Furopyridines. XXIII [1]. Synthesis and Reactions of Chloropyridine Derivatives of Furo[2,3-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine

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Chlorination of the *N*-oxides of furo[2,3-*b*]- **1a**, -[2,3-*c*]- **1b** and -[3,2-*c*]pyridine **1c** with phosphorus oxychloride afforded compounds substituted normally at the α- or γ-position to the ring nitrogen, **2a**, **2'a**, **2b**, **2c**, **2'c** and **2''c**, and in addition, in the case of **1b**, compounds substituted on the furan ring, **2'b** and **2''b**. The structures of these compounds were confirmed from their ir, nmr and mass spectra. The major chlorinated products **2a**, **2b** and **2c** were converted to methoxy- **5a**, **5b** and **5c**, *N*-pyrrolidyl- **7a**, **7b** and **7c**, and phenylthiofuropyridines **8a**, **8b**, and **8c**.

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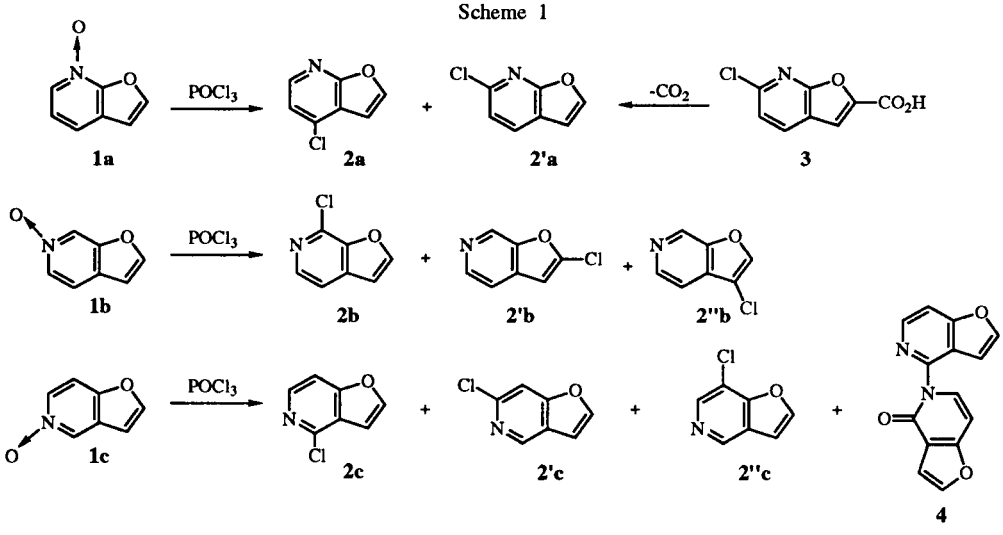
In our continuing studies on the synthesis and reactivity of furopyridines, we recently reported the chlorination, cyanation and nitration of furo[3,2-*b*]pyridine *N*-oxide [2] and acetoxylation of furo[2,3-*b*]-, -[3,2-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine *N*-oxides [3]. The chlorination of furo[3,2-*b*]pyridine *N*-oxide with phosphorus oxychloride afforded a mixture of 2-chloro, 3-chloro-, 5-chloro and 7-chlorofuro[3,2-*b*]pyridine. The major product, the 7-chloro derivative, was substituted with several nucleophiles. The 7-methoxy, 7-*N*-pyrrolidyl, 7-dimethylamino and 7-(1-cyano-1-ethoxycarbonyl)methylene compounds were prepared.

To compare the reactivity of the *N*-oxides of furo[2,3-*b*]- (**1a**), -[2,3-*c*]- (**1b**) and -[3,2-*c*]pyridine (**1c**) with that of furo[3,2-*b*]pyridine *N*-oxide towards chlorination with phosphorus oxychloride and in nucleophilic substitution of the chlorine atom in the chloro compounds, we describe in this paper the chlorination of **1a**, **1b** and **1c** and conversion of the chloro compounds into derivatives having another substituent.

Compound **1a** was refluxed with phosphorus oxychloride in chloroform to yield a light brown syrup from which two compounds, **2a** (mp 45-50°, bp 110-120°/21 mm Hg) and **2'a** (mp 45-48°, bp 110-130°/6 mm Hg) were isolated in yields of 65% and 5% by column chromatography on silica gel. In the ^{1}H-nmr spectrum, compound **2a** showed signals of the two protons of the furan ring at δ 7.74 (d) and 6.88 (d) (J = 2.6 Hz) and two protons of the pyridine ring at δ 8.24 (d) and 7.26 (d) (J = 5.6 Hz), and **2'a** the signals of the furan proton at δ 7.70 (d) and 6.79 (d) (J = 2.6 Hz) and the pyridine proton at δ 7.89 (d) and 7.28 (d) (J = 8.2 Hz). Though it was difficult to determine the position of the chlorine atom in both compounds from these spectral data, compound **2'a** was identified with the sample obtained by decarboxylation of 6-chlorofuro[2,3-*b*]pyridine-2-carboxylic acid **3** which was synthesized by the method of Weis [4]. Thus, the structures of **2a** and **2'a** were confirmed to be 4-chloro- and 6-chlorofuro[2,3-*b*]pyridine respectively.

