Furopyridines. VI. Preparation and Reactions of 2- and 3-Substituted Furo[2,3-*b*]pyridines

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Received March 10, 1986

This paper describes the synthesis and chemical properties of some 2- and 3-substituted furo[2,3-*b*]pyridines. Reaction of ethyl 2-chloronicotinate **1** with sodium ethoxycarbonylmethoxide or 1-ethoxycarbonyl-1-ethoxide gave β-keto ester **2** or ketone **5**, respectively. Ketonic hydrolysis of **2** afforded ketone **3**, from which furo[2,3-*b*]pyridine **4** was obtained by the method of Sliwa. While, 2-methyl derivative **7** was prepared from **5** by reduction, *O*-acetylation and the subsequent pyrolysis. Reaction of ketone **3** with methyllithium gave tertiary alcohol **8** which was *O*-acetylated and pyrolyzed to give 3-methyl derivative **9**. Formylation of **4**, *via* lithio intermediate, with DMF yielded 2-formyl derivative **10**, from which **7**, was obtained by Wolff-Kishner reduction. Dehydration of the oxime **11** of **10** gave 2-cyano derivative **12**, which was hydrolyzed to give 2-carboxylic acid **13**. Reaction of 3-bromo compound **14** with copper(I) cyanide gave 3-cyano derivative **15**. Alkaline hydrolysis of **15** afforded compound **16** and **17**, while acidic hydrolysis gave carboxamide **18**. Reduction of **15** with DIBAL-H afforded 3-formyl derivative **19**. Wolff-Kishner reduction of **19** gave no reduction product **9** but hydrazone **20**. Reduction of tosylhydrazone **21** with sodium borohydride in methanol afforded 3-methoxymethylfuro[2,3-*b*]pyridine **22**.

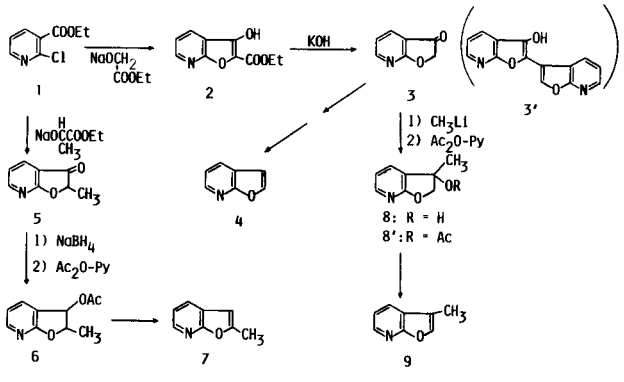
J. Heterocyclic Chem., **23**, 1465 (1986).

As part of our continuing investigation in the chemistry of furopyridines we are particularly interested in the synthesis and reactions of 2- and 3-substituted furopyridines which can be the important intermediates for the preparation of derivatives having further functional groups. In this paper we describe an improved synthesis of furo[2,3-*b*]pyridine (**4**), and preparation and chemical properties of 2- and 3-cyano derivatives.

The parent compound **4** has been synthesized by two different methods. McFarland *et al* [1] obtained this compound from ethyl 5-aminofuro[2,3-*b*]pyridine-2-carboxylate, which was synthesized by Snyder and Ebentino [2] from 2-furoic acid through several steps, by removal of the amino group, hydrolysis of the ester and pyrolysis of the carboxylic acid. Sliwa [3] prepared compound **4** from furo[2,3-*b*]pyridin-3(2*H*)-one (**3**) by reduction with lithium aluminumhydride, acetylation of the hydroxy group and pyrolysis of the acetoxy derivative. The intermediate **3** was prepared from 2-hydroxynicotinic acid through a series of reactions including chlorination of the hydroxy group, Claisen condensation with ethyl acetate to give ethyl (2-ethoxynicotinoyl)acetate, bromination, hydrolysis to give 3-bromoacetylpyridin-3-ol and cyclization of the bromoacetyl derivative with silver oxide. These methods, however, are insufficient for the preparative scale of more than two grams, because of the lower overall yield and multistep procedure (the former in less than 3% for eleven steps, the latter in 14% for eight steps from the material commercially available).

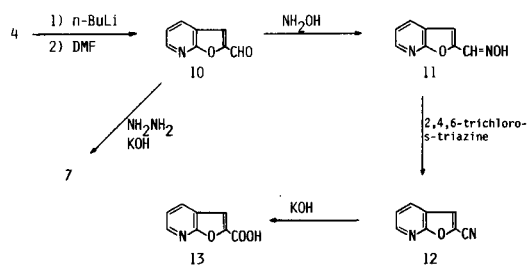
We recently reported [4] the facile synthesis of furo[3,2-*b*]- and furo[2,3-*c*]pyridin-3(2*H*)-one from ethyl 3-hydroxypicolinate and ethyl 3-hydroxyisonicotinate by

Scheme 1



reaction with ethyl bromoacetate, cyclization and ketonic hydrolysis of the β-keto ester, respectively. By utilization of this method we found that furo[2,3-*b*]pyridin-3(2*H*)-one (**3**) is readily obtained from ethyl 2-chloronicotinate (**1**). Compound **1** prepared from 2-hydroxynicotinic acid by Sliwa's method [3a] was treated with 2.5 equivalent of sodium ethoxycarbonylmethoxide in 1,2-dimethoxyethane to yield ethyl 3-hydroxyfuro[2,3-*b*]pyridine-2-carboxylate (**2**) in 70% yield. The β-keto ester **2** was converted to ketone **3** by refluxing with potassium hydroxide for 20 minutes in 80% yield [5]. Thus, furo[2,3-*b*]pyridine **4** was obtained in 28% overall yield for six steps from 2-hydroxynicotinic acid. Analogously, treatment of compound **1** with sodium 1-ethoxycarbonyl-1-ethoxide afforded 2-methylfuro[2,3-*b*]pyridin-3(2*H*)-one (**5**). Ketone **5** was reduced with sodium borohydride and subsequently acetylated to give 2-methyl-3-acetoxy-2,3-dihydrofuro[2,3-*b*]pyridine (**6**). Pyrolysis of compound **6** yielded 2-methylfuro[2,3-*b*]pyri-

