Furopyridines. XXIV [1]. Nitration, Chlorination, Acetoxylation and Cyanation of 2,3-Dihydrofuro[2,3-*b*]-, -[3,2-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine *N*-Oxides

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Nitration of 2,3-dihydrofuro[3,2-*b*]- *N*-oxide **3b** and -[2,3-*c*]pyridine *N*-oxide **3c** afforded the nitropyridine compounds **4b**, **5b** and **6** from **3b** and **4c**, **5c**, **5'c** and **7** from **3c**, while -[2,3-*b*]- *N*-oxide **3a** and -[3,2-*c*]pyridine *N*-oxide **3d** did not give the nitro compound. Chlorination of **3b** and **3c** with phosphorus oxychloride yielded mainly the chloropyridine derivatives **15b**, **15'b** from **3b** and **15c** and **15'c** from **3c**, whereas **3a** and **3d** gave pyridine derivatives formed through fission of the 1-2 ether bond of the furopyridines **13a**, **14** and **13d**. Acetoxylation of **3b** and **3c** gave 3-acetoxy derivatives **18b** and **18c** and the parent compound **1b** and **1c**. Acetoxylation of **3a** yielded compounds formed through fission of the 1-2 bond **16** and **17** and **3d** gave furopyridones **19** and **19'**. Cyanation of **3b** and **3c** yielded mainly the cyanopyridine compounds **20b**, **20c** and **20'c**. Cyanation of **3a** and **3d** gave the cyanopyridine compounds **20a**, **20d** and **20'd** accompanying formation of the pyridine derivatives **21a**, **21d** and **21'd**.

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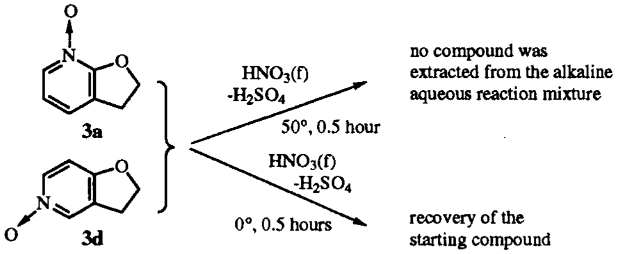
In the course of the study of the chemistry of furopyridines, we previously reported the chlorination, acetoxylation and cyanation of the *N*-oxides of furopyridines, from which derivatives having a chloro, acetoxy or cyano group at the α- or γ-position of the ring nitrogen of furopyridines were obtained [1-4]. These compounds seemed to be suitable precursors for further chemical modifications and were converted into other functional groups such as alkoxy, dialkylamino, hydroxy, carboxy and formyl which were expected to lead to useful, pharmacologically active compounds [1-5]. However, nitration of the *N*-oxides of furopyridines did not give the compounds having a nitro group attached to the pyridine ring [2]. Thus, we intended to synthesize nitropyridine derivatives of furopyridines by nitration of the *N*-oxides of 2,3-dihydrofuropyridines and the subsequent dehydrogenation. In this paper we report the nitration, acetoxylation, chlorination and cyanation of the *N*-oxides of 2,3-dihydrofuropyridines to compare the reactivity of the 2,3-dihydro compounds with that of full aromatic furopyridines.

Scheme 1

The *N*-oxides **3a-d** of the 2,3-dihydrofuropyridines were prepared in excellent yields by the catalytic hydrogenation of furopyridines **1a-d** over palladium-charcoal and the subsequent *N*-oxidation with *m*-chloroperbenzoic acid in chloroform.

Scheme 2



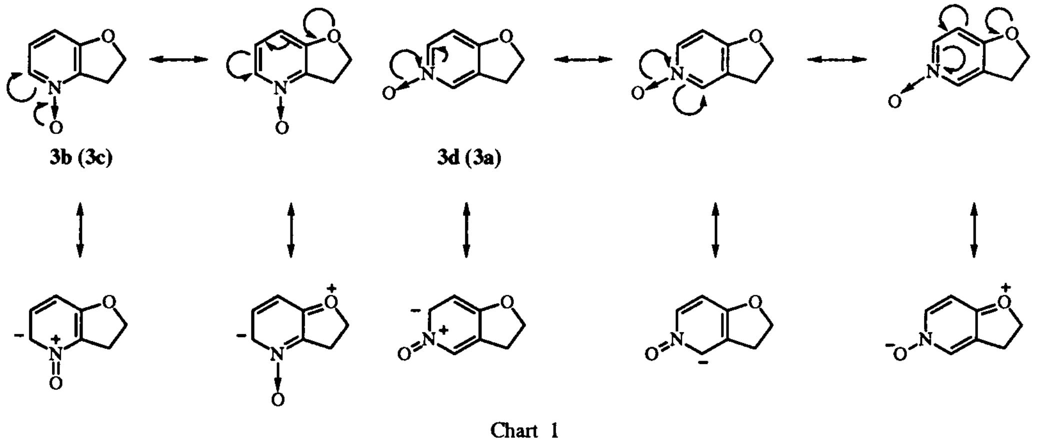
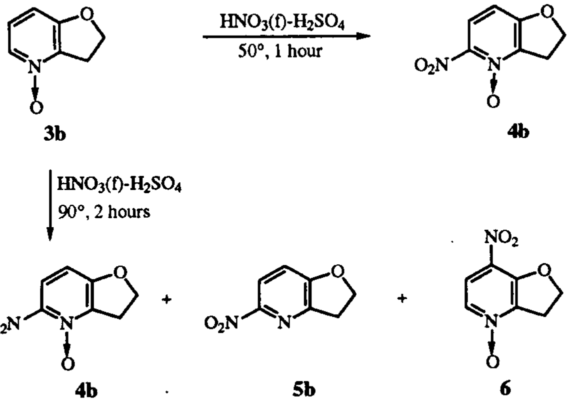


Chart 1

The nitration of **3a** and **3d** with fuming nitric acid and sulfuric acid at 50° gave no organic compound extractable from the basified aqueous reaction mixture, and the nitration at 0° resulted in recovery of the starting *N*-oxide. In contrast, the nitration of **3b** at 50° yielded 5-nitro-2,3-dihydrofuro[3,2-*b*]pyridine *N*-oxide **4b** in 90% yield, and the nitration at 90° gave a mixture of **4b** (44%), 5-nitro-2,3-dihydrofuro[3,2-*b*]pyridine **5b** (2%) and 7-nitro-2,3-dihydrofuro[3,2-*b*]pyridine *N*-oxide **6** (15%). The position of the nitro group in **4b** and **6** was determined by comparison of the chemical shift of the pyridine protons of **4b** (δ 7.75 and 6.74 (d, J = 8.8 Hz)) and **6** (δ 7.88 and 7.74 (d, J = 7.3 Hz)) with that of **3b** (δ 7.79 (d, J = 6.4 Hz, H-5)), 7.04 (dd, J = 6.4, 8.2 Hz, H-6) and 6.71 (d, J = 8.2 Hz, H-7)).

Scheme 3



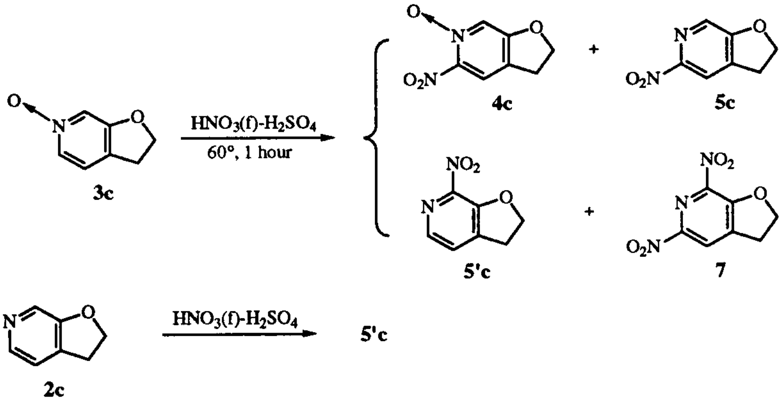
The nitration of **3c** at 60° afforded 5-nitro-2,3-dihydrofuro[2,3-*c*]pyridine *N*-oxide **4c** (32%), 5-nitro-2,3-dihydrofuro[2,3-*c*]pyridine **5c** (5%), 7-nitro-2,3-dihydrofuro[2,3-*c*]pyridine **5'c** (2%) and 5,7-dinitro-2,3-dihydrofuro[2,3-*c*]pyridine **7** (5%). These results indicated that the reactivity of the α- and γ-position to the ring nitrogen for nitration is apparently affected by the electron donating mesomeric effect of the ring oxygen. In the case of **3b** and **3c**, in which the ring oxygen is at the β-position to the ring nitrogen, the mesomeric effect and the back-donating effect of the *N*-oxide oxygen efficiently enhance the electrophilic reactivity of the α- and γ-position to the ring nitrogen. While, in **3a** and **3d**, the mesomeric effect and the back-donating effect counteract each other at α- and γ-position to the ring nitrogen (Chart 1).

Interestingly, treatment of nitro *N*-oxide **4b** with phosphorus trichloride yielded the deoxygenated compound **5b** (60%) accompanying the dehydrogenated compound, 5-nitrofuro[3,2-*b*]pyridine **8b** (23%). This fact strongly suggested that the dehydrogenated compound **8b** was yielded by the reaction of *N*-oxide **4b** with phosphorus oxychloride formed through deoxygenation of the *N*-oxide. Thus, *N*-oxide **4b** was refluxed with phosphorus oxychloride in chloroform to give compound **8b** in 65% yield. Reaction of the 7-nitro derivative **6** with phosphorus oxychloride also yielded the dehydrogenated compound **8'b** (42%) accompanying formation of 5-chloro-7-nitro-2,3-dihydrofuro[3,2-*b*]pyridine **11b** (40%). Likewise, refluxing of the 5-nitro *N*-oxide **4b** with acetic anhydride gave **8b** (24%), 3-acetoxy-5-nitro-2,3-dihydrofuro[3,2-*b*]pyridine **9** (33%) and 7-acetoxy-5-nitro-2,3-dihydrofuro[3,2-*b*]pyridine **10b** (15%). Reduction of the nitro group of **8b** with aluminum amalgam yielded the amino compound, which was successively converted into the acetamide compound **12**.

