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A convenient synthesis of furo[3,2-*b*]pyridine and its 2- and 3-methyl derivatives from ethyl 3-hydroxypicinate (**1**) is described. The hydroxy ester **1** was *O*-alkylated with ethyl bromoacetate or ethyl 2-bromopropionate to give the diester **2a** or **2b**. Cyclization of compound **2a** afforded ethyl 3-hydroxyfuro[3,2-*b*]pyridine-2-carboxylate (**3**) which in turn was hydrolyzed and decarboxylated to give furo[3,2-*b*]pyridin-3-(2*H*)-one (**4a**). Cyclization of **2b** gave the 2-methyl derivative **4b**. Reduction of **4a** and **4b** with sodium borohydride yielded the corresponding hydroxy derivative **5a** and **5b** respectively, which were dehydrated with phosphoric acid to give furo[3,2-*b*]pyridine (**6a**) and its 2-methyl derivative (**6b**). 2-Acetylpyridin-3-ol (**8**) was converted to the ethoxycarbonylmethyl ether (**9**) by *O*-alkylation with ethyl bromoacetate, which was cyclized to give 3-methylfuro[3,2-*b*]pyridine-2-carboxylic acid (**10**). Decarboxylation of **10** afforded 3-methylfuro[3,2-*b*]pyridine (**11**).

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We have been interested in the chemical properties of furopyridines which are expected to be new moieties of biologically active compounds, and have investigated the fundamental electrophilic reactions of furo[2,3-*b*]-, furo[3,2-*b*]-, furo[2,3-*c*]- and furo[3,2-*c*]pyridine [1].

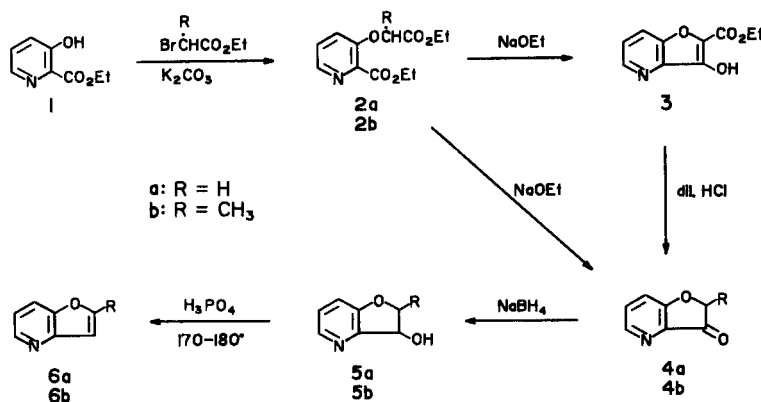
In order to develop the chemistry of furopyridines, it is essential to prepare the parent molecules and/or simple substituted derivatives in moderate quantities by a simple procedure. Two synthetic routes to the parent molecule furo[3,2-*b*]pyridine (**6a**) from 2-furoic acid [2], or furufural [3] as starting material have been reported. These routes, however, are inconvenient for the preparative scale of more than two grams, because the former involves multistep procedure (in lower than 3% overall yield for seven steps) and the latter high-vacuum pyrolysis of 3-(2-furanyl)propenal *O*-methyloxime (in 10% overall yield for four steps). Weis [4] has reported the synthesis of 5-methylfuro[3,2-*b*]pyridine-2-carboxylic acid from 6-methyl-3-hydroxypyridine through a series of reactions, including

hydroxymethylation at the 2-position, oxidation of the hydroxymethyl group to aldehyde and condensation with diethyl bromomalonate. This procedure as a route to **6a** or 2-alkylated derivatives becomes attractive if one has a source of 3-hydroxy-2-pyridinecarboxaldehyde, but several workers have reported the production of this intermediate was arduous and sometimes capricious [5].

