Furopyridines. XXVI [1]. Reactions of Cyanopyridine Derivatives of Furo[2,3-*b*]-, -[3,2-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine

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Bromination of α-cyanopyridine derivatives of furopyridines **1a-d** gave the 2,3-dibromo-2,3-dihydro compounds **2a-d** in excellent yields. Treatment of **2a-d** with sodium hydroxide in methanol yielded compounds formed through the dehydrobromination and solvolysis of the nitrile. *N*-Oxidation of **1a** and **1b** gave *N*-oxide in much poor yield, while **1c** and **1d** gave the *N*-oxide **13c** and **13d** in good yields. The nucleophilic reactions (cyanation, chlorination and acetoxylation) of **13c** and **13d** through a Reissert-Henze type reaction gave poor results, which would be caused by the strong electron withdrawing effect of the cyano group.

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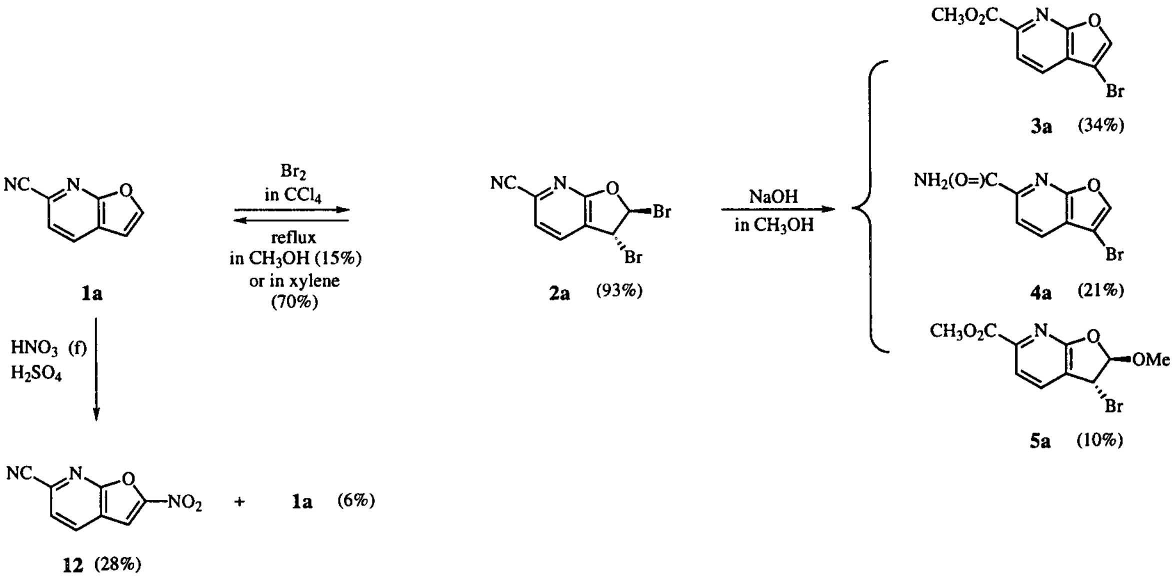
We have been continuously interested in the chemistry of furopyridines, and have reported the syntheses and the reactivities of furo[2,3-*b*]-, -[3,2-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine and their *N*-oxides. Now, we intend to see the effects of a functional group on the furan or the pyridine ring upon the reactivity of the monosubstituted furopyridines for the second electrophilic and/or nucleophilic reaction. In this paper we report bromination and nitration of four furopyridines having a cyano group at the α-position to the ring nitrogen, and cyanation with trimethylsilyl cyanide, chlorination with phosphorus oxychloride and acetoxylation with acetic anhydride of the *N*-oxides of the α-cyanopyridine derivative of the furopyridines.

Bromination of 6-cyanofuro[2,3-*b*]- (**1a**) [2], 5-cyanofuro[3,2-*b*]- (**1b**) [3], 7-cyanofuro[2,3-*c*]- (**1c**) [2] and 4-cyanofuro[3,2-*c*]pyridine (**1d**) [2] with molecular bromine in carbon tetrachloride afforded the corresponding *trans*-2,3-dibromo-2,3-dihydro derivative **2a-d** in good yield.

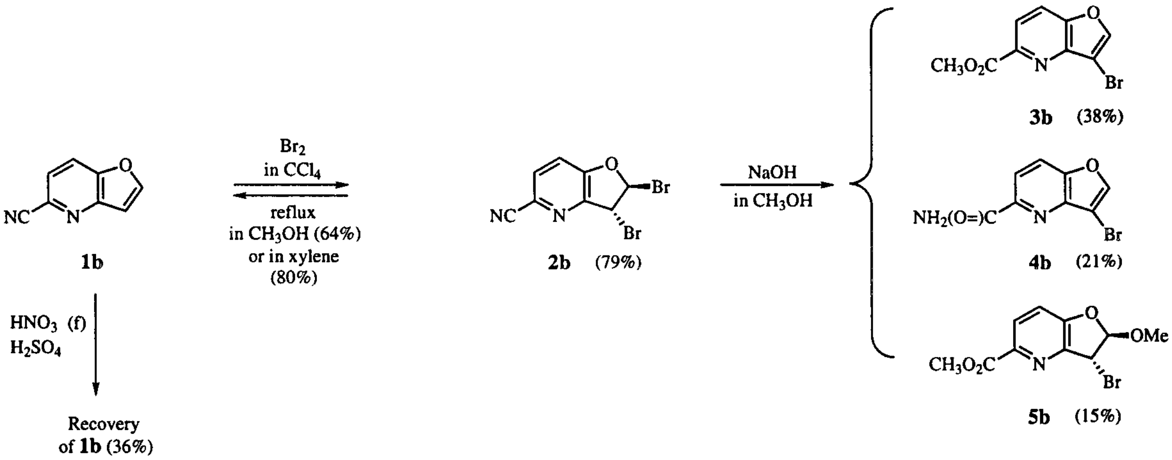
When the dibromo addition products were treated with diluted sodium hydroxide solution in methanol at room temperature, each dibromodihydrofuropyridine afforded several compounds formed through the dehydrobomination and methanolysis of the cyano group. Compound **2a** afforded methyl 3-bromofuro[2,3-*b*]pyridine-6-carboxylate (**3a**) (34%), 3-bromofuro[2,3-*b*]pyridine-6-carboxamide (**4a**) (21%) and methyl *trans*-2-methoxy-3-bromo-2,3-dihydrofuro[2,3-*b*]pyridine-6-carboxylate (**5a**) (10%) (Scheme 1). Compound **2b** yielded methyl 3-bromofuro[3,2-*b*]pyridine-5-carboxylate (**3b**) (38%), 3-bromofuro[3,2-*b*]pyridine-5-carboxamide (**4b**) (21%) and *trans*-2-methoxy-3-bromo-2,3-dihydrofuro[3,2-*b*]pyridine-5-carboxylate (**5b**) (15%) (Scheme 2). Compound **2c** gave methyl 3-bromofuro[2,3-*c*]pyridine-7-carboxylate (**3c**) (7%), 3-bromofuro[2,3-*c*]pyridine-7-carboxamide (**4c**) (9%), methyl 3-bromofuro[2,3-*c*]pyridine-7-imidate (**6**) (62%) and 2-methoxy-3-bromo-7-cyanofuro[2,3-*c*]pyridine (**7**) (6%) (Scheme 3). Compound **2d** gave methyl *trans*-2-methoxy-3-bromofuro[3,2-*c*]pyridine-4-carboxylate (**5d**) (33%), 3-bromo-4-cyanofuro[3,2-*c*]pyridine (**8**) (21%) and 2-methoxy-3-bromofuro[3,2-*c*]pyridine-4-carboxamide (**9**) (9%) (Scheme 4). These results were compared with the methanolysis of α-cyanofuropyridine **1a** and **1c**, 2-cyanopyridine (**1e**) and 3-cyanopyridine (**1f**) with diluted aqueous sodium hydroxide in methanol. Compound **1a**, **1c** and **1e**, α-cyanopyridine compounds, gave the corresponding methyl imidates **10a**, **10c** and **10e** and amide **11c** in excellent yield, while **1f**, β-cyanopyridine, resulted in recovery of the staring **1f** and yielded the amide **11f** in poor yield. Thus, it was found that the cyano group at the α-postion to the ring nitrogen is more easily methanolyzed than that at the β-position (Scheme 5).