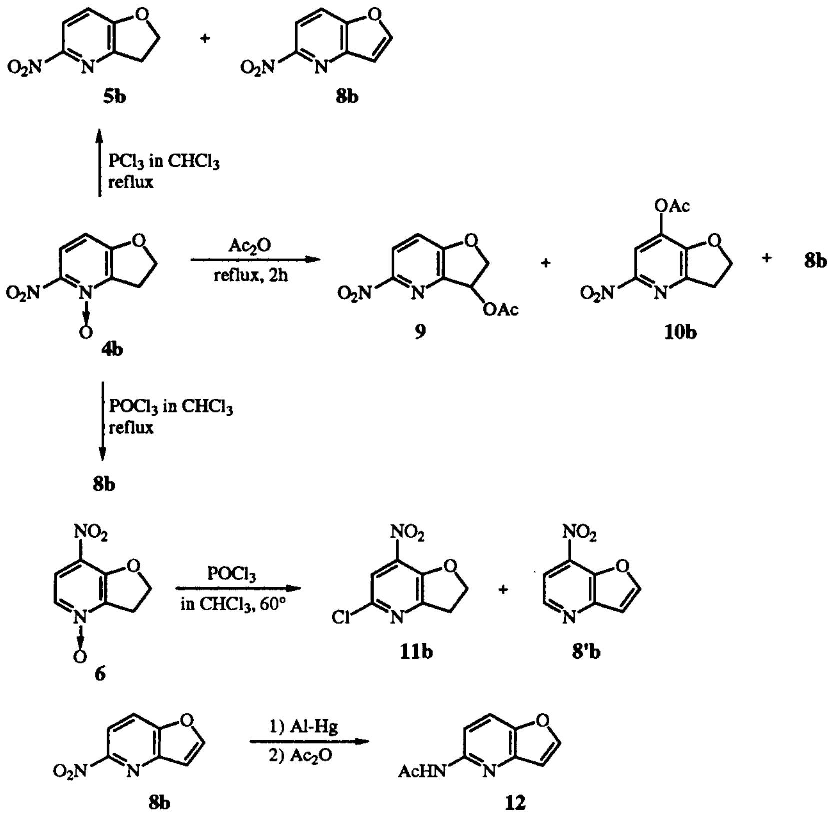
The reaction course of formation of **8b** and **8'b** would be interpreted as follows. Attack of phosphorus oxychloride at the oxygen of the *N*-oxide would give a phosphonated pyridinium ion **i**. Electron transfer from C-H bond at 3-position would give an intermediate **ii** and proton, and further electron transfer from bond C-3-C-3a to bond C-3a-N-4, the subsequent fission of N-O bond and attack of chloride ion at C-3 from the chlorophosphonate moiety would give 3-chloro derivative **iii** (or its 7-nitro isomer). Dehydrochlorination from **iii** (or its 7-nitro isomer) would give compound **8b** or **8'b** (Chart 2).

Reactions of 5-nitro-2,3-dihydrofuro[2,3-*c*]pyridine *N*-oxide **4c** with phosphorus oxychloride and with acetic anhydride afforded normally substituted-pyridine products, 7-chloro **11c** (99%) and 7-acetoxy compound **10c** (99%), respectively.

Scheme 4



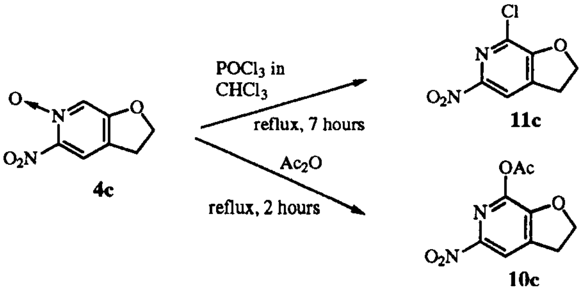
Scheme 5



The chlorination of *N*-oxides **3b** and **3c** with phosphorus oxychloride gave the normally chlorinated-pyridine products, 5-chloro **15b** (8%) and 7-chloro compound **15'b** (24%) accompanying formation of **1b** (16%) from **3b** and 5-chloro **15c** (22%) and 7-chloro compound **15'c** (22%) from **3c**, whereas the chlorination of **3a** and **3d** yielded complex mixtures of products, from which the unexpected products, 2,6-dichloro-3-(2'-chloroethyl)pyridine **13a** (6.5%) and 2,4-dichloro-3-(2'-chloroethyl)pyridine **14** (2.3%) from **3a** and 6-chloro-2,3-dihydrofuro[3,2-*c*]pyridine **15d** (61), 2,4-dichloro-3-(2'-chloroethyl)pyridine **13d** (10%) and **14** (12%) from **3d**, were isolated. The position of the chlorine atom in **15b** and **15'b** was determined again by comparison of the chemical shift of the pyridine protons. Compound **15b** exhibited signals of two pyridine protons at δ 7.03 and 6.98 (d, J = 8.0 Hz) and compound **15'b** at δ 7.05 and 7.93 (d, J = 5.4 Hz). The signal at δ 7.93 of **15'b** and the signal at δ 6.98 of **15b** could be assigned to the proton at the α- and γ-position to the ring nitrogen respectively; therefore, the structure of **15b** was determined as 5-chloro and **15'b** 7-chloro compound. The structures of compound **13a, 13d** and **14** were confirmed from the mass and ^{1}H-nmr spectral data. The high resolution mass spectra of these compounds showed the same molecular formula, $C_7H_6NCl_3$. In the ^{1}H-nmr spectrum, **13a** showed signals of two pyridine protons at δ 7.60 and 7.25 as doublet of J = 7.9 Hz, **14** at δ 8.20 and 7.29 as doublet of J = 5.3 Hz and **13d** at δ 8.29 and 7.39 as singlet. Thus, the structure of **13a** was determined as 2,6-dichloro-3-(2'-chloroethyl)-, **13d** as 2,4-dichloro-5-(2'-chloroethyl)- and **14** as 2,4-dichloro-3-(2'-chloroethyl)pyridine.

Formation of **13a**, **13d** and **14** can be explained as follows. At the first stage, the *N*-oxide **3a** and **3d** is normally chlorinated at the α- or γ-position by phosphorus oxychloride, then the ring nitrogen of the chlorinated 2,3-dihydrofuropyridine is protonated to form an ammonium ion. Electron transfer by mesomeric effect of the ring oxygen and the successive attack of chloride ion at C-2 yield 3-(2'-chloroethyl)-2-pyridinol compound, and then the hydroxyl group of the 2-pyridinol is chlorinated by phosphorus oxychloride to give **13a**, **13d** and **14** (Chart 3).

Scheme 6



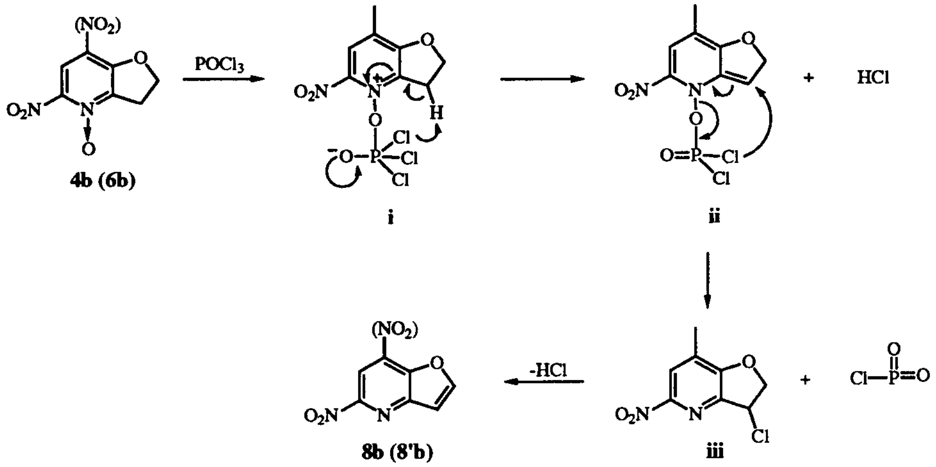


Chart 2

Reaction of the *N*-oxides **3a-d** with acetic anhydride gave again unexpected results: **3a** yielded 1-acetoxy-3-(2'-acetoxyethyl)pyridin-2(1*H*)-one **16** (6%) and 3-(2'-acetoxyethyl)-2-pyridinol *N*-oxide **17** (13%), **3b** yielded 3-acetoxy derivative **18b** (59%) and the parent compound **1b** (9%), **3c** gave **18c** (44%) and the parent compound **1c** (32%), and **3d** gave 2,3-dihydrofuro[3,2-*c*]pyridin-4(5*H*)-one **19** (10%) and 2,3-dihydrofuro[3,2-*c*]pyridin-6(5*H*)-one **19'** (6.5%). Compound **16**, an oil, was somewhat unstable to heat and decomposed into compound **17** by standing at room temperature in the air for 1 to 2 days, and its structure was characterized from the ^{1}H-nmr (signals of two acetoxy methyl at 2.38 and 2.02 and three aromatic protons at δ 7.27 (2H) and 6.25 (1H)) and ir (three carbonyl absorptions at 1808, 1738 and 1660 cm^{-1}) spectra. Formation of **16** and **17** would be interpreted as follows: the positive charge of the *N*-acetoxyammonium ion intermediate (a) would be directly affected by the mesomeric effect of the ring oxygen to form the resonance structure and therefore the first attack of the acetoxy anion occurs at C-2 by the inductive effect of the oxonium cation to form compound **16** and the hydrolysis of the N-O bond of **16** would give **17** (Chart 4).

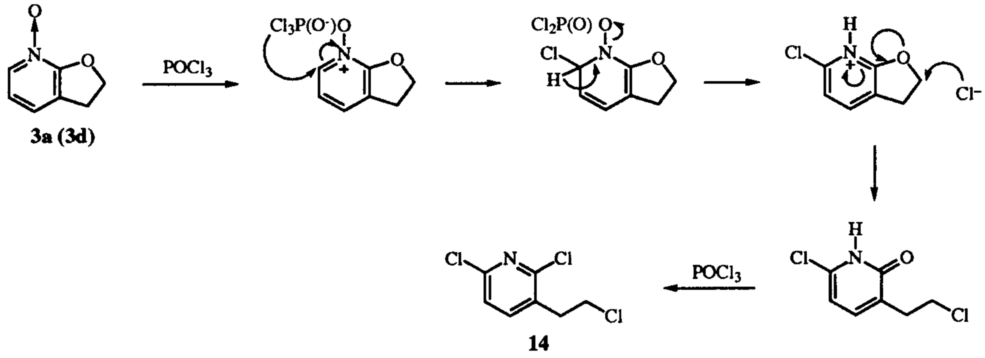


Chart 3

Reaction path for the formation of **18b**, **18c**, **1b** and **1c** from **3b** and **3c** can be explained by the mechanism argued for the chlorination of the 5-nitro *N*-oxide **4b** with phosphorus oxychloride in the above.