The chlorination of compound **1b** with phosphorus oxychloride in chloroform gave a brown syrup from which three products, **2b** (mp 63-65°), **2'b** (mp 49-53°) and **2''b** (mp 91-95°) were isolated in yields of 30%, 5.5% and 3.1% by column chromatography on silica gel.

Scheme 1



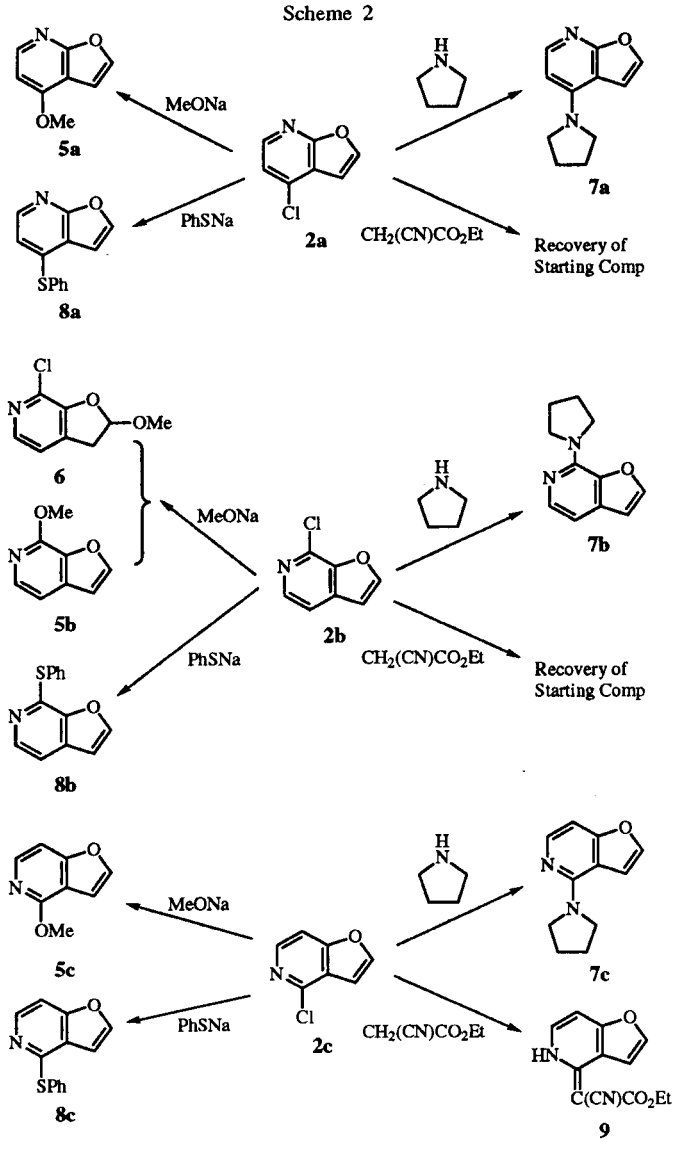
Compound **2b** showed, in its ^{1}H-nmr spectrum, two doublets of the furan protons at δ 7.81 and 6.88 (J = 2.1 Hz) and those of the pyridine protons at δ 8.19 and 7.49 (J = 5.3 Hz), **2'b** exhibited a doublet of the furan proton at δ 6.63 (J = 0.9 Hz) and three signals of the pyridine protons at δ 8.80 (t, J = 0.9 Hz), 8.43 (d, J = 5.3 Hz) and 7.45 (dd, J = 0.9, 5.3 Hz) and **2"b** exhibited a singlet of the furan proton at δ 7.77 and three signals of the pyridine protons at δ 8.90 (d, J = 0.9 Hz), 8.52 (d, J = 5.3 Hz) and 7.45 (dd, J = 0.9, 5.3 Hz). Compound **2b** was identified as 7-chlorofuro[2,3-*c*]pyridine by comparison of ir and ^{1}H-nmr spectral data with those of the authentic sample previously synthesized in our laboratory [5]. The structures of **2'b** and **2"b** were confirmed unequivocally to be 2-chloro- and 3-chlorofuro[2,3-*c*]pyridine by comparison of these ^{1}H-nmr spectra.

