 (7a), 147.34 (4), 126.56 (4a), 114.47 (CN), 99.61 (3), 32.20 (7), 29.59 (5), 23.24 (6); ms: m/z (relative intensity) 160 (59) (M$^+$), 159 (100), 132 (6), 131 (16), 116 (2), 105 (4), 104 (13), 77 (8), 63 (2), 52 (7), 51 (5), 39 (6).

2-Bromo-6,7-dihydro-5*H*-1-pyrindine-3-carbonitrile (**5c**).

This compound was prepared from cyanopyridone **4c** and boiling phosphorus tribromide, as for **5a**, in yields of 33 to 43%. Recrystallized for analysis from ethyl acetate, mp 117-121° (recrystallized at 119°); ^{1}H nmr (deuteriochloroform): δ 2.24 (2H, quintet, J = 7.6 Hz), 3.02 (2H, t, J = 7.5 Hz), 3.10 (2H, t, J = 7.8 Hz), 7.76 (H, s); ^{13}C nmr (deuteriochloroform at 77.31): δ 171.82 (7a), 141.52 (2), 137.53 (4), 137.00 (4a), 116.51 (CN), 110.53 (3), 34.55 (7), 29.92 (5), 22.88 (6); ms: m/z (relative intensity) 225 (7), 224 (75) [M$^+$, ^{81}Br], 223 (53), 222 (79) [M$^+$, ^{79}Br], 221 (51), 144 (12), 143 (76), 142 (34), 141 (25), 116 (34), 115 (15), 114 (14), 90 (7), 89 (22), 88 (28), 76 (8), 75 (7), 65 (10), 64 (20), 63 (25), 62 (15), 61 (9), 52 (16), 51 (28), 50 (22), 41 (15), 40 (15), 39 (100), 38 (37), 37 (22).

Anal. Calcd. for $C_9H_7BrN_2$: C, 48.46; H, 3.16; N, 12.56; Br, 35.82. Found: C, 48.37; H, 3.15; N, 12.56; Br, 35.53.

6,7-Dihydro-5*H*-1-pyrindine-3-carbonitrile (**6c**) [14].

This compound was prepared from bromonitrile (**5c**), zinc duct, and ethanolic acetic acid, as for **6a**, yield 73%, mp 90.0-91.6°, (lit [14] 88°); ^{1}H nmr (deuteriochloroform): δ 2.20 (2H, quintet, J = 7.5 Hz), 3.01 (2H, t, J = 7.5 Hz), 3.10 (2H, t, J = 7.5 Hz), 7.73 (H, d, J = 1.8 Hz), 8.62 (H, d, J = 1.8 Hz); ^{13}C nmr (deuteriochloroform at 77.33): δ 170.68 (7a), 150.74 (2), 137.65 (4a), 134.53 (4), 117.47 (CN), 107.06 (3), 34.64 (7), 30.45 (5), 22.82 (6); ms: m/z (relative intensity) 145 (8), 144 (100) [M$^+$], 143 (88), 142 (20), 117 (10), 116 (30), 115 (9), 90 (13), 89 (22), 88 (12), 76 (11), 65 (8), 64 (18), 63 (24), 62 (18), 52 (12), 51 (17), 50 (11), 39 (32), 38 (15).

Ethyl 6,7-Dihydro-5*H*-1-pyrindine-3-carboxylate (**8c**) [14].

This compound was prepared from nitrile **6c** as for **6a** on a 0.015 mole scale, yield 1.70 g (59%), as a low-melting oil, (lit [14] mp 42°); ^{1}H nmr (deuteriochloroform): δ 1.40 (3H, t, J = 7.1 Hz, C*H*$_3$CH$_2$O), 2.18 (2H, quintet, J = 7.5 Hz, 6-CH$_2$), 2.99 (2H, t, J = 7.5 Hz, 5-CH$_2$), 3.07 (2H, t, J = 7.5 Hz, 7-CH$_2$), 4.39 (2H, q, J = 7.1 Hz, CH$_3$C*H*$_2$O), 8.08 (H, s, 4-H), 8.97 (H, bs, 2-H); ^{13}C nmr (deuteriochloroform at 77.34): δ 170.45 (7a), 165.82 (CO), 149.21 (2), 136.95 (4a), 132.70 (4), 124.09 (3), 61.13 (CH$_3$*C*H$_2$O), 34.39 (7), 30.39 (5), 23.11 (6), 14.32 (*C*H$_3$CH$_2$O); ms: m/z (relative intensity) 192 (2), 191 (40) [M$^+$], 163 (50), 147 (12), 146 (100), 118 (50), 117 (22), 91 (22), 90 (12), 89 (12), 65 (17), 63 (20), 51 (9), 39 (20).

