Furopyridines. XXI [1]. Synthesis of Cyano Derivatives of Furo-[2,3-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine and Their Conversion to Derivatives Having Another Carbon-substituent

Shunsaku Shiotani* and Katsunori Taniguchi

Department of Chemistry, Faculty of Science, Toyama University, Gofuku 3190, Toyama 930, Japan
Received September 4, 1996

Cyanation of furo[2,3-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine *N*-oxides **1a**, **1b** and **1c** by the Reissert-Henze method, reaction with benzoyl chloride and trimethylsilyl cyanide in dichloromethane and the reaction with trimethylsilyl cyanide and triethylamine in acetonitrile afforded 6-cyanofuro[2,3-*b*]- **2a**, 7-cyanofuro[2,3-*c*]- **2b** and 4-cyanofuro[3,2-*c*]pyridine **2c** in moderate to excellent yield. The cyano group in **2a**, **2b** and **2c** was converted to carboxamides **3a**, **3b** and **3c**, ethyl imidates **5a**, **5b** and **5c** and ethyl carboxylates **6a**, **6b** and **6c**. Reaction of the *N*-oxides with trimethylsily bromide in acetonitrile gave the deoxygenated furopyridine **7a** and **7d**, bifuropyridyl **8b** and **8c**, and the *N*-oxide **9** of **8c**.

J. Heterocyclic Chem., **34**, 493 (1997).

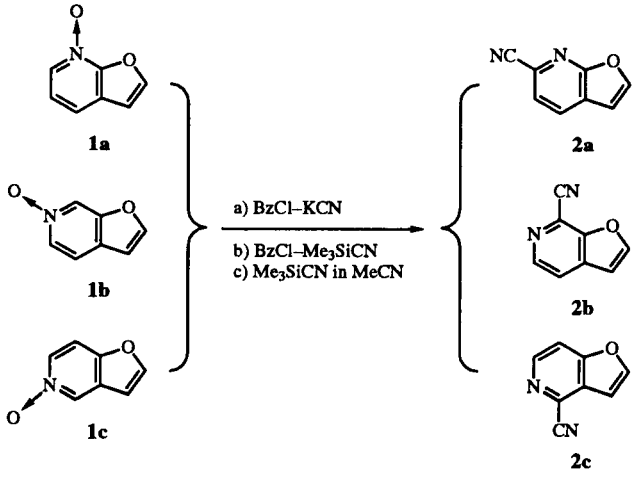
In our studies of the synthesis and reactivity of furopyridines, we have recently reported cyanation, chlorination and nitration of furo[3,2-*b*]pyridine *N*-oxide [2] and acetoxylation of furo[2,3-*b*]-, -[3,2-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine *N*-oxides [3]. The cyanation of furo-[3,2-*b*]pyridine *N*-oxide by the Reissert-Henze method and with benzoyl chloride and trimethylsilyl cyanide in dichloromethane afforded the 5-cyano compounds selectively, from which the corresponding carboxamides, carboxylic acids and ethyl esters were derived.

To compare the reactivity of furo[2,3-*b*]- **1a**, -[2,3-*c*]- **1b** and -[3,2-*c*]pyridine *N*-oxides (**1c**) with that of furo[3,2-*b*]-pyridine in cyanation and with the aim to find new compounds with possible biological activity we describe in this paper the cyanation of **1a**, **1b** and **1c** and conversion of the cyano group to several carbon substituents.

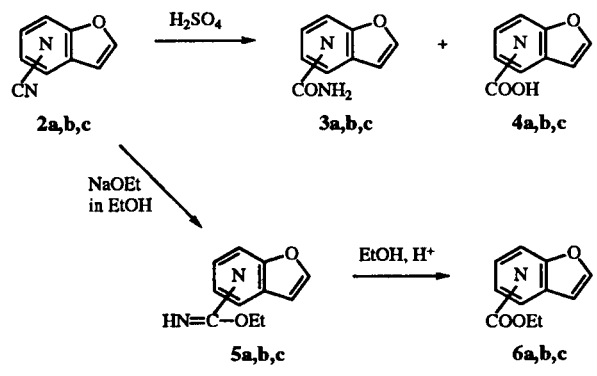
Reissert-Henze cyanation of **1a**, **1b** and **1c** with benzoyl chloride and potassium cyanide in dichloromethane and water afforded 6-cyanofuro[2,3-*b*]- **2a**, 7-cyanofuro-[2,3-*c*]- **2b** and 4-cyanofuro[3,2-*c*]pyridine (**2c**) in yields of 50%, 88% and 71% respectively. The cyanation with trimethylsilyl cyanide and benzoyl chloride in dichloromethane gave the same products in lower yields (40% for **2a**, 57% for **2b** and 51% for **2c**). While, the cyanation with trimethylsilyl cyanide and triethylamine in acetonitrile [4] gave the same products in much better yields (77% for **2a**, 99% for **2b** and 98% for **2c**) [5].