Scheme 2

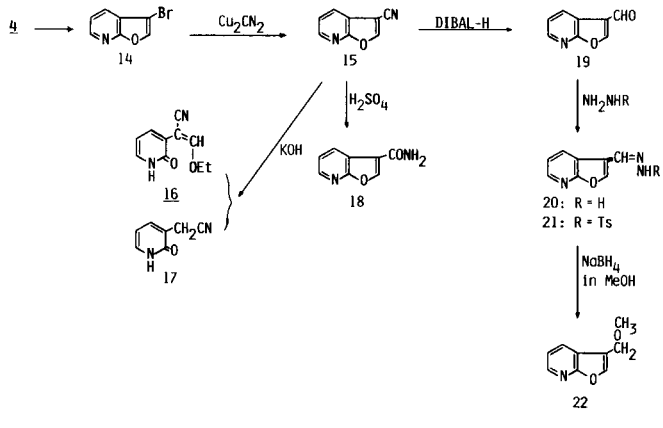


dine (**7**). Reaction of ketone **3** with methyllithium in 1,2-dimethoxyethane gave 3-methyl-2,3-dihydrofuro[2,3-*b*]-pyridin-3-ol (**8**), which in turn was acetylated and pyrolyzed to afford 3-methylfuro[2,3-pyridine (**9**).

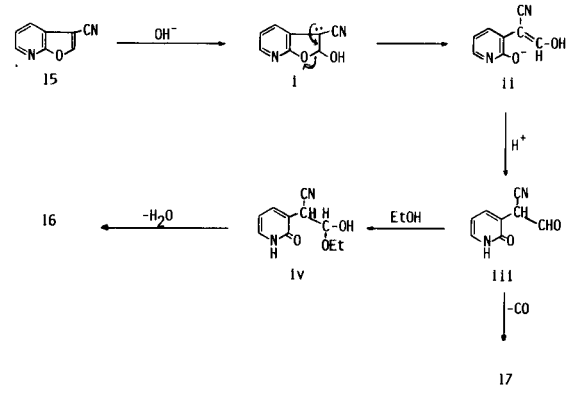
The availability of appreciable quantities of furo[2,3-*b*]-pyridine (**4**) allowed us to proceed with a systematic study of synthesis and chemical properties of 2- and 3-substituted furo[2,3-*b*]pyridines. Treatment of compound **4** with *n*-butyllithium in tetrahydrofuran and the subsequent reaction with *N,N*-dimethylformamide gave 2-formyl derivative (**10**). Aldehyde **10** was easily reduced to 2-methyl compound **7** by refluxing with hydrazine and potassium hydroxide in aqueous ethanol. The oxime **11** of aldehyde **10** was obtained in the usual manner, and was dehydrated by treatment with 2,4,6-trichloro-1,3,5-triazine [6] to give nitrile **12**. Hydrolysis of nitrile **12** with potassium hydroxide in aqueous ethanol gave furo[2,3-*b*]-pyridine-2-carboxylic acid (**13**).

On the other hand, 3-cyano derivative **15** was prepared from 3-bromofuro[2,3-*b*]pyridine (**14**) [7] by refluxing with copper(I) cyanide in *N,N*-dimethylformamide. Reaction of compound **15** with potassium hydroxide in aqueous ethanol gave a mixture of 1-[3-(2-hydroxypyridyl)]-2-ethoxyacrylonitrile (**16**) and 3-cyanomethylpyridin-2-ol (**17**). The former was isolated by extraction of the alkaline aqueous reaction mixture with chloroform and the latter

Scheme 3



Scheme 4



from the acidified aqueous solution. The structural assignments were made from their elemental analyses, ir and ^{1}H nmr spectra. Compound **16** and **17** showed ν CN and ν C=O (pyridone) absorption at 2210 and 1640 cm^{-1}, and at 2260 and 1655 cm^{-1}, respectively. The ^{1}H nmr spectrum of **16** in deuteriochloroform exhibited signals assignable to protons on pyridine nucleus at δ 6.32 (dd, J = 6.2, 6.8 Hz, 1H, H-5), 7.17 (dd, J = 1.8, 6.2 Hz, 1H, H-4) and 7.61 (dd, J = 1.8, 6.8 Hz, 1H, H-6), olefinic proton at δ 8.73 (s, 1H), and protons of ethoxy group at δ 1.40 (t, J = 7.0 Hz, 3H, OCH_2CH_3) and 4.19 (q, J = 7.0 Hz, 2H, OCH_2CH_3). Compound **17** in deuteriomethanol exhibited signals of protons on pyridine ring at δ 6.31 (t, J = 6.5 Hz, 1H, H-5), 7.33 (ddd, J = 0.5, 2.0, 6.5 Hz, 1H, H-4) and 7.60 (ddd, J = 1.0, 2.0, 6.5 Hz, 1H, H-6), and protons of methylene at δ 3.62 (dd, J = 0.5, 1.0 Hz, 2H). This unexpected result may be interpreted as follows: The carbon at 2-position of compound **15** is highly reactive for nucleophilic attack due to the electron withdrawing effect of the 3-cyano group and oxygen at 1-position. Therefore, the intermediate **i** is easily formed by attack of hydroxide ion. Cleavage of the 1-2 bond of **i** yields intermediate **ii** which gives compound **17** through isomerization to intermediate **iii** and decarbonylation. Attack of ethanol molecule at the carbonyl carbon of **iii** gives intermediate **iv** from which compound **16** is afforded by dehydration (Scheme 4). In contrast, hydrolysis with sulfuric acid gave carboxamide **18** in good yield.