1,2,5,6,7,8-Hexahydro-2-oxo-3-quinolinecarbonitrile (**4d**) [13,14].

A solution of sodium methoxide (132.1 g, 2.45 moles) in ethanol (223 ml) and absolute diethyl ether (2530 ml) was treated, in portions, with a mixture of cyclohexanone (**1d**) (239.6 g, 2.441 moles) and ethyl formate (192.7 g, 2.601 moles) over 2.5 hours. The mixture was allowed to stand overnight. To avoid a tedious filtration, the product **3d** was extracted into water (1500 ml) and reacted at once with 2-cyanoacetamide (207.1 g, 2.463 moles) in two lots in the usual manner. The combined yield of crude product was 149.1 g (35%). It was recrystallized (Soxhlet extractor) from glacial acetic acid, mp 253.5-254.5° or 250.0-257.0° (irreproducible, slight dec), (lit [13] 249° dec); ^{1}H nmr (10% w/w trifluoroacetic acid-deuteriochloroform): δ 1.87 (4H, m, 6 & 7-CH$_2$), 2.65 (2H, t, J = 5.4 Hz, 5-CH$_2$), 2.82 (2H, t, J = 5.6 Hz, 8-CH$_2$), 7.89 (H, s, 4-H), 12.17 (CF$_3$CO$_2$H, NH); ^{13}C nmr (10% w/w trifluoroacetic acid deuteriochloroform): (deuteriochloroform at 77.25, trifluoroacetic acid at 114.86 and 160.82) δ 162.56 (2), 151.53 (8a), 151.42 (4), 120.27 (5), 114.03 (CN), 100.42 (3), 27.60 (8), 25.90 (5), 21.71 (7), 20.81 (6); ms: m/z (relative intensity) 174 (77) [M$^+$], 173 (22), 159 (1), 147 (4), 146 (100), 118 (15), 104 (6), 91 (7), 77 (4), 52 (5), 41 (6), 39 (7).

2-Bromo-5,6,7,8-tetrahydro-3-quinolinecarbonitrile (**5d**).

This compound was obtained from the cyanoquinolone **4d** and boiling phosphorus tribromide as for **5a** in 48% yield after two Kugelrohr distillations and crystallization from ethyl acetate, mp 155-159°, recrystallizing at 158°; ^{1}H nmr (deuteriochloroform): δ 1.81-1.97 (4H, m, 6 & 7-CH$_2$), 2.80 (2H, t, J = 6 Hz, 5-CH$_2$), 2.97 (2H, t, J = 6 Hz, 8-CH$_2$), 7.64 (H, s, 4-H); ^{13}C nmr (deuteriochloroform at 77.19): δ 163.64 (8a), 142.54 (4), 139.28 (2), 132.32 (4a), 116.11 (CN), 110.61 (3), 32.69 (8), 27.83 (5), 22.09 (1), 21.80 (6); ms: m/z (relative intensity) 239 (8), 238 (68) [M$^+$, ^{81}Br], 237 (35), 236 (63) [M$^+$, ^{79}Br], 235 (32), 223 (8), 221 (9), 210 (35), 208 (37), 197 (4), 195 (5), 157 (39), 156 (12), 155 (16), 142 (15), 141 (12), 131 (14), 129 (35), 103 (16), 102 (22), 101 (10), 88 (11), 78 (15), 77 (31), 76 (19), 75 (16), 65 (12), 64 (18), 63 (20), 62 (11), 53 (12), 52 (28), 51 (54), 50 (32), 41 (49), 40 (16), 39 (100), 38 (26).

Anal. Calcd. for $C_{10}H_9BrN_2$: C, 50.66; H, 3.83; N, 11.82; Br, 33.70. Found: C, 50.55; H, 3.98; N, 11.74; Br, 33.79.

5,6,7,8-Tetrahydro-3-quinolinecarbonitrile (**6d**) [14].

This compound was obtained from the bromonitrile **5d**, zinc dust, and ethanolic acetic acid as for **6a**, yield 59%. The product, after two Kugelrohr distillations, was crystallized from ethyl acetate-hexane, mp 81.5-83.7°, (lit [14] 81-82°); ^{1}H nmr (deuteriochloroform): δ 1.80-1.97 (4H, m, 6 & 7-CH$_2$), 2.81 (2H, t, J = 6 Hz, 5-CH$_2$), 2.98 (2H, t, J = 6 Hz, 8-CH$_2$), 7.62 (H, d, J = 2.1 Hz, 4-H), 8.61 (H, d, J = 2.1 Hz, 2-H); ^{13}C nmr (deuteriochloroform at 77.19): δ 162.47 (8a), 149.17 (2), 139.45 (4), 133.05 (4a), 117.07 (CN), 106.85 (3), 32.80 (8), 28.43 (5), 22.41 (7), 22.07 (6); ms:

m/z (relative intensity) 159 (9), 158 (82), [M⁺], 157 (100), 155 (12), 143 (39), 142 (31), 131 (12), 130 (83), 129 (26), 117 (15), 104 (18), 103 (28), 90 (11), 78 (13), 77 (25), 76 (26), 75 (14), 64 (17), 63 (25), 62 (11), 52 (21), 51 (30), 50 (20), 41 (21), 39 (40), 38 (11).