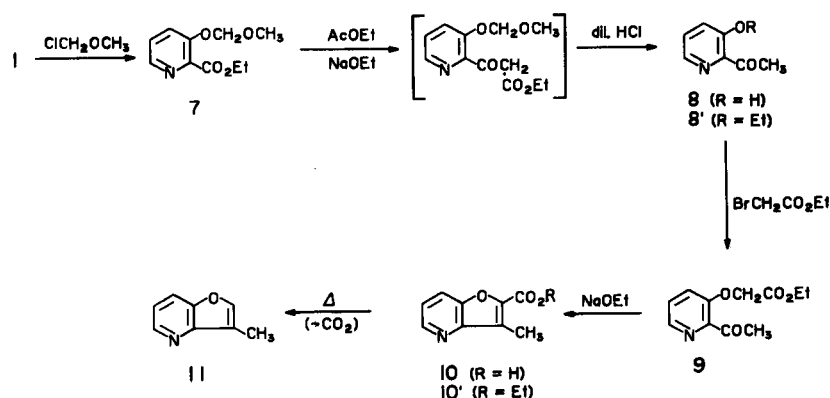
Meanwhile, we have now developed an alternative route which gives compound **6a** in 10-g quantities in 60% overall yield for five steps and is applicable to the synthesis of 2- or 3-alkyl furo[3,2-*b*]pyridine.

Our preparative synthesis starts with 3-hydroxypicolinic acid available commercially. The ethyl ester **1** of the acid was *O*-alkylated with ethyl bromoacetate in refluxing acetone in the presence of potassium carbonate to give ethyl 2-(2-ethoxycarbonyl-3-pyridyloxy)acetate (**2a**). The diester **2a** was treated with sodium ethoxide in refluxing toluene to afford ethyl 3-hydroxyfuro[3,2-*b*]pyridine-2-carboxylate (**3**). Heating of the hydroxy ester **3** with

Scheme 1



Scheme 2



hydrochloric acid gave furo[3,2-*b*]pyridin-3(2*H*)-one (**4a**) (The ir and <sup>1</sup>H nmr spectra of the hydrochloride showed that the salt exists completely in enol form). The furopyridone **4a** was reduced with sodium borohydride in methanol to give 2,3-dihydrofuro[3,2-*b*]pyridin-3-ol (**5a**). Sliwa [6] has reported that the direct dehydration of 2,3-dihydrofuro[2,3-*b*]pyridin-3-ol using *p*-toluenesulfonic acid or copper(II) sulfate did not give furo[2,3-*b*]pyridine and resulted in resinification or recovery of the starting hydroxy compound. Dehydration of compound **5a** with phosphoric acid, however, yielded furo[3,2-*b*]pyridine (**6a**) in excellent yield. The ir and <sup>1</sup>H nmr spectra were completely identical with those of the sample prepared by the method of Gronowitz [2].

Analogously, 2-methyl derivative **6b** was synthesized in 30% overall yield. Compound **1** was *O*-alkylated with ethyl 2-bromopropionate to give ethyl 2-(2-ethoxycarbonyl-3-pyridyloxy)propionate (**2b**), which was cyclized with sodium ethoxide to 2-methylfuro[3,2-*b*]pyridin-3-(2*H*)-one (**4b**). Reduction of the ketone **4b** with sodium borohydride gave a mixture of *cis* and *trans*-2-methyl-2,3-dihydrofuro[3,2-*b*]pyridin-3-ol (**5b**) (ratio: *ca.* 1:1). Dehydration of the isomeric mixture of hydroxy derivatives gave 2-methylfuro[3,2-*b*]pyridine (**6b**). Structural assignment for the compound **6b** is based on the ir and <sup>1</sup>H nmr spectra and the elemental analysis of the free base and its methiodide **6b-MeI**.

Compound **1** was converted to 2-acetyl-3-pyridinol (**8**) by a Claisen condensation of the methoxymethyl ether of **1** with ethyl acetate and the subsequent hydrolysis and decarboxylation. *O*-Alkylation of **8** with ethyl bromoacetate afforded ethyl 2-(2-acetyl-3-pyridyloxy)acetate (**9**).

Treatment of compound **9** with sodium ethoxide in refluxing toluene afforded 3-methylfuro[3,2-*b*]pyridine-2-carboxylic acid (**10**) in 47% yield along with 13% yield of the ethyl ester (**10'**) which was easily saponified to give **10**.

The carboxylic acid **10** was decarboxylated to 3-methylfuro[3,2-*b*]pyridine (**11**) by heating with copper powder. The structure of compound **11** was confirmed by its ir and <sup>1</sup>H nmr spectra and elemental analysis of the free base and the methiodide **11-MeI**.

## EXPERIMENTAL

Melting points were determined by using micro melting point apparatus (Yanagimoto). All melting points are uncorrected. Infrared (ir) spectra were taken on a JASCO A-102 spectrometer. Proton nuclear magnetic resonance (<sup>1</sup>H nmr) spectra were recorded on a JEOL JNM-PMX 60 spectrometer. Chemical shifts are reported in part per million related to tetramethylsilane as an internal standard.