The structures of these compounds **3-9** were confirmed from their ^{1}H-nmr and ir spectra. Compounds **3a**, **3b** and **3c** showed signals for a proton of the furan (2-position) as a singlet, at δ 7.92 for **3a**, 8.00 for **3b** and 7.93 for **3c**, signals of the pyridine ring as a pair of doublets, at δ 8.24 and 8.04 for **3a**, 8.24 and 7.90 for **3b** and 8.66 and 7.75 for **3c**, and a signal of the methyl protons of methyl ester at δ 4.05 for **3a**, 4.05 for **3b** and 4.10 for **3c**; and in the ir spectra **3a**, **3b** and **3c** showed carbonyl absorptions at 1721, 1705 and 1734 cm^{-1} respectively. Compounds **4a**, **4b** and **4c** also exhibited signals of the furan proton at δ 7.88 for **4a**, 8.00 for **4b** and 7.96 **4c**, the signals of the pyridine protons at δ 8.31 and 8.06 for **4a**, 8.32 and 7.91 for **4b** and 8.49 and 7.72 for **4c** in the ^{1}H-nmr spectra; and the carbonyl absorptions of the amide at 1696, 1698 and 1704 cm^{-1} respectively in their ir spectra. The ^{1}H-nmr spectra of **5a**, **5b** and **5d** exhibited signals of two aliphatic protons at δ 5.81 and 5.15 for **5a**, 5.82 and 5.20 for **5b** and 5.86 and 5.64 for **5d**, two pyridine protons at δ 7.84 for **5a**, 8.11 and 7.28 for **5b** and 8.58 and 7.06 for **5d**, and two signals of methoxy protons at δ 3.99 and 3.61 for **5a**,