The structures of **2a**, **2b** and **2c** were confirmed from their ir and nmr spectra. The ir spectrum of **2a** showed ν_{CN} at 2233 cm^{-1}, the ^1H nmr spectrum showed signals of the protons of the pyridine ring at δ 8.08 (H-4 or H-6, d, J = 7.9 Hz) and δ 7.66 (H-5, d, J = 7.9 Hz) and the protons of the furan ring at δ 7.92 (H-2, d, J = 2.4 Hz) and δ 6.91 (H-3, d, J = 2.4 Hz). The pyridine proton signals were compared with those (H-6, δ 8.35; H-5, δ 7.19; H-4, δ 7.92) of the parent furo[2,3-*b*]pyridine [6] by considering the substituent effect of the cyano group on the chemical shifts; the signal at δ 8.08 was assigned to H-4. The ^{13}C nmr spectrum showed four signals of the aromatic methine carbons at δ 148.4, 131.0, 124.1 and 106.4, and four aromatic quaternary carbons at δ 161.0, 126.6, 123.3 and 117.4. The ^1H-^{13}C COSY spectrum revealed that the methine carbon at δ 148.4 is attached to H-2, 131.0 to H-4, 124.1 to H-5 and 106.4 to H-3. Comparison of the signals of the quaternary carbons with the ^{13}C nmr spectrum of furo[2,3-*b*]pyridine [7] by considering the substituent effect of cyano group on the chemical shift suggested the assignment of the signal at δ 161.0 to C-7a, 126.6 to C-6, 123.3 to C-3a and 117.4 to CN. From these facts, compound **2a** was confirmed as being 6-cyanofuro-[2,3-*b*]pyridine. Compound **2b** exhibited absorption of ν_{CN} at 2234 cm^{-1} in its ir spectrum, and signals of pyridine-protons at δ 8.54 (H-5, d, J = 5.3 Hz) and δ 7.86 (H-4, d, J = 5.3 Hz) and of furan-protons at δ 7.96 (H-2, d, J = 2.3 Hz) and δ 7.03 (H-3, d, J = 2.3 Hz) in the ^1H nmr spectrum. The coupling pattern of the pyridine-protons confirmed the position of the cyano group in **2b**. The ir spectrum of **2c** showed ν_{CN} at 2239 cm^{-1}, the ^1H nmr spectrum showed signals of protons of pyridine ring at δ

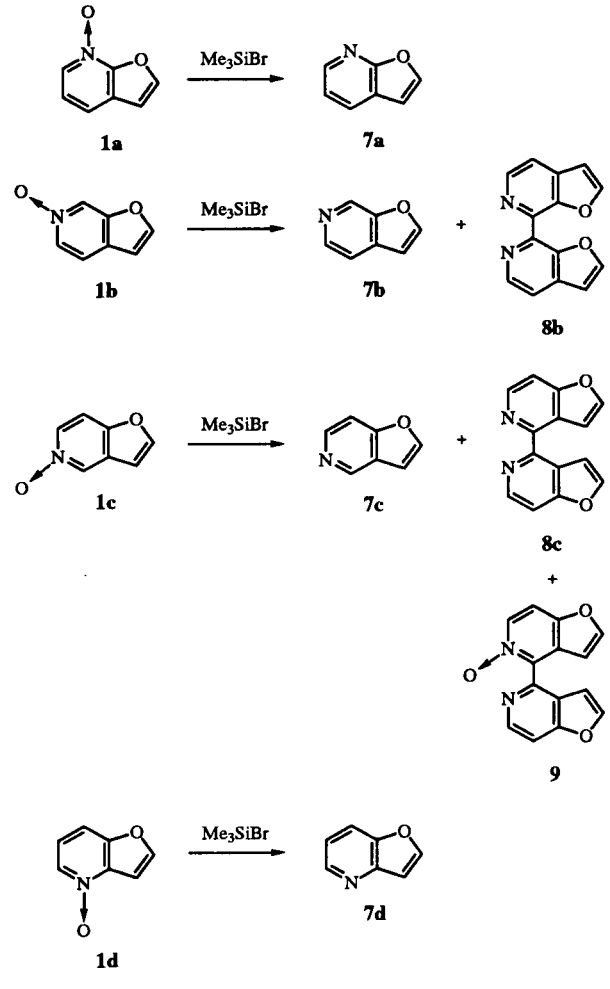
Scheme I



Scheme II



Scheme III



8.62 (d, J = 5.8 Hz) and δ 7.67 (dd, J = 0.9, 5.8 Hz) and signals of protons of the furan ring at δ 7.85 (d, J = 2.5 Hz) and δ 7.07 (dd, J = 0.9, 2.5 Hz). From the coupling pattern of pyridine-protons and zig-zag coupling between signals at δ 7.67 and 7.07, the position of the cyano group in **2c** was determined.

Hydrolysis of the nitriles **2a**, **2b** and **2c** with sulfuric acid afforded the corresponding carboxamides **3a** (57%), **3b** (73%) and **3c** (31%), accompanying formation of the carboxylic acids **4a** (18%), **4b** (2%) and **4c** (11%). Treatment of nitriles **2a**, **2b** and **2c** with sodium ethoxide in ethanol afforded the corresponding imidates **5a**, **5b** and **5c** in excellent yield, from which esters **6a**, **6b** and **6c** were obtained in high yield by treatment with a catalytic amount of hydrogen chloride in ethanol.