### Ethyl 3-Hydroxypicolinate (**1**).

In a flask with condenser and water separator, a mixture of 3-hydroxypicolinic acid (25.0 g, 0.18 mole), ethanol (600 ml), benzene (200 ml) and 98% sulfuric acid (10 ml) was refluxed for 40 hours. After evaporation of the excess ethanol and benzene *in vacuo*, the slightly yellow residue was dissolved in 500 ml of water, neutralized with sodium bicarbonate and extracted with chloroform. After drying over magnesium sulfate and evaporation of the solvent, the yellow oily residue was distilled to give 19.8 g (66%) of **1**, bp 85-93° (0.7 mm Hg).

Concentration of the aqueous layer after chloroform extraction to 100 ml and acidification with hydrochloric acid to pH 4-4.5 led to precipitation of 7 g of unreacted acid, which was resubjected to the esterification procedure to bring the overall esterification yield to 85%; ir (liquid film): 3150 (broad, m), 3060 (m), 3030 (w), 2980 (m), 2930 (w), 2870 (w), 1670 (s), 1590 (m), 1445 (s), 1440 (m), 1375 (m), 1340 (m), 1305 (s), 1240 (m), 1200 (s), 1130 (w), 1100 (s), 1050 (w), 1015 (m), 860 (m), 805 (s) cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 1.43 (t, J = 7.5 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 4.46 (q, J = 7.5 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 7.26 (d, J = 2.4 Hz, 1H, H-4), 7.27 (d, J = 3.2 Hz, 1H, H-5), 8.17 (dd, J = 2.4, 3.2 Hz, 1H, H-6), 10.77 (s, 1H, OH).

*Anal.* Calcd. for C<sub>8</sub>H<sub>9</sub>NO<sub>3</sub>: C, 57.47; H, 5.42; N, 8.38. Found: C, 57.12; H, 5.40; N, 8.12.

### Ethyl 2-(2-Ethoxycarbonyl-3-pyridyloxy)acetate (**2a**).

A mixture of compound **1** (18.92 g, 0.113 mole), ethyl bromoacetate (22.0 g, 0.132 mole) and anhydrous potassium carbonate (20 g) in dry acetone (200 ml) was refluxed with stirring for 15 hours. After cooling, the inorganic materials were filtered off, and the filtrate was dissolved in chloroform, washed with water and dried (magnesium sulfate). The residue of the chloroform solution was distilled to give 23.95 g (84%) of

**2a** as a colorless oil, bp 163-164° (0.7 mm Hg); ir (liquid film): 3060 (w), 2980 (m), 2930 (m), 2900 (w), 2860 (w), 1755 (s), 1730 (s), 1580 (m), 1450 (s), 1390 (w), 1380 (m), 1365 (m), 1300 (s), 1200 (s), 1140 (w), 1100 (s), 1070 (w), 1050 (w), 1020 (m), 860 (m), 800 (s) cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 1.26 (t, J = 7.0 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.40 (t, J = 7.0 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 4.21 (q, J = 7.0 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.41 (q, J = 7.0 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.67 (s, 2H, OCH<sub>2</sub>COOEt), 7.20 (dd, J = 8.0, 2.0 Hz, 1H, H-4), 7.27 (dd, J = 8.0, 3.6 Hz, 1H, H-5), 8.22 (dd, J = 3.6, 2.0 Hz, 1H, H-6).

Anal. Calcd. for C<sub>12</sub>H<sub>13</sub>NO<sub>5</sub>: C, 56.91; H, 5.97; N, 5.53. Found: C, 56.67; H, 5.97; N, 5.59.

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

A mixture of **2a** (23.0 g, 0.091 mole), sodium ethoxide (13.6 g, 0.2 mole) in toluene (350 ml) was refluxed with stirring for 18 hours. After cooling, the crystalline precipitates were filtered, dissolved in water (200 ml) and acidified with acetic acid. The crystalline product was filtered and dried *in vacuo* to give 17.1 g (91%) of **3**, mp 188-193°. Recrystallization from ethanol gave an analytically pure sample of mp 191-194° (slightly yellow prisms); ir (potassium bromide): 3450 (broad, m), 3070 (m), 3030 (w), 2980 (m), 2920 (w), 2900 (w), 2700 (broad, m), 1700 (s), 1625 (m), 1600 (w), 1570 (w), 1470 (m), 1440 (m), 1395 (s), 1370 (s), 1350 (m), 1260 (s), 1220 (m), 1160 (m), 1140 (s), 1025 (m), 940 (m), 880 (w), 860 (w), 800 (s), 780 (w), 760 (m) cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 1.46 (t, J = 7.5 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 4.48 (q, J = 7.5 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 7.32 (dd, J = 8.4, 4.4 Hz, 1H, H-6), 7.72 (dd, J = 8.4, 1.2 Hz, 1H, H-7), 8.58 (dd, J = 4.4, 1.2 Hz, 1H, H-5).

