Furopyridines. XVII [1]. Cyanation, Chlorination and Nitration of Furo[3,2-*b*]pyridine *N*-Oxide

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Received November 2, 1995

The *N*-oxide **2** of furo[3,2-*b*]pyridine (**1**) was cyanated by the Reissert-Henze reaction with potassium cyanide and benzoyl chloride to give 5-cyano derivative **3**, which was converted to the carboxamide **4**, carboxylic acid **5**, ethyl ester **6** and ethyl imidate **8**. Chlorination of **2** with phosphorus oxychloride yielded 2-**9a**, 3- **9b**, 5- **9c** and 7-chloro derivative **9d**. Reaction of **9d** with sodium methoxide, pyrrolidine, *N,N*-dimethylformamide and ethyl cyanoacetate afforded 7-methoxy- **10**, 7-(1-pyrrolidyl)- **11** and 7-dimethylaminofuro[3,2-*b*]pyridine (**14**) and 7-(1-cyano-1-ethoxy-carbonyl)methylene-4,7-dihydrofuro[3,2-*b*]pyridine (**12**). Nitration of **2** with a mixture of fuming nitric acid and sulfuric acid gave 2-nitrofuro[3,2-*b*]pyridine *N*-oxide (**15**).

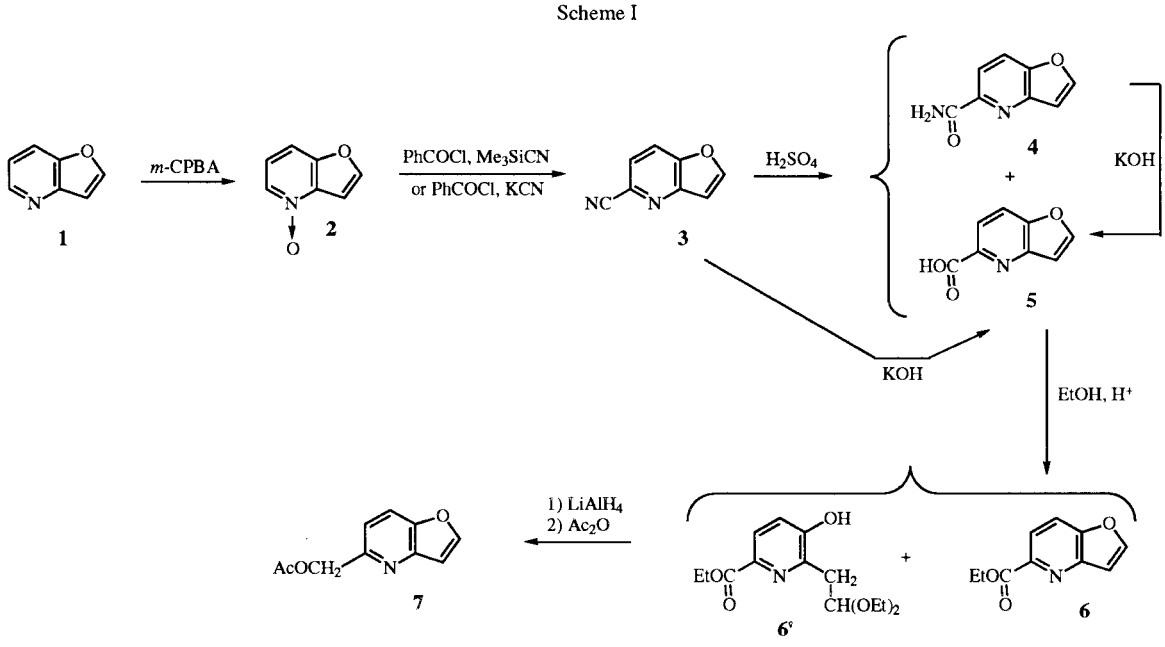
J. Heterocyclic Chem., **33**, 1051 (1996).

In the previous papers we had reported the electrophilic reactions and lithiation of furopyridines [2], which preferentially occur at the furan ring. In order to extend the chemistry of furopyridines, it was desired to synthesize derivatives having substituents at the pyridine ring. Although several furopyridines possessing a substituent at the pyridine ring had been synthesized from the preformed pyridine or furan derivatives [3], the substitution at the pyridine ring of furopyridines had never been reported except the chlorination of furo[3,2-*c*]pyridine *N*-oxide with phoshporus oxychloride by McFarland *et al* [4]. It had been well known that conversion of an aromatic azine ring into its *N*-oxide facilitates the attack of both nucleophiles and electrophiles at the aromatic ring. Thus, we planned to examine the actual reactivity of the *N*-oxides of furopyridines. In this paper we report the cyanation by Reissert-Henze reaction, chlorination and nitration of furo[3,2-*b*]pyridine *N*-oxide.

New *et al* reported that the conversion of furo-[3,2-*c*]pyridine into its Reissert products was unsuccessful, while thieno[3,2-*c*]pyridine, -[2,3-*d*]pyridazine and -[2,3-*d*]-pyrimidine systems yielded the Reissert compounds [5]. Meanwhile, the Reissert-Henze reaction had been widely used to introduce a cyano group into an α-(or occasionally γ-) position to the hetero-nitrogen atom of many types of azine rings [6-11]. This reaction seemed to be applicable for the introduction of a cyano group to the pyridine ring of furopyridines because the *O*-acyl intermediate of the *N*-oxide would be more susceptible to the attack of a nucleophile at the α-position to the nitrogen of pyridine ring.