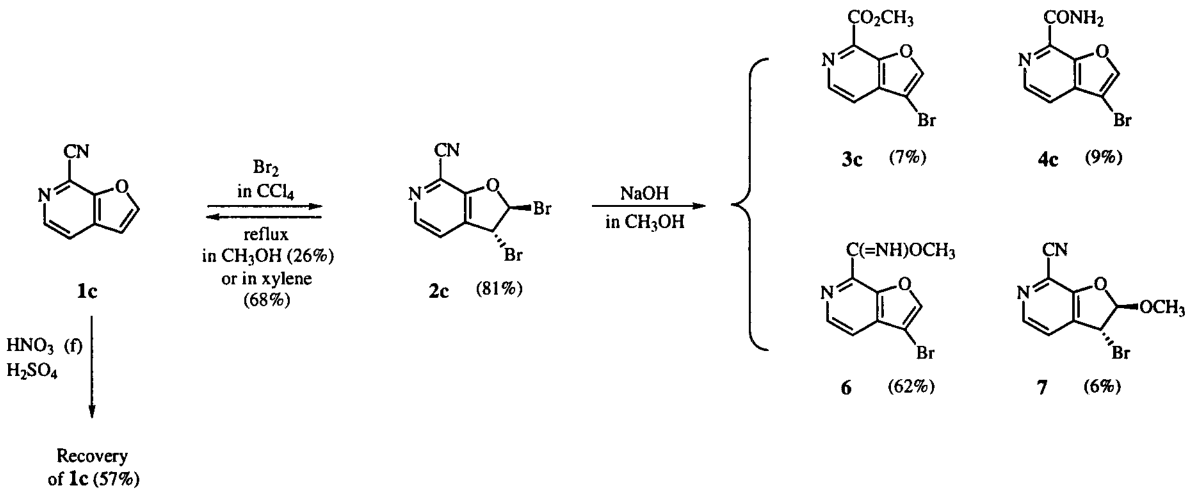
Scheme 1



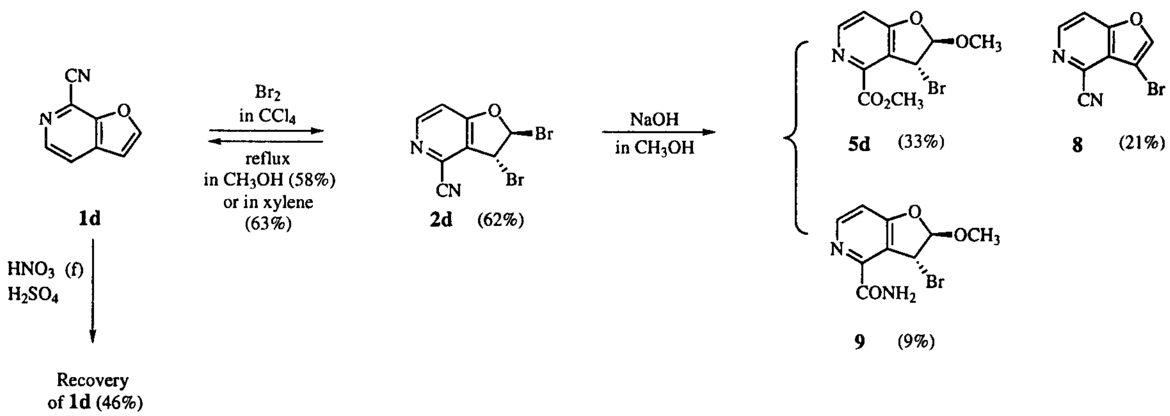
Scheme 2



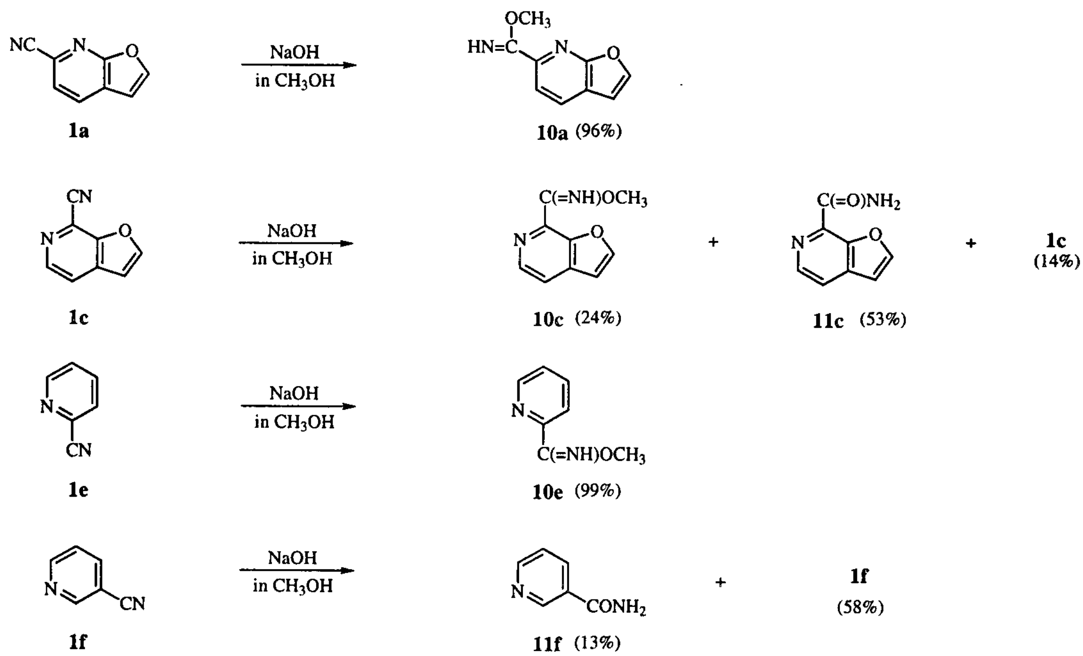
Scheme 3



Scheme 4



Scheme 5



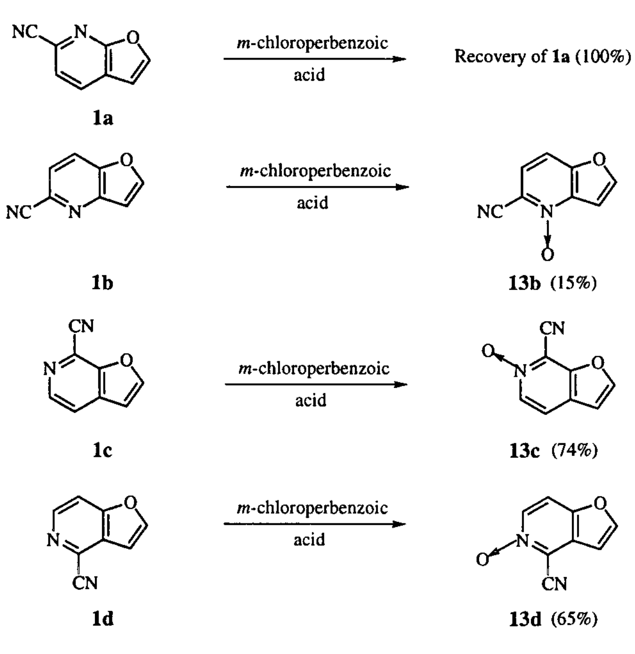
3.99 and 3.60 for **5b** and 4.08 and 3.57 for **5d**, respectively. Compound **6** exhibited a signal for a furan proton at δ 7.87, two pyridine protons at δ 8.56 and 7.63, and the methoxy protons at δ 4.13 in its ^{1}H-nmr spectrum. Compound **8** also showed in its ^{1}H-nmr spectrum a signal of a furan proton at δ 7.85 and of two pyridine protons at δ 8.68 and 7.69; and in the ir spectrum absorption of cyano group at 2240 cm^{-1}. The ^{1}H-nmr spectrum of **7** showed signals of two aliphatic protons at δ 5.90 and 5.10, of two pyridine protons at δ 8.38 and 7.51 and of the methoxy protons at δ 3.65; and the ir spectrum showed absorption of cyano group at 2237 cm^{-1}. Compound **9** also showed signals of two aliphatic protons at δ 5.87 and 5.82, of two pyridine protons at δ 8.41 and 7.03, and of methoxy protons at δ 3.56 in the ^{1}H-nmr spectrum; and the carbonyl absorption at 1696 cm^{-1} in the ir spectrum. The coupling constant (J = 0.0 Hz) between the aliphatic protons of **7** and **9** indicated that the configuration of the aliphatic protons of these compounds is *trans* [4].

It is of interest that the starting compound **1b** was obtained by distillation of compound **2b** under reduced pressure as a sole distillate in good yield. Thus, the dibromodihydrofuropyridines **2a-d** were refluxed in methanol for 4-7 hours to give the cyanofuropyridine **1a-d** in yield of 15%, 64%, 26% and 58% respectively, accompanying recovery of the dibromodihydro compound (85% for **2a**, 31% for **2b**, 68% for **2c** and 41% for **2d**). Moreover, refluxing of **2a-d** in xylene for 24 hours yielded the debrominated compound **1a-d**, in 70%, 80%, 68% and 63% respectively, as a sole product [5]. These results are very interesting but difficult to explain. We cannot postulate any reaction course at the present.

Nitration of compound **1a-d** with a mixture of fuming nitric acid and sulfuric acid afforded really poor results: **1a** yielded 2-nitro derivative **12** (28%) and the starting **1a** (6%); **1b**, **1c** and **1d** gave no nitro compound but each starting compound in 36%, 57% and 46% yield respectively.

N-Oxidation of **1a** by refluxing with *m*-chloroperbenzoic acid in chloroform for 2 days resulted in complete recovery of the starting **1a**. Compound **1b** gave the *N*-oxide **13b** (15%) by refluxing with *m*-chloroperbenzoic acid in chloroform for 3 days, while **1c** and **1d** yielded the *N*-oxides **13c** (74%) and **13d** (65%) by refluxing for 1 day. These results apparently indicated that the *N*-oxidation is affected by the basicity of the furopyridines [4], and the cyano group diminished the basicity of the furopyridines (Scheme 6).

Scheme 6



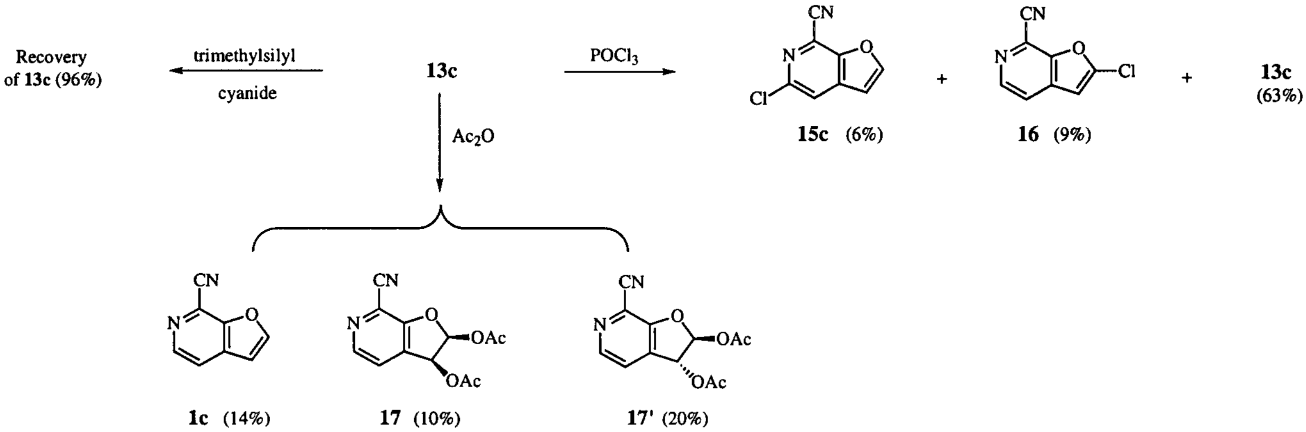
The cyanation of **13c** with trimethylsilyl cyanide and triethylamine in acetonitrile did not yield any dicyano derivative but recovered the starting **13c** (96%). The same cyanation of **13d** gave 4,6-dicyano compound **14** (5%), **1d** (7%) and the starting **13d** (70%). The position of the second cyano group in **14** was confirmed by its ^{1}H-nmr spectrum showing signal of a pyridine proton as a doublet coupled by zig-zag coupling (J = 1.0 Hz) with 3-proton. These results suggested that the electron density of the *N*-oxide oxygen of **13c** and **13d** is much reduced by the strong electron withdrawing effect of the cyano group at the α-position, and the attack of trimethylsilyl cyanide at the oxygen to form Si-O bond is prevented.

The chlorination of **13c** with phosphorus oxychloride gave 5-chloro-7-cyanofuro[2,3-*c*]pyridine (**15c**) (6%) and 2-chloro-7-cyano compound **16** (9%) in very low yield. The same reaction of **13d** afforded 4-cyano-6-chlorofuro[3,2-*c*]pyridine (**15d**) (76%) and **13d** (23%). Compound **15c** showed, in its ^{1}H-nmr spectrum, signals of a pyridine proton at δ 7.80 as a singlet and furan protons as a pair of doublet at δ 7.94 and 6.92 (J = 2.1 Hz); **15d** signals of a pyridine proton at δ 7.71 (d, J = 1.0 Hz) and furan protons at δ 7.86 (d, J = 2.3 Hz) and 7.06 (dd, J = 1.0, 2.3 Hz); **16** signal of pyridine protons at δ 8.54 and 7.69 as a pair of doublet (J = 5.0 Hz) and a furan proton at δ 6.78 as a singlet. These ^{1}H-nmr spectral data supported the structure of these compounds.