Ethyl 5,6,7,8-Tetrahydro-3-quinolinecarboxylate (**8d**) [14].

This compound was prepared from the nitrile **6d** as for **8a**, yield 31% (probably improvable); ^{1}H nmr (deuteriochloroform); δ 1.40 (3H, t, J = 7.2 Hz, C*H*$_3$CH$_2$O), 1.83 (2H, m, 6-CH$_2$), 1.92 (2H, m, 7-CH$_2$), 2.82 (2H, t, J = 6.2 Hz, 5-CH$_2$), 2.98 (2H, t, J = 6.4 Hz, 8-CH$_2$), 4.39 (2H, q, J = 7.2 Hz, CH$_3$C*H*$_2$O), 7.96 (H, s, 4-H), 8.94 (H, s, 2-H); ^{13}C nmr (deuteriochloroform at 77.22): δ 165.68 (CO), 162.07 (8a), 147.74 (2), 137.65 (4), 132.12 (4a), 123.71 (3), 61.13 (CH$_3$*C*H$_2$O), 32.72 (8), 28.61 (5), 22.76 (7), 22.44 (6), 14.32 (*C*H$_3$CH$_2$O); ms: m/z (relative intensity) 206 (2), 205 (32) [M⁺], 177 (38), 176 (23), 161 (14), 160 (100), 149 (6), 133 (10), 132 (82), 130 (18), 117 (22), 105 (7), 104 (10), 103 (20), 91 (7), 90 (8), 79 (18), 78 (12), 77 (51), 65 (14), 64 (11), 63 (23), 53 (11), 52 (11), 51 (28), 50 (10), 41 (14), 39 (28).

Acknowledgments.

The encouragement of Dr. Edward B. Sanders throughout this work was greatly appreciated. Also acknowledged are John Naworal (Mass Spectroscopy), Ronald Bassfield (NMR), Jim Day (Graphic Arts), and Anne Donathan and Patricia Sinkiewicz (Word Processing).

REFERENCES AND NOTES

[1] J. I. Seeman, H. V. Secor, C. G. Chavdarian, E. B. Sanders, R. L. Bassfield and J. F. Whidby, *J. Org. Chem.*, **46**, 3040 (1981).

[2] M. W. Hu, W. E. Bondinell and D. Hoffman, *J. Labelled Comp.*, **10**, 79 (1974).

[3] H. Meislich, in "Pyridine and Derivatives", Part Three, E. Klingsberg, ed, Interscience, New York, NY, 1962, p 525.

[4] H. E. Mertel, in "Pyridine and Derivatives", Part Two, E. Klingsberg, ed, Interscience, New York, NY, 1961, p 326.

[5] H. E. Mertel, *Loc. Cit.*, p 347.

[6] M. M. Robinson, *J. Am. Chem. Soc.*, **80**, 5481 (1958).

[7a] S. M. McElvain and M. A. Goese, *J. Am. Chem. Soc.*, **63**, 2283 (1941); [b] H. O. Burrus and G. Powell, *ibid.*, **67**, 1468 (1945); [c] H. Gilman and H. S. Broadbent, *ibid.*, **70**, 2755 (1948); [d] M. C. Kloetzel and F. L. Chubb, *ibid.*, **79**, 4226 (1957).

[8] H. Cohen and J. D. Mier, *Chem. Ind.*, 349 (1965).

[9] E. C. Royals and K. C. Brannock, *J. Am. Chem. Soc.*, **76**, 1180 (1954).

[10] H. Falk, O. Hofer and H. Lehner, *Monats. Chem.*, **104**, 925 (1973).

[11] C. A. Lipinski, T. E. Blizniak and R. N. Craig, *J. Org. Chem.*, **49**, 566 (1984).

[12] R. P. Mariella, *J. Am. Chem. Soc.*, **69**. 2670 (1947).

[13] H. K. Sen-Gupta, *J. Chem. Soc.*, **107**, 1347 (1915).

[14] E. M. Godar and R. P. Mariella, *J. Org. Chem.*, **25**, 557 (1960).