Reduction of 3-cyano compound **15** with diisobutylaluminum hydride in ether gave 3-formyl derivative **19**. Wolff-Kishner reduction of aldehyde **19** to 3-methyl derivative **9** was unsuccessful. Refluxing of **19** with hydrazine and potassium hydroxide in aqueous ethanol gave only the corresponding hydrazone **20** and no reduction product. The same reduction in triethylene glycol at 180° did not give any organic compound extractable with chloroform or ethyl acetate. Such a difference in the Wolff-Kishner reduction of 2- and 3-aldehyde can be ex-

plained as follows: From the argument based on the reaction mechanism for Wolff-Kishner reduction [8], it is suggested that negative charge of the hydrazone anion of **20**, a key intermediate for Wolff-Kishner reduction, is highly delocalized due to the inductive effect of the oxygen at 1-position and conjugation through the 2-3 bond, and the charge density on the formyl carbon is much reduced. Therefore, the reduction can not proceed.

Reduction of tosylhydrazone **21** of **19** with sodium borohydride in methanol afforded 3-methoxymethylfuro-[2,3-*b*]pyridine (**22**).

EXPERIMENTAL

Melting points were determined by using a micro melting point apparatus (Yanagimoto) and are uncorrected. The ir spectra were taken on a JASCO A-102 spectrometer. The ^{1}H nmr spectra were recorded on a JEOL JNM-PMX-60 instrument. Chemical shifts are reported in part per million related to tetramethylsilane as an internal standard. Mass spectra were obtained on an ESCO EMD-05B instrument.

Ethyl 3-Hydroxyfuro[2,3-*b*]pyridine-2-carboxylate (**2**).

To a suspension of sodium hydride (20 g of 60% dispersion in mineral oil, 0.5 moles) in 450 ml of 1,2-dimethoxyethane was added ethyl glycolate (50 g, 0.48 moles) during 15 minutes with ice-cooling and stirring. After stirring for 30 minutes at room temperature, to this mixture was added ethyl 2-chloronicotinate (**1**) (35.5 g, 0.192 moles) [3a] in 100 ml of 1,2-dimethoxyethane over a period of 10 minutes. The mixture was stirred and heated at 60-70° for 12 hours. After evaporation of the solvent, the residual solid mass was dissolved in 500 ml of water, washed with benzene, acidified with acetic acid (35 ml) and extracted with chloroform (5 x 200 ml). Drying (magnesium sulfate) and evaporation of the solvent gave 30.5 g of crude **2**. Recrystallization from ether afforded 27.7 g (70%) of pure sample, mp 92-95° ir (potassium bromide): 3330 (OH), 3060, 2970, 2925, 2850, 1665 (C=O), 1605, 1580, 1470, 1445, 1395, 1345, 1315, 1290, 1265, 1245, 1230, 1190, 1155, 1100, 1040, 1020, 920, 880, 805, 780, 760 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.45 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 4.47 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 7.26 (dd, J = 4.8, 7.8 Hz, 1H, H-5), 8.08 (dd, J = 1.7, 7.8 Hz, 1H, H-4), 8.50 (dd, J = 1.7, 4.8 Hz, 1H, H-6).

Anal. Calcd. for $C_{10}H_9NO_4$: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.84; H, 4.38; N, 6.81.

Furo[2,3-*b*]pyridin-3(2*H*)-one (**3**).

A mixture of **2** (3.2 g, 15.4 mmoles) in 100 ml of ethanol and potassium hydroxide (2.3 g, 41.1 mmoles) in 10 ml of water was refluxed on a water bath for 20 minutes. After evaporation of the solvent, the yellow-orange crystalline mass was dissolved in 50 ml of water, acidified with hydrochloric acid (8 ml) and heated on a water bath for 10 minutes. The cooled solution was neutralized with sodium bicarbonate and extracted with chloroform. After drying (magnesium sulfate), the solvent was evaporated to give 1.73 g of almost pure **3** as a slightly yellow crystalline mass of mp 93-94° (literature [3b], mp 95°). Recrystallization from methanol-ether gave 1.67 g (80%) of pure **3**, mp 94.5-95.5°. The ir and ^{1}H nmr spectra were identical with those of the sample prepared by the method of Sliwa [3b]; ir (potassium bromide): 3050, 2930, 1705 (C=O), 1585, 1470, 1415, 1335, 1300, 1260, 1220, 1180, 1100, 990, 850, 795, 770, 735 cm^{-1}; ^{1} nmr (deuteriochloroform): δ 4.70 (s, 2H, 2 x H-2), 7.09 (dd, J = 4.8, 7.6 Hz, 1H, H-5), 8.01 (dd, J = 2.0, 7.6 Hz, 1H, H-4), 8.53 (dd, J = 2.0, 4.8 Hz, 1H, H-6).

2-Methylfuro[2,3-*b*]pyridin-3(2*H*)-one (**5**).