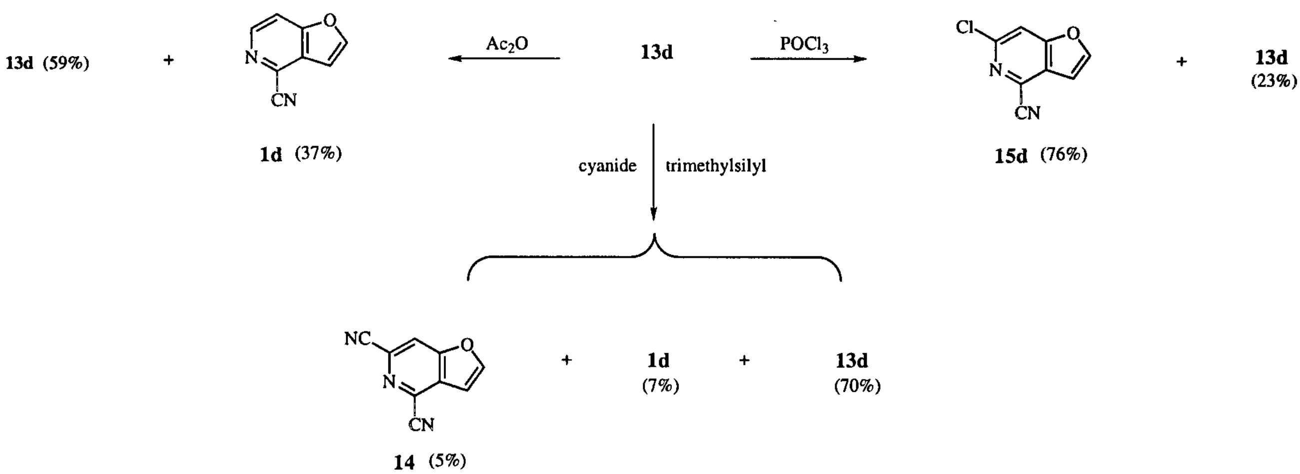
Acetoxylation of **13c** with acetic anhydride yielded *cis*-**17** (10%) and *trans*-2,3-diacetoxy-7-cyano-2,3-dihydrofuro[2,3-*c*]pyridine (**17'**) (20%) and **1c** (14%), while the same reaction of **13d** resulted in recovery of **13d** (59%) and **1d** (37%). The ^{1}H-nmr spectra **17** and **17'** exhibited signals of pyridine protons at δ 8.43 (d, J = 4.7) and 7.53 (dd, J = 4.7, 1.2 Hz), aliphatic methine protons at δ 7.01 (d, J = 6.0 Hz) and 6.23 (dd, J = 6.0, 1.2 Hz) and methyl protons at δ 2.20 (s) and 2.15 (s) for **17** and at δ 8.43 (d, J = 4.5 Hz) and 7.65 (dd, J = 4.5, 0.5 Hz), aliphatic methine protons at δ 6.82 (d, J = 1.2 Hz) and 6.09 (d, J = 1.2, 0.5 Hz) and methyl protons at δ 2.17 (s) and 2.14 (s) for **17'**. The smaller coupling constant of 1.2 Hz between the aliphatic methine protons of compound **17'** indicated the configuration of the acetoxyl groups at 2- and 3-position to be *trans*.

Formation of compounds having the second substituent at the pyridine carbon **14**, **15c** and **15d** is interpreted by the well known mechanism for the chlorination and cyanation of the *N*-oxides of pyridine, quinoline and isoquinoline [6]; and formation of the compounds having the substituent at the furan ring **16**, **17** and **17'** would be interpreted by the mechanism postulated in our previous paper [7]. While, formation of the deoxygenated compounds **1c** and **1d** by the acetoxylation of the corresponding *N*-oxide can be interpreted as follows. The electron withdrawing

Scheme 7



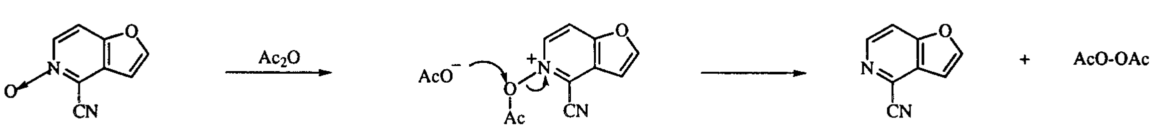
Scheme 8



effect of the cyano group at the α-position to the acetoxylated nitrogen cation is efficiently exerted upon the N-O bond, and the acetate anion formed in the initial step would attack the partially positive-charged oxygen of the N-O bond to give diacetylperoxide (Chart 1).

From these results, it can be concluded that the cyano group at the pyridine ring of furopyridines diminishes the basicity but does not decrease the reactivity of the furan moiety, and that the nucleophilic reactivity of *N*-oxide of α-cyanopyridine derivative of furo[2,3-*c*]- and -[3,2-*c*]pyridine through a Reissert-Henze type reaction is much reduced by the electron withdrawing effect of cyano group at the α-position to the ring nitrogen in each furopyridine.

Chart 1



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 taken on a JEOL A-400 (400 MHz) or a JEOL MAC-FX (90 MHz) instrument with tetramethylsilane as an internal reference in deuteriochloroform. The mass spectra were obtained by using JEOL JMS-OISG-2 spectrometer. Column chromatography was conducted on silica gel (Chromatography Silica Gel, BW-820MH, Fuji Silysia Chemical Ltd).

General Procedure for the Bromination of 6-Cyanofuro[2,3-*b*]- **1a**, 5-Cyanofuro[3,2-*b*]- **1b**, 7-Cyanofuro[2,3-*c*]- **1c** and 4-Cyanofuro[3,2-*c*]pyridine **1d**.

To a solution of cyano compound **1a**, **1b**, **1c** or **1d** (130 mg, 0.9 mmole) in carbon tetrachloride (7 ml) was added a solution of bromine (430 mg, 2.7 mmoles) in carbon tetrachloride (5 ml) by syringe over a period of 5 minutes below 0° with stirring. After being stirred at room temperature for 15 hours, the mixture was evaporated to dryness. The residual solid mass was recrystallized from acetone for crude **2a**, ether for crude **2b**, ether-chloroform for crude **2c** and **2d** to give the pure sample in 93% yield from **1a**, 79% from **1b**, 81% from **1c** and 62% from **1d**.

trans-2,3-Dibromo-2,3-dihydro-6-cyanofuro[2,3-*b*]pyridine **2a**.

This compound had mp 115-118° (colorless crystals); ir (potassium bromide): 3092, 3042, 3024, 2924, 2953, 2238 (CN), 1605, 1590, 1422, 1338, 1316, 1212, 1034, 959, 844, 834 cm^{-1}; ^{1}H-nmr δ 7.99 (d, J = 7.2 Hz, 1H, H-5), 7.55 (d, J = 7.2 Hz, 1H, H-4), 6.90 (s, 1H, H-2), 5.75 (s, 1H, H-3).

Anal. Calcd. for $C_8H_4N_2OBr_2$: C, 31.61; H, 1.33; N, 9.22. Found: C, 31.89; H, 1.37; N, 9.14.

trans-2, 3-Dibromo-2,3-dihydro-5-cyanofuro[3,2-*b*]pyridine **2b**.

This compound had mp 88-90° (colorless crystals); ir (potassium bromide): 3087, 3027, 2239 (CN), 1602, 1582, 1445, 1423, 1247, 1213, 1015, 945, 843 cm^{-1}; ^{1}H-nmr δ 7.72 (d, J = 8.4 Hz, 1H, H-7), 7.46 (d, J = 8.4 Hz, 1H, H-6), 6.91 (s, 1H, H-2), 5.69 (s, 1H, H-3).

Anal. Calcd. for $C_8H_4N_2OBr_2$: C, 31.61; H, 1.33; N, 9.22. Found: C, 32.01; H, 1.40; N, 9.42.

trans-2,3-Dibromo-2,3-dihydro-7-cyanofuro[2,3-*c*]pyridine **2c**.

This compound had mp 140-145° (colorless crystals); ir (potassium bromide): 3026, 2923, 2853, 2241 (CN), 1592, 1426, 1302, 1217, 1173, 1065, 1014, 940, 853, 806 cm^{-1}; ^{1}H-nmr δ 8.54 (d, J = 4.8 Hz, 1H, H-5), 7.68 (d, J = 4.8 Hz, 1H, H-4), 6.93 (s, 1H, H-2), 5.70 (s, 1H, H-3).