Anal. Calcd. for C<sub>10</sub>H<sub>9</sub>NO<sub>4</sub>: C, 57.97; H, 4.38; N, 6.76. Found: C, 58.05; H, 4.25; N, 6.84.

### Furo[3,2-*b*]pyridin-3(2*H*)-one (**4a**).

Compound **3** (17.0 g, 0.082 mole) was heated with 10% hydrochloric acid (120 ml) under reflux for 3 hours. Evaporation of the excess hydrochloric acid gave 14.0 g (100%) of crude hydrochloride of **4a**, which was recrystallized from methanol to afford a pure sample of **4a**·HCl, mp 141-144°; ir (potassium bromide): 3370 (s), 3300 (s), 3090 (w), 2980 (w), 2700 (broad, s), 1640 (w), 1620 (m), 1575 (s), 1495 (s), 1370 (s), 1295 (m), 1275 (s), 1215 (s), 1130 (w), 1100 (w), 1075 (s), 960 (w), 895 (w), 860 (m), 790 (m), 780 (s) cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 7.82 (dd, J = 8.4, 5.6 Hz, 1H, H-6), 8.02 (s, 1H, H-2), 8.57 (dd, J = 8.4, 1.0 Hz, 1H, H-7), 8.65 (dd, J = 5.6, 1.0 Hz, 1H, H-5).

Anal. Calcd. for C<sub>7</sub>H<sub>6</sub>ClNO<sub>2</sub>: C, 49.00; H, 3.52; N, 8.16. Found: C, 48.90; H, 3.56; N, 7.99.

### 2,3-Dihydrofuro[3,2-*b*]pyridin-3-ol (**5a**).

To a stirred solution of **4a**·HCl (14.0 g, 0.0816 mole) in methanol (300 ml) was added portionwise sodium borohydride (10 g, 0.265 mole) with ice-cooling, and the mixture was stirred at room temperature for 30 minutes. After evaporation of the solvent *in vacuo*, the slightly orange syrup was treated with water and extracted with chloroform. Drying (magnesium sulfate) and evaporation of the solvent gave 10.1 g (90%) of **5a** as a slightly brown solid mass. The analytical sample was obtained by recrystallization from methanol-acetone as colorless needles, mp 112-113°; ir (potassium bromide): 3150 (s), 2980 (w), 2940 (w), 2910 (m), 2840 (w), 1600 (w), 1580 (m), 1455 (m), 1420 (s), 1340 (w), 1300 (s), 1255 (m), 1225 (m), 1160 (w), 1110 (w), 1080 (s), 940 (s), 860 (w), 790 (m) cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 4.50 (dd, J = 10.4, 6.2 Hz, 1H, one of the methylene proton at C-2), 4.71 (dd, J = 10.4, 4.4 Hz, 1H, another proton of the methylene at C-2), 5.45 (dd, J = 6.2, 4.4 Hz, 1H, H-3), 7.10 (d, J = 3.0 Hz, 2H, H-6 and H-7), 8.03 (t, J = 3.0 Hz, 1H, H-5), 4.70 (broad s, 1H, OH, disappeared by addition of deuteriooxide).

Anal. Calcd. for C<sub>7</sub>H<sub>7</sub>NO<sub>2</sub>: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.44; H, 5.12; N, 9.91.

### Furo[3,2-*b*]pyridine (**6a**).

A solution of **5a** (10.0 g, 0.073 mole) in 85% phosphoric acid (50 ml) was heated at 170-180° with stirring for 15 hours. After cooling, the slightly brown mixture was diluted with 200 ml of water, made alkaline with concentrated aqueous ammonia, extracted with ether (five times)

and dried (potassium carbonate). After removal of most of the solvent under atmospheric pressure, the pale brown residue was distilled *in vacuo* to give 8.2 g (94%) of compound **6a** as a colorless oil, bp 110-115° (27 mm Hg) (literature [2], bp 79-80° (12 mm Hg)). The ir and <sup>1</sup>H nmr spectra were completely identical with those of the sample prepared by the method of Gronowitz *et al* [2].