The results of cyanation of the *N*-oxides **3a-d** with trimethylsilyl cyanide also varied from system to system of the furopyridines. The *N*-oxide **3a** yielded the 7-cyano derivative **20a** (40%) and 3-(2'-cyanoethyl)-2-pyridinol *N*-oxide **21a** (19%); **3b** gave 5-cyano compound **20b**

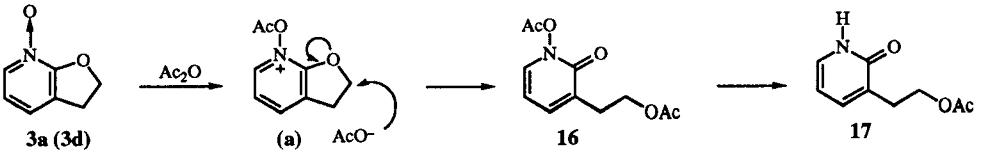
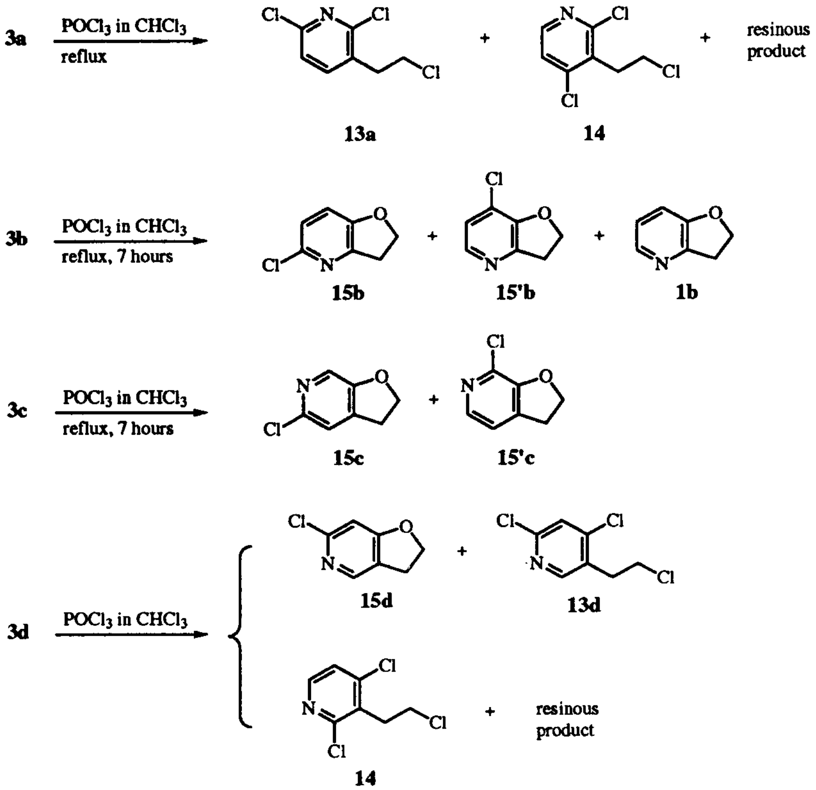


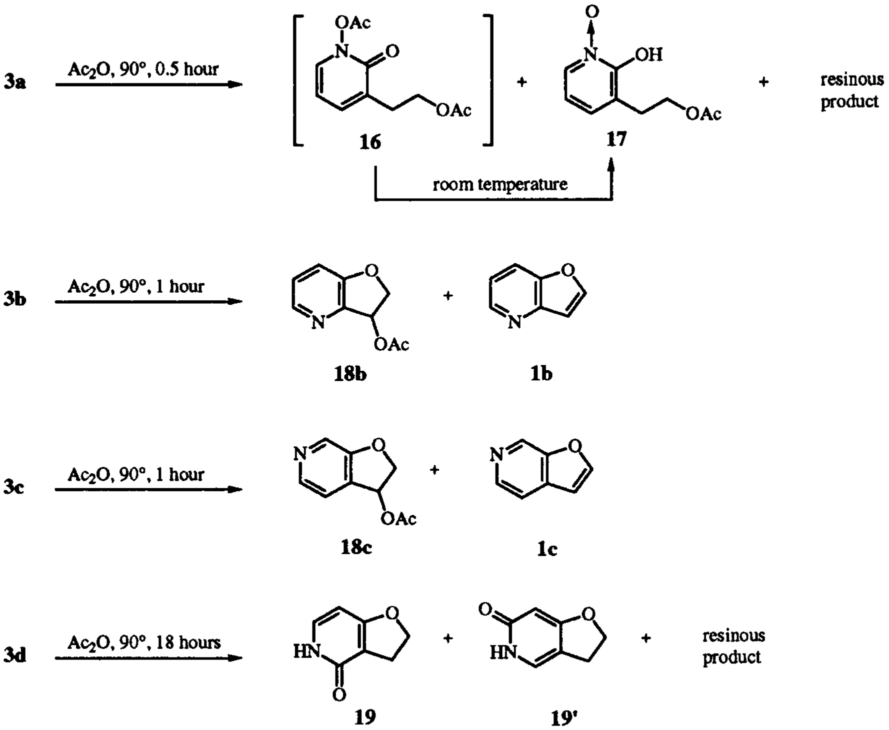
Chart 4

Scheme 7

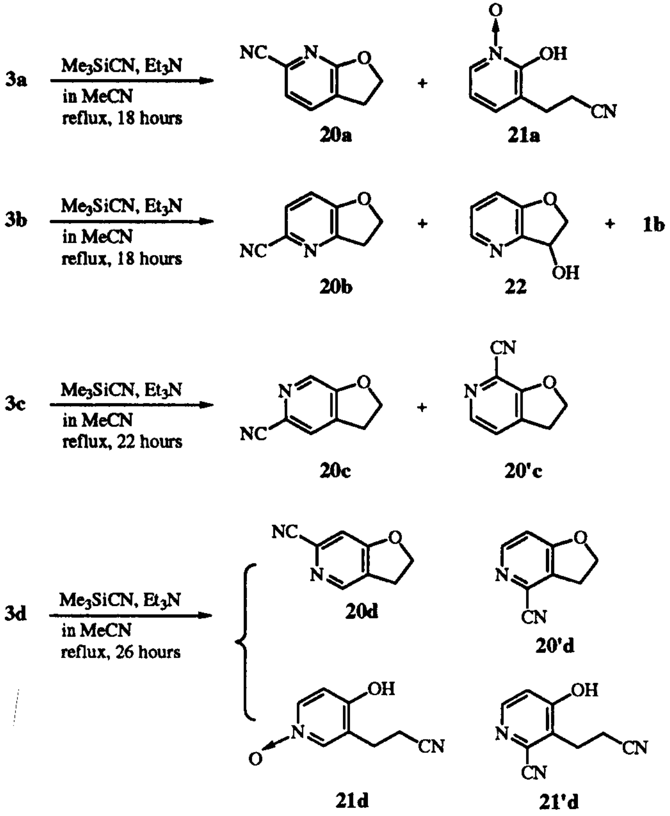


(18%), 3-hydroxy compound **22** (18%) and **1b** (18%); **3c** gave 5-cyano **20c** (34%) and 7-cyano compound **20'c** (63%); likewise **3d** gave 6-cyano **20d** (27%), 4-cyano compound **20'd** (2.2%), 3-(2'-cyanoethyl)-4-pyridinol *N*-oxide

Scheme 8



Scheme 9



21d (15%) and 2-cyano-3-(2'-cyanoethyl)-4-pyridinol **21'd** (33%). Compounds **21a**, **21d** and **21d'** would be formed by a similar reaction pathway for that of **17** from **3a**. Compound **22** would be formed by a similar reaction pathway as for the chlorination of the 5-nitro *N*-oxide **4b** with phosphorus oxychloride as above: attack of trimethylsilanol at the 3-position of the intermediate from **3d**, which corresponds to the intermediate **ii** for the chlorination of **4b**, and the subsequent hydrolysis of the silyl ether.

Chlorination, acetoxylation and cyanation of **3a-d** gave the substituted-pyridine products in considerably lower yields than these reactions of fully aromatic furopyridine *N*-oxides reported in previous papers [1,2,3]. Moreover, compounds **3a** and **3d**, in which the ring oxygen is at α- and γ-position to the ring nitrogen, yielded products formed through fission of 1-2 bond, and compounds **3b** and **3c**, in which the ring oxygen is at β-position to the ring nitrogen, accompanied formation of 3-substituted products. These results suggested that the nucleophilic reactivity at the α- and γ-position of the phosphonated, acetoxylated or siloxylated ammonium cation is much reduced by the mesomeric electron-donating effect of the ring oxygen as illustrated in Chart 5. In the cases of **3b** and **3c**, the electron-withdrawing effect of the ammonium cation intermediate **a'** would affect at C-3 as shown in Chart 5.

Thus, by comparing results described in this paper with those of the *N*-oxides of fully aromatic furopyridines it would be concluded that the electronic effect of the ring oxygen of *N*-oxides of 2,3-dihydrofuropyridines upon the pyridine ring is mesomeric and electron-donating and that of *N*-oxides of furopyridine is rather electron-withdrawing.

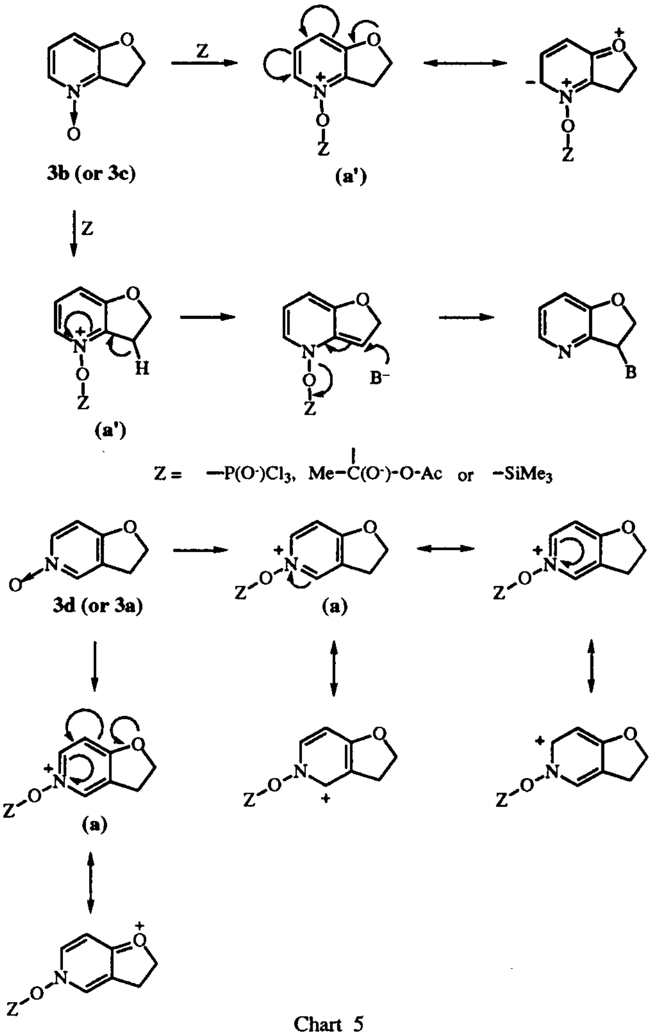


Chart 5

EXPERIMENTAL

Melting points were determined by using a Yanagimoto micro melting point apparatus and are uncorrected. The ir spectra were recorded on a JASCO FT/IR 7300 spectrometer. The ^{1}H-nmr spectra were recorded on a JEOL-PMX 60 (60 MHz), JEOL MAC-FX (90 MHz) and/or JEOL JNM FX-A400 (400 MHz) spectrometer in deuteriochloroform with tetramethylsilane as an internal reference. The mass spectra were taken by using JEOL JMS-OISG-2 instrument. Column chromatography was performed with silica gel (Chromatography Silica Gel, BW-820MH, Fuji Silysia Chemical Ltd) or alumina (Merck, Aluminium Oxide 90 active, neutral).