The *N*-oxides **1a**, **1b**, **1c** and furo[3,2-*b*]pyridne *N*-oxide (**1d**) were reacted with trimethylsilyl bromide and triethylamine in acetonitrile, expecting formation of bromo derivatives of furopyridines. Compound **1a** and **1d**, however, yielded no brominated compound, but the deoxygenated furopyridine **7a** and **7d** in yield of 59% and 50% respectively. While the reaction **1b** gave the deoxygenated furopyridine **7b** (23%) and 7,7'-bifuro[2,3-*c*]pyridyl (**8b**) (27%), and **1c** gave the deoxygenated furopyridine **7c** (11%), 4,4'-bifuro[3,2-*c*]pyridyl (**8c**) (70%), 4,4'-bifuro[3,2-*c*]pyridyl mono-*N*-oxide (**9**) (15%) and the starting compound **1c** (3.5%). The structures of **8b**, **8c** and **9** were determined by their spectral data. The elemental analyses and high resolution mass spectra suggested compounds **8b** and **8c** to have the molecular formula $C_{14}H_8N_2O_2$. In the ir spectra both the compounds showed no characteristic absorption in the function region. The ^1H nmr spectrum of **8b** exhibited signals of two pridine protons at δ 8.69 (d, J = 5.3 Hz) and δ 7.67 (d, J = 5.3 Hz) and two furan protons at δ 7.87 (d, J = 2.1 Hz) and δ 6.89 (d, J = 2.1 Hz). The ^1H nmr of **8c** exhibited signals of two pyridine protons at δ 8.66 (d, J = 5.6 Hz) and δ 7.50 (d, J = 5.6 Hz) and two furan protons at δ 7.85 (d, J = 2.0 Hz) and δ 7.75 (d, J = 2.0 Hz). Thus, compound **8b** and **8c** were suggested to be a symmetrically bonded bifuropyridyl. The lack of the signal of the proton at the 7-position of furo[2,3-*c*]-pyridne for **8b** and the 4-position of furo[3,2-*c*]pyridne for **8c** indicated that both the compound to be 7,7'-bifuro[2,3-*c*]pyridyl and 4,4'-bifuro[3,2-*c*]pyridyl respectively. The elemental analysis and high resolution mass spectrum of **9** suggested the molecular formula $C_{14}H_8N_2O_3$. The ^1H nmr spectrum of **9** showed signals of four pyridine protons at δ 8.68 (d, J = 5.6 Hz), δ 8.34 (d, J = 7.2 Hz), δ 7.59 (dd, J = 0.4, 5.6 Hz) and δ 7.49 (dd, J = 0.4, 7.2 Hz) and four furan protons at δ 7.74 (d, J = 2.0 Hz), δ 7.72 (d, J = 2.0 Hz), δ 7.07 (dd, J = 0.4, 2.0 Hz) and δ 6.93 (dd, J = 0.4, 2.0 Hz). The spin decoupled spectrum established the assignment of the proton signals; irradiation at δ 8.68, which is unequivocally assigned to H-6', changed the signal at δ 7.59 to a doublet (J = 0.4 Hz); irradiation at δ 7.07 changed the signal at δ 7.72 to a singlet and the signal at δ 7.59 to a doublet (J = 5.6 Hz). Thus, the signals at δ 8.68, 7.72, 7.59 and

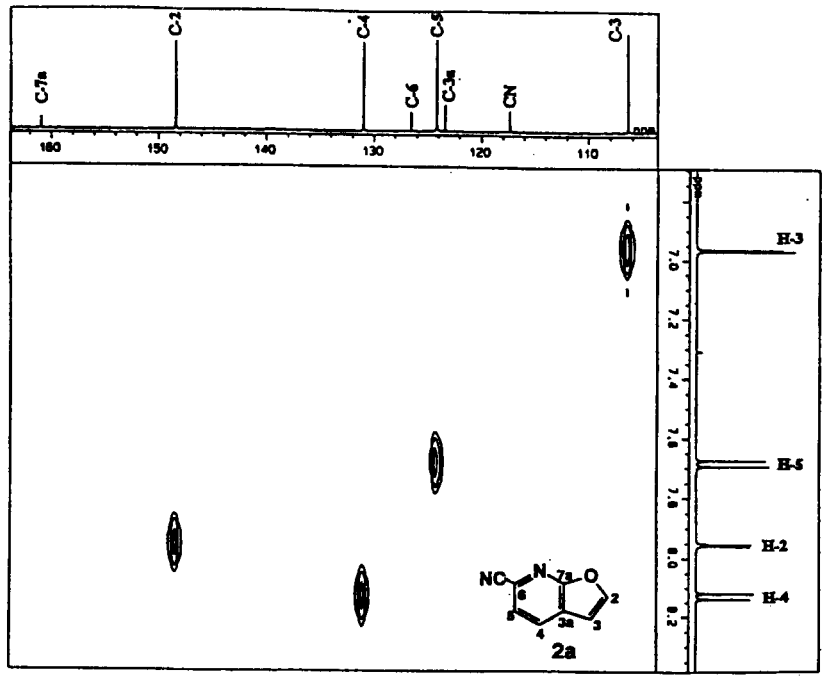


Figure 1. ^{1}H-^{13}H COSY spectrum of **2a**.

7.07 were assigned to H-6', H-2', H-7' and H-3', and signals at δ 8.34, 7.74, 7.49 and 6.93 to H-6, H-2, H-7 and H-3. The ^{13}C nmr spectrum exhibited signals of eight aromatic methine carbons and six quaternary carbons. These carbon signals were assigned to the corresponding carbon in compound **9** by comparison of the spectrum with those of furo[3,2-*c*]pyridine [7] and its *N*-oxide [3] and from the ^{1}H-^{13}C cosy spectrum. Formation of these compounds may be interpreted as follows (Chart 1): At the first stage, trimethylsilyl bromide would attack the *N*-oxide oxygen to form trimethylsiloxylammonium bromide. The hard bromide ion can not bond to the soft