### Ethyl 2-(2-Ethoxycarbonyl-3-pyridyloxy)propionate (**2b**).

A mixture of compound **1** (1.16 g, 6.95 mmoles), ethyl 2-bromopropionate (1.47 g, 8.12 mmoles) and anhydrous potassium carbonate (1.7 g) in dry acetone (15 ml) was stirred and refluxed for 6 hours. After cooling, the inorganic materials and the solvent were removed to give a brown oil which was dissolved in chloroform, washed with water and dried (magnesium sulfate). After evaporation of the solvent, the residual oil was distilled to afford 1.2 g (65%) of **2b**, bp 170° (bath temperature) (0.1 mm Hg); ir (liquid film): 3060 (w), 2980 (m), 2940 (w), 2900 (w), 2870 (w), 1750 (s), 1735 (s), 1580 (m), 1445 (s), 1390 (w), 1375 (w), 1365 (m), 1300 (s), 1275 (m), 1200 (s), 1130 (m), 1105 (s), 1065 (w), 1050 (m), 1010 (m), 945 (w), 860 (m), 800 (m) cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 1.23 (t, J = 7.2 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.41 (t, J = 7.2 Hz, 3H, OCH<sub>2</sub>CH<sub>3</sub>), 1.64 (d, J = 7.0 Hz, 3H, -CH(CH<sub>3</sub>)COOEt), 4.17 (q, J = 7.2 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.42 (q, J = 7.2 Hz, 2H, OCH<sub>2</sub>CH<sub>3</sub>), 4.72 (q, J = 7.0 Hz, 1H, -CH(CH<sub>3</sub>)COOEt), 7.23 (dd, J = 8.6, 1.1 Hz, 1H, H-4), 7.30 (dd, J = 8.6, 3.6 Hz, 1H, H-5), 8.27 (dd, J = 3.6, 1.1 Hz, 1H, H-6).

Anal. Calcd. for C<sub>13</sub>H<sub>17</sub>NO<sub>5</sub>: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.13; H, 6.34; N, 5.44.

### 2-Methylfuro[3,2-*b*]pyridin-3(2*H*)-one (**4b**).

A mixture of **2b** (4.95 g, 18.5 mmoles), sodium ethoxide (1.54 g, 22.6 mmoles) in toluene (40 ml) was refluxed under stirring for 17 hours. After cooling, 150 ml of water was added to the mixture. The aqueous layer was acidified with acetic acid, and the resulting solid precipitates were filtered and dried in a desiccator to give 1.94 g (70%) of crude **4b** which was unstable and no suitable solvent could be found for recrystallization.

### 2-Methyl-2,3-dihydrofuro[3,2-*b*]pyridin-3-ol (**5b**).

To a solution of crude **4b** (1.94 g, 13 mmoles) in methanol (50 ml) was added portionwise sodium borohydride (2.0 g, 53 mmoles) with ice-cooling and stirring. The mixture was stirred at room temperature for 30 minutes. After evaporation of the solvent *in vacuo*, the orange semisolid was treated with water (50 ml) and extracted with chloroform. Drying (magnesium sulfate) and evaporation of the solvent afforded 1.7 g of brown syrup, which was distilled *in vacuo* to give 1.53 g (78%) of **5b** as a colorless oil, bp 150-155° (bath temperature) (0.1 mm Hg); <sup>1</sup>H nmr (deuteriochloroform): δ 1.45 (d, J = 6.4 Hz, 1.5H, ½ CH<sub>3</sub>), 1.55 (d, J = 6.4 Hz, 1.5H, ½ CH<sub>3</sub>), 4.69 (dq, J = 6.4, 4.0 Hz, 0.5H, H-2 of the *trans* isomer), 4.70 (qn, J = 6.4 Hz, 0.5H, H-2 of the *cis* isomer), 4.96 (d, J = 4.0 Hz, 0.5H, H-3 of the *trans* isomer), 5.13 (d, J = 6.4 Hz, 0.5H, H-3 of the *cis* isomer), 5.43 (broad s, OH), 6.98 (d, J = 3.0 Hz, 2H, H-6 and H-7), 7.91 (t, J = 3.0 Hz, 1H, H-5).