To a suspension of sodium hydride (4.0 g of 60% dispersion, 0.1 moles) in 50 ml of 1,2-dimethoxyethane was added ethyl lactate (9.8 g, 0.083 mole) over a period of 20 minutes with ice-cooling and stirring. After stirring at room temperature for 30 minutes, to this mixture was added ethyl 2-chloronicotinate (6.0 g, 0.032 mole) at room temperature during 10 minutes. The mixture was stirred at 70-80° for 19 hours. After evaporation of the solvent, the light brown solid was dissolved in 250 ml of water, washed with benzene, acidified with acetic acid, extracted with chloroform and dried over magnesium sulfate. The residue of the chloroform solution was distilled to give 2.42 g (50%) of **5**, bp 100-110° (0.1 mm Hg). The distillate solidified on cooling, mp 50-53°; ir (liquid film): 3060, 2990, 2940, 2870, 1725 (C=O), 1605, 1950, 1550, 1480, 1420, 1370, 1340, 1290, 1270, 1225, 1185, 1100, 1075, 1060, 1035, 970, 895, 855, 810, 780, 740 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.56 (d, J = 7.2 Hz, 3H, 2-CH_3), 4.74 (q, J = 7.2 Hz, 1H, H-2), 7.04 (dd, J = 6.8, 7.2 Hz, 1H, H-5), 7.95 (dd, J = 2.0, 7.2 Hz, 1H, H-4), 8.50 (dd, J = 2.0, 6.8 Hz, 1H, H-6).

Anal. Calcd. for $C_8H_7NO_2$: C, 64.42; H, 4.47; N, 9.39. Found: C, 64.30; H, 4.47; N, 9.40.

2-Methyl-3-acetoxy-2,3-dihydrofuro[2,3-*b*]pyridine (**6**).

To a solution of **5** (2.0 g, 13.4 mmoles) in 100 ml of ethanol was added portionwise sodium borohydride (0.6 g, 15.8 mmoles) under ice-cooling and stirring. After stirring for 30 minutes at room temperature, ammonium chloride (1.0 g) was added and stirring was continued for 30 minutes. After evaporation of the solvent *in vacuo*, the residual syrup was dissolved in a mixture of 25 ml of pyridine and 25 ml of acetic anhydride. The reaction mixture was left for 1.5 days at room temperature, and then evaporated the pyridine and acetic anhydride. The brown syrupy residue was dissolved in chloroform, washed with water and dried over magnesium sulfate. The dried solution was evaporated *in vacuo* to give a brown syrup. Distillation of the residue gave 2.15 g (81%) of **6** as a colorless viscous oil, bp 100° (0.1 mm Hg); ir (liquid film): 3080, 3030, 2990, 2940, 2880, 1740 (C=O), 1600, 1470, 1430, 1375, 1300, 1290, 1230, 1190, 1100, 1085, 1040, 1020, 980, 925, 910, 885, 825, 790, 775 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.44 (d, J = 6.6 Hz, 1.5H, ½ CH_3), 1.52 (d, J = 6.6 Hz, 1.5H, ½ CH_3), 2.05 (s, 3H, $OCOCH_3$), 4.74 (dq, J = 2.4, 6.6 Hz, 0.5H, H-2 of the *trans* isomer), 4.80 (qn, J = 6.6 Hz, H-2 of the *cis* isomer), 5.78 (dt, J = 0.7, 2.4 Hz, 0.5H, H-3 of the *trans* isomer), 6.10 (d, J = 6.6 Hz, 0.5H, H-3 of the *cis* isomer), 6.80 (dd, J = 5.0, 7.0 Hz, 0.5H, H-5 of the *cis* isomer), 6.81 (dd, J = 5.0, 7.0 Hz, 0.5H, H-5 of the *trans* isomer), 7.70 (dd, J = 1.8, 7.0 Hz, 0.5H, H-4 of the *cis* isomer), 7.71 (ddd, J = 0.7, 1.7, 7.0 Hz, 0.5H, H-4 of the *trans* isomer), 8.01 (dd, J = 1.8, 5.0 Hz, 0.5H, H-6 of the *cis* isomer), 8.02 (ddd, J = 0.7, 1.7, 5.0 Hz, 0.5H, H-6 of the *trans* isomer).

Anal. Calcd. for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 61.93; H, 5.77; N, 6.96.

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

A mixture of **6** (1.7 g, 8.8 mmoles) and slumina (4.0 g) in a 20-ml flask equipped with a condenser was heated at 150-200° under reduced pressure (150-160 mm Hg). The distillate was dissolved in ether, washed with aqueous sodium bicarbonate solution, dried over potassium carbonate and evaporated the solvent. The residual oil was distilled *in vacuo* to give 1.1 g (94%) of **7**, bp 145° (25 mm Hg); ir (liquid film): 3100, 3050, 3010, 2950, 2910, 2840, 1600, 1585, 1465, 1440, 1380, 1335, 1315, 1265, 1240, 1170, 1140, 1105, 1040, 995, 940, 880, 820, 805, 765 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.37 (d, J = 0.9 Hz, 3H, 2-CH_3), 6.20 (q, J = 0.9 Hz, 1H, H-3), 6.95 (dd, J = 4.6, 7.2 Hz, 1H, H-5), 7.58 (dd, J = 1.6, 7.2 Hz, 1H, H-4), 8.04 (dd, J = 1.6, 4.6 Hz, 1H, H-6); ms: m/e 133 (M^+, 100), 132 (M - H, 66), 106 (M - HCN, 35), 104 (M - H - CO, 53), 79 (M - CO - C_2H_2, 53), 78 (M - CO - HCN, 70).

Anal. Calcd. for C_8H_7NO: C, 72.18; H, 5.30; N, 10.52. Found: C, 72.17; H, 5.62; N, 10.13.

The methiodide had mp 175-176° (slightly yellow needles from methanol-acetone).

Anal. Calcd. for $C_9H_{10}INO$: C, 39.29; H, 3.66; N, 5.09. Found: C, 39.46; H, 3.53; N, 5.22.