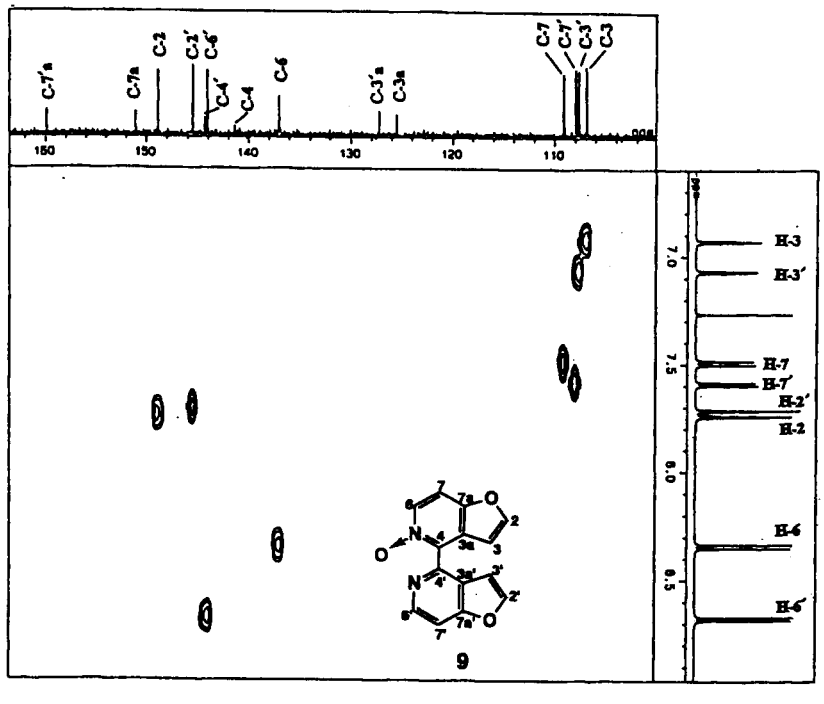
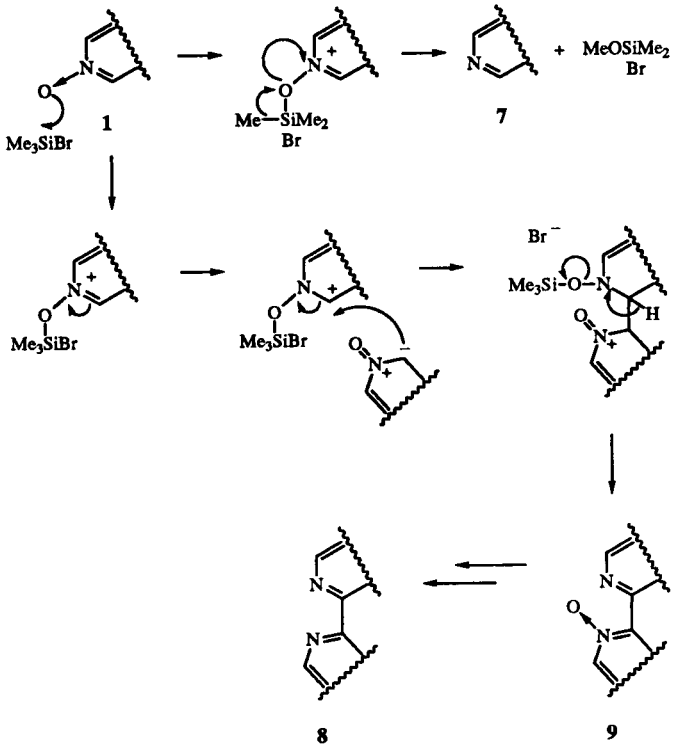


Figure 2. ^{1}H-^{13}H COSY spectrum of **9**.

Chart 1



α-carbon atom, and the strong affinity of the hard silyl group for the hard *N*-oxide oxygen would cause elimination of dimethylmethoxysilyl bromide to give the deoxygenated furopyridine. While, in the cases of **1b** and **1c**, the dimeric products would be formed by attack of the positively charged α-carbon of the trimethylsily adduct at the negatively charged α-carbon of furopyridine *N*-oxide, followed by elimination of trimethylsilanol to give the bifuropyridyl *N*-oxide, which would be subsequently deoxygenated to afford the symmetric dimer **8b** and **8c** by the same process as described above.

EXPERIMENTAL

All melting points were determined on a micro-hot stage (Yanagimoto) and are uncorrected. Infrared spectra were recorded on a JASCO FT/IR 7300 spectrometer. The ^{1}H nmr spectra were recorded on a JEOL PMX 60 (60 MHz), a JEOL MAC-FX (90 MHz) or a JEOL JNM FX A400 spectrometer (400 MHz), and the ^{13}C (100 MHz) spectra were taken on a JEOL JNM FX A400 spectrometer with tetramethylsilane as an internal standard. Mass spectra were obtained by using JEOL JMS-OISG-2 spectrometer.

General Procedure for the Cyanation of Furopyridine *N*-Oxides **1a**, **1b** and **1c**.

A) To a solution of potassium cyanide (500 mg, 7.7 mmoles) in water (0.7 ml) was added a solution of the *N*-oxide hydrate **1**•H_2O (107 mg, 0.7 mmole) in dichloromethane (4 ml) and then a solution of benzoyl chloride (0.86 mmole) in dichloromethane (4 ml) dropwise. After vigorous stirring at room temperature for 2 days, the organic layer of the reaction mixture was separated and the aqueous layer was extracted with chloroform. After drying over magnesium sulfate, the combined organic layers were evaporated.

Further processing of the residue of the organic layers is described in the subsequent paragraph.

6-Cyanofuro[2,3-*b*]pyrdine (**2a**).

The residue from **1a** (100 mg) was chromatographed on silica gel (30 g) column. The second fraction eluted with hexane-ethyl acetate (3:1) gave 51 mg (50%) of pure **2a** as a colorless crystal. Recrystallization from ether gave an analytical sample, mp 106-110°; ir (potassium bromide): 3151, 2233, 1655, 1583, 1525, 1407 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.08 (d, J = 7.9 Hz, 1H, H-4), 7.92 (d, J = 2.4 Hz, H-2), 7.66 (d, J = 7.9 Hz, H-5), 6.91 (d, J = 2.4 Hz, H-3); ^{13}C nmr (deuteriochloroform): δ 161.0 (s, C-7a), 148.4 (d, C-2), 131.0 (d, C-4), 126.6 (s, C-6), 124.1 (d, C-5), 123.3 (s, C-3a), 117.4 (s, CN), 106.4 (d, C-3); hrms Calcd. for $C_8H_4N_2O$: m/z M$^+$ 144.0323. Found: 144.0327.

Anal. Calcd. for $C_8H_4N_2O$: C, 66.67; H, 2.80; N, 19.44. Found: C, 67.00; H, 3.12; N, 19.33.