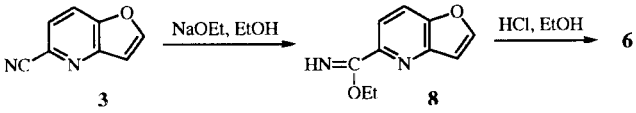
Treatment of furo[3,2-*b*]pyridine **1** with *m*-chloroperbenzoic acid in dichloromethane [12] yielded the *N*-oxide

Scheme I



2 in high yield, which could be purified by distillation under reduced pressure and obtained in colorless crystalline solid of monohydrate.

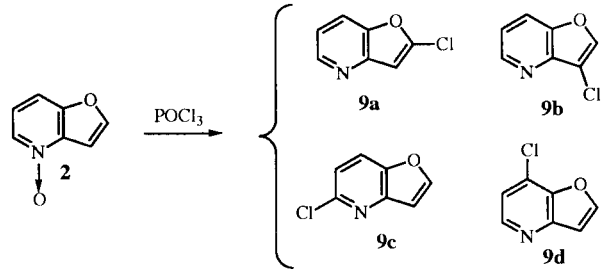
Scheme II



Reissert-Henze cyanation of the *N*-oxide **2** with benzoyl chloride and potassium cyanide in dichloromethane and water afforded the α-cyano compound **3** in a yield of 70%. The cyanation with trimethylsilyl cyanide and benzoyl chloride in dichloromethane [13] gave the same product in less yield (45%). The structure of **3** was confirmed from its ir and pmr spectra; the ir spectra of compound **3** showed ν_{CN} at 2236 cm^{-1}, the pmr spectra showed signals of the protons at the pyridine ring at δ 7.84 (H-7) and 7.57 (H-6) as an AB quartet, and protons at furan ring at δ 7.95 (H-2) and 7.00 (H-3). The signals at δ 7.84 and 7.00 couple each other by 0.8 Hz (zigzag coupling between H-7 and H-3), by which the position of the cyano group was confirmed. Hydrolysis of the nitrile with sulfuric acid afforded a mixture of furo[3,2-*b*]pyridine-5-caboxamide (**4**) and the carboxylic acid **5** in 70% and 7% yield. Alkaline hydrolysis of the nitrile and the amide gave the carboxylic acid **5** (70%). Treatment of the carboxylic acid **5** with sulfuric acid in ethanol afforded the corresponding ethyl ester **6** in low yield (20%) accompanying ethyl 6-(2,2-diethoxyethyl)-5-hydroxypyridine-2-carboxylate (**6'**) in 20% yield. Reduction of ester **6** with lithium aluminam hydride yielded the hydroxymethyl compound, which was unstable in the air at room temperature and slowly polymerized to form a chloroform-insoluble resinous product. Acetylation of the hydroxymethyl compound yielded the *O*-acetyl derivative **7**, stable in the air, as colorless crystals. Reaction of the nitrile **3** with sodium ethoxide in ethanol afforded the imidate **8**, from which ester **6** was obtained in high yield by treatment with a catalytic amount of hydrogen chloride in ethanol.

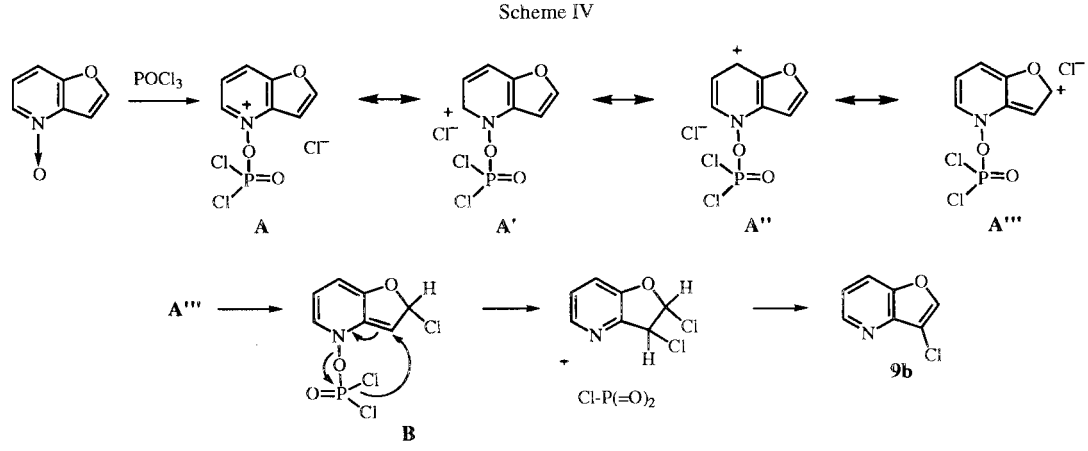
Chlorination of *N*-oxide **2** with phosphorous oxychloride yielded a light brown solid mass, from which monochloro derivatives **9a** (mp 44-50°), **9b** (mp 75-77.5°), **9c** (mp 51.5-52.5°) and **9d** (mp 84.5-86°) were isolated in yield of 3%, 13%, 17% and 47% respectively. These compounds, except **9a**, were stable in the air. Compound **9a** was somewhat unstable and discolored rapidly in the air, but stable in solution under the nitrogen atmosphere. The structure of each compound was confirmed from the pmr spectra. The 2-chloro compound **9a** showed a signal of a furan proton at δ 6.67 as a doublet (J = 0.8 Hz, zig-zag coupling with H-7) assignable to H-3 and three pyridine protons at δ 8.88 (dd, H-5), 7.47 (ddd, H-7) and 6.98 (dd, H-6). The 3-chloro compound **9b** exhibited signals of three pyridine protons at δ 8.53 (dd, H-5), 7.78 (s, H-2), 7.68 (dd, H-7) and 7.19 (dd, H-6) a furan proton at δ 7.78 as a singlet assignable to H-2. Compound **9c** and **9d** showed signals of two furan protons and two pyridine protons at δ 7.75 (dd, H-2), 6.93 (d, H-3), 7.75 (dd, H-7) and 7.23 (d, H-6) for **9c** and 7.99 (d, H-2), 7.10 (d, H-3), 8.53 (d, H-5) and 7.32 (d, H-6) for **9d**, respectively. Thus, the compound exhibits the pyridine protons at higher field was assigned to 5-chloro **9c** and the lower to 7-chloro derivative **9d**.