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

To a solution of **3** (1.4 g, 10.4 mmoles) in 150 ml of dry ether was added methyllithium in ether (16 ml of 1.6*M* solution, 25.6 mmoles) over a

period of 20 minutes with ice-cooling and stirring under nitrogen atmosphere. After stirring for 2 hours at room temperature, the reaction mixture was treated with 10 ml of water. The aqueous layer was extracted with chloroform (6 x 50 ml). The organic layers were combined, dried (potassium carbonate) and evaporated. Distillation of the residue gave 0.36 g (23%) of **8**, bp 140-150° (bath temperature) (0.6 mm Hg); ir (liquid film): 3250 (broad, OH), 3020, 2970, 2930, 2900, 1610, 1470, 1425, 1375, 1355, 1315, 1275, 1235, 1195, 1160, 1145, 1120, 1070, 1040, 985, 940, 875, 855, 800, 780, 730 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.59 (s, 3H, 3-CH_3), 4.20, 4.43 (AB-q, J = 9.8 Hz, 2H, 2 x H-2), 5.30 (s, 1H, OH), 6.66 (dd, J = 5.0, 7.0 Hz, 1H, H-5), 7.51 (dd, J = 1.8, 7.0 Hz, 1H, H-4), 7.69 (dd, J = 1.8, 5.0 Hz, 1H, H-6). Compound **8** is somewhat hygroscopic and gave poor elemental analyses (Calcd. for C, H and N: 63.57, 6.00 and 9.27; found were 62.45; 5.91 and 8.44).

Compound **8** (0.36 g, 2.28 mmoles) was dissolved in a mixture of 5 ml of pyridine and 5 ml of acetic anhydride and was allowed to stand for 2 days at room temperature. After evaporation of the pyridine and acetic anhydride *in vacuo*, the syrupy residue was dissolved in ether, washed with water, dried over magnesium sulfate and the solvent evaporated. Distillation of the residue gave 0.4 g of a mixture of **8'** and **9** (roughly in ratio of 4:1 (from ^1H nmr)). A mixture of the distillate (0.4 g) and alumina (3 g) in a 10-ml flask equipped with an air condenser was heated at 160-170° under reduced pressure (150-160 mm Hg). The distillate was dissolved in ether, washed with aqueous sodium bicarbonate solution, dried (potassium carbonate) and the solvent evaporated. Distillation of the residue gave 0.3 g (95%) of **9** as a colorless oil, bp 120-130° (bath temperature) (15 mm Hg); ir (liquid film): 3120, 3070, 3030, 2990, 2960, 2930, 2890, 2870, 1610, 1590, 1570, 1450, 1440, 1410, 1400, 1385, 1350, 1330, 1280, 1245, 1190, 1135, 1090, 1080, 1040, 995, 870, 800, 775, 760, 720 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.15 (d, J = 1.2 Hz, 3H, 3-CH_3), 7.06 (dd, J = 4.8, 7.6 Hz, 1H, H-5), 7.35 (q, J = 1.2 Hz, 1H, H-2), 7.71 (dd, J = 1.6, 7.6 Hz, 1H, H-4), 8.19 (dd, J = 1.6, 4.8 Hz, 1H, H-6); ms: m/e 133 (M^+, 100), 132 (M - H, 60), 104 (M - H - CO, 64), 79 (22), 78 (40), 77 (30).

Anal. Calcd. for C_8H_7NO: C, 72.18; H, 5.30; N, 10.52. Found: C, 71.90; H, 5.38; N, 10.13.

The methiodide had mp 225.5-227° dec (colorless cubes from methanol-acetone).

Anal. Calcd. for $C_9H_{10}INO$: C, 39.29; H, 3.66; N, 5.09. Found: C, 39.19; H, 3.63; N, 4.84.

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

A solution of compound **4** (5.0 g, 42 mmoles) in 60 ml of dry tetrahydrofuran was stirred under nitrogen atmosphere and maintained at −70° while a solution of *n*-butyllithium in hexane (30 ml, 1.6*M*, 48 mmoles) was added dropwise by syringe over a period of 10 minutes and for 5 minutes longer. The dark-green mixture was treated with *N,N*-dimethylformamide (6.0 g, 82 mmoles). The reaction mixture was stirred for 4 hours after removal of the cooling bath. Then, the mixture was treated with 10% hydrochloric acid (20 ml), made alkaline with sodium bicarbonate and extracted with dichloromethane. After evaporation of the solvent *in vacuo*, the solid residue (6.1 g) was recrystallized from ethyl acetate-hexane to give 6.0 g (97%) of pure **10**, mp 136.5-137°; ir (potassium bromide): 3110, 3090, 2840 (aldehyde CH), 1680 (C=O), 1585, 1550, 1480, 1405, 1340, 1315, 1290, 1255, 1115, 940, 890, 860, 840, 790, 770 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.34 (dd, J = 4.8, 8.0 Hz, 1H, H-5), 7.53 (s, 1H, H-3), 8.13 (dd, J = 1.8, 8.0 Hz, 1H, H-4), 8.54 (dd, J = 1.8, 4.8 Hz, 1H, H-6), 9.90 (s, 1H, -C*H*O); ms: m/e 147 (M^+, 100), 146 (M - H, 49), 119 (M - CO, 55), 118 (M - H - CO, 8.3), 91 (M - 2CO, 31), 90 (M - H - 2CO, 50), 64 (57), 63 (67).

Anal. Calcd. for $C_8H_5NO_2$: C, 65.31; H, 3.43; N, 9.52. Found: C, 65.19; H, 3.63; N, 9.64.

Wolff-Kishner Reduction of **10**.