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

The residue (120 mg) from **2a** was chromatographed on a silica gel (30 g) column. The second fraction eluted with hexane-ethyl acetate (3:1) gave 89 mg (88%) of pure **2b**, which was recrystallized from ether-hexane to give an analytical sample of mp 128-130° (in a sealed tube) as colorless needles; ir (potassium bromide): 3157, 2234, 1604, 1422, 1185 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.54 (d, J = 5.3 Hz, H-5), 7.96 (d, J = 2.3 Hz, H-2), 7.86 (d, J = 5.3 Hz, H-4), 7.03 (d, J = 2.3 Hz, H-3).

Anal. Calcd. for $C_8H_4N_2O$: C, 66.67; H, 2.80; N, 19.44. Found: C, 66.63; H, 3.04; N, 19.37.

4-Cyanofuro[3,2-*c*]pyridine (**2c**).

The residue from **1c** (120 mg) was chromatographed on a silica gel (30 g) column. The second fraction eluted with hexane-ethyl acetate (3:1) gave 71.5 mg (71%) of pure **2c**, which was recrystallized from hexane to give an analytical sample of mp 99-100° (in a sealed tube) as colorless crystals; ir (potassium bromide): 3133, 3112, 2239, 1607, 1531, 1427, 1237, 1139 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.62 (d, J = 5.8 Hz, 1H, H-6), 7.85 (d, J = 2.5 Hz, 1H, H-2), 7.67 (dd, J = 0.9, 5.8 Hz, 1H, H-7), 7.07 (dd, J = 0.9, 2.5 Hz, 1H, H-3); hrms Calcd. for $C_8H_4N_2O$: m/z M$^+$ 144.0323. Found: 144.0319.

Anal. Calcd. for $C_8H_4N_2O$: C, 66.67; H, 2.80; N, 19.44. Found: C, 66.47; H, 3.19; N, 19.18.

B) A solution of the *N*-oxide hydrate **1**•H_2O (460 mg, 3.0 mmoles) in dichloromethane (5 ml) was treated with a molecular sieve (5A, 2 g) for 5 hours at room temperature to cause dehydration. To the dried solution was added triethylamine (920 mg, 6.5 mmoles) and trimethylsilyl cyanide (2.2 ml, 16.5 mmoles) with stirring under nitrogen atmosphere. After stirring for 5 minutes, to this mixture was added benzoyl chloride (0.75 ml, 6.5 mmoles), and stirring was continued for 20 to 24 hours at room temperature. The reaction mixture was stirred with 10% aqueous solution of potassium carbonate (1.5 g) for 15 minutes. The organic layer was dried (potassium carbonate) and evaporated to leave a light brown solid (400-450 mg). Purification of the crude

residue by chromatography on a silica gel column (45 g) eluting with hexane-ethyl acetate (3:1) yielded **2a** (173 mg, 40%), **2b** (247 mg, 57%) and **2c** (221 mg, 51%), respectively.

C) A solution of the *N*-oxide hydrate **1**•H_2O (187 mg, 1.22 mmoles) in acetonitrile (4 ml) was treated with a molecular sieve (5A, 1 g) for 5 hours at room temperature to cause dehydration. To the dried solution was added triethylamine (0.25 ml, 1.83 mmoles) and trimethylsilyl cyanide (0.41 ml, 3.06 mmoles) with stirring under a nitrogen atmosphere. After being heated at 100-110° for 18 hours, the reaction mixture was evaporated, and the residue was treated with chloroform and water. The aqueous layer was extracted with chloroform. The combined chloroform layers were dried (magnesium sulfate) and evaporated to leave a light brown solid mass (180-200 mg), which was chromatographed on an alumina (Merck, neutral, 20 g) column eluting with chloroform to give pure **2a** (127.5 mg, 77%) from **1a**, **2b** (163 mg, 99%) from **1b** and **2c** (162 mg, 98%) from **1c**.

Hydrolysis of 6-Cyanofuro[2,3-*b*]- **2a**, 7-Cyanofuro[2,3-*c*]- **2b** and 4-Cyanofuro[3,2-*c*]pyridine (**2c**) with Sulfuric Acid.

General Procedure.

Nitrile **2** (276 mg, 1.92 mmoles) was heated with a mixture of sulfuric acid (2.8 ml) and water (0.5 ml) on a water bath for 20 minutes. The cooled reaction mixture was diluted with water (15 ml), basified with sodium bicarbonate, extracted with chloroform. Evaporation of the dried (magnesium sulfate) extract gave furopyridinecarboxamide as a colorless solid mass.

Further processing of the crude product is indicated in the following paragraph.

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

The crude product (190 mg) from **2a** was recrystallized from acetone to give 177 mg (57%) of **3a** as colorless crystals, mp 167-170°; ir (potassium bromide): 3448, 1679, 1588, 1389, 1349, 1137 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.13 and 7.95 (AB-q, J = 7.8 Hz, 2H, H-5 and H-4), 7.73 (d, J = 2.5 Hz, 1H, H-2), 6.74 (d, J = 2.5 Hz).

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.44; H, 3.93; N, 17.30.

Furo[2,3-*c*]pyridine-7-carboxamide (**3b**).

The crude product (250 mg) from **2b** was recrystallized from acetone to give 227 mg (73%) of pure **3b**, mp 173-175°; ir (potassium bromide): 3396, 1660, 1593, 1426, 1267, 1179 cm^{-1}; ^1H nmr (deuteriochloroform): 8.40 (d, J = 5.0 Hz, 1H, H-5), 7.94 (d, J = 2.1 Hz, 1H, H-2), 7.74 (d, J = 5.0 Hz, 1H, H-4), 6.88 (d, J = 2.1 Hz, 1H, H-3).

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.26; H, 3.78; N, 17.21.

Furo[3,2-*c*]pyridine-4-carboxamide (**3c**).