Scheme III



Formation of **9a**, **9c** and **9d** is understood by the quaternary ammonium ion intermediate **A** and its resonance

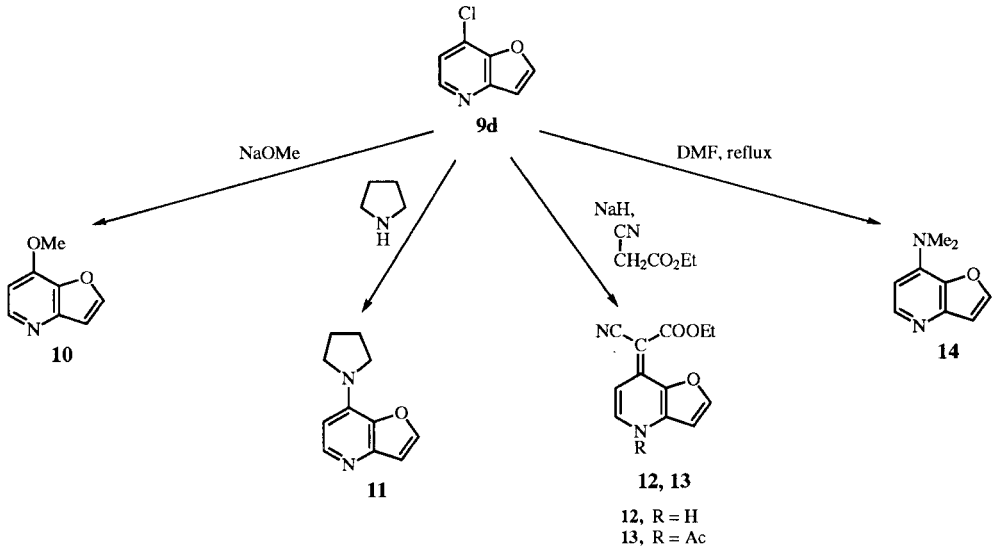
Scheme IV



structures (**A'**, **A"**, **A"'**), attack of chloride ion at the positively charged position, and the successive deprotonation. While, formation of **9b** would be rationalized by the attack of chloride ion at the 3-position of the intermediate **B** to form 2,3-dichloro-2,3-dihydro compound and the subsequent dehydrochlorination (Scheme IV).

at the pyridine ring but 2-nitrofuro[3,2-*b*]pyridine *N*-oxide (**15**) in 30% yield. This result is different from the nitration of thieno[3,2-*b*]pyridine *N*-oxide, and indicates that the furan ring of the *N*-oxide **2** is still more reactive than the pyridine ring for the electrophilic attack.

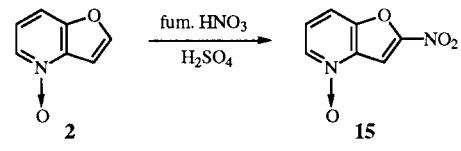
Scheme V



The major product, 7-chloro derivative **9d**, was submitted to substitution with several nucleophiles. The reaction with sodium methoxide in methanol afforded 7-methoxyfuro-[3,2-*b*]pyridine (**10**) (70%). Refluxing of **9d** with pyrrolidine gave 7-(1-pyrrolidyl)derivative **11** (75%). The reaction with ethyl sodio-cyanoacetate yielded 7-(1-cyano-1-ethoxycarbonyl)methylene-4,7-dihydrofuro[3,2-*b*]pyridine **12** in 60% yielded. Though it was expected that compound **12** occurs in two tautomeric forms [14], the pmr spectrum in dimethyl sulfoxide-d_6 indicated that **12** is present in the 4,7-dihydro structure in polar solvent. The infrared absorptions in a potassium bromide pellet at 3464 cm^{-1} for NH, at 2185 cm^{-1} for a conjugated enaminonitrile [15], and at both 1655 (weak) and 1605 cm^{-1} (strong) for ester carbonyl group suggested that **12** may be also present in the solid state (yellow needles) in the 4,7-dihydro structure. Acetylation of **12** with acetic anhydride afforded *N*-acetyl derivative **13**. Attempts to convert 5-chloro **9c** and 7-chloro compound **9d** into the corresponding cyano compound with copper(I) cyanide in *N,N*-dimethylformamide at reflux temperature resulted in recovery of most of the starting compound accompanying formation of 5-cyano derivative **3** in less than 1% yield for compound **9c**, and 7-dimethylaminofuro[3,2-*b*]pyridine (**14**) in 48% yield for **9d**, which would be caused by substitution of the chlorine with dimethylamine formed by decomposition of *N,N*-dimethylformamide at higher temperature.