A solution of compound **10** (0.50 g, 3.4 mmoles), hydrazine hydrate (1.7 g, 34 mmoles) and potassium hydroxide (0.95 g) in 15 ml of ethanol was refluxed on a water bath for 1 hour. The reaction mixture was diluted with 50 ml of water and extracted with dichloromethane. After drying (magnesium sulfate) and evaporation of the solvent, the residual oil was distilled to give 0.40 g (88%) of **7**, bp 130-140° (bath temperature (22 mm Hg). The ir and ^1H nmr spectra were identical with those of the sample obtained by the method described above.

2-Cyanofuro[2,3-*b*]pyridine (**12**).

A solution of **10** (1.0 g, 6.8 mmoles), hydroxylamine hydrochloride (1.0 g, 14.4 mmoles) and potassium carbonate (1.0 g, 7.2 mmoles) in 15 ml of 70% ethanol was allowed to stand for 2 hours at room temperature. The mixture was diluted with 50 ml of water and stored in a refrigerator overnight. Filtration and drying of the crystalline precipitates afforded 1.04 g (95%) of almost pure **11**, mp 204-205°. Analytical sample was obtained by recrystallization from methanol as colorless needles, mp 205-206°; ir (potassium bromide): 3200 (broad, OH, 3080, 3010, 2890, 1590, 1480, 1450, 1430, 1410, 1290, 1265, 1250, 1140, 1115, 980, 945, 865, 775 cm^{-1}; ^1H nmr (deuteriochloroform-deuteriodimethyl sulfoxide): δ 6.91 (s, ¾H, H-3 of the (*Z*)-isomer), 7.18 (dd, J = 4.8, 7.2 Hz, ¾H, H-5 of the (*Z*)-isomer), 7.19 (dd, J = 4.8, 7.6 Hz, ¼H, H-5 of the (*E*)-isomer), 7.57 (s, ¼H, H-3 of the (*E*)-isomer), 7.61 (s, ¼H, formyl H of the (*E*)-isomer), 7.91 (dd, J = 6.1, 7.2 Hz, ¾H, H-4 of the (*Z*)-isomer), 7.96 (dd, J = 2.0, 7.6 Hz, ¼H, H-4 of the (*E*)-isomer), 8.03 (s, ¾H, formyl H of the (*Z*)-isomer), 8.23 (dd, J = 1.6, 4.8 Hz, ¾H, H-6 of the (*Z*)-isomer), 8.28 (dd, J = 2.0, 4.8 Hz, ¼H, H-6 of the (*E*)-isomer), 11.60 (s, ¾H, OH of the (*Z*)-isomer), 12.16 (s, ¼H, OH of the (*E*)-isomer); ms: m/e 162 (M^+, 18.5), 146 (18), 145 (17), 144 (M - H_2O, 93), 132 (6.4), 119 (13.5), 118 (6), 117 (11), 116 (100), 91 (15), 90 (36), 89 (55), 88 (11), 65 (17), 64 (52), 63 (74), 62 (45), 61 (21).

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.43; H, 3.66; N, 17.01.

The aldoxime **11** (150 mg, 0.926 mmole) was dissolved in 30 ml of dichloromethane and 0.3 ml of pyridine. The solution was treated with nitrogen gas, then 2,4,6-trichloro-1,3,5-triazine (200 mg, 1.08 mmoles) was added in one batch with stirring and nitrogen inlet. After stirring and refluxing for 1.5 hours, the reaction mixture was treated with 6 ml of 1*N* sodium hydroxide solution. The aqueous layer was extracted with chloroform (3 x 30 ml) and the organic layers were combined and dried over magnesium sulfate. Evaporation of the solvent gave 120 mg of crude **12**, which was recrystallized from ether to give 100 mg (75%) of pure sample of **12**, mp 74.5-76°; ir (potassium bromide): 3150, 3130, 3090, 2240 (CN), 1590, 1555, 1475, 1400, 1315, 1260, 1240, 1175, 1130, 1115, 940, 895, 850, 820, 790, 770 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.30 (dd, J = 4.8, 7.6 Hz, 1H, H-5), 7.41 (s, 1H, H-3), 8.01 (dd, J = 1.6, 7.6 Hz, 1H, H-4), 8.45 (dd, J = 1.6, 4.8 Hz, 1H, H-6); ms: m/e 144 (M^+, 100), 116 (M - H_2CN, 96), 90 (M - 2 x HCN, 18), 89 (M - H_2CN - HCN, 78), 65 (19), 64 (45), 63 (62), 62 (45).

Anal. Calcd. for $C_8H_4N_2O$: C, 66.67; H, 2.80; N, 19.44. Found: C, 66.40; H, 3.01; N, 19.15.

Furo[2,3-*b*]pyridine-2-carboxylic Acid (**13**).

A solution of **12** (70 mg, 0.49 mmole) and potassium hydroxide (90 mg, 1.6 mmoles) in 1 ml of ethanol was refluxed for 2 hours. After evaporation of the solvent, the crystalline residue was dissolved in 1 ml of water and acidified with hydrochloric acid (*p*H 2-3). Filtration of the cooled mixture gave 50 mg (63%) of **13**, mp 281-282° dec (literature [1] mp 280°). The ir and ^1H nmr spectra were identical with those of the sample prepared by the method of McFarland [1].

3-Cyanofuro[2,3-*b*]pyridine (**15**).

A mixture of 3-bromofuro[2,3-*b*]pyridine (**14**) [7] (1.9 g, 9.6 mmoles) and copper(I) cyanide (1.9 g, 21.2 mmoles) in 50 ml of *N,N*-dimethylformamide was refluxed with stirring for 3 hours. The cooled brown mixture was treated with a solution of potassium cyanide (3 g) in 60 ml of water, extracted with ether (4 x 50 ml). The ethereal extracts were combined, washed with water, dried over potassium carbonate and evaporated the solvent *in vacuo* to give 1.16 g of crystalline residue. Recrystallization from ether gave 1.05 g (76%) of pure sample of **15**, mp 127-129°; ir (potassium bromide): 3150, 3060, 2930, 2240 (CN), 1590, 1545, 1400, 1340, 1280, 1180, 1130, 1060, 860, 845, 800, 770 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.37 (dd, J = 4.8, 7.6 Hz, 1H, H-5), 8.06 (dd, J = 1.6, 4.8

Hz, 1H, H-4), 8.20 (s, 1H, H-2), 8.41 (dd, J = 1.6, 4.8 Hz, 1H, H-6).