The crude product (100 mg) from **2c** was purified by recrystallization from ether to give 86 mg (31%) of **3c**, mp 156-158°; ir (potassium bromide): 3413, 1708, 1604, 1440, 1266, 1117, 1019 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.36 (d, J = 5.0 Hz, 1H, H-6), 7.64 (d, J = 2.0 Hz, 1H, H-2), 7.58 (dd, J = 2.0, 1.0 Hz, 1H, H-3), 7.51 (dd, J = 5.0, 1.0 Hz, 1H, H-7).

Anal. Calcd. for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.64, H, 4.00; N, 17.50.

The aqueous layer was acidified with acetic acid and extracted with chloroform. Evaporation of the dried (magnesium sulfate) chloroform extract afforded a crystalline mass, which was recrystallized from methanol to give 56 mg (18%) of **4a**, 6.2 mg (2%) of **4b** and 34.4 mg (11%) of **4c**.

Furo[2,3-*b*]pyridine-6-carboxylic Acid (**4a**).

This compound had mp 135-138°; ir (potassium bromide): 3435, 3200-2500 (broad), 1690, 1586, 1275 cm^{-1}; ^1H nmr (deuteriomethanol): δ 8.22 and 8.15 (AB-q, J = 7.9 Hz, 2H, H-5 and H-4), 8.07 (d, J = 2.6 Hz, 1H, H-2), 7.03 (d, J = 2.6 Hz).

Anal. Calcd. for $C_8H_5NO_3$: C, 58.90; H, 3.09; N, 8.59. Found: C, 59.25; H, 3.20; N, 8.60.

Furo[2,3-*c*]pyridine-7-carboxylic Acid (**4b**).

This compound had mp >300°; ir (potassium bromide): 3458, 3100-2500 (broad), 1667, 1627, 1608, 1354 cm^{-1}; ^1H nmr (deuteriomethanol): δ 8.44 (d, J = 5.1 Hz, 1H, H-5), 8.28 (d, J = 2.2 Hz, 1H, H-2), 8.04 (d, J = 5.1 Hz, 1H, H- 4), 7.17 (d, J = 2.2 Hz, 1H, H-3).

Anal. Calcd. for $C_8H_5NO_3$•$1.5H_2O$: C, 50.53; H, 4.24; N, 7.37. Found: C, 50.90; H, 3.92; N, 7.59.

Furo[3,2-*c*]pyridine-4-carboxylic Acid (**4c**).

This compound had mp >300°; ir (potassium bromide): 3475, 3250-2600 (broad), 1620, 1615, 1598, 1580, 1396 cm^{-1}; ^1H nmr (deuteriomethanol): δ 8.58 (d, J = 6.2 Hz, 1H, H-6), 8.13 (d, J = 2.3 Hz, 1H, H-2), 7.94 (dd, J = 6.2, 0.6 Hz, 1H, H-7), 7.58 (dd, J = 2.3, 0.6 Hz, 1H, H-3).

Anal. Calcd. for $C_8H_5NO_3$: C, 58.90; H, 3.09; N, 8.59. Found: C, 58.63; H, 3.32; N, 8.32.

Preparation of Ethyl Furo[2,3-*b*]pyridine-6-imidate **5a**, -[2,3-*c*]-pyridine-7-imidate **5b** and -[3,2-*c*]pyridine-4-imidate **5c**.

General Procedure.

To a solution of sodium ethoxide prepared from sodium (180 mg, 7.8 mmoles) in absolute ethanol (10 ml) was added a solution of nitrile **2** (540 mg, 3.8 mmoles) in absolute ethanol (30 ml) with stirring at room temperature. After being stirred for 17 hours at room temperature, the mixture was evaporated and the residue was treated with chloroform and water. The chloroform extract was dried (magnesium sulfate) and evaporated to give a yellow crystalline mass.

Further processing of the crude product is described in the following paragraph.

Ethyl Furo[2,3-*b*]pyridine-6-imidate (**5a**).

The residue from **2a** was recrystallized from ether to give 670 mg (94%) of **5a**, mp 87-90°; ir (potassium bromide): 3318, 3120, 3082, 2977, 1647, 1584, 1405, 1374, 1332 cm^{-1}; ^1H nmr (deuteriochloroform): 9.10 (broad s, 1H, =NH), 8.05 and 7.88 (AB-q, J = 7.8 Hz, 2H, H-4 and H-5), 7.82 (d, J = 2.6 Hz, 1H, H-2), 6.85 (d, J = 2.6 Hz, 1H, H-3), 4.48 (q, J = 7.0 Hz, 2H, O-CH_2CH_3), 1.47 (t, J = 7.0 Hz, 3H, O-CH_2CH_3).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: 63.37; H, 5.37; N, 14.48.

Ethyl Furo[2,3-*c*]pyridine-7-imidate (**5b**).

The crude product from **2b** was recrystallized from hexane to give 677 mg (95%) of pure **5b** as colorless crystals, mp 125-129°; ir (potassium bromide): 3279, 3094, 2991, 1640, 1593, 1535, 1411, 1343, 1182 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.04 (broad s, 1H, =NH), 8.31 (d, J = 4.8 Hz, 1H, H-5), 7.75 (d, J = 2.0 Hz, 1H, H-2), 7.53 (d, J = 4.8 Hz, 1H, H-4), 6.77 (d, J = 2.0 Hz, 1H, H-3), 4.51 (q, J = 7.0 Hz, 2H, O-CH_2CH_3), 1.50 (t,

J = 7.0 Hz, 3H, O-CH_2CH_3); hrms Calcd. for $C_{10}H_{10}N_2O_2$: m/z M^+ 190.0742. Found: 190.0736.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.28; H, 5.31; N, 14.66.

Ethyl Furo[3,2-*c*]pyridine-4-imidate (**5c**).