General Procedure for the Preparation of *N*-Oxides of 2,3-Dihydrofuro[2,3-*b*]- **3a**, -[3,2-*b*]- **3b**, -[2,3-*c*]- **3c** and -[3,2-*c*]pyridine **3d**.

A mixture of furopyridine 1 (1.27 g, 10.7 mmoles), palladium-charcoal (5%, 1.0 g), acetic acid (5 ml) in methanol (15 ml) was shaken in a hydrogen atmosphere at room temperature for 25 hours (the hydrogenation of **1a** ceased within 3 hours). After removal of the catalyst and solvent, the syrupy residue was dissolved in chloroform, washed with 5% sodium bicarbonate solution and water, and dried over magnesium sulfate. The residual oil was distilled to give **2a** (1.25 g, 97%) (bp 160-165°/40 mm Hg) from **1a**, **2b** (1.23 g, 95%) (bp 115°/40 mm Hg) from **1b**, **2c** (1.21 g, 95%) (bp 135-145°/40 mm Hg) from **1c** and **2d** (1.15 g, 89%) (bp 135-140°/45 mm Hg) from **1d**, which were used for the next step without any purification.

A mixture of **2** (1.23 g, 10.2 mmoles) and *m*-chloroperbenzoic acid (75% purity, 2.8 g, 12.2 mmoles) in chloroform (50 ml) was stirred at room temperature for 18 hours. The reaction mixture was filtered slowly with an alumina (basic, 100 g) pad to remove the acidic components. The filtrate was evaporated to give a solid mass which was purified by distillation to afford **3b•1/2H$_2$O** (1.3 g, 88%) from **2b** and **3c** (1.13 g, 81%) from **2c** and by recrystallization from acetone-methanol to give **3a•3/4H$_2$O** (1.36 g, 89%) from **2a** and **3d•1/3H$_2$O** (1.21 g, 83%) from **2d**.

Compound **3a**.

This compound had mp 92-95° (colorless crystals); ir (potassium bromide): 2950, 1845, 1599, 1500, 1440, 1329, 1240, 1217, 1030, 926, 782 cm^{-1}; ^{1}H-nmr: δ 7.97 (d, J = 7.0 Hz, 1H, H-6), 7.14 (dq, J = 7.0, 1.2 Hz 1H, H-4), 6.81 (t, J = 7.0 Hz, 1H, H-5), 4.89 (t, J = 8.8 Hz, 2H, 2 x H-2), 3.41 (td, J = 8.8, 1.2 Hz, 2H, 2 x H-3); ms: m/z (relative intensity) 137 (M$^+$, 40), 121 (100), 120 (20), 93 (18); hrms: 137.0466. M$^+$, Calcd. for $C_7H_7NO_2$: 137.0476.

Anal. Calcd. for $C_7H_7NO_2$•3/4H_2O: C, 55.81; H, 5.69; N, 9.30. Found: C, 55.64; H, 5.65; N, 9.27.

Compound **3b**.

This compound had mp 103-104°; ir (potassium bromide): 3114, 3090, 2926, 2856, 1636, 1616, 1585, 1486, 1477, 1447, 1284, 1248, 1237, 1183, 1039, 979, 793 cm^{-1}; ^{1}H-nmr: δ 7.79 (d, J = 6.4 Hz, 1H, H-5), 7.04 (dd, J = 8.2, 6.4 Hz, 1H, H-6), 6.71 (d, J = 8.2 Hz, 1H, H-7), 4.76 (t, J = 9.0 Hz, 2H, 2 x H-2), 3.48 (t, J = 9.0 Hz, 2H, 2 x H-3); ms: m/z (relative intensity) 137 (M$^+$, 100), 121 (22), 120 (61), 92 (46); hrms: 137.0477. M$^+$, Calcd. for $C_7H_7NO_2$: 137.0476.

Anal. Calcd. for $C_7H_7NO_2$•1/2H_2O: C, 57.53; H, 5.52; N, 9.58. Found: C, 57.13; H, 5.86; N, 9.44.

Compound **3c**.

This compound had mp 92-94° (colorless crystals); 3111, 3065, 2982, 2913, 1625, 1579, 1487, 1473, 1453, 1441, 1304, 1278, 1195, 1151, 1108, 996, 974, 878, 822, 778 cm^{-1}; ^{1}H-nmr: δ 7.85 (s, 1H, H-7), 7.82 (d, J = 6.7 Hz, 1H, H-5), 7.06 (d, J = 6.7 Hz, 1H, H-4), 4.75 (t, J = 8.8 Hz, 2H, 2 x H-2), 3.23 (t, J = 8.8 Hz, 2H, 2 x H-3).

Anal. Calcd. for $C_7H_7NO_2$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.05; H, 5.34; N, 10.21.

Compound **3d**.

This compound had mp 178-181° (colorless crystals); ir (potassium bromide): 3075, 2872, 1632, 1493, 1457, 1443, 1240, 1204, 1127, 1113, 981, 937, 842, 825, 764 cm^{-1}; ^{1}H-nmr: δ 8.10 (s, 1H, H-4), 8.02 (d, J = 7.0 Hz, 1H, H-6), 6.70 (d, J = 7.0 Hz, 1H, H-7), 4.76 (t, J = 8.8 Hz, 2H, 2 x H-2), 3.29 (t, J = 8.8 Hz, 2H, 2 x H-3); ms: m/z (relative intensity) 137 (M$^+$, 56), 121 (100), 120 (69), 71 (62), 57 (99); hrms: 137.0473. M$^+$, Calcd. for $C_7H_7NO_2$: 137.0476.

Anal. Calcd. for $C_7H_7NO_2$•1/3H_2O: C, 58.74; H, 5.40; N, 9.79. Found: C, 58.39; H, 5.15; N, 9.69.

Nitration of 2,3-Dihydrofuro[3,2-*b*]pyridine *N*-Oxide **3b**.

a) Compound **3b** (127 mg, 0.9 mmole) was cooled to -10°, then 0.6 ml of sulfuric acid was added with stirring. To this solution was added fuming nitric acid (0.5 ml), and the mixture was stirred at 50° for 1 hour. To the yellow mixture was added ice and ice-water, basified with potassium carbonate, and extracted with chloroform. The residue of the dried (magnesium sulfate) chloroform solution was recrystallized from acetone to give 147 mg (90%) of **4b**, mp 161-165° (light yellow crystals); ir (potassium bromide): 3139, 3053, 3013, 2923, 2854, 1572, 1531, 1483, 1469, 1412, 1355, 1286, 1240, 1195, 1068, 974, 911, 853 cm^{-1}; ^{1}H-nmr: δ 7.75 (d, J = 8.8 Hz, 1H, H-6), 6.76 (d, J = 8.8 Hz, 1H, H-7), 4.90 (t, J = 9.0 Hz, 2H, 2 x H-2), 3.53 (t, J = 9.0 Hz, 2H, 2 x H-3); ms: m/z (relative intensity) 182 (M$^+$, 100), 120 (37), 119 (17), 118 (34), 82 (17), 80 (43); hrms: 182.0311. M$^+$, Calcd. for $C_7H_6N_2O_4$: 182.0327.

Anal. Calcd. for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.22; H, 3.37; N, 15.28.

b) Compound **3b** (400 mg, 2.9 mmoles) was cooled to -10°, then 2.0 ml of sulfuric acid was added with stirring. To this solution was added fuming nitric acid (1.6 ml), and the mixture was stirred at 90° for 2 hours. After being cooled, to the yellow mixture was added ice and ice-water, basified with potassium carbonate, and extracted with chloroform. The residue of the dried (magnesium sulfate) chloroform solution was chromatographed on an alumina (30 g) column eluting with hexane-ethyl acetate (2:3) to yield compound **4b** (11 mg, 2%), 5-nitro-2,3dihydrofuro[3,2-*b*]pyridine **5b** (212 mg, 44%) and 7-nitro-2,3-dihydrofuro[3,2-*b*]pyridine *N*-oxide **6** (77 mg, 14%).

Compound **5b**.

This compound had mp 160-160.5° (from acetone, pale yellow crystals); ir (potassium bromide): 3114, 3068, 3041, 3013, 2915, 2853, 1572, 1521, 1450, 1427, 1353, 1258, 1089, 922, 859 cm^{-1}; ^{1}H-nmr: δ 8.14 (d, J = 8.8 Hz, 1H, H-6), 7.18 (d, J = 8.8 Hz, 1H, H-7), 4.88 (t, J = 9.0 Hz, 2H, 2 x H-2), 3.45 (t, J = 9.0 Hz, 2H, 2 x H-3).

Anal. Calcd. for $C_7H_6N_2O_3$: C, 50.61; H, 3.63; N, 16.86. Found: C, 50.44; H, 3.76; N, 16.85.

Compound **6**.

This compound had mp 181-183° (from acetone, yellow crystals); ir (potassium bromide): 3100, 3078, 3008, 2924, 2854, 1612, 1590, 1525, 1516, 1437, 1426, 1356, 1336, 1285, 1243, 1204, 1177, 1049, 906, 842, 758 cm^{-1}; ^{1}H-nmr: δ 7.88 (d, J = 7.3 Hz, 1H, H-5), 7.74 (d, J = 7.3 Hz, 1H, H-6), 5.03 (t, J = 9.0 Hz, 2H, 2 x H-2), 3.53 (t, J = 9.0 Hz, 2H, 2 x H-3).

Anal. Calcd. for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.26; H, 3.46; N, 15.43.

Nitration of 2,3-Dihydrofuro[2,3-*c*]pyridine *N*-Oxide **3c**.

Compound **3c** (100 mg, 0.73 mmole) was cooled to -10°, then 0.5 ml of sulfuric acid was added with stirring. To this solution was added fuming nitric acid (0.4 ml), and the mixture was stirred at 50° for 1 hour. To the yellow mixture was added ice and ice-water, basified with potassium carbonate, and extracted with chloroform. The residue of the dried (magnesium sulfate) chloroform solution was chromatographed on a silica gel (23 g) column eluting with hexane-ethyl acetate (1:1) to give 5-nitro-**5c** (first fraction, 10 mg, 8%), 7-nitro- **5'c** (second fraction, 4 mg, 3%), 5,7-dinitro-2,3-dihydrofuro[2,3-*c*]pyridine **7** (third fraction, 10 mg, 7%) and 5-nitro-2,3-dihydrofuro[2,3-*c*]pyridine *N*-oxide **4c** (last fraction, 76 mg, 57%).