Anal. Calcd. for C<sub>8</sub>H<sub>9</sub>NO<sub>2</sub>: C, 63.56; H, 6.00; N, 9.27. Found: C, 63.50; H, 6.02; N, 8.87.

### 2-Methylfuro[3,2-*b*]pyridine (**6b**).

Compound **5b** (1.73 g, 12.6 mmoles) was dissolved in 85% phosphoric acid (20 ml) and heated at 170-180° for 18 hours. After cooling, the slightly brown mixture was diluted with 100 ml of water and basified with concentrated aqueous ammonia with ice-cooling. The mixture was extracted with chloroform, and the chloroform layer was dried over magnesium sulfate. After removal of most of the solvent under atmospheric pressure, the residual oil was distilled *in vacuo* to give 1.21 g (90%) of **6b** as a colorless oil, bp 120-130° (bath temperature) (23 mm Hg); ir (liquid film): 3110 (w), 3060 (w), 3030 (w), 3010 (w), 2950 (w), 2860 (w), 2840 (w), 1600 (s), 1560 (m), 1475 (w), 1435 (m), 1410 (s), 1380 (w), 1290 (w), 1260 (s), 1240 (s), 1190 (w), 1165 (s), 1140 (w), 1100 (w), 1030 (w), 1015 (w), 995 (w), 960 (w), 935 (s), 890 (w), 815 (m), 800 (m), 780 (s) cm<sup>-1</sup>; <sup>1</sup>H nmr (deuteriochloroform): δ 2.42 (d, J = 1.0 Hz, 3H, 2-CH<sub>3</sub>), 6.53 (qn, J = 1.0 Hz, 1H, H-3), 7.01 (dd, J = 8.2, 4.6 Hz, 1H, H-6), 7.54 (ddd, J =

8.2, 1.4, 1.0 Hz, 1H, H-7), 8.35 (dd,  $J = 4.6, 1.4$  Hz, 1H, H-5).

*Anal.* Calcd. for  $C_8H_7NO$ : C, 72.17; H, 5.30; N, 10.52. Found: C, 71.98; H, 5.69; N, 10.26.

The methiodide had mp 192-195° (from methanol-acetone), colorless cubes.

*Anal.* Calcd. for  $C_8H_{10}INO$ : C, 39.29; H, 3.66; N, 5.09. Found: C, 39.10; H, 3.67; N, 4.85.

### 2-Acetylpyridin-3-ol (8).

To a solution of sodium ethoxide prepared from 1.2 g (0.052 mole) of sodium and 50 ml of ethanol was added 8.5 g (0.051 mole) of compound **1** in 20 ml of ethanol with ice-cooling and stirring. After stirring for 30 minutes, the colorless mixture was evaporated *in vacuo* to dryness. The sodium salt of **1** in 300 ml of chloroform was cooled in an ice bath and treated dropwise with 4.5 g (0.056 mol) of chloromethyl methyl ether. The reaction mixture, after stirring at room temperature for 15 hours, was washed with 200 ml of 5% sodium hydroxide solution and water. After drying (magnesium sulfate), the solution was evaporated to leave 11.3 g of slightly yellow oil which was distilled to give 8.88 g (83%) of compound **7** as an almost colorless oil, bp 140-150° (bath temperature) (0.1 mm Hg); <sup>1</sup>H nmr (deuteriochloroform):  $\delta$  1.40 (t,  $J = 7.0$  Hz, 3H,  $OCH_2CH_3$ ), 3.47 (s, 3H,  $-OCH_3$ ), 4.42 (q,  $J = 7.0$  Hz, 2H,  $OCH_2CH_3$ ), 5.22 (s, 2H,  $-OCH_2O-$ ), 7.30 (dd,  $J = 8.4, 4.4$  Hz, 1H, H-5), 7.56 (dd,  $J = 8.4, 1.6$  Hz, 1H, H-4), 8.28 (dd,  $J = 4.4, 1.6$  Hz, 1H, H-6).

*Anal.* Calcd. for  $C_{10}H_{13}NO_2$ : C, 56.87; H, 6.20; N, 6.63. Found: 56.64; H, 6.28; N, 6.44.