The nitration of *N*-oxide **2** with a mixture of fuming nitric acid and sulfuric acid gave no compound nitrated

Scheme VI



EXPERIMENTAL

All melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. Infrared spectra were recorded on a JASCO FT/IR 7300 spectrometer. The nmr spectra were taken on a JEOL-PMX 60 (60 MHZ) or a JEOL JNM FX-A400 (400 MHz) spectrometer in deuteriochloroform unless otherwise stated, with tetramethylsilane as an internal reference. The mass spectra were obtained by using JEOL JMS-OISG-2 spectrometer.

Furo[3,2-*b*]pyridine *N*-Oxide (**2**).

A mixture of furo[3,2-*b*]pyridine (**1**) (1.0 g, 8.4 mmoles) and *m*-chloroperbenzoic acid (2.5 g, purity 70%, 10.1 mmoles) in dichloromethane was stirred at room temperature for 20 hours. The mixture was filtered slowly through a sintered glass filter with an alumina (70 g) pad, and the filtrate was evaporated. The residual crystalline mass was recrystallized from ether to give 1.1 g (97%) of **2**•1/2H_2O, mp 83-85°; ir (potassium bromide): 3454 (broad), 3155, 3098, 2957, 2925, 2854, 1651, 1617, 1467, 1440, 1375, 1312, 1270, 1249, 1063, 1048, 771 cm^{-1}; pmr (60

MHz): δ 8.16 (d, J = 6.0 Hz, 1H, H-5), 7.72 (d, J = 2.5 Hz, 1H, H-2), 7.43 (d, J = 8.0 Hz, 1H, H-7), 7.19 (d, J = 2.5 Hz, 1H, H-3), 7.13 (dd, J = 6.0, 8.0 Hz, 1H, H-6), 3.01 (s, 1H, 1/2H_2O) .

Anal. Calcd. for $C_7H_5NO_2$•1/2H_2O: C, 58.33; H, 4.20; N, 9.72. Found: C, 58.66; H, 4.35; N, 9.74.

5-Cyanofuro[3,2-*b*]pyridine (**3**).

A) To a solution of potassium cyanide (500 mg, 7.7 mmoles) in water (0.7 ml) was added a solution of the *N*-oxide **2** (100 mg, 0.7 mmole) in dichloromethane (4 ml) and then a solution of benzoyl chloride (0.86 ml, 7.4 mmoles) in dichloromethane (4 ml) dropwise. After vigorous stirring at room temperature for 2 days, the organic layer of the reaction mixture was separated and the aqueous layer was extracted with chloroform. After drying, the combined organic layers were evaporated, and the crude crystalline solid was chromatographed on a silica gel (30 g) column. The second fraction eluted with hexane-ethyl acetate (3:1) gave 91 mg of crude **3**, which was purified by recrystallization from ether to give 71 mg (71%) of pure **3** as colorless needles, mp 175-176°; ir (potassium bromide): 3148, 3123, 3069, 3051, 2924, 2853, 2236 (CN), 1607, 1535, 1409, 1275, 1222, 1114, 1018, 851, 801 cm^{-1}; pmr (60 MHz): δ 7.95 (d, J = 2.2 Hz, 1H, H-2), 7.84 (dd, J = 0.8, 7.6 Hz, 1H, H-7), 7.57 (d, J = 7.6 Hz, 1H, H-6), 7.00 (dd, J = 0.8, 2.2 Hz, 1H, H-3).

Anal. Calcd. for $C_8H_4N_2O$: C, 66.67; H, 2.80; N, 19.44. Found; C, 66.71; H, 3.06; N, 19.36.

B) A solution of the *N*-oxide hemihydrate **2**•1/2H_2O (590 mg, 4.1 mmoles) in dichloromethane (10 ml) was treated with molecular sieve (5A, 2 g) for 4 hours at room temperature to dehydrate. To the dried solution was added triethylamine (1.22 ml, 8.7 mmoles) and trimethylsilyl cyanide (2.9 ml, 21.9 mmoles) with stirring under nitrogen atmosphere. After stirring for 5 minutes, to this mixture was added benzoyl chloride (1.0 ml, 8.7 mmoles), and stirring was continued for 20 hours at room temperature. The reaction mixture was stirred with 10% aqueous solution of potassium carbonate (1.7 g) for 15 minutes. The organic layer was dried (potassium carbonate) and evaporated to leave a light brown solid (1.25 g). The crude residue was chromatographed on a silica gel (130 g) column eluting with chloroform to give 370 mg of crude **3**. Recrystallization from ether gave pure sample (283 mg, 45%) of **3**, mp 175-176°; the ir and pmr spectra of this sample were identical with those of the sample prepared in the above.

Furo[3,2-*b*]pyridine-5-carboxamide (**4**) and Furo[3,2-*b*]pyridine-5-carboxylic Acid (**5**).