Compound **4c**.

This compound had mp 176-179° (from methanol, yellow crystals); ir (potassium bromide): 3115, 3055, 2925, 2855, 1622, 1525, 1493, 1479, 1426, 1342, 1299, 1193, 1155, 1072, 931, 904, 863, 779 cm^{-1}; ^1H-nmr: δ 7.88 (s, 1H, H-7), 7.62 (t, J = 1.2 Hz, 1H, H-4), 4.86 (t, J = 8.8 Hz, 2H, 2 x H-2), 3.33 (dt, J = 8.8, 1.2 Hz, 2H, 2 x H-3).

Anal. Calcd. for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.13; H, 3.41; N, 15.42.

Compound **5c**.

This compound had mp 120-123° (from ether-acetone, slightly yellow crystals); ir (potassium bromide): 3113, 3060, 2924, 2835, 1527, 1488, 1353, 1262, 1073, 977, 928, 918, 889, 828, 763 cm^{-1}; ^1H-nmr: δ 8.17 (t, J = 1.2 Hz, 1H, H-4), 8.05 (s, 2H, H-7), 4.84 (t, J = 8.8, 2H, 2 x H-2), 3.39 (dt, J = 8.8, 1.2 Hz, 2H, 2 x H-3).

Anal. Calcd. for $C_7H_6N_2O_3$: C, 50.61; H, 3.64; N, 16.86. Found: C, 50.54; H, 3.79; N, 16.80.

Compound **5'c**.

This compound had mp 135-136° (from ether-acetone, almost colorless crystals); ir (potassium bromide): 3115, 3050, 2926, 2853, 1614, 1538, 1482, 1416, 1360, 1318, 1211, 1073, 911, 856 cm^{-1}; ^1H-nmr: δ 7.99 (d, J = 4.2 Hz, 1H, H-5), 7.40 (dt, J = 4.2, 1.2 Hz, 1H, H-4), 4,84 (t, J = 8.8, Hz, 2H, 2 x H-2), 3.39 (dt, J = 8.8, 1.2 Hz, 2H, 2 x H-3).

Anal. Calcd. for $C_7H_6N_2O_3$: C, 50.61; H, 3.64; N, 16.86. Found: C, 50.66; H, 3.66; N, 17.00.

Compound **5'c** was also synthesized by the following procedure from **2c** as a single product. Sulfuric acid (0.7 ml) was added slowly to compound **2c** (150 mg, 1.2 mmoles) below 0° with stirring. Then, to this mixture was added a mixture of sulfuric acid (0.5 ml) and nitric acid (1.3 ml) at 0° and stirred for 1.5 hours at this temperature. The reaction mixture was poured onto ice, made alkaline with sodium bicarbonate and extracted with chloroform. The residue of the dried chloroform extract was recrystallized from ether-acetone to give 140 mg (69%) of **5'c**, which was identified with the sample obtained in the above by comparison of ir and ^1H-nmr spectra.

Compound **7**.

This compound had mp 187-187.5° (from ether-acetone, slightly yellow crystals); ir (potassium bromide): 3116, 2924, 2845, 1611, 1542, 1379, 1355, 1319, 1252, 1111, 919, 825, 725 cm^{-1}; ^1H-nmr: δ 8.43 (t, J = 1.2 Hz, 1H, H-4), 5.13 (t, J = 8.8 Hz, 2H, 2 x H-2), 3.35 (dt, J = 8.8, 1.2 Hz, 2H, 2 x H-3); ms: m/z (relative intensity) 211 (M^+, 24), 165 (100), 89 (30), 65 (19), 64 (20), 52 (44); hrms: 211.0238. M^+, Calcd. for $C_7H_5N_3O_5$: 211.0229.

Anal. Calcd. for $C_7H_5N_3O_5$: C, 39.82; H, 2.39; N, 19.90. Found: C, 40.10; H, 2.67; N, 19.79.

Reaction of 5-Nitro-2,3-dihydrofuro[3,2-*b*]pyridine *N*-Oxide **4b** with Phosphorus Trichloride.

A mixture of **4b** (150 mg, 0.82 mmole) and phosphorus trichloride (0.32 ml, 3.6 mmoles) in chloroform (6 ml) was refluxed for 2 hours. After being cooled, the mixture was treated with ice-water, basified with sodium bicarbonate and separated the layers. The organic layer was dried over magnesium sulfate and evaporated to give 170 mg of a yellow solid mass which was chromatographed on a silica gel (15 g) column eluting with hexane-ethyl acetate (3:1) to give 81 mg (60%) of 5-nitro-2,3-dihydrofuro[3,2-*b*]pyridine **5b** and 31 mg (23%) of 5-nitrofuro[3,2-*b*]pyridine **8b**.

Compound **8b**.

This compound had mp 155-157° (from acetone-ether, pale yellow crystals); ir (potassium bromide): 3149, 3132, 3085, 2922, 2853, 1530, 1407, 1374, 1338, 1324, 1278, 1103, 1012, 857, 835, 799 cm^{-1}; ^1H-nmr: δ 8.36 (d, J = 8.8 Hz, 1H, H-6), 8.13 (d, J = 2.3 Hz, 1H, H-2), 8.06 (dd, J = 8.8, 0.9 Hz, 1H, H-7), 7.21 (dd, J = 2.3, 0.9 Hz, 1H, H-3); ms: m/z (relative intensity) 164 (M^+, 22), 118 (100), 90 (42), 64 (23), 63 (61); hrms: 164.0220. M^+, Calcd. for $C_7H_4N_2O_3$: 164.0222.

Anal. Calcd. for $C_7H_4N_2O_3$: C, 51.23; H, 2.46; N, 17.07. Found: C, 51.44; H, 2.74; N, 16.89.

Reaction of Compound **4b** and **6b** with Phosphorus Oxychloride.

A solution of compound **4b** or **6b** (168 mg, 0.92 mmole) and phosphorus oxychloride (0.34 ml, 3.7 mmoles) in chloroform (8 ml) was refluxed for 4 hours. After being cooled, the reaction mixture was poured on to ice, basified with potassium carbonate and separated the layers. The organic layer was dried (magnesium sulfate) and evaporated to leave a yellow solid mass. Chromatography of the residue from **4b** on an alumina (Merck, neutral, 70 g) column eluting with hexane-ethyl acetate (1:1) yielded 97 mg (64%) of **8b**. The residue from **6b** was chromatographed on a silica gel (35 g) column eluting with chloroform-methanol (99:1) to give compound **8'b** (35 mg, 44%) and 5-chloro-7-nitro-2,3-dihydrofuro[3,2-*b*]pyridine **11b** (38 mg, 39%).

Compound **8'b**.

This compound had mp 75-80° (from ether, slightly yellow crystals); ir (potassium bromide): 3127, 3084, 3097, 2924, 2854, 1606, 1560, 1383, 1228, 1170, 1127, 1022, 834, 813, 793, 754 cm^{-1}; ^1H-nmr: δ 8.44 (d, J = 5.3 Hz, 1H, H-5), 7.91 (d, J = 2.3 Hz, 1H, H-2), 7.26 (d, J = 5.3 Hz, 1H, H-6), 7.04 (d, J = 2.3 Hz, 1H, H-3); ms: m/z (relative intensity) 164 (M^+, 4), 119 (5), 118 (40), 98 (6), 90 (30), 64 (16), 63 (33); hrms: 164.0215. M^+, Calcd. for $C_7H_4N_2O_3$: 164.0222.

Compound **11b**.

This compound had mp 84-86° (from ether, yellow crystals); ir (potassium bromide): 3092, 3032, 2920, 2852, 1615, 1517, 1404, 1360, 1346, 1189, 919, 894, 730 cm^{-1}; ^1H-nmr: δ 7.78 (s, 1H, H-6), 5.02 (t, J = 9.0 Hz, 2H, 2 x H-2), 3.51 (t, J = 9.0 Hz, 2H, 2 x H-3); ms: m/z (relative intensity) 202 (M^++2, 33), 200 (M^+, 100), 154 (24), 126 (20), 99 (36), 91 (34), 90 (24), 63 (23); hrms: 199.9988. M^+, Calcd. for $C_7H_5N_2O_3Cl$: 199.9988.

Anal. Calcd. for $C_7H_5N_2O_3Cl$: C, 41.92; H, 2.51; N, 13.97. Found: C, 42.22; H, 2.68; N, 14.02.

5-Acetamidofuro[3,2-*b*]pyridine **12**.

A mixture of compound **8b** (53 mg, 0.32 mmole), small pieces of aluminum foil (23 mg, 0.85 mmole), mercury(II) chloride (10 mg, 0.04 mmole) and water (0.1 ml) in tetrahydrofuran (10 ml) was stirred at room temperature for 5 hours. The reaction mixture was filtered through a sintered glass filter with a Celite pad. The filtrate was dried over magnesium sulfate and evaporated to give 36 mg (91%) of the 5-amino compound, which was heated with acetic anhydride (1 ml) on a water bath for 1 hour. After evaporation of the excess acetic anhydride, the residual syrup was dissolved in chloroform. The chloroform solution was washed with sodium bicarbonate aqueous solution several times and dried over magnesium sulfate. The solid residue (45 mg) of the chloroform solution was recrystallized from acetone-ether to give the pure sample of 5-acetamido-2,3-dihydrofuro[3,2-*b*]pyridine **12** (40 mg, 701), mp 161-165°; 3254, 3203, 3145, 3107, 3040, 2987, 2935, 2854, 1688, 1618, 1555, 1529, 1421, 1371, 1346, 1279, 1259, 1141, 1102, 1035, 1019, 824, 791 cm^{-1}; ^{1}H-nmr: δ 8.28 (broad s, 1H, NH), 8.23 (dd, J = 9.0, 0.8 Hz, 1H, H-7), 7.83 (d, J = 2.1 Hz, 1H, H-2), 7.80 (d, J = 9.0 Hz, 1H, H-6), 6.81 (dd, J = 2.1, 0.8 Hz, H-3), 2.22 (s, 3H, -COCH$_3$).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.09; H, 4.83; N, 15.61.

Reaction of 5-Nitro-2,3-dihydrofuro[2,3-*c*]pyridine *N*-Oxide **4c** with Phosphorus Oxychloride.

A mixture of **4c** (30 mg, 0.16 mmole) and phosphorus oxychloride (0.06 ml, 0.66 mmole) in chloroform was stirred and refluxed for 4 hours. After being cooled, the reaction mixture was treated with ice, basified with sodium bicarbonate and separated the layers. The chloroform layer was dried (magnesium sulfate) and evaporated to give a light yellow solid mass which was recrystallized from ether-acetone to yield 33 mg (99%) of **11c**, mp 106-109°; ir (potassium bromide): 3085, 2980, 2925, 2850, 1537, 1457, 1351, 1312, 1277, 1189, 1099, 982, 919, 824 cm^{-1}; ^{1}H-nmr: δ 8.12 (t, J = 1.2 Hz, 1H, H-4), 4.94 (t, J = 9.0 Hz, 2H, 2 x H-2), 3.49 (dt, J = 9.0, 1.2 Hz, 2H, 2 x H-3).