Anal. Calcd. for $C_8H_4N_2O$: C, 66.67; H, 2.80; N, 19.44. Found: C, 66.78; H, 2.82; N, 19.12.

Hydrolysis of **15** with Potassium Hydroxide.

A mixture of **15** (200 mg, 1.4 mmoles), potassium hydroxide (100 mg, 1.8 mmoles), 5 ml of water and 10 ml of ethanol was refluxed on a water bath for 1 hour. After evaporation of the solvent, the semi-solid residue was treated with water and chloroform. The chloroform layer was dried over magnesium sulfate and evaporated to give 0.15 g of crystalline residue, which was recrystallized from methanol to afford 100 mg (38%) of compound **16**, mp 195-198°; ir (potassium bromide): 3430 (broad, NH), 3000-2400 (NH), 3130, 3060, 2990, 2880, 2820, 2210 (CN), 1640 (C=O of pyridone), 1615, 1595, 1555, 1485, 1390, 1365, 1355, 1305, 1260, 1220, 1190, 1145, 1110, 1065, 1040, 985, 940, 920, 885, 860, 760 cm^{-1}; ^1H nmr (deuteriochloroform): δ 1.40 (t, J = 7.0 Hz, 3H, OCH_2CH_3), 4.19 (q, J = 7.0 Hz, 2H, OCH_2CH_3), 6.32 (dd, J = 6.2, 6.8 Hz, 1H, H-5), 7.37 (dd, J = 1.8, 6.2 Hz, 1H, H-4), 7.61 (dd, J = 1.8, 6.8 Hz, 1H, H-5), 8.73 (s, 1H, olefinic H), 12.56 (broad s, 1H, NH); ms: m/e 190 (M^+, 16.5), 162 (M - C_2H_4, 5), 161 (M - C_2H_5, 2.6), 145 (M- OC_2H_5, 6), 144 (M - C_2H_5OH, 12), 135 (M - HCN -C_2H_4, 5.6), 134 (M - HCN - C_2H_5, 100), 133 (16), 116 (22), 106 (7), 105 (16), 89 (11), 79 (20), 78 (16).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.85; H, 5.48; N, 14.73.

The aqueous layer after chloroform extraction was evaporated *in vacuo*, treated the residue with 1 ml of 1*N* hydrochloric acid (*p*H 3) and extracted with chloroform. The chloroform solution was dried over magnesium sulfate and evaporated to give 110 mg of orange crystalline mass. Recrystallization from methanol gave 100 mg (53.7%) of **17**, mp 195-197°; ir (potassium bromide): 3450 (broad, NH), 3150, 3080, 3040, 3000-2400 (NH), 2950, 2920, 2260 (CN), 1655 (C=O of pyridone), 1620, 1570, 1480, 1400, 1370, 1260, 1220, 1060, 980, 950, 940, 880, 775 cm^{-1}; ^1H nmr (deuteriomethanol): δ 3.62 (dd, J = 0.5, 1.0 Hz, 2H, $-CH_2-$), 6.31 (t, J = 6.5 Hz, 1H, H-5), 7.33 (ddd, J = 0.5, 2.0, 6.5 Hz, 1H, H-4), 7.60 (ddd, J = 1.0, 2.0, 6.5 Hz, 1H, H-6); ms: m/e 134 (M^+, 100), 117 (M - OH, 5), 116 (M - H_2O, 39), 106 (M - CO, 37), 105 (M - H - HCN, 58), 80 (45), 79 (M - CO - HCN, 89), 52 (96), 51 (74).

Anal. Calcd. for $C_7H_6N_2O$: C, 62.68, H, 4.51; N, 20.88. Found: C, 62.49; H, 4.57; N, 20.58.

Furo[2,3-*b*]pyridine-3-carboxamide (**18**).

A mixture of **15** (100 mg, 0.69 mmoles), 0.2 g of water and 1 ml of concentrated sulfuric acid was heated on a water bath for 3 hours. The cooled mixture was diluted with water, neutralized with sodium bicarbonate and extracted with chloroform. The chloroform extract was dried (magnesium sulfate) and evaporated to give 110 mg of crude **18**. Recrystallization from methanol gave 100 mg (89%) of **18**, mp 204-205°; ir (potassium bromide): 3350 (NH), 1660 (C=O), 1600, 1550, 1480, 1420, 1400, 1325, 1245, 1170, 1130, 1110, 1040, 1030, 865, 840, 805, 775 cm^{-1}; ^1H nmr (deuteriomethanol): δ 7.35 (dd, J = 4.8, 7.6 Hz, 1H, H-5), 8.27 (dd, J = 1.6, 7.6 Hz, 1H, H-4), 8.39 (s, 1H, H-2), 8.43 (dd, J = 1.6, 7.6 Hz, 1H, H-6).

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.13; H, 3.86; N, 17.04.

3-Formylfuro[2,3-*b*]pyridine (**19**).