A) Compound **3** (184 mg, 1.28 mmoles) was heated with a mixture of sulfuric acid (1.84 ml) and water (0.34 ml) on a water bath for 20 minutes. The cooled reaction mixture was diluted with 10 ml of water, basified with sodium bicarbonate, extracted with chloroform. Evaporation of the dried (magnesium sulfate) extract gave a colorless solid, which was purified by recrystallization from acetone to give 146 mg (71%) of compound **4**, mp 176-178°; ir (potassium bromide): 3382, 3266, 3138, 3115, 3103, 2922, 1690, 1655, 1604, 1401, 1310, 1274, 1196, 1103, 1032, 846, 783, 774 cm^{-1}; pmr (60 MHz): δ 8.13 (d, J = 8.4 Hz, 1H, H-6), 7.85 (d, J = 2.0 Hz, 1H, H-2), 7.78 (dd, J = 0.8, 8.4 Hz, 1H, H-7), 6.93 (dd, J = 0.8, 2.0 Hz, 1H, H-3), 5.97 (broad s, 2H, -NH 2).

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.56; H, 3.77; N, 17.26.

The aqueous layer was acidified with acetic acid and extracted with chloroform. Evaporation of the dried (magnesium sulfate) chloroform extract afforded 14 mg (7%) of the carboxylic acid **5**. Recrystallization from acetone gave pure sample of **5•H_2O**, mp 151-154°; ir (potassium bromide): 3496, 3148, 3128, 2926, 2499 (broad), 1926 (broad), 1682, 1613, 1538, 1418, 1357, 1289, 1192, 1104, 1016, 785 cm^{-1}; pmr (60 MHz): δ 8.25 (d, J = 8.8 Hz, 1H, H-6), 7.97 (d, J = 2.0 Hz, 1H, H-2), 7.90 (d, J = 8.8 Hz, 1H, H-7), 7.40 (broad s, 3H, COOH and H_2O), 7.02 (d, J = 2.0 Hz, 1H, H-3).

Anal. Calcd. for $C_8H_5NO_3$•H_2O: C, 53.04; H, 3.89; N, 7.73. Found: C, 53.16; H, 3.97; N, 7.67.

B) Compound **3** (418 mg, 2.9 mmoles) was refluxed with potassium hydroxide (1.6 g, 19 mmoles) in 80% ethanol (22 ml) for 2 hours. After evaporation of the solvent under reduced pressure, the residue was dissolved in water (10 ml), acidified with acetic acid and extracted with ethyl acetate. The extract was dried over magnesium sulfate and evaporated to give 400 mg of crude **5**, which was recrystallized from acetone to give pure sample of **5•H_2O** (375 mg, 71%). The ir and pmr spectra were identical with those of the sample obtained in the above.

Esterification of Furo[3,2-*b*]pyridine-5-carboxylic Acid (**5**) with Ethanol and Sulfuric Acid.

A solution of **5** (266 mg, 1.63 mmoles) and sulfuric acid (0.5 ml) in ethanol (50 ml) was refluxed for 15 hours. After evaporation of the solvent, the residual syrup was dissolved in water (10 ml), basified with sodium bicarbonate and extracted with chloroform. The extract was dried (magnesium sulfate) and evaporated to leave a light brown oil (200 mg), which chromatographed on a silica gel (25 g) column eluting with chloroform. The first fraction (75 mg) was purified by recrystallization from hexane to give 63 mg (20%) of pure ethyl furo[3,2-*b*]pyridine-5-carboxylate (**6**) (colorless needles), mp 95-96.5°; ir (potassium bromide): 3137, 3102, 2948, 2923, 2852, 1712, 1417, 1370, 1341, 1284, 1263, 1182, 1111, 1033, 1010, 808, 779 cm^{-1}; pmr (60 MHz): δ 8.07 (d, J = 8.4 Hz, 1H, H-6), 7.82 (d, J = 2.4 Hz, 1H, H-2), 7.71 (dd, J = 0.8, 8.4 Hz, 1H, H-7), 7.04 (dd, J = 0.8, 2.4 Hz, 1H, H-3), 4.46 (q, J = 7.0 Hz, 2H, O-CH_2-CH_3), 1.45 (t, J = 7.0 Hz, 3H, O-CH_2-CH_3).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.66; H, 4.97; N, 7.30.

The second fraction (100 mg) was recrystallized from hexane to give compound **6'** (87 mg, 20%) as colorless crystals, mp 105-107.5°; ir (potassium bromide): 3150-2850 (broad), 2977, 2903, 2654 (broad), 1723, 1578, 1373, 1320, 1269, 1184, 1126, 1069, 862 cm^{-1}; pmr (60 MHz): δ 7.83 (d, J = 8.0 Hz, 1H, H-3), 7.16 (d, J = 8.0 Hz, 1H, H-4), 4.84 (t, J = 5.0 Hz, 1H, -CH_2-CH(OEt)$_2$), 4 32 (q, J = 7.0 Hz, 2H, O-C$H_2$$CH_3$), 3.70 (q, J = 7.0 Hz, 2H, O-C$H_2$$CH_3$), 3.56 (q, J = 7.0 Hz, 2H, O-C$H_2$$CH_3$), 3.18 (d, J = 5.0 Hz, 2H, -CH_2-CH(OEt)$_2$), 1.40 (t, J = 7.0 Hz, 3H, O-CH_2CH_3), 1.15 (t, J = 7.0 Hz, 6H, 2xO-CH_2CH_3).

Anal. Calcd. for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.45; H, 7.32; N, 4.94.

5-Acetoxymethylfuro[3,2-*b*]pyridine (**7**).