Recrystallization of crude **5c** from hexane yielded 641 mg (90%) of the pure sample, mp 65-70°; ir (potassium bromide): 3291, 3117, 3079, 2903, 1642, 1604, 1575, 1535, 1407, 1329, 1269 cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.06 (broad s, 1H, =NH), 8.30 (d, J = 5.0 Hz, 1H, H-6), 7.50 (d, J = 2.0 Hz, 1H, H-2), 7.32 (dd, J = 5.0, 0.8 Hz, 1H, H-7), 7.08 (dd, J = 2.0, 0.8 Hz, 1H, H-3), 4.43 (q, J = 7.0 Hz, 2H, O-CH_2CH_3), 1.48 (t, J = 7.0 Hz, 3H, O-CH_2CH_3).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.37; H, 5.41; N, 14.57.

Preparation of Ethyl Furo[2,3-*b*]pyridine-6-carboxylate **6a**, -[2,3-*c*]-pyridine-7-carboxylate **6b** and -[3,2-*c*]pyridine-4-carboxylate **6c**.

General Procedure.

A solution of imidate **5** (380 mg, 2.0 mmoles) in 90% ethanol (20 ml) containing 0.1 ml of 10% hydrochloric acid was stirred at room temperature for 15 hours. After evaporation of the solvent, the mixture was basified with sodium bicarbonate and extracted with chloroform. The residue of the dried (magnesium sulfate) extract was recrystallized from ether to give 348 mg (91%) of **6a**, 359 mg (94%) of **6b** and 317 (83%) of **6c**.

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

This compound had mp 86-88°; ir (potassium bromide): 3129, 2993, 2902, 1712, 1588, 1520, 1372, 1320, 1277, 1179 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.16 and 8.06 (AB-q, J = 8.0 Hz, 2H, H-4 and H-5), 7.88 (d, J = 2.6 Hz, 1H, H-2), 6.87 (d, J = 2.6 Hz, 1H, H-3), 4.50 (q, J = 7.0 Hz, 2H, O-CH_2CH_3), 1.47 (t, J = 7.0 Hz, 3H, O-CH_2CH_3).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 63.03; H, 4.82; N, 7.31.

Ethyl Furo[2,3-*c*]pyridine-7-carboxylate (**6b**).

This compound had mp 86-90°; ir (potassium bromide): 3132, 3060, 2983, 1720, 1601, 1532, 1421, 1295, 1165 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.57 (d, J = 5.0 Hz, 1H, H-5), 7.91 (d, J = 2.0 Hz, 1H, H-2), 7.76 (d, J = 5.0 Hz, 1H, H-4), 6.91 (d, J = 2.0 Hz, 1H, H-3), 4.59 (q, J = 7.0 Hz, 2H, O-CH_2CH_3), 1.53 (t, J = 7.0 Hz, 3H, O-CH_2CH_3).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.84; H, 4.81; N, 7.27.

Ethyl Furo[3,2-*c*]pyridine-4-carboxylate (**6c**).

This compound had mp 51-55°; ir (potassium bromide): 3091, 3029, 2982, 2927, 1709, 1609, 1429, 1299, 1263, 1178, 1036 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.50 (d, J = 5.0 Hz, 1H, H-6), 7.63 (d, J = 2.2 Hz, 1H, H-2), 7.47 (dd, J = 5.0, 0.8 Hz, 1H, H-7), 7.30 (dd, J = 2.2, 0.8 Hz, 1H, H-3), 4.48 (q, J = 7.0 Hz, 2H, O-CH_2CH_3), 1.46 (t, J = 7.0 Hz, 3H, O-CH_2CH_3).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.99; H, 4.75; N, 7.35.

Reaction of Furo[2,3-*b*]- **1a**, -[2,3-*c*]- **1b**, -[3,2-*c*]- **1c** and -[3,2-*b*]pyridine *N*-Oxide **1d** with Trimethylsilyl Bromide.

General Procedure.

A solution of the *N*-oxide hydrate **1**•H_2O (201 mg, 1.31 mmoles) in acetonitrile (6 ml) was treated with molecular sieve (5A, 1 g) for 17 hours at room temperature to dehydrate. To the dried solution was added triethylamine (0.82 ml, 5.96 mmoles) and then trimethylsilyl bromide (0.49 ml, 3.72 mmoles) with stirring at room temperature. The brown red mixture was refluxed for 42 hours. After evaporation of the solvent, the mixture was treated with chloroform and water. The residue of the dried (magnesium sulfate) chloroform extract was chromatographed on an alumina (Merck, neutral activity II, 35 g) column eluting with chloroform-methanol (99:1). In the cases of the product from **1a** and **1d**, the deoxygenated furopyridine **7a** (92 mg, 59%) and **7d** (78 mg, 55%) were isolated by the chromatography.

The chromatography of the crude product from **1b** yielded furo[2,3-*c*]pyridine **7b** (first fraction, 36 mg, 23%) and dimeric compound **8b** (second fraction, 43 mg, 28%). By the chromatography of the product from **1c**, the dimeric compound **8c** (first fraction, 109 mg, 70%), furo[3,2-*c*]pyridine **7c** (second fraction, 17.2 mg, 11%), *N*-oxide **9** of **8c** (27 mg, 15%) and the starting **1c** (7 mg, 3.5%).

The structures of the deoxygenated furopyridine **7a**, **7b**, **7c** and **7d** were confirmed by comparison of the ir and ^1H nmr spectral data [6,9,8,10] of the authentic samples respectively.

7,7'-Bifuro[2,3-*c*]pyridyl (**8b**).

Recrystallization of **8b** from acetone-ether gave an analytical sample of mp 233-237°; ir (potassium bromide): 3129, 3092, 3039, 3006, 1583, 1528, 1396, 1331, 1193, 1133 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.68 (d, J = 5.3 Hz, 2H, H-5 and H-5'), 7.88 (d, J = 2.1 Hz, 2H, H-2 and H-2'), 7.67 (d, J = 5.3 Hz, 2H, H-4 and H-4'), 6.90 (d, J = 2.1 Hz, 2H, H-3 and H-3').