To a suspension of **15** (1.3 g, 9.0 mmoles) in 50 ml of dry ether cooled at −70° was added diisobutylaluminum hydride (14 ml of 1.5*M* solution in toluene, 21 mmoles) under nitrogen atmosphere with stirring. After stirring for 1.5 hours at −70°, the temperature of the mixture was raised to −40° and stirred for 2 hours. The mixture was treated with 20 ml of 1*N* sulfuric acid, stirred for 10 minutes at room temperature, basified with sodium bicarbonate and Rochelle salt, and separated the layers. The aqueous layer was extracted with ether (3 x 50 ml). The organic layers were combined, dried over magnesium sulfate and evaporated to leave 1.2 g of a crystalline mass. Recrystallization from methanol-ether gave 1.1 g (82%) of **19**, mp 121-124°; ir (potassium bromide): 3130, 3070, 2920, 2850, 2750 (aldehyde CH), 1675 (C=O), 1590, 1550, 1475, 1400, 1265, 1245, 1195, 1120, 1075, 1030, 860, 790, 770, 740 cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.29 (dd, J = 4.8, 7.2 Hz, 1H, H-5), 8.27 (s, 1H, H-2), 8.34 (dd, J = 1.8, 4.8 Hz, 1H, H-4), 8.41 (dd, J = 1.8, 7.2 Hz, 1H, H-6), 10.01 (s, 1H, C*H*O).

Anal. Calcd. for $C_8H_5NO_2$: C, 65.31; H, 3.43; N, 9.52. Found: C, 65.20; H, 3.49; N, 9.54.

Hydrazone **20** and Tosylhydrazone **21** of **19**.

A solution of compound **19** (100 mg, 0.68 mmole), hydrazine hydrate (100 mg, 2.0 mmoles) and potassium hydroxide (100 mg) in 3 ml of ethanol was refluxed on a water bath for 2 hours. After evaporation of the solvent, the residual mass was treated with 10 ml of water. The crystalline precipitates were filtered and dried. Recrystallization from methanol gave 95 mg (88%) of **20**, mp 288-292°.

Anal. Calcd. for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.06. Found: C, 59.40; H, 4.40; N, 26.11.

A solution of **19** (600 mg, 4.1 mmoles), tosylhydrazine (900 mg, 4.8 mmoles) in 20 ml of methanol was refluxed for 3 hours. After evaporation of the solvent, the crystalline residue was recrystallized from methanol-water to give 850 mg (66%) of **21**, mp 178-180°; ^1H nmr (deuteriomethanol): δ 2.33 (s, 3H, $-CH_3$), 7.25, 7.78 (A_2B_2-m, J_{AB} = 8.2 Hz, 4H, aromatic H of the tosyl group), 7.30 (dd, J = 4.8, 7.4 Hz, 1H, H-5), 7.90 (s, 1H, H-2), 7.94 (s, 1H, -C*H*=NNH-), 8.22 (dd, J = 1.8, 4.8 Hz, 1H, H-4), 8.36 (dd, J = 1.8, 7.4 Hz, 1H, H-6).

Anal. Calcd. for $C_{15}H_{13}N_3O_3S$: C, 57.13; H, 4.15; N, 13.33. Found: C, 57.42; H, 4.38; N, 13.54.

3-Methoxymethylfuro[2,3-*b*]pyridine (**22**).

To a solution of **21** (200 mg, 0.63 mmole) in 20 ml of methanol was added sodium borohydride (200 mg, 5.6 mmoles) in 10 ml of methanol with ice-cooling and stirring. The mixture was refluxed for 7 hours on a water bath. After evaporation of the solvent, the orange residue was treated with water and extracted with ether. Drying (magnesium sulfate) and evaporation of the solvent yielded 140 mg of yellow oil, which was distilled under reduced pressure to give 65 mg (60%) of **22**, bp 160-170° (bath temperature) (10 mm Hg); ir (liquid film): 3110, 3060, 3050, 3000, 2900, 2850, 2825, 1590, 1570, 1470, 1400, 1360, 1285, 1250, 1190, 1135, 1110, 1090, 955, 910, 865, 800, 780 cm^{-1}; ^1H nmr (deuteriochloroform): δ 3.38 (s, 3H, O-CH_3), 4.57 (d, J = 0.8 Hz, 2H, $-CH_2OCH_3$), 7.15 (dd, J = 4.8, 7.6 Hz, 1H, H-5), 7.59 (t, J = 0.8 Hz, 1H, H-2), 7.93 (dd, J = 1.6, 7.6 Hz, 1H, H-4), 8.26 (dd, J = 1.6, 4.8 Hz, 1H, H-6).

Anal. Calcd. for $C_9H_9NO_2$: C, 66.25; H, 5.56; N, 8.58. Found: C, 65.85; H, 5.66; N, 8.23.

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[5] When the alkaline hydrolysis was carried out for a longer time (2-5 hours), 2-(3-furo[2,3-*b*]pyridyl)furo[2,3-*b*]pyridin-3-ol (**3'**), a ketol condensation product, was formed in 40-60% yield besides compound **3** (in 30-50% yield). Compound **3'** had mp 206-210° dec (yellow prisms from methanol); ir (potassium bromide): 3000 (broad, OH), ^1H nmr (deuteriodimethyl sulfoxide): δ 7.31 (dd, J = 4.8, 7.6 Hz, 1H, H-5), 7.45 (dd, J = 4.8, 7.6 Hz, 1H, H-5'), 8.15 (dd, J = 1.6, 7.6 Hz, 1H, H-6), 8.23 (dd, J = 1.6, 4.8 Hz, 1H, H-4), 8.35 (dd, J = 1.6, 4.8 Hz, 1H, H-4'), 8.44 (s, 1H, H-2'), 8.62 (dd, J = 1.6, 7.6 Hz, 1H, H-6').

Anal. Calcd. for $C_{14}H_8N_2O_3$: C, 66.67; H, 3.20; N, 11.11. Found: C, 66.43; H, 3.26; N, 11.39.

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