Anal. Calcd. for $C_7H_5N_2O_3Cl$: C, 41.92; H, 2.51; N, 13.97. Found: C, 42.20; H, 2.74; N, 13.84.

Reaction of Compound **4b** with Acetic Anhydride.

A solution of **4b** (50 mg, 0.28 mmole) in acetic anhydride (1 ml) was stirred and refluxed for 2 hours. After being cooled, 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 slightly brown solid mass. Chromatography of the solid mass on a silica gel (13 g) eluting with hexane-ethyl acetate (3:1) afforded **8b** (10 mg, 24%), 3-acetoxy-5-nitro-2,3-dihydrofuro[3,2-*b*]pyridine **9** (33 mg, 33%) and 7-acetoxy-5-nitro-2,3-dihydrofuro[3,2-*b*]pyridine **10b** (10 mg, 15%).

Compound **9**.

This compound had mp 143-144° (from ether-acetone, colorless crystals); ir (potassium bromide): 3101, 3069, 2986, 2927, 1742, 1612, 1439, 1356, 1269, 1230, 1211, 1100, 1066, 941, 867, 835 cm^{-1}; ^{1}H-nmr: δ 8.32 (d, J = 8.8 Hz, 1H, H-6), 7.41 (d, J = 8.8 Hz, 1H, H-7), 6.20 (dd, J = 7.2, 3.2 Hz, 1H, H-3), 5.01 (dd, J = 12.0, 7.2 Hz, 1H, H-2), 4.68 (dd, J = 12.0, 3.2 Hz, 1H, H-2'), 2.15 (s, 3H, OAc).

Anal. Calcd. for $C_9H_8N_2O_5$: C, 48.22; H, 3.60; N, 12.50. Found: C, 48.44; H, 3.77; N, 12.60.

Compound **10b**.

This compound had mp 124-125° (from ether-acetone, colorless crystals); ir (potassium bromide): 3100, 2948, 2922, 2860, 1774, 1625, 1552, 1429, 1372, 1355, 1327, 1269, 1221, 1203, 1056, 911, 902 cm^{-1}; ^{1}H-nmr: δ 8.00 (s, 1H, H-6), 4.91 (t, J = 8.8 Hz, 2H, 2 x H-2), 3.50 (t, J = 8.0 Hz, 2H, 2 x H-3).

Anal. Calcd. for $C_9H_8N_2O_5$: C, 48.22; H, 3.60; N, 12.50. Found: C, 48.60; H, 3.75; N, 12.23.

Reaction of **4c** with Acetic Anhydride.

A solution of **4c** (75 mg, 0.42 mmole) in acetic anhydride (1.5 ml) was stirred and refluxed for 2 hours. After being cooled, 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 slightly brown solid mass. Recrystallization of the crude product from ether-acetone yielded 91 mg (99%) of 7-acetoxy-5-nitro-2,3-dihydrofuro[2,3-*c*]pyridine **10c**, mp 111-112° (colorless crystals); ir (potassium bromide): 3102, 3005, 2989, 2929, 2854, 1775, 1585, 1532, 1484, 1460, 1363, 1318, 1294, 1232, 1216, 1185, 1110, 1048, 924, 883 cm^{-1}; ^{1}H-nmr: δ 8.15 (t, J = 1.2 Hz, 1H, H-4), 4.89 (t, J = 9.0 Hz, 2H, 2 x H-2), 3.46 (td, J = 9.0, 1.2 Hz, 2H, 2 x H-3).

Anal. Calcd. for $C_9H_8N_2O_5$: C, 48.22; H, 3.60; N, 12.50. Found: C, 48.45; H, 3.68; N, 12.45.

General Procedure for the Chlorination of 2,3-Dihydrofuropyridine *N*-Oxide **3a**, **3b**, **3c** and **3d** with Phosphorous Oxychloride.

To obtain each anhydrous *N*-oxide, each individual *N*-oxide hydrate **3a•3/4H$_2$O**, **3b•1/2H$_2$O** or **3d•1/3H$_2$O** was dissolved in dry tetrahydrofuran, dehydrated over molecular sieves 4A for 15 hours and the solvent was evaporated. A mixture of each 2,3-dihydrofuropyridine *N*-oxide **3** (100 mg, 0.73 mmole) and phosphorus oxychloride (1.0 ml, 10.75 mmoles) in chloroform (1.0 ml) was stirred and refluxed for 7 hours (2 hours for **3a**). After being cooled, the reaction mixture was poured onto ice, basified with sodium bicarbonate and extracted with chloroform. Further processing of the residue of the dried (magnesium sulfate) chloroform solution in indicated in a subsequent paragraph.

2,6-Dichloro-3-(2'-chloroethyl)- **13a** and 2,4-Dichloro-3-(2'-chloroethyl)pyridine **14**.

The residue (100 mg) from **3a** was chromatographed on a silica gel (10 g) column. The first fraction eluted with chloroform gave 10 mg (6.5%) of **13a** and the second 2 mg (1.3%) of **14**.

Compound **13a**.

This compound had bp 110-120° (bath temperature) (20 mm Hg) (colorless oil); ir (neat): 3102, 3005, 2955, 2919, 2850, 1581, 1552, 1426, 1362, 1225, 1139, 1070, 829, 757 cm^{-1}; ^{1}H-nmr: δ 7.60 (d, J = 7.9 Hz, 1H, H-5), 7.25 (d, J = 7.9 Hz, 1H, H-4), 3.78 (t, J = 6.7 Hz, 2H, -C*H*$_2$-CH$_2$-Cl), 3.17 (t, J = 6.7 Hz, 2H, -CH$_2$-C*H*$_2$-Cl); ms: m/z (relative intensity) 213 (M$^+$+4, 5), 211 (M$^+$+2, 16), 209 (M$^+$, 16), 164 (11), 162 (68), 160 (100), 125 (6), 124 (10), 102 (9); hrms: 208.9563. M$^+$, Calcd. for $C_7H_6NCl_3$: 208.9555.

Compound **14**.

This compound had bp 120-130° (bath temperature) (20 mm Hg) (colorless oil); ir (neat): 2958, 2920, 2850, 1562, 1547, 1440, 1378, 1260, 1133, 1114, 1025, 828, 794, 770 cm^{-1}; ^{1}H-nmr: δ 8.20 (d, J = 5.3 Hz, 1H, H-6), 7.29 (d, J = 5.3 Hz, 1H, H-5), 3.85-3.66 (m, 2H, -C*H*$_2$-CH$_2$-Cl), 3.51-3.32 (m, 2H, -CH$_2$-C*H*$_2$-Cl); ms: m/z (relative intensity) 213 (M$^+$+4, 6), 211 (M$^+$+2, 21), 209 (M$^+$, 22), 164 (10), 162 (67), 160 (100), 124 (8), 102 (10); hrms: 208.9559. M$^+$, Calcd. for $C_7H_6NCl_3$: 208.9555.

5-Chloro- **15b**, 7-Chloro-2,3-dihydrofuro[3,2-*b*]pyridine **15'b** and Furo[3,2-*b*]pyridine **1b**.

The residue (100 mg) from **3b** was chromatographed on a hplc column (LiChrosorb Si 60) eluting with hexane-ethyl acetate (1:1) to give **15b** (the first fraction, 11 mg, 9%), **1b** (the second, 14 mg, 16%) and **15'b** (the third, 30 mg, 26%). The structure of compound **1b** was confirmed by comparison of the ir and ^{1}H-nmr spectra with those of the authentic sample [6].

Compound **15b**.

This compound had mp 52-55° (bp 135-140° (bath temperature) (15 mm Hg), colorless crystals); ir (potassium bromide): 2958, 2924, 2850, 1647, 1541, 1508, 1437, 1240, 1182, 1110, 1078, 966, 940 cm^{-1}; ^{1}H-nmr: δ 7.03 (dt, J = 8.0, 0.8 Hz, 1H, H-7), 6.98 (d, J = 8.0 Hz, 1H, H-6), 4.69 (t, J = 9.0 Hz, 2H, 2 x H-2), 3.31 (td, J = 9.0, 0.8 Hz, 2H, 2 x H-3).

Anal. Calcd. for C_7H_6NOCl: C, 54.04; H, 3.89; N, 9.00. Found: C, 53.93; H, 3.88; N, 8.78.

Compound **15'b**.

This compound had mp 45-47° (colorless crystals) (bp 120-130°) (bath temperature) (15 mm Hg); ir (potassium bromide): 3076, 2981, 2924, 1595, 1566, 1478, 1418, 1325, 1225, 1198, 1160, 986, 939, 904, 810 cm^{-1}; ^{1}H-nmr: δ 7.93 (d, J = 5.4 Hz, 1H, H-5), 7.05 (td, J = 5.4, 0.7 Hz, 1H, H-6), 4.76 (t, J = 9.0 Hz, 2H, 2 x H-2), 3.41 (td, J = 9.0, 0.7 Hz, 2H, 2 x H-3).

Anal. Calcd. for C_7H_6NOCl: C, 54.04; H, 3.89; N, 9.00. Found: C, 53.78; H, 3.91; N, 8.90.

5-Chloro- **15c** and 7-Chloro-2,3-dihydrofuro[2,3-*c*]pyridine **15'c**.

The residue (120 mg) from **3c** was chromatographed on a silica gel (20 g) column eluting with hexane-ethyl acetate (1:1) to give **15c** (the first fraction, 41 mg, 36%) and **15'c** (the second, 43 mg, 37%).

Compound **15c**.

This compound had mp 101-102° (from hexane-ether, colorless crystals); ir (potassium bromide): 3087, 3054, 3023, 2974, 2952, 2903, 1599, 1575, 1481, 1468, 1457, 1430, 1367, 1291, 1236, 1160, 1074, 978, 941, 884, 814 cm^{-1}; ^{1}H-nmr: δ 7.87 (s, 1H, H-7), 7.15 (s, 1H, H-4), 4.65 (t, J = 8.8 Hz, 2H, 2 x H-2), 3.24 (t, 8.8 Hz, 2H, 2 x H-3).

Anal. Calcd. for C_7H_6NOCl: C, 54.04; H, 3.89; N, 9.00. Found: C, 54.07; H, 3.84; N, 9.03.

Compound **15'c**.