A mixture of the methoxymethyl ether (**7**) (8.88 g, 0.042 mole), sodium ethoxide (10.3 g, 0.15 mole) in 100 ml of ethyl acetate was refluxed under stirring for 14 hours. After evaporation of the excess ethyl acetate, the brown mass was dissolved in 70 ml of water, and the resultant solution was neutralized with hydrochloric acid. The dark oil was dissolved by addition of a further 15 ml of concentrated hydrochloric acid and the hydrolysis was completed by refluxing for 3 hours. The cold solution was basified with sodium hydroxide solution and extracted with ether. The ethereal extract was dried over magnesium sulfate and evaporated to give 1.8 g (25%) of 2-acetyl-3-ethoxypyridine (**8**), bp 120° (bath temperature) (0.5 mm Hg); <sup>1</sup>H nmr (deuteriochloroform):  $\delta$  1.44 (t,  $J = 7.2$  Hz, 3H,  $OCH_2CH_3$ ), 2.60 (s, 3H,  $-COCH_3$ ), 4.08 (q,  $J = 7.2$  Hz, 2H,  $OCH_2CH_3$ ), 7.18 (dd,  $J = 8.0, 2.0$  Hz, 1H, H-4), 7.31 (dd,  $J = 8.0, 3.4$  Hz, 1H, H-5), 8.13 (dd,  $J = 3.4, 2.0$  Hz, 1H, H-6).

*Anal.* Calcd. for  $C_9H_{11}NO_2$ : C, 65.44; H, 6.71; N, 8.48. Found: C, 65.05; H, 6.81; N, 8.29.

The aqueous layer after ether extraction was acidified with acetic acid, and extracted with chloroform. After drying (magnesium sulfate), the chloroform solution was evaporated to leave 3.5 g of brown semisolid, which was distilled to give 2.3 g (40%) of **8**, bp 110-130° (bath temperature) (0.3 mm Hg). The distillate solidified on standing, mp 56-58° (literature [7], mp 58°). The ir and <sup>1</sup>H nmr (deuteriochloroform):  $\delta$  2.70 (s, 3H,  $-COCH_3$ ), 7.23 (dd,  $J = 8.0, 2.0$  Hz, 1H, H-4), 7.32 (dd,  $J = 8.0, 3.4$  Hz, 1H, H-5), 8.12 (dd,  $J = 3.4, 2.0$  Hz, 1H, H-6), 11.73 (s, 1H,  $-OH$ ) spectral data were identical with those reported by Dejardin *et al* [7].

A solution of the ethoxy compound **8** (1.7 g, 0.01 mole) in 20 ml of 48% hydrobromic acid was refluxed for 19 hours. After evaporation of the hydrobromic acid *in vacuo*, the mixture was dissolved in water (20 ml), made alkaline with sodium bicarbonate and extracted with chloroform. Evaporation of the solvent afforded 0.7 g (50%) of compound **8**.

### Ethyl 2-(2-Acetyl-3-pyridyloxy)acetate (9).

A mixture of compound **8** (2.2 g, 0.016 mole), anhydrous potassium carbonate (4 g) and ethyl bromoacetate (3.3 g, 0.02 mole) in dry acetone (35 ml) was stirred and refluxed for 2 hours. After cooling, the inorganic materials were filtered off, and the brown filtrate was evaporated to leave a brown syrupy residue. The residue was treated with 30 ml of water, extracted with chloroform, and dried (magnesium sulfate). The residue of the chloroform solution was distilled *in vacuo* to give 2.9 g (81%) of compound **9**, bp 140-150° (bath temperature) (0.1 mm Hg); ir (liquid film):

3060 (w), 2990 (m), 2940 (m), 2900 (w), 1755 (s), 1700 (s), 1575 (s), 1455 (s), 1440 (s), 1390 (w), 1380 (m), 1355 (s), 1300 (s), 1265 (m), 1200 (s), 1140 (m), 1090 (s), 1055 (s), 1020 (m), 950 (m), 860 (w), 840 (w), 800 (s), 760 (m)  $cm^{-1}$ ; <sup>1</sup>H (deuteriochloroform):  $\delta$  1.24 (t,  $J = 7.0$  Hz, 3H,  $OCH_2CH_3$ ), 2.61 (s, 3H,  $-COCH_3$ ), 4.18 (q,  $J = 7.0$  Hz, 2H,  $OCH_2CH_3$ ), 4.63 (s, 2H,  $OCH_2COOEt$ ), 7.15 (dd,  $J = 8.2, 2.0$  Hz, 1H, H-4), 7.27 (dd,  $J = 8.0, 3.6$  Hz, 1H, H-5), 8.17 (dd,  $J = 3.6, 2.0$  Hz, 1H, H-6).