Anal. Calcd. for $C_8H_4N_2OBr_2$: C, 31.61; H, 1.33; N, 9.22. Found: C, 31.48; H, 1.37; N, 8.99.

trans-2,3-Dibromo-2,3-dihydro-4-cyanofuro[3,2-*c*]pyridine **2d**.

This compound was a colorless viscous oil which could not be distilled without decomposition, and was chromatographed on a silica gel column eluting with chloroform to give pure sample of **2d**; ir (neat): 3094, 3019, 2926, 2854, 1607, 1585, 1449, 1275, 1259, 1228, 1153, 1011, 990, 947, 864, 843, 725 cm^{-1}; ^{1}H-nmr δ 8.66 (d, J = 5.6 Hz, 1H, H-6), 7.23 (d, J = 5.6 Hz, 1H, H-7), 6.92 (s, 1H, H-2), 5.85 (s, 1H, H-3).

Anal. Calcd. for $C_8H_4N_2OBr_2$: C, 31.61; H, 1.33; N, 9.22. Found: C, 31.95; H, 1.53; N, 8.99.

General Procedure for the Reaction of **2a**, **2b**, **2c** and **2d** with Sodium Hydroxide in Methanol.

To a solution of compound **2a**, **2b**, **2c** or **2d** (160 mg, 0.5 mmole) in methanol (10 ml) was added a solution of sodium hydroxide (2 ml, 10% in water) at room temperature. After standing at room temperature for 20 minutes, the mixture was evaporated at room temperature. The residue was dissolved in chloroform and washed with water. The crystalline residue of the dried chloroform solution was chromatographed on a silica gel (20 g) column eluting with hexane-ethyl acetate (5:1 for the product from **2a** and **2b**, 6:1 for the product from **2c** and 3:1 for the product from **2d**) to afford compound **3a** (34%), **4a** (21%) and **5a** (10%) from **2a**, compound **3b** (38%), **4b** (21%) and **5b** (15%) from **2b**, compound **3c** (7%), **4c** (9%), **6** (62%) and **7** (6%) from **2c**, and compound **5d** (33%), **8** (21%) and **9** (9%) from **2d**.

Methyl 3-Bromofuro[2,3-*b*]pyridine-6-carboxylate **3a**.

This compound had mp 107-110° (from ether, colorless crystals); ir (potassium bromide): 3153, 3115, 3097, 2967, 2925, 1721 (C=O), 1585, 1388, 1312, 1257, 1120, 1100, 984, 859, 795 cm^{-1}; ^{1}H-nmr δ 8.24 (d, J = 8.2 Hz, 1H, H-5), 8.04 (d, J = 8.2 Hz, 1H, H-4), 7.92 (s, 1H, H-2), 4.05 (s, 3H, $-OCH_3$).

Anal. Calcd. for $C_9H_6NO_3Br$: C, 42.22; H, 2.36; N, 5.47. Found: C, 41.95; H, 2.34; N, 4.95.

3-Bromofuro[2,3-*b*]pyridine-6-carboxamide **4a**.

This compound had mp 228-229° (from acetone, colorless crystals); ir (potassium bromide): 3454, 3281, 3138, 2924, 1696 (C=O), 1592, 1531, 1462, 1390, 1338, 1280, 1114, 1085, 986, 851, 745 cm^{-1}; ^{1}H-nmr δ 8.31 (d, J = 7.9 Hz, 1H, H-5), 8.06 (d, J = 7.9 Hz, 1H, H-4), 7.88 (s, 1H, H-2).

Anal. Calcd. for $C_8H_5N_2O_2Br$: C, 39.86; H, 2.09; N, 11.62. Found: C, 39.94; H, 2.37; N, 11.57.

Methyl 2-Methoxy-3-bromo-2,3-dihydrofuro[2,3-*b*]pyridine-6-carboxylate **5a**.

This compound had mp 50-55° (from ether-hexane, colorless crystals); ir (potassium bromide): 2955, 2926, 2854, 1733 (C=O), 1649, 1614, 1467, 1438, 1300, 1199, 1115, 1006, 822, 763 cm^{-1}; ^{1}H-nmr δ 7.84 (s, 2H, H-4 and H-5), 5.81 (d, J = 0.9 Hz, 1H, H-2), 5.15 (d, J = 0.9 Hz, 1H, H-3), 3.99 (s, 3H, $-OCH_3$), 3.61 (s, 3H, $-OCH_3$); ms: m/z (relative intensity) 289 (M^++2, 0.1), 287 (M^+, 0.1), 267 (34), 238 (38), 135 (33), 103 (100); hrms: 286.9802; M^+, Calcd. for $C_{10}H_{10}NO_4Br$: 286.9794.

Methyl 3-Bromofuro[3,2-*b*]pyridine-5-carboxylate **3b**.

This compound had mp 135-137° (from acetone, colorless crystals); ir (potassium bromide): 3123, 3059, 3017, 2944, 2846, 1705 (C=O), 1605, 1542, 1413, 1345, 1306, 1264, 1173, 1123, 1078, 1015, 844, 771, 754 cm^{-1}; ^{1}H-nmr δ 8.24 (d, J = 8.6 Hz, 1H, H-6), 8.00 (s, 1H, H-2), 7.90 (d, J = 8.6 Hz, 1H, H-7), 4.05 (s, 3H, $-OCH_3$).

Anal. Calcd. for $C_9H_6NO_3Br$: C, 42.22; H, 2.36; N, 5.47. Found: C, 42.34; H, 2.37; N, 5.48.

3-Bromofuro[3,2-*b*]pyridine-5-carboxamide **4b**.

This compound had mp 240-243° (from acetone); ir (potassium bromide): 3460, 3272, 3192, 3134, 3063, 1698 (C=O), 1589, 1399, 1317, 1278, 1194, 1079, 1015, 841, 794 cm^{-1}; ^{1}H-nmr δ 8.32 (d, J = 8.5 Hz, 1H, H-6), 8.00 (s, 1H, H-2), 7.91 (d, J = 8.5 Hz, 1H, H-7), 5.65 (broad s, 2H, $-NH_2$).

Anal. Calcd. for $C_8H_5N_2O_2Br$: C, 39.86; H, 2.09; N, 11.62. Found: C, 40.18; H, 2.26; N, 11.78.

Methyl 2-Methoxy-3-bromo-2,3-dihydrofuro[3,2-*b*]pyridine-5-carboxylate **5b**.

This compound had 81-83° (from ether-hexane, colorless crystals); ir (potassium bromide): 3021, 2948, 1723 (C=O), 1581, 1434, 1344, 1327, 1269, 1167, 1117, 1098, 897, 853, 811, 791 cm^{-1}; ^{1}H-nmr δ 8.11 (d, J = 8.6 Hz, 1H, H-6), 7.28 (d, J = 8.6 Hz, 1H, H-7), 5.82 (s, 1H, H-2), 5.20 (s, 1H, H-3), 3.99 (s, 3H, $-OCH_3$), 3.60 (s, 3H, $-OCH_3$).

Anal. Calcd. for $C_{10}H_{10}NO_4Br$: C, 41.69; H, 3.50; N, 4.86. Found: C, 41.88; H, 3.53; N, 4.93.

Methyl 3-Bromofuro[2,3-*c*]pyridine-7-carboxylate **3c**.

This compound had mp 110-115° (from ether, colorless crystals); ir (potassium bromide): 3146, 3046, 2953, 2924, 2853, 1734 (C=O), 1596, 1539, 1405, 1301, 1263, 1201, 1186, 1143, 1103, 973, 799, 782 cm^{-1}; ^{1}H-nmr δ 8.66 (d, J = 5.0 Hz, 1H, H-5), 7.93 (s, 1H, H-2), 7.75 (d, J = 5.0 Hz, 1H, H-4), 4.10 (s, 3H, $-OCH_3$); ms: m/z (relative intensity) 257 (M^++2, 10), 256 (12), 255 (M^+, 10), 254 (10), 227 (25), 226 (11), 225 (41), 224 (26), 223 (15), 222 (26), 199 (85), 197 (100), 83 (10); hrms: 254.9521; M^+, Calcd. for $C_9H_6NO_3Br$: 254.9530.