This compound had mp 105-105° (from hexane-ether, colorless crystals); 2994, 2974, 2938, 2876, 1601, 1569, 1475, 1459, 1418, 1353, 1301, 1236, 1206, 1165, 1065, 982, 945, 907, 829 cm^{-1}; ^{1}H-nmr: δ 7.92 (d, J = 4.9 Hz, 1H, H-5), 7.12 (d, J = 4.9 Hz, 1H, H-4), 4.71 (t, J = 9.0 Hz, 2H, 2 x H-2), 3.34 (t, J = 9.0 Hz, 2H, 2 x H-2).

Anal. Calcd. for C_7H_6NOCl: C, 54.04; H, 3.89; N, 9.00. Found: C, 54.04; H, 3.88; N, 8.96.

6-Chloro-2,3-dihydrofuro[3,2-*c*]pyridine **15d**, 2,4-Dichloro-5-(2'-chloroethyl)pyridine **13d** and 2,4-dichloro-3-(2'-chloroethyl)pyridine **14**.

The residue (98 mg) from **3d** was chromatographed on a silica gel (10 g) column. The first fraction eluted with chloroform gave a mixture of **13d** and **14** (50 mg) and the second **15d** (6.5 mg, 6%). The first fraction was again chromatographed on a hplc column (LiChrosorb Si 60) eluting with hexane-ethyl acetate (25:1) to give **13d** (15 mg, 10%) and **14** (19 mg, 12%). Compound **14** was identified with that obtained from **3a** by comparison of the ir and ^{1}H-nmr spectra.

Compound **13d**.

This compound had bp 135-140° (bath temperature) (20 mm Hg) (colorless oil); 3049, 2962, 2927, 2955, 1573, 1542, 1450, 1346, 1326, 1148, 1123, 1056, 860, 837, 782, 707 cm^{-1}; ^{1}H-nmr: δ 8.29 (s, 1H, H-6), 7.39 (s, 1H, H-3), 3.74 (t, J = 6.8 Hz, 2H, -CH_2-$\mathrm{CH_2}$-Cl), 3.19 (t, J = 6.8 Hz, 2H, -$\mathrm{CH_2}$-CH_2-Cl); ms: m/z (relative intensity) 213 (M$^+$+4, 6), 211 (M$^+$+2, 18), 209 (M$^+$, 18), 164 (10), 162 (63), 160 (100), 124 (8), 75 (8); hrms: 208.9559. M$^+$, Calcd. for $C_7H_6NCl_3$: 208.9555.

Compound **15d**.

This compound had mp 44-47° (colorless crystals) (bp 100-120°) (bath temperature) (20 mm Hg); ir (potassium bromide): 3059, 2978, 2952, 2913, 2869, 1578, 1483, 1462, 1445, 1288, 1219, 1053, 945, 883, 700 cm^{-1}; ^{1}H-nmr: δ 8.09 (s, 1H, H-4), 6.75 (s, 1H, H-7), 4.72 (t, J = 9.0 Hz, 2H, -CH_2-$\mathrm{CH_2}$-Cl), 3.23 (t, J = 9.0 Hz, 2H, -$\mathrm{CH_2}$-CH_2-Cl).

Anal. Calcd. for C_7H_6NOCl: C, 54.04; H, 3.89; N, 9.00. Found: C, 53.83; H, 3.84; N, 8.91.

General Procedure for the Acetoxylation of **3a**, **3b**, **3c** and **3d** with Acetic Anhydride.

To obtain the anhydrous *N*-oxide, the *N*-oxide hydrate **3a•3/4H$_2$O**, **3b•1/2H$_2$O** or **3a•1/3H$_2$O** was dissolved in dry tetrahydrofuran, dehydrated over molecular sieves 4A for 15 hours and the solvent was evaporated. A solution of 2,3-dihydrofuropyridine *N*-oxide **3** (200 mg, 1.5 mmoles) in acetic anhydride (2 ml) was stirred at 90° for 1 hour (0.5 hours for **3a**). After evaporation of the excess acetic anhydride, the reaction mixture was diluted with water, basified with sodium bicarbonate and extracted with chloroform. Further processing of the residue of the dried (magnesium sulfate) chloroform solution from **3a**, **3b**, **3c** and **3d** is indicated in a subsequent paragraph.

1-Acetoxy-3-(2'-acetoxyethyl)pyridin-2(1*H*)-one **16** and 3-(2'-Acetoxyethyl)-2-pyridinol *N*-Oxide **17**.

The residue (150 mg) from **3a** was chromatographed on a silica gel (20 g) column eluting with hexane-ethyl acetate (2:1) to give 20 mg (6%) of **16** and 141 mg (49%) of **17**.

Compound **16**.

This compound was a colorless oil, but could not be purified by distillation because of decomposition by heating, and gradually changed to compound **17** on standing at room temperature in the air; ir (neat): 3111, 3083, 3032, 2928, 2855, 1808, 1738, 1660, 1604, 1556, 1434, 1376, 1243, 1164, 1038, 837, 761 cm^{-1}; ^{1}H-nmr: δ 7.27 (d, J = 7.0 Hz, 2H, H-4 and H-6), 6.15 (t, J = 7.0 Hz, 1H, H-5), 4.32 (t, J = 6.7 Hz, 2H, -$\mathrm{CH_2}$-CH_2-OAc), 2.90 (t, J = 6.7 Hz, 2H, -CH_2-$\mathrm{CH_2}$-OAC), 2.38 (s, 3H, -OAc), 2.02 (s, 3H, -OAc).

Compound **17**.

This compound had mp 95-98° (from acetone-ether, pale yellow crystals); ir (potassium bromide): 3200-2560 (broad), 2968, 2926, 2852, 1732, 1638, 1579, 1560, 1508, 1436, 1277, 1246, 1213, 1045, 820, 753 cm^{-1}; ^{1}H-nmr: δ 7.71 (d, J = 7.0 Hz, 1H, H-6), 7.26 (d, J = 7.0 Hz, 1H, H-4), 6.28 (t, J = 7.0 Hz, 1H, H-5), 4.32 (t, J = 6.6 Hz, 2H, -$\mathrm{CH_2}$-CH_2-OAc), 2.94 (t, J = 6.6 Hz, 2H, -CH_2-$\mathrm{CH_2}$-OAc), 2.02 (s, 3H, -OAc).

Anal. Calcd. for $C_9H_{11}NO_4$: C, 54.82; H, 5.62; N, 7.10. Found: C, 55.06; H, 5.57; N, 7.13.

3-Acetoxy-2,3-dihydrofuro[3,2-*b*]pyridine **18b** and Furo[3,2-*b*]pyridine **1b**.

The residue (220 mg) from **3b** was distilled under reduced pressure to give 16 mg (9%) of **1b** and 154 mg (59%) of **18b**. Compound **1b** (bp 105° (bath temperature) (20 mm Hg)) was identified with the authentic sample [6] by comparison of the ir and ^{1}H-nmr spectra.

Compound **18b**.

This compound had bp 80-85° (bath temperature) (0.1 mm Hg) (colorless oil); ir (neat): 307, 3030, 3010, 2963, 2890, 1739, 1584, 1458, 1434, 1372, 1265, 1236, 1158, 1062, 1033, 957, 799, 753 cm^{-1}; ^{1}H-nmr: δ 8.24 (dd, J = 4.1, 2.0 Hz, 1H, H-5), 7.22 (dd, J = 8.3, 4.1 Hz, 1H, H-5), 7.20 (dd, J = 8.3, 2.0 Hz, 1H, H-7), 6.21 (dd, J = 7.1, 3.2 Hz, 1H, H-3), 4.80 (dd, J = 11.7, 7.1 Hz, 1H, H-2), 4.51 (dd, J = 11.7, 3.2 Hz, 1H, H-2'); ms: m/z (relative intensity) 179 (M^+, 18), 137 (67), 136 (91), 120 (58), 119 (89), 109 (23), 108 (30), 92 (33), 91 (33); hrms: 179.0586. M^+, Calcd. for $C_9H_9NO_3$: 179.0582.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 59.98; H, 5.01; N, 7.99.

3-Acetoxy-2,3-dihydrofuro[2,3-*c*]pyridine **18c** and Furo[2,3-*c*]pyridine **1c**.

The residue (230 mg) from **3c** was distilled under reduced pressure to give 49 mg (29%) of **1c** and 107 mg (41%) of **18c**. Compound **1c** (bp 90-115° (bath temperature) (18 mm Hg)) was identified with the authentic sample [7] by comparison of the ir and ^{1}H-nmr spectra.

Compound **18c**.

This compound had bp 80-90°(bath temperature) (0.1 mm Hg) (colorless oil); ir (neat): 3045, 3001, 2959, 2891, 1740, 1589, 1483, 1423, 1373, 1229, 1182, 1033, 956, 831 cm^{-1}; ^{1}H-nmr: δ 8.34 (s, 1H, H-7), 8.26 (d, J = 4.7 Hz, 1H, H-5), 7.40 (d, J = 4.7 Hz, 1H, H-4), 6.26 (dd, J = 6.8, 2.9 Hz, 1H, H-3), 4.67 (dd, J = 11.5, 6.8 Hz, 1H, H-2), 4.55 (dd, J = 11.5, 2.9 Hz, 1H, H-2').

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.60; H, 5.13; N, 7.85.

2,3-Dihydrofuro[3,2-*c*]pyridin-4(5*H*)-one **19** and 2,3-Dihydrofuro[3,2-*c*]pyridin-6(5*H*)-one **19'**.

The residue (75 mg) from **3d** was chromatographed on a silica gel (7 g) column eluting with ethyl acetate-methanol (97:3) to give compound **19** (20 mg, 10%) and **19'** (13 mg, 6.5%).

Compound **19**.

This compound had mp 221-223° (from ether-acetone, colorless crystals); ir (potassium bromide): 3119, 3054, 2973, 2932, 2866, 2804, 1657, 1609, 1577, 1439, 1257, 1220, 1079, 1057, 969, 928, 897 cm^{-1}; ^{1}H-nmr: δ 7.29 (d, J = 7.0 Hz, 1H, H-6), 6.05 (d, J = 7.0 Hz, 1H, H-7), 4.69 (t, J = 9.1 Hz, 2H, 2 x H-2), 3.13 (t, J = 9.1 Hz, 2H, 2 x H-3).

Anal. Calcd. for $C_7H_7NO_2$: C, 61.31; H, 5.14; N, 10.21. Found: C, 60.93; H, 5.11; N, 9.90.

Compound **19'**.

This compound had mp 222-224° (from acetone-ether, colorless crystals); ir (potassium bromide): 3251, 3189, 3131, 2955, 2924, 2850, 2818, 1667, 1633, 1480, 1456, 1456, 1345, 1256, 1201, 1145, 986, 957, 910 cm^{-1}; ^{1}H-nmr: δ 7.14 (s, 1H, H-4), 5.87 (s, 1H, H-7), 4.64 (t, J = 8.1 Hz, 2H, 2 x H-2), 3.05 (t, J = 8.1 Hz, 2H, 2 x H-3).

Anal. Calcd. for $C_7H_7NO_2$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.67; H, 5.36; N, 9.89.