To a suspension of lithium aluminum hydride (42 mg, 1.1 mmoles) in dry ether (2 ml) was added a solution of ester **6** (106 mg, 0.55 mmole) in ether (8 ml) with ice-cooling and stirring. After being stirred for 5 hours at room temperature, the reaction mixture was treated with 0.2 ml of water, filtered through a sintered glass filter with a Celite pad. The filter cake was washed with

dichloromethane (5 x 5 ml). Combined organic solution was dried over magnesium sulfate and concentrated to about 2 ml under reduced pressure. To this solution was added pyridine (0.1 ml) and acetic anhydride (0.15 ml, 1.47 mmoles), and the mixture stood over night at room temperature. The mixture was diluted with ethyl acetate (20 ml), washed with brine and dried (magnesium sulfate). The residual light brown paste (93 mg) was chromatographed to give 41 mg (48%) of pure **7**, mp 58-63°; ir (potassium bromide): 3135, 3119, 3070, 3045, 1739, 1611, 1577, 1536, 1419, 1381, 1253, 1116, 1058, 1019, 927, 880, 820, 790 cm^{-1}; pmr (60 MHz): δ 7.87 (d, J = 2.2 Hz, 1H, H-2), 7.67 (dd, J = 0.8, 8.4 Hz, 1H, H-7), 7.22 (d, J = 8.4 Hz, 1H, H-6), 6.87 (dd, J = 0.8, 2.2 Hz, 1H, H-3), 5.28 (s, 2H, -O-CH_2-), 2.16 (s, 3H, CH_3CO-); ms: m/z 191.0586 (M^+, Calcd. for $C_{10}H_9NO_3$: 191.0582).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 63.07; H, 4.74; N, 7.35.

Ethyl Furo[3,2-*b*]pyridine-5-imidate (**8**) and Its Conversion to Compound **6**.

A) To a solution of sodium ethoxide prepared from sodium (90 mg, 3.9 mmoles) in anhydrous ethanol (5 ml) was added a solution of nitrile **3** (270 mg, 1.9 mmoles) in anhydrous ethanol (22 ml) with stirring at room temperature. After being stirred for 15 hours at room temperature, the mixture was evaporated and treated with chloroform and water. The residue (yellow crystalline mass) (296 mg) of the dried chloroform extract was recrystallized from hexane to give imidate **8** (275 mg,78%) as colorless prisms, mp 67-68.5°; ir (potassium bromide): 3275, 3110, 2975, 1650, 1606, 1415, 1377, 1332, 1323, 1271, 1203, 1148, 1091, 1032, 880, 830, 801 cm^{-1}; pmr (60 MHz): δ 7.86 (d, J = 2.4 Hz, 1H, H-2), 7.82 (d, J = 8.4 Hz, 1H, H-6), 7.78 (dd, J = 0.8, 8.4 Hz, 1H, H-7), 7.00 (dd, J = 0.8, 2.4 Hz, 1H, H-3), 4.43 (q, J = 7.0 Hz, 2H, -O-C$H_2$$CH_3$), 1.45 (t, J = 7.0 Hz, 3H, O-CH_2CH_3).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.91; H, 5.25; N, 14.71.

When a crude sample of imidate **8** was chromatographed on a silica gel column eluting with chloroform-ethanol (97:3), no imidate **8** but the caboxamide **4** and ethyl carboxylate **6** were obtained (1:2) in 60% yield, which would be caused by hydrolysis of the imino group or ethoxy group of **8**.

B) A solution of imidate **8** in 50% ethanol (10 ml) containing 0.05 ml of 10% hydrochloric acid was stirred at room temperature for 14 hours. After evaporation of the solvent, the mixture was basified with sodium bicarbonate and extracted with chloroform. The residue of the dried chloroform extract was recrystallized from hexane to give 80 mg (97%) of ethyl caboxylate **6**, mp 94.5-96.5°. The ir and pmr spectra were identical with those of the sample obtained by esterification of carboxylic acid **5**.

2-Chloro- **9a**, 3-Chloro- **9b**, 5-Chloro- **9c** and 7-Chlorofuro-[3,2-*b*]pyridine (**9d**).

A mixture of **2** (1.0 g, 7.4 mmoles), phosphorus oxychloride (5.4 ml, 60 mmoles) and chloroform (2 ml) was refluxed for 1.5 hours. After being cooled, the mixture was poured into ice-water (20 ml), basified with sodium bicarbonate and extracted with chloroform. The residue of the dried chloroform extract was chromatographed on a silica gel (70 g) column. Elution with chloroform-methanol (97:3) gave four fractions. Recrystallization of each fraction from hexane-ether gave pure sample of **9a** (33 mg, 3%), **9b** (147 mg, 13%), **9c** (194 mg, 17%) and **9d** (535 mg, 47%).

2-Chlorofuro[3,2-*b*]pyridine (**9a**).

This compound had mp 44-50°; ir (potassium bromide): 3137, 3049, 2920, 2851, 1610, 1573, 1544, 1411, 1259, 1156, 1073, 927, 786 cm^{-1}; pmr (carbon tetrachloride, 60 MHz): δ 8.88 (dd, J = 1.2, 4.6 Hz, 1H, H-5), 7.47 (ddd, J = 0.8, 1.2, 8.4 Hz, 1H, H-7), 6.98 (dd, J = 4.6, 8.4 Hz, 1H, H-6), 6.67 (d, J= 0.8 Hz, 1H, H-3); ms: m/z 152.9981 (M^+, Calcd. for C_7H_4NOCl: 152.9981).