Anal. Calcd. for $C_9H_6NO_3Br$: C, 42.22; H, 2.36; N, 5.47. Found: C, 42.54; H, 2.51; N, 5.23.

3-Bromofuro[2,3-*c*]pyridine-7-carboxamide **4c**.

This compound had mp 155-160° (from acetone, colorless crystals); ir (potassium bromide): 3449, 3270, 3114, 2924, 1704 (-C=O), 1607, 1589, 1538, 1419, 1386, 1337, 1165, 1047, 910, 874, 836, 802 cm^{-1}; ^{1}H-nmr δ 8.49 (d, J = 5.0 Hz, 1H, H-5), 7.96 (s, 1H, H-2), 7.72 (d, J = 5.0 Hz, 1H, H-4), 5.72 (broad s, 2H, $-NH_2$); ms: m/z (relative intensity) 242 (M^++2, 40), 240 (M^+, 44), 224 (18), 222 (22), 199 (86), 197 (100); hrms: 239.9531; M^+, Calcd. for $C_8H_5N_2O_2Br$: 239.9534.

Methyl 3-Bromofuro[2,3-*c*]pyridine-7-imidate **6**.

This compound had mp 178-181° (from acetone, colorless crystals); ir (potassium bromide): 3292, 3140, 3054, 3026, 2996, 2952, 2854, 1651, 1593, 1539, 1467, 1442, 1406, 1372, 1331, 1267, 1165, 1109, 1092, 965, 845 cm^{-1}; ^{1}H-nmr δ 9.20 (broad s, 1H, NH), 8.56 (d, J = 5.0 Hz, 1H, H-5), 7.87 (s, 1H, H-2), 7.63 (d, J = 5.0 Hz, 1H, H-4), 4.13 (s, 3H, $-OCH_3$).

Anal. Calcd. for $C_9H_7N_2O_2Br$: C, 42.38; H, 2.77; N, 10.98. Found: C, 42.37; H, 2.79; N, 11.02.

2-Methoxy-3-bromo-7-cyano-2,3-dihydrofuro[2,3-*c*]pyridine **7**.

This compound had mp 60-65° (from ether, colorless crystals); ir (potassium bromide): 3085, 3034, 2971, 2935, 2840, 2237 (-CN), 1588, 1452, 1426, 1363, 1300, 1217, 1156, 1108, 1059, 978, 862, 854, 774 cm^{-1}; ^{1}H-nmr δ 8.38 (d, J = 4.5 Hz, 1H, H-5), 7.51 (d, J = 4.5 Hz, 1H, H-4), 5.90 (s, 1H, H-2), 5.10 (s, 1H, H-3), 3.65 (s, 3H, $-OCH_3$); ms: m/z (relative intensity) 256 (M^++2, 26), 254 (M^+, 27), 176 (15), 175 (100), 139 (23); hrms: 253.9682; M^+, Calcd. for $C_9H_7N_2O_2Br$: 253.9690.

Methyl 2-Methoxy-3-bromo-2,3-dihydrofuro[3,2-*c*]pyridine-4-carboxylate **5d**.

This compound had mp 28-34°; ir (neat): 2927, 2852, 1725 (C=O), 1604, 1588, 1455, 1304, 1207, 1107, 916, 861 cm^{-1}; ^{1}H-nmr δ 8.58 (d, J = 5.3 Hz, 1H, H-6), 7.06 (d, J = 5.3 Hz, 1H, H-7), 5.86 (s, 1H, H-2), 5.64 (s, 1H, H-3), 4.08 (s, 3H, $-OCH_3$), 3.57 (s, 3H, $-OCH_3$); ms: m/z (relative intensity) 289 (M^++2, 1), 287 (M^+, 1), 229 (7), 208 (59), 176 (67), 148 (100), 120 (14); hrms: 286.9813; M^+, Calcd. for $C_{10}H_{10}NO_4Br$: 286.9792.

3-Bromo-4-cyanofuro[3,2-*c*]pyridine **8**.

This compound had mp 161-163° (from ether, colorless crystals); ir (potassium bromide): 3123, 3094, 3044, 2240 (CN), 1602, 1568, 1534, 1439, 1426, 1415, 1316, 1273, 1231, 1187, 1062, 995, 986, 837 cm^{-1}; ^{1}H-nmr δ 8.68 (d, J = 5.8 Hz, 1H, H-6), 7.85 (s, 1H, H-2), 7.69 (d, J = 5.8 Hz, 1H, H-7); ms: m/z (relative intensity) 224 (M^++2, 96), 222 (M^+, 100), 115 (70), 88 (30); hrms: 221.9427; M^+, Calcd. for $C_8H_3N_2OBr$: 221.9423.

Anal. Calcd. for $C_8H_3N_2OBr$: C, 43.08; H, 1.36; N, 12.56. Found: C, 43.213 H, 1.40; N, 12.46.

2-Methoxy-3-bromo-2,3-dihydrofuro[3,2-*c*]pyridine-4-carboxamide **9**.

This compound had mp 222-224° (from acetone, colorless crystals); ir (potassium bromide): 3399, 3289, 3200, 3030, 3018, 2957, 2925, 2852, 2840, 1696 (C=O), 1602, 1457, 1389, 1359, 1226, 1215, 1110, 982, 915, 864, 840, 781 cm^{-1}; ^{1}H-nmr δ 8.41 (d, J = 5.5 Hz, 1H, H-6), 7.03 (d, J = 5.5 Hz, 1H, H-7), 5.87 (s, 1H, H-2), 5.82 (s, 1H, H-3), 3.56 (s, 3H, $-OCH_3$).

Anal. Calcd. for $C_9H_9N_2O_3Br$: C, 39.58; H, 3.32; N, 10.26. Found: C, 39.67; H, 3.45; N, 10.21.

Solvolysis of 6-Cyanofuro[2,3-*b*]pyridine **1a**, 7-Cyanofuro[2,3-*c*]pyridine **1c**, 2-Cyanopyridine **1e** and 3-Cyanopyridine **1f** with Sodium Hydroxide in Methanol.

A mixture of the cyano compound **1a**, **1c**, **1e** or **1f** (1.0 mmole) and aqueous sodium hydroxide solution (10%, 2 ml, 5.0 mmoles) in methanol (10 ml) was stirred for 20 minutes at room temperature. After evaporation of the solvent under reduced pressure, the residual mass was treated with chloroform and water.

The residue from **1a** was recrystallized from ether to give methyl furo[2,3-*b*]pyridine-6-imidate **10a** (118 mg, 96%), and the residue from **1e** was distilled to give methyl pyridine-2-imidate **10e** (130 mg, 99%), bp 105-110°/20 mm Hg (literature, bp 103-104°/15 mm Hg [8]).

The residues of the dried chloroform layer from **1c** and **1f** were chromatographed on a silica gel column eluting with hexane-ethyl acetate (1:1) to give furo[2,3-*c*]pyridine-7-carboxamide **11c** (60 mg, 53%), methyl furo[2,3-*c*]pyridine-7-imidate **10c** (29 mg, 24%) and the starting compound **1c** (13.5 mg, 14%) from **1c**, and nicotinamide **11f** (15 mg, 13%) and the starting compound **1f** (58 mg, 58%) from **1f** respectively.

Compounds **10e** and **11c** were identified by comparison of the ^{1}H-nmr and ir spectra with those of each authentic sample [2,8].

Compound **10a**.

This compound had mp 100-102° (colorless crystals); ir (potassium bromide): 3305, 3133, 3098, 3040, 3009, 2961, 2924, 2954, 1647, 1584, 1535, 1475, 1438, 1410, 1350, 1270, 1197, 1141, 1097, 1024, 993, 883, 841 cm^{-1}; ^{1}H-nmr δ 8.03 (d, J = 8.0 Hz, 1H, H-5), 7.84 (d, J = 8.0 Hz, 1H, H-4), 7.81 (d, J = 2.3 Hz, 1H, H-2), 6.84 (d, J = 2.3 Hz, 1H, H-3), 4.04 (S, 3H, $-OCH_3$).