Anal. Calcd. for $C_{14}H_8N_2O_2$: C, 71.18; H, 3.41; N, 11.86. Found: C, 71.20; H, 3.53; N, 11.74.

4,4'-Bifuro[3,2-*c*]pyridyl (**8c**).

The analytical sample was obtained by recrystallization from acetone-ether, mp 189-191°; ir (potassium bromide): 3174, 3140, 1598, 1568, 1532, 1445, 1400, 1263, 1015 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.65 (d, J = 5.6 Hz, 2H, H-6 and H-6'), 7.85 (dd, J = 2.1, 0.9 Hz, 2H, H-3 and H-3'), 7.74 (d, J = 2.1 Hz, 2H, H-2 and H-2'), 7.49 (dd, J = 5.6, 0.9 Hz, 2H, H-7 and H-7'); ^{13}C nmr (deuteriochloroform): δ 160.7 (s, C-7a and C-7'a), 151.5 (s, C-4 and C-4'), 145.9 (d, C-2 and C-2'), 143.61 (d, C-6 and C-6'), 123.6 (s, C-3a and C-3'a), 108.1 (d, C-3 and C-3'), 107.1 (d, C-7 and C-7').

Anal. Calcd. for $C_{14}H_8N_2O_2$: C, 71.18; H, 3.41; N, 11.86. Found: C, 71.21; H, 3.62; N, 11.83.

4,4'-Bifuro[3,2-*c*]pyridyl *N*-Oxide (**9**).

The crude sample was recrystallized from acetone to give the pure sample of **9**, mp 209-210°; ir (potassium bromide): 3390 (broad), 3151, 3117, 1611, 1576, 1525, 1406, 1266, 1212, 1127 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.68 (d, J = 5.6 Hz, 1H, H-6'), 8.35 (d, J = 7.2 Hz, 1H, H-6), 7.74 (d, J = 2.0 Hz, 1H, H-2), 7.72 (d, J = 2.0 Hz, 1H, H-2'), 7.59 (dd, J = 5.6, 0.4 Hz, 1H, H-7'), 7.49 (dd, J = 7.2 Hz, 1H, H-7), 7.07 (dd, J = 2.0, 0.4 Hz, 1H, H-3'), 6.93 (dd, J = 2.0, 0.4 Hz, 1H, H-3); ^{13}C nmr (deuteriochloroform): δ 159.9 (s, C-7'a), 151.1 (s, C-7a), 148.9 (d, C-2), 145.5 (d, C-2'), 144.4 (s, C-4'), 144.1 (d, C-6'), 141.4 (s, C-4), 137.1 (d, C-6), 127.3 (s, C-3'a), 125.5 (s, C-3a), 109.2 (d, C-7), 108.0 (d, C-7'), 107.7 (d, C-3'), 106.9 (d, C-3).

Anal. Calcd. for $C_{14}H_8N_2O_3$•H_2O: C, 62.22; H, 3.73; N, 10.73. Found: C, 62.35; H, 3.81; N, 10.37.

REFERENCES AND NOTES

[1] Part XX. S. Shiotani and Y. Tsukamoto, *J. Heterocyclic Chem.*, **34**, 129 (1997).

[2] S. Shiotani and K. Taniguchi, *J. Heterocyclic Chem.*, **33**, 1051 (1996).

[3] S. Shiotani, K. Taniguchi, T. Ishida and Y. In, *J. Heterocyclic Chem.*, **33**, 647 (1996).

[4a] H. Vorbruggen and K. Krolikiewicz, *Synthesis*, 316 (1983); [b] T. Hirota, T. Matsushita, K. Sasaki and S. Kashino, *Heterocycles*, **41**, 2565 (1995).

[5] The reaction of furo[3,2-*b*]pyridine *N*-oxide with trimethylsilyl cyanide under the same condition yielded 5-cyanofuro[3,2-*b*]pyridine in 95% yield accompanying the formation of 7-cyano derivative (2%), which were isolated by chromatography on a silica gel column eluting with hexane-ethyl acetate (1:1). The structure of the former was confirmed by comparison of the ir and 1H nmr spectra with those of the sample prepared by Reissert-Henze method previously reported [2]. The structure of the latter was determined from the following spectral data, mp 61-65° (from ether); ir (potassium bromide): 3139, 2241, 1612, 1562, 1381, 1262 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.71 (d, J = 5.0 Hz, 1H, H-5), 8.02 (d, J = 2.3 Hz, 1H, H-2), 7.47 (d, J = 5.0 Hz, 1H, H-6), 7.13 (d, J = 2.3 Hz, 1H, H-3); ms: m/z (relative intensity) 145 (10), 144 (M^+, 100), 116 (4); hrms: Calcd. for $C_8H_4N_2O$: m/z M^+ 144.0323. Found: 144.0313.

[6a] J. W. McFarland, R. P. Wollerman, W. C. Sadler and G. N. Coleman, *J. Heterocyclic Chem.*, **8**, 735 (1971); [b] H. Sliwa, *Bull. Soc. Chim. France*, 646 (1970).

[7] S. Shiotani and H. Morita, *J. Heterocyclic Chem.*, **28**, 1469 (1991).

[8a] F. Eloy and A. Deryckere, *J. Heterocyclic Chem.*, **8**, 57 (1971); [b] G. Lhommet, H. Sliwa and P. Maitte, *Bull. Soc. Chim. France*, 1442 (1972).

[9] S. Shiotani and H. Morita, *J. Heterocyclic Chem.*, **19**, 1207 (1982).

[10] S. Gronowitz, C. Westerlund and A.-B. Hornfeldt, *Acta Chem. Scand., Ser.* **B29**, 233 (1975).