3-Chlorofuro[3,2-*b*]pyridine (**9b**).

This compound had mp 75-77.5° (in a sealed tube); ir (potassium bromide): 3116, 3065, 2921, 2851, 1609, 1550, 1409, 1271, 1159, 1078, 1027, 845, 768 cm^{-1}; pmr (60 MHz): δ 8.53 (dd, J = 1.0, 4.8 Hz, 1H, H-5), 7.78 (s, 1H, H-2), 7.68 (dd, J = 1.0, 8.6 Hz, 1H, H-7), 7.19 (dd, J = 4.8, 8.6 Hz, 1H, H-6); ms: m/z 152.9985 (M^+, Calcd. for C_7H_4NOCl: 152.9981).

5-Chlorofuro[3,2-*b*]pyridine (**9c**).

This compound had mp 51.5-52.5° (in a sealed tube); ir (potassium bromide): 3124, 3062, 2923, 1606, 1564, 1408, 1279, 1182, 1118, 1022, 817, 780, 744 cm^{-1}; pmr (60 MHz): δ 7.82 (d, J = 2.4 Hz, 1H, H-2), 7.75 (dd, J = 0.9, 9.4 Hz, 1H, H-7), 7.23 (d, J = 9.4 Hz, 1H, H-6), 6.93 (dd, J = 0.9, 2.4 Hz, 1H, H-3); ms: m/z 152.9979 (M^+, Calcd. for C_7H_4NOCl: 152.9981).

7-Chlorofuro[3,2-*b*]pyridine (**9d**).

This compound had mp 84.5-86° (in a sealed tube); ir (potassium bromide): 3127, 3097, 2923, 2854, 1606, 1560, 1383, 1170, 1127, 1022, 834, 812, 755 cm^{-1}; pmr (60 MHz): δ 8.53 (d, J = 5.6 Hz, 1H, H-5), 7.99 (d, J = 2.4 Hz, 1H, H-2), 7.32 (d, J = 5.6 Hz, 1H, H-6), 7.10 (d, J = 2.4 Hz, 1H, H-3); ms: m/z 152.9981 (M^+, Calcd. for C_7H_4NOCl: 152.9981). Sublimation occurred resulting in poor elemental analysis.

7-Methoxyfuro[3,2-*b*]pyridine (**10**).

A solution of **9d** (50 mg, 0.33 mmole) and sodium methoxide prepared from 83 mg (3.6 mmoles) of sodium in methanol (2.5 ml) was refluxed for 3 hours. After evaporation of the solvent, the residue was treated with water and chloroform. The chloroform layer was dried (magnesium sulfate) and evaporated to leave a colorless oil which was distilled to give pure sample of **14** (34 mg, 70%), bp 110-120° (bath temperature) (20 mm Hg); ir (neat): 3037, 2945, 2854, 1625, 1572, 1492, 1406, 1296, 1209, 1111, 971, 809, 749 cm^{-1}; pmr (60 MHz): δ 8.22 (d, J = 5.2 Hz, 1H, H-5), 7.60 (d, J = 2.0 Hz, 1H, H-2), 6.13 (d, J = 2.0 Hz, 1H, H-3), 6.58 (d, J = 5.2 Hz, 1H, H-6), 3.95 (s, 3H, OMe); ms: m/z 149.0471 (M^+, Calcd. for $C_8H_7NO_2$: 149.0476).

7-(1-Pyrrolidyl)furo[3,2-*b*]pyridine (**11**).

A solution of **9d** (70 mg, 0.46 mmole) in dry pyrrolidine (1 ml) was refluxed for 5 hours. After evaporation of the excess pyrrolidine, the residual syrup was dissolved in chloroform. The chloroform solution was washed with water, dried over magnesium sulfate, and evaporated to leave a pale brown solid mass. Recrystallization of the crude solid from hexane-ether gave 65 mg (75%) of **11**, mp 102-105°; ir (potassium bromide): 3067, 2968, 2866, 1619, 1538, 1497, 1417, 1214, 1110, 1036, 923, 797 cm^{-1}; pmr (carbon tetrachloride, 60 MHz): δ 7.91 (d, J = 5.6 Hz, 1H, H-5), 7.50 (d, J = 2.4 Hz, 1H, H-2), 6.71 (d, J = 2.4 Hz, 1H, H-3), 6.00 (d, J = 5.6 Hz, 1H, H-6), 3.60 (m, 4H, -CH_2NCH_2-), 1.98 (m, 4H, -CH_2-CH_2-).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.28; H, 6.53; N, 15.22.

7-(1-Cyano-1-ethoxycarbonyl)methylenefuro[3,2-*b*]pyridine (**12**) and Its *N*-Acetyl Derivative **13**.