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.22; H, 4.50; N, 15.78.

Compound **10c**.

This compound had mp 84-86° (from ether-hexane, colorless crystals); ir (potassium bromide): 3280, 3140, 3103, 3013, 2923, 2852, 1651, 1595, 1536, 1439, 1416, 1381, 1352, 1274, 1186, 1113, 1038, 948, 882, 837 cm^{-1}; ^{1}H-nmr δ 8.48 (d, J = 5.0 Hz, 1H, H-5), 7.86 (d, J = 2.3 Hz, 1H, H-2), 7.67 (d, J = 5.0 Hz, 1H, H-4), 6.88 (d, J = 2.3 Hz, 1H, H-3), 4.13 (s, 3H, -OCH_3); ms: m/z (relative intensity) 176 (M^+, 9), 175 (4), 147 (4), 144 (100), 133 (4), 119 (14); hrms: 176.0564; M^+, Calcd. for $C_9H_9N_2O_2$: 176.0585.

Anal. Calcd. for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.13; H, 4.44; N, 15.52.

Debromination of Compound **2a**, **2b**, **2c** and **2d**.

a) A solution of **2a**, **2b**, **2c** or **2d** (100 mg, 0.33 mmole) in methanol (10 ml) was refluxed (for 4 hours for **2a**, 6 hours for **2b** and 7 hours for **2c** and **2d**). After evaporation of the solvent, the residue was treated with chloroform and water. The residue of the dried (magnesium sulfate) chloroform layer was chromatographed on a silica gel column eluting with hexane-ethyl acetate (5:1) to give **1a** (7 mg, 15%) and **2a** (85 mg, 85%) from **2a**, **1b** (30 mg, 64%) and **2b** (31 mg, 31%) from **2b**, **1c** (12 mg, 26%) and **2c** (68 mg, 68%) from **2c**, and **1d** (27 mg, 58%) and **2d** (41 mg, 41%) from **2d**.

b) A solution of **2a**, **2b**, **2c** or **2d** (58 mg, 0.19 mmole) in xylene (3 ml) was refluxed for 24 hours. After evaporation of the solvent, the mixture was treated with chloroform and water. The residue of the dried (magnesium sulfate) chloroform layer was chromatographed on a silica gel column eluting with hexane-ethyl acetate (5:1) to give **1a** (20 mg, 70%) from **2a**, **1b** (21 mg, 80%) from **2b**, **1c** (19 mg, 68%) from **2c**, and **1d** (18 mg, 63%) from **2d**.

Nitration of Compound **1a**, **1b**, **1c** and **1d**.

Sulfuric acid (1.2 ml) was added to cyanopyridine derivative **1a**, **1b**, **1c** or **1d** (108 mg, 0.75 mmole) at -10° over 5 minutes. To this mixture was added fuming nitric acid (d, 1.50, 1.0 ml) dropwise to maintain the temperature 0-5°. After being stirred for 1 hour at room temperature, the mixture was poured onto 2 g of ice, made alkaline with sodium bicarbonate, extracted with ethyl acetate several times, dried (magnesium sulfate) and evaporated the solvent.

The residue from **1b**, **1c** and **1d** gave the starting cyanopyridine compound in 36%, 57% and 46% yield respectively.

The residue from **1a** was chromatographed on a silica gel column to give 2-nitro-6-cyanofuro[2,3-*b*]pyridine **12** (37 mg, 28%) and the starting **1a** (3 mg, 6%).

Compound **12**.

This compound had mp 139-143° (from acetone, slightly yellow crystals); ir (potassium bromide): 3140, 3105, 2925, 2853, 2235 (-CN), 1609, 1588, 1568, 1534, 1401, 1368, 1286, 1234, 1103, 979, 939, 858, 796 cm^{-1}; ^{1}H-nmr δ 8.38 (d, J = 8.2 Hz, 1H, H-5), 7.86 (d, J = 8.2 Hz, 1H, H-4), 7.74 (s, 1H, H-3).

Anal. Calcd. for $C_8H_3N_3O_3$: C, 50.81; H, 1.60; N, 22.22. Found: C, 51.07; H, 1.82; N, 21.97.

General Procedure for the Preparation of 5-Cyanofuro[3,2-*b*]- **13b**, 7-Cyanofuro[2,3-*c*]- **13c** and 4-Cyanofuro[3,2-*c*]pyridine *N*-Oxide **13d**.

A mixture of cyanopyridine **1b**, **1c** or **1d** (500 mg, 3.5 mmoles) and *m*-chloroperbenzoic acid (1.03 g, purity 70%, 4.2 mmoles) in chloroform (20 ml) was refluxed for 48 hours. The mixture was filtered slowly through a sintered glass filter with an alumina (50 g) pad, and the filtrate was evaporated. The crystalline residue was recrystallized from acetone to give the pure sample of *N*-oxide **13b** (83 mg, 15%), **13c** (412 mg, 74%) and **13d** (362 mg, 65%). The *N*-oxidation of **1a** by the same procedure resulted in complete recovery of the starting compound.

Compound **13b** had mp 205-210° (colorless crystals); ir (potassium bromide): 3145, 3127, 3072, 2924, 2853, 2241, 1608, 1582, 1453, 1423, 1369, 1251, 1129, 1073, 1015, 817, 778 cm^{-1}; ^{1}H-nmr δ 7.86 (d, J = 2.2 Hz, 1H, H-2), 7.59 (d, J = 8.8 Hz, 1H, H-6), 7.52 (dd, J = 8.8, 1.0 Hz, 1H, H-7), 7.30 (dd, J = 2.2, 1.0 Hz, 1H, H-3); ms: m/z (relative intensity) 160 (M^+, 100), 144 (54), 116 (19), 108 (14), 80 (20), 77 (27); hrms: 160.0274; M^+, Calcd. for $C_8H_4N_2O_2$: 160.0272.

Anal. Calcd. for $C_8H_4N_2O_2$: C, 60.01; H, 2.52; N, 17.49. Found: C, 59.59; H, 2.55; H, 17.30.

Compound **13c** had mp 233-240° (colorless crystals); ir (potassium bromide): 3138, 3106, 3067, 3004, 2240 (-CN), 1536, 1476, 1433, 1345, 1300, 1198, 1163, 1036, 1029, 986, 870, 852, 791 cm^{-1}; ^{1}H-nmr δ 8.37 (d, J = 7.5 Hz, 1H, H-5), 8.12 (d, J = 2.0 Hz, 1H, H-2), 7.88 (d, J = 7.5 Hz, 1H, H-4), 7.12 (d, J = 2.0 Hz, 1H, H-3); ms: m/z (relative intensity) 160 (M^+, 100), 144 (91), 77 (51), 76 (25); hrms: 160.0271; M^+, Calcd. for $C_8H_4N_2O_2$: 160.0272.

Anal. Calcd. for $C_8H_4N_2O_2$: C, 60.01; H, 2.52; N, 17.49. Found: C, 59.94; H, 2.53; N, 17.40.

Compound **13d** had mp 253-253° (colorless crystals); ir (potassium bromide): 3140, 3119, 3049, 2924, 2854, 2236 (-CN), 1616, 1519, 1423, 1251, 1196, 1127, 1041, 982, 885, 822, 790 cm^{-1}; ^{1}H-nmr δ 8.21 (d, J = 7.0 Hz, 1H, H-6), 7.89 (d, J = 2.1 Hz, 1H, H-2), 7.62 (d, J = 7.0 Hz, 1H, H-7), 6.92 (d, J = 2.1 Hz, 1H, H-3); ms: m/z (relative intensity) 160 (M^+, 100), 144 (83), 116 (14), 105 (17), 104 (15), 89 (17), 77 (51), 76 (25); hrms: 160.0271; M^+, Calcd. for $C_8H_4N_2O_2$: 160.0272.