*Anal.* Calcd. for  $C_{11}H_{13}NO_4$ : C, 59.19; H, 5.87; N, 6.27. Found: 58.99; H, 5.80; N, 6.42.

### 3-Methylfuro[3,2-*b*]pyridine-2-carboxylic Acid (10) and Its Ethyl Ester (10').

A mixture of sodium ethoxide (0.82 g, 12 mmoles) and compound **9** (1.88 g, 8.4 mmoles) in toluene (50 ml) was refluxed and stirred for 14 hours. After cooling, the dark brown mixture was extracted with water (50 ml). The aqueous layer was acidified with acetic acid, and chilled in an ice bath for 5 hours to complete the precipitation. The crystalline precipitates were filtered and dried to give 0.7 g (47%) of **10**, mp 245-251° dec. The analytical sample was obtained by recrystallization from methanol, mp 251-254° dec; <sup>1</sup>H nmr (deuteriomethanol):  $\delta$  2.58 (s, 3H, 3- $CH_3$ ), 7.38 (dd,  $J = 8.0, 4.5$  Hz, 1H, H-6), 7.88 (dd,  $J = 8.0, 2.0$  Hz, 1H, H-7), 8.49 (dd,  $J = 4.5, 2.0$  Hz, 1H, H-5).

*Anal.* Calcd. for  $C_9H_7NO_3 \cdot \frac{1}{2}H_2O$ : C, 58.07; H, 4.33; N, 7.52. Found: C, 57.61; H, 4.12; N, 7.61.

The toluene layer after water extraction was dried (magnesium sulfate) and evaporated to give 0.3 g of pale brown syrup which was distilled to give 0.22 g (13%) of the ethyl ester **10'**, bp 140-150° (bath temperature) (0.3 mm Hg) (the distillate solidified on standing); <sup>1</sup>H nmr (deuteriochloroform):  $\delta$  1.47 (t,  $J = 7.0$  Hz, 3H,  $OCH_2CH_3$ ), 2.65 (s, 3H, 3- $CH_3$ ), 4.47 (q,  $J = 7.0$  Hz, 2H,  $OCH_2CH_3$ ), 7.30 (dd,  $J = 8.4, 4.2$  Hz, 1H, H-6), 7.78 (dd,  $J = 8.4, 1.8$  Hz, 1H, H-7), 8.60 (dd,  $J = 4.2, 1.8$  Hz, 1H, H-5).

*Anal.* Calcd. for  $C_{11}H_{11}NO_3$ : C, 64.38; H, 5.40; N, 6.83. Found: C, 64.46; H, 5.36; N, 6.58.

A solution of potassium hydroxide (0.3 g, 5.4 mmoles) and the ester **10'** (0.22 g, 1.07 mmoles) in ethanol (15 ml) was refluxed for 3 hours. After evaporation of the ethanol, the residue was dissolved in 5 ml of water, and acidified with hydrochloric acid to pH 3.0. The crystalline precipitates were filtered and dried to give 0.15 g (79%) of **10**.

### 3-Methylfuro[3,2-*b*]pyridine (11).

A mixture of the carboxylic acid **10** (0.62 g, 3.5 mmoles) and copper powder (1.0 g) in a 5-ml flask equipped with an air condenser was heated to pyrolyze using a soft flame. The distillate was dissolved in chloroform. The insoluble material was removed by filtration and the chloroform from the filtrate by distillation at atmospheric pressure. Distillation of the residue *in vacuo* afforded 0.42 g (90%) of **11**, bp 150° (bath temperature) (15 mm Hg); <sup>1</sup>H nmr (deuteriochloroform):  $\delta$  2.27 (d,  $J = 1.2$  Hz, 3H, 3- $CH_3$ ), 7.11 (dd,  $J = 8.0, 4.6$  Hz, 1H, H-6), 7.54 (q,  $J = 1.2$  Hz, 1H, H-2), 7.62 (dd,  $J = 9.0, 1.2$  Hz, 1H, H-7), 8.46 (dd,  $J = 4.6, 1.2$  Hz, 1H, H-5).

*Anal.* Calcd. for  $C_8H_7NO$ : C, 72.17; H, 5.30; N, 10.52. Found: C, 71.92; H, 5.63; N, 10.80.

The methiodide had mp 192-195° dec (from methanol-acetone).

*Anal.* Calcd. for  $C_8H_{10}INO$ : C, 39.29; H, 3.66; N, 5.09. Found: C, 39.10; H, 3.67; N, 4.85.

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