General Procedure for Cyanation of **3a**, **3b**, **3c** and **3d** with Trimethylsilyl Cyanide.

Prior to use for the reaction, the *N*-oxide hydrate, **3a•3/4H$_2$O**, **3b•1/2H$_2$O** or **3d•1/3H$_2$O** was dehydrated by treatment of the solution in dry tetrahydrofuran over molecular sieves 4A for 30 hours and evaporation of the solvent.

A mixture of *N*-oxide **3** (100 mg, 0.73 mmole), trimethylsilyl cyanide (0.2 ml, 1.8 mmoles) and triethylamine (0.15 ml, 1.1 mmoles) in acetonitrile (10 ml) was stirred and refluxed for 20 hours (70 hours for **3d**). After evaporation of the solvent, the reaction mixture was dissolved in chloroform, washed with water and dried over magnesium sulfate. Further processing of the residue of the dried (magnesium sulfate) chloroform solution from **3a**, **3b**, **3c** and **3d** is indicated in a subsequent paragraph.

6-Cyano-2,3-dihydrofuro[2,3-*b*]pyridine **20a** and 3-(2'-Cyanoethyl)2-pyridinol *N*-Oxide **21a**.

The residue (95 mg) from **3a** was chromatographed on a silica gel (7 g) column using chloroform as eluent to give 43 mg (40%) of **20a** and 23 mg (19%) of **21a**.

Compound **20a**.

This compound had mp 103-104° (from acetone-ether, colorless crystals); ir (potassium bromide): 3093, 3076, 2988, 2975, 2921, 2852, 2235, 1603, 1585, 1484, 1448, 1431, 1256, 1139, 1105, 1001, 832, 785 cm^{-1}; ^{1}H-nmr: δ 7.57 (d, J = 7.3 Hz, 1H, H-4), 7.23 (d, J = 7.3 Hz, 1H, H-5), 4.72 (t, J = 8.5 Hz, 2H, 2 x H-2), 3.35 (t, J = 8.5 Hz, 2H, 2 x H-3).

Anal. Calcd. for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.45; H, 4.30; N, 19.07.

Compound **21a**.

This compound had mp 118-120° (from acetone-ether, colorless crystals); (potassium bromide): 3050-2400 (broad), 3094, 2975, 2855. 2247, 1638, 1554, 1432, 1382, 1264, 1220, 1177, 1077, 971, 880, 765 cm^{-1}; ^{1}H-nmr: δ 7.60 (d, J = 7.1 Hz, 1H, H-6), 7.37 (d, J = 7.1 Hz, 1H, H-4), 6.33 (t, J = 7.1 Hz, 1H, H-5), 2.93 (t, J = 7.0 Hz, 2H, -CH$_2$-*C*H$_2$-CN), 2.76 (t, J = 7.0 Hz, 2H, -*C*H$_2$-CH$_2$-CN).

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C,58.31; H, 4.90; N, 16.99.

5-Cyano-2,3-dihydrofuro[3,2-*b*]pyridine **20b**, 3-Hydroxy-2,3-dihydrofuro[3,2-*b*]pyridine **22** and Furo[3,2-*b*]pyridine **1b**.

The residue (95 mg) was chromatographed on a silica gel (20 g) column eluting with hexane-ethyl acetate (3:1) to give **20b** (19 mg, 18%), **22** (19 mg, 19%) and **1b** (15 mg, 18%). Compound **1b** (bp 105°(bath temperature) (20 mm Hg)) was identified with the authentic sample [6] by comparison of the ir and ^{1}H-nmr spectra.

Compound **20b**.

This compound had mp 123-124° (from ether-hexane, colorless crystals); ir (potassium bromide): 3057, 3026, 3001, 2927, 2853, 2228, 1597, 1575, 1482, 1452, 1437, 1315, 1252, 1110, 977, 933, 924, 876 cm^{-1}; ^{1}H-nmr: δ 7.43 (d, J = 8.3 Hz, 1H, H-7), 7.05 (d, J = 8.3 Hz, 1H, H-6), 4.78 (t, J = 9.0 Hz, 2H, 2 x H-2), 3.38 (t, J = 9.0 Hz, 2H, 2 x H-3); ms: m/z (relative intensity) 146 (M^+, 95), 145 (100), 118 (20), 117 (15), 92 (13), 91 (17), 90 (12), 64 (37), 63 (21); hrms: 146.0479. M^+, Calcd. for $C_8H_6N_2O$: 146.0480.

Anal. Calcd. for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 66.19; H, 4.54; N, 18.79.

Compound **22**.

This compound had mp 109-111° (from hexane-ether, colorless crystals); ir (potassium bromide): 3400-2950 (broad), 2960, 2924, 2858, 1606, 1587, 1461, 1431, 1309, 1262, 1236, 1166, 1115, 1087, 1019, 950, 801 cm^{-1}; ^1H-nmr: δ 8.10 (t, J = 3.2 Hz, 1H, H-5), 7.18 (d, J = 3.2 Hz, 2H, H-6 and H-7), 5.50 (dd, J = 6.8, 3.8 Hz, 1H, H-3), 4.71 (dd, J = 10.8, 6.8 Hz, 1H, H-2), 4.57 (dd, J = 10.8, 3.8 Hz, 1H, H-2').

Anal. Calcd. for $C_7H_7NO_2$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.33; H, 5.05; N, 10.24.

5-Cyano- **20c** and 7-Cyano-2,3-dihydrofuro[2,3-*c*]pyridine **20'c**.

The residue (130 mg) from **3c** was chromatographed on a silica gel (25 g) column eluting with hexane-ethyl acetate (3:1) to afford 36 mg (34%) of **20c** (first fraction) and 67 mg (63%) of **20'c** (second fraction).

Compound **20c**.

This compound had mp 129-131° (from acetone-ether, colorless crystals); ir (potassium bromide): 3059, 3024, 3001, 2953, 2942, 2920, 2238, 1594, 1576, 1486, 1475, 1286, 1270, 249, 1193, 1104, 930, 901, 731 cm^{-1}; ^1H-nmr: δ 8.21 (d, J = 1.0 Hz, 1H, H-7), 7.56 (q, J = 1.0 Hz, 1H, H-4), 4.75 (t, J = 9.0 Hz, 2H, 2 x H-2), 3.32 (td, J = 9.0, 1.0 Hz, 2H, 2 x H-3).

Anal. Calcd. for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.59; H, 4.30; N, 19.20.

Compound **20'c**.

This compound had mp 141-143° (from acetone-ether, colorless crystals); ir (potassium bromide): 3086, 2981, 2922, 2853, 2234, 1600, 1582, 1477, 1458, 1434, 1216, 1192, 1059, 912, 861, 851 cm^{-1}; ^1H-nmr: δ 8.21 (d, J = 4.6 Hz, 1H, H-5), 7.36 (d, J = 4.6 Hz, 1H, H-4), 4.79 (t, J = 9.0 Hz, 2H, 2 x H-2), 3.54 (t, J = 9.0 Hz, 2H, 2 x H-3).

Anal. Calcd. for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.85; H, 4.34; N, 19.25.

6-Cyano- **20d** and 4-Cyano-2,3-dihydrofuro[3,2-*c*]pyridine **20'd**, 3-(2'-Cyanoethyl)-4-pyridinol *N*-Oxide **21a** and 2-Cyano-3-(2'-cyanoethyl)-4-pyridinol **21'd**.

The residue (120 mg) from **3d** was chromatographed on a silica gel (12 g) column eluting with hexane-ethyl acetate (3:1) to afford 2.3 mg (2.2%) of **20'd** (first fraction), 29 mg (27%) of **20d** (second fraction), 18 mg (15%) of **21d** (third fraction) and 42 mg (33%) of **21'd** (fourth fraction).

Compound **20d**.

This compound had mp 84-85° (from ether-hexane, colorless crystals); ir (potassium bromide): 3093, 3060, 3004, 2981, 2915, 2852, 2240, 1595, 1573, 1489, 1468, 1436, 1399, 1299, 1278, 1239, 1106, 982, 959, 881 cm^{-1}; ^1H-nmr: δ 8.41 (d, J = 0.9 Hz, 1H, H-4), 7.10 (d, J = 0.9 Hz, 1H, H-7), 4.77 (t, J = 9.1 Hz, 2H, 2 x H-2), 3.34 (t, J = 9.1 Hz, 2H, 2 x H-3).

Anal. Calcd. for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.79; H, 4.28; N, 19.13.

Compound **20'd**.

This compound had mp 60-63° (from ether-hexane, colorless crystals); ir (potassium bromide): 3095, 3060, 2955, 2920, 2850, 2231, 1601, 1582, 1459, 1380, 1290, 1241, 1055, 999, 973, 930, 846 cm^{-1}; ^1H-nmr: δ 8.37 (d, J = 5.6 Hz, 1H, H-6), 6.89 (d, J = 5.6 Hz, 1H, H-7), 4.77 (t, J = 9.1 Hz, 2H, 2 x H-2), 3.45 (t, J = 9.1 Hz, 2H, 2 x H-3); ms: m/z (relative intensity) 146 (M^+, 100), 145 (80), 119 (76); hrms: 146.0479. M^+, Calcd. for $C_8H_6N_2O$: 146.0478 .

Anal. Calcd. for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.89; H, 4.38; N, 18.83.

Compound **21d**.

This compound had mp 167-170° (from ether, colorless crystals); ir (potassium bromide): 3435, 3213, 3158, 3081, 2991, 2925, 2869, 2229, 1624, 1612, 1578, 1273, 1258, 1010, 964, 939 cm^{-1}; H-nmr: δ 8.07 (s, 1H, H-2), 7.04 (d, J = 15.9 Hz, 1H, H-6), 5.77 (d, J = 15.9 Hz, 1H, H-5), 4.51 (t, J = 9.5 Hz, 2H, $-CH_2-\mathit{CH}_2-CN$), 3.12 (t, J = 9.5 Hz, 2H, $-\mathit{CH}_2-CH_2-CN$).

Anal. Calcd. for $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 58.67; H, 4.93; N, 17.12.

Compound **21'd**.

This compound had mp 92-93° (from ether-acetone, colorless crystals); ir (potassium bromide): 3331, 3088, 2960, 2948, 2888, 2244, 1582, 1410, 1379, 1245, 1223, 1092, 1053, 952, 865, 846, 817 cm^{-1}; ^1H-nmr: δ 8.77 (d, J = 5.0 Hz, 1H, H-6), 7.74 (d, J = 5.0 Hz, 1H, H-5), 4.07 (t, J = 6.0 Hz, 2H, $-CH_2-\mathit{CH}_2-CN$), 3.33 (t, J = 6.0 Hz, 2H, $-\mathit{CH}_2-CH_2-CN$).

Anal. Calcd. for $C_9H_7N_3O$: C, 62.42; H, 4.07; N, 24.26. Found: C, 62.16; H, 4.13; N, 24.21.

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