Anal. Calcd. for $C_8H_4N_2O_2$: C, 60.01; H, 2.52; N, 17.49. Found: C, 59.93; H, 2.47; N, 17.31.

Reaction of Compound **13c** and **13d** with Trimethylsilyl Cyanide.

A mixture of *N*-oxide **13c** or **13d** (102 mg, 0.63 mmole), trimethylsilyl cyanide (0.15 ml, 0.94 mmole) and triethylamine (0.1 ml, 0.7 mmoles) in acetonitrile (6 ml) was refluxed for 48 hours. After evaporation of the solvent, the residue was dissolved in chloroform, washed with water and dried (magnesium sulfate). The residue (98 mg, 96%) from **13c** was identified as the starting compound **13c**.

The residue from **13d** (95 mg) was chromatographed on a silica gel (10 g) column eluting with chloroform to give compound **1d** (7 mg, 7%), 4,6-dicyanofuro[3,2-*c*]pyridine **14** (7.5 mg, 5%) and the starting compound **13d** (71 mg, 70%).

Compound **14** had mp 176-176.5° (from ether, colorless crystals); ir (potassium bromide): 3161, 3122, 3101, 2242 (-CN), 1562, 1550, 1447, 1336, 1298, 1132, 1046, 1000, 940, 891, 882, 810 cm^{-1}; ^{1}H-nmr δ 8.08 (d, J = 1.0 Hz, 1H, H-7), 8.07 (d, J = 2.1 Hz, 1H, H-2), 7.20 (dd, J = 2.1, 1.0 Hz, 1H, H-3).

Anal. Calcd. for $C_9H_3N_3O$: C, 63.91; H, 1.79; N, 24.84. Found: C, 63.89; H, 1.91; N, 24.72.

Reaction of Compound **13c** and **13d** with Phosphorus Oxychloride.

A mixture of the *N*-oxide **13c** or **13d** (80 mg, 0.5 mmole) in phosphorus oxychloride (1 ml) was heated on a water bath for 15 minutes. After being cooled, the mixture was poured onto ice (5 g), basified with sodium bicarbonate, extracted with chloroform.

The residue (95 mg) of the dried chloroform extract from **13c** was chromatographed on a silica gel column eluting with chloroform to give 5-chloro-7-cyanofuro[2,3-*c*]pyridine **15c** (5 mg, 6%), 2-chloro-7-cyanofuro[2,3-*c*]pyridine **16** (8 mg, 9%) and the starting **13c** (50 mg, 63%).

The residue (100 mg) of the dried chloroform extract from **13d** was chromatographed on a silica gel (12 g) column eluting with chloroform to give 6-chloro-4-cyanofuro[3,2-*c*]pyridine **15d** (68 mg, 76%) and the starting **13d** (18 mg, 23%).

Compound **15c** had mp 141-143° (from ether); ir (potassium bromide): 3150, 3111, 3095, 3036, 2924, 2236 (-CN), 1603, 1573, 1427, 1266, 1210, 1126, 1100, 1039, 1018, 894, 883, 873, 800 cm^{-1}; ^{1}H-nmr δ 7.94 (d, J = 2.1 Hz, 1H, H-2), 7.80 (s, 1H, H-4), 6.92 (d, J = 2.1 Hz, 1H, H-3); ms: m/z (relative intensity) 180 (M^++2, 33), 178 (M^+, 100), 143 (68); hrms: 177.9923; M^+, Calcd. for $C_8H_3N_2OCl$: 177.9934.

Compound **16** had mp 144-145° (from ether, colorless crystals); ir (potassium bromide): 3150, 3112, 3095, 3080, 2923, 2853, 2235 (-CN), 1607, 1547, 1416, 1262, 1174, 1080, 1062, 923, 952 cm^{-1}; ^{1}H-nmr δ 8.54 (d, J = 5.0 Hz, 1H, H-5), 7.69 (d, J = 5.0 HZ, 1H, H-4), 6.78 (s, 1H, H-3).

Anal. Calcd. for $C_8H_3N_2OCl$: C, 53.81; H, 1.69; N, 15.69. Found: C, 53.93; H, 1.86; N, 15.56.

Compound **15d** had mp 157-158° (from ether-acetone, colorless crystals); ir (potassium bromide); 3153, 3114, 3090, 3017, 2923, 2852, 2239 (-CN), 1601, 1530, 1427, 1380, 1342, 1292, 1138, 1082, 1037, 996, 908, 884, 876 cm^{-1}; ^{1}H-nmr δ 7.86 (d, J = 2.3 Hz, 1H, H-2), 7.71 (d, J = 1.0 Hz, 1H, H-7), 7.06 (dd, J = 2.3, 1.0 Hz, 1H, H-3) .

Anal. Calcd. for $C_8H_3N_2OCl$: C, 53.81; H, 1.69; N, 15.69. Found: C, 53.86; H, 1.64; N, 15.59.

Reaction of Compound 13c and 13d with Acetic Anhydride.

A mixture of the *N*-oxide **13c** or **13d** (100 mg, 0.63 mmole) in acetic anhydride (1 ml) was heated at 90-100° with stirring for 7 hours for **13c** (45 hours for **13d**). After being cooled, the excess acetic anhydride was evaporated under reduced pressure. The residual deep brown syrup was treated with water, basified with sodium bicarbonate, extracted with chloroform.

The residue (190 mg) of the dried chlorofrom solution from **13c** was chromatographed on a silica gel (20 g) column eluting with chloroform to give **1c** (12 mg, 14%) and a mixture of **17** and **17'** (60 mg). The mixture of **17** and **17'** was subjected to hplc (column: Lichrosorb Si 60 (5 μm); eluent: hexane-ethyl acetate 2:1) to give pure sample of *cis*- (**17**) (17 mg, 10%) and *trans*-2,3-diacetoxy-2,3-dihydro-7-cyanofuro[2,3-*c*]pyridine (**17'**) (32 mg, 20%).

The residue (120 mg) from **13d** was chromatographed on a silica gel column eluting with chloroform to give compound **1d** (33 mg, 37%) and the starting compound **13d** (59 mg, 59%).

Compound **17**.

This compound was an oil, which decomposed on distillation under reduced pressure, and was characterized from its ir, ^{1}H-nmr and mass spectra; ir (neat): 3092, 3027, 2938, 2855, 2238, (-CN), 1759, 1605, 1591, 1433, 1374, 1290, 1206, 1046, 947, 856 cm^{-1}; ^{1}H-nmr δ 8.43 (d, J = 4.7 Hz, 1H, H-5), 7.53 (dd, J = 4.7, 1.2 Hz, 1H, H-4), 7.01 (d, J = 6.0 Hz, 1H, H-2), 6.23 (dd, J = 6.0, 1.2 Hz, 1H, H-3), 2.20 (s, 3H, $-COCH_3$), 2.15 (s, 3H, $-COCH_3$); ms: m/z (relative intensity) 262 (M^+, 11), 192 (47), 151 (9), 150 (100), 149 (34); hrms 262.0570; M^+, Calcd. for $C_{12}H_{10}N_2O_5$: 262 0589.

Compound **17'**.

This compound was an oil, which decomposed on distillation under reduced pressure, and was characterized from its ir, ^{1}H-nmr and mass spectra; ir (neat): 3091, 3027, 2940, 2238 (-CN), 1750, 1592, 1456, 1373, 1182, 1062, 949, 857 cm^{-1}; ^{1}H-nmr δ 8.43 (d, J = 4.5 Hz, 1H, H-5), 7.65 (dd, J = 4.5, 0.5 Hz, 1H, H-4), 6.82 (d, J = 1.2 Hz, 1H, H-2), 6.09 (dd, J = 1.2, 0.5 Hz, 1H, H-3), 2.17 (s, 3H, $-COCH_3$), 2.14 (s, 3H, $-COCH_3$); ms: m/z (relative intensity) 262 (M^+, 2), 192 (7), 150 (16), 149 (6), 43 (100); hrms: 262.0601; M^+, Calcd. for $C_{12}H_{10}N_2O_5$: 262.0589.

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