To a suspension of sodium hydride (277 mg, 60% in mineral oil, 6.9 mmoles, washed with hexane) in *N,N*-dimethylformamide (0.5 ml) was added ethyl cyanoacetate (740 mg, 6.6 mmoles) with stirring. After being stirred for 30 minutes at room temperature, to this mixture was added a solution of **9d** (100 mg, 0.65 mmole) in *N,N*-dimethylformamide (1.0 ml), and the mixture was stirred at 120° for 20 hours. After being cooled, the reaction mixture was diluted with water, acidified with hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with brine, dried over magnesium sulfate and evaporated to give 100 mg of yellow solid mass. The residue was recrystallized from ethanol to give pure sample of **12** (88 mg, 60%), mp 233-236°; ir (potassium bromide): 3250-2750 (broad), 3131, 2978, 2185, 1655, 1605, 1533, 1463, 1285, 1205, 1121, 1025, 883, 802 cm^{-1}; pmr (dimethyl sulfoxide-d_6, 400 MHz): δ 13.10 (broad s, 1H, NH), 8.30 (d, J = 2.0 Hz, 1H, H-2), 8.23 (d, J = 7.2 Hz, 1H, H-5), 7.88 (d, J = 7.2 Hz, 1H, H-6), 7.00 (d, J = 2.0 Hz, 1H, H-3), 4.11 (q, J = 7.2 Hz, 2H, O-CH_2CH$_3$), 1.23 (t, J = 7.2 Hz, 3H, O-CH$_2$CH_3).

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.31; H, 4.54; N, 12.01.

A mixture of **12** (52 mg, 0.23 mmole), acetic anhydride (1 ml) and pyridine (1 ml) was stirred for 20 hours at 90°. After evaporation of the excess of acetic anhydride and pyridine, the residue was dissolved in chloroform, and the extract was washed with 2% hydrochloric acid and water, dried over magnesium sulfate, and evaporated to give a yellow crystalline mass. Recrystallization of the solid from chloroform gave 55 mg (90%), mp 201-204° dec; ir (potassium bromide): 3185, 3148, 2982, 2931, 2194, 1743, 1686, 1628, 1539, 1475, 1374, 1263, 1250, 1224, 1130, 1034, 1007, 822, 784 cm^{-1}; pmr (deuteriochloroform, 400 MHz): δ 8.30 (d, J = 8.0 Hz, 1H, H-5), 7.87 (d, J = 2.0 Hz, 1H, H-2), 7.59 (d, J = 8.0 Hz, 1H, H-6), 7.56 (d, J = 2.0 Hz, 1H, H-3), 4.30 (q, J = 7.2 Hz, 2H, O-CH_2CH$_3$), 2.69 (s, 3H, Ac), 1.38 (t, J = 7.2 Hz, 3H, O-CH$_2$CH_3).

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.71; H, 4.79; N, 10.44.

Reaction of 7-Chlorofuro[3,2-*b*]pyridine (**9d**) with Copper(I) Cyanide in *N,N*-Dimethylformamide.

A mixture of **9d** (100 mg, 0.65 mmole) and copper(I) cyanide (300 mg, 3.35 mmoles) in freshly distilled *N,N*-dimethylformamide (5 ml) was refluxed for 20 hours. After being cooled, to the mixture was added a solution of potassium cyanide (15%, 10 ml), and extracted with chloroform. The residue of the chloroform extract was dissolved in ether, and the ethereal solution was washed with brine, dried (magnesium sulfate) and evaporated. After evaporation of the solvent, the semi-solid mass was chromatographed on a silica gel (12 g) column eluting with ether to give 45 mg (45%) of **9d** and 50 mg (48%) of 7-(dimethylamino)furo[3,2-*b*]pyridine (**14**), mp 52-55°; ir (potassium bromide): 3098, 2930, 1622, 1543, 1417, 1254, 1097, 921, 799, 751 cm^{-1}; pmr (carbon tetrachloride, 60 MHz): δ 7.91 (d, J = 5.6 Hz, 1H, H-5), 7.50 (d, J = 2.2 Hz, 1H, H-2), 6.68 (d, J = 2.2 Hz, 1H, H-3), 6.09 (d, J = 5.6 Hz, 1H, H-6), 3.10 (s, 6H, NMe_2); ms: m/z 162.0792 (M^+, Calcd. for $C_9H_{10}N_2O$: 162.0793).

Refluxing of **9d** in *N,N*-dimethylformamide for 20 hours afforded a mixture of **9d** and **14** (*ca.* 1:1, by integration of the pmr spectrum).

2-Nitrofuro[3,2-*c*]pyridine 4-Oxide (**15**).

Compound **2** (100 mg, 0.74 mmole) was dissolved in 1.0 ml of sulfuric acid by addition of the acid keeping the temperature below -5°. Fuming nitric acid (d, 1.52, 0.5 ml) was added slowly to keep the temperature below 0°. After being stirred for 6 hours at room temperature, the reaction mixture was diluted with ice-water, basified with sodium bicarbonate, and extracted with chloroform. The chloroform extract was dried (magnesium sulfate) and evaporated to leave a yellow solid mass. Recrystallization from methanol yielded 41 mg (30%) of **15**, mp 196-199° dec; ir (potassium bromide): 3065, 2923, 1565, 1522, 1461, 1434, 1376, 1266, 1119, 1062, 894, 820, 780, 740 cm^{-1}; pmr (deuteriomethanol, 60 MHz): δ 8.45 (dd, J = 1.0, 6.2 Hz, 1H, H-5), 8.11 (d, J = 1.2 Hz, 1H, H-3), 7.92 (ddd, J = 1.0, 1.2, 8.0 Hz, 1H, H-7), 7.71 (dd, J = 6.2, 8.0 Hz, 1H, H-6).

Anal. Calcd. for $C_7H_4N_2O_4$: C, 46.68; H, 2.24; N, 15.55. Found: C, 46.86; H, 2.54; N, 15.38.

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