Refluxing of **1c** with phosphorus oxychloride in chloroform gave a light brown syrup from which four compounds, **2c** (mp 39-41°, bp 110-125°/20 mm Hg), **2'c** (mp 67-68.5°), **2"c** (bp 115-120°/20 mm Hg) and **4** (mp 234-237°), were isolated in yields of 65%, 2.4%, 7% and 5% respectively. In the ^{1}H-nmr spectrum, **2c** showed signals of two furan protons at δ 7.57 (d, J = 2.0 Hz) and 6.80 (dd, J = 0.8, 2.0 Hz) and two pyridine protons at δ 8.16 (d, J = 5.4 Hz) and 7.30 (dd, J = 5.4, 0.8 Hz). Compounds **2'c** and **2"c** exhibited, in their ^{1}H-nmr spectra, signals of two furan protons at δ 7.68 (d, J = 2.2 Hz) and 6.80 (dd, J = 2.2, 0.8 Hz) and at δ 7.53 (d) and 6.72 (d) (J = 2.2 Hz) and signals of two pyridine protons at δ 8.63 (s) and 7.45 (d, J = 0.8 Hz) and at δ 8.63 (s) and 8.28 (s) respectively. Compound **4** showed a carbonyl absorption at 1692 cm^{-1}. The ^{1}H-nmr spectrum of **4** showed two pairs of signals of furan protons at 7.69 (d, J = 2.0 Hz) and 6.81 (d 1, J = 2.0, 0.8 Hz) and at δ 7.58 (d, J = 2.0) and 7.05 (dd, J = 2.0, 1.2 Hz), and two pairs of pyridine protons at δ 7.68 (d, J = 8.0 Hz) and 6.72 (dd, J = 8.0, 0.8 Hz) and at δ 8.47 (d, J = 5.6 Hz) and 7.56 (dd, J = 5.6, 1.2 Hz). Compound **2c** and **4** were identified with 4-chlorofuro[3,2-*c*]pyridine [6] and 5-(4'-furo[3,2-*c*]pyridyl)furo[3,2-*c*]pyridin-4(5*H*)one [3] by comparison of the ir and ^{1}H-nmr spectra with those of the authentic samples. The structures of **2'c** and **2"c** were determined to be 6-chloro- and 7-chlorofuro[3,2-*c*]pyridine by comparison of the ^{1}H-nmr spectral data.

It is worth noting that furopyridine *N*-oxides having the ring oxygen at the α- or γ-position to the ring nitrogen (**1a** and **1c**) did not give a compound chlorinated at the furan ring, while those having the oxygen at the β-position (**1b** and furo[3,2-*b*]pyridine *N*-oxide [2]), yielded the products chlorinated at the furan ring, though the yields were not so high. Formation of compounds substituted at the pyridine ring **2a**, **2'a**, **2b**, **2c**, **2'c** and **2"c** and the dimeric product **4** from **1c** is interpreted by the well known mechanism for the chlorination of the *N*-oxides of pyridine, quinoline and isoquinoline [7], and formation of compounds substituted at the furan ring would be understood by the mechanism postulated for the formation of the furan-chlorinated products from furo[3,2-*b*]pyridine *N*-oxide [2] and the acetoxylated furan compounds from furo[2,3-*b*]-, -[3,2-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine *N*-oxide in the previous paper [3].

The major products, 4-chlorofuro[2,3-*b*]- **2a**, 7-chlorofuro[2,3-*c*]- **2b** and 4-chlorofuro[3,2-*c*]pyridine **2c**, were substituted with several nucleophiles.

Scheme 2



The reaction with sodium methoxide in methanol afforded the corresponding methoxy derivatives **5a**, **5b** and **5c** in yields of 82%, 49% and 62% respectively. In the case of **2b**, this reaction accompanied the formation of 2-methoxy-7-chloro-2,3-dihydrofuro[2,3-*c*]pyridine **6** (13%) and recovery of the starting **2b** (13%). The structure

of **6** was confirmed from its elemental analysis, mass spectrum and ^{1}H- and ^{13}C-nmr spectra. The mass spectrum of **6** showed M^+ peak at m/e 185 and M^++2 287 (ratio of intensity: ca. 10:3) and the high resolution mass spectrum indicated the M^+ to be $C_8H_8NO_2Cl$. The elemental analysis also supported the molecular formula. In the ^{1}H-nmr spectrum **6** exhibited signals of two pyridine protons at δ 7.98 (d, J = 4.7 Hz) and 7.12 (1H, ddd, J = 4.7, 1.2, 0.9 Hz) and four signals of aliphatic protons at δ 5.77 (1H, dd, J = 6.4, 2.6 Hz), 3.44 (1H, ddd, J = 17.6, 6.2, 1.2 Hz), 3.10 (ddd, J = 17.6, 2.6, 0.9 Hz) and 3.59 (3H, s). The ^{13}C-nmr spectrum showed three signals of aromatic quarternary carbons at δ 151.5, 136.6 and 132.8, two signals of aromatic methine carbon at δ 141.9 and 119.5, and three signals of aliphatic carbons at δ 107.6, 56.4 and 37.1. Formation of compound **6** can be understood by the following consideration. The electron-withdrawing effect of the ring nitrogen is efficiently exerted upon C-2 through the C-3-C-3a bond in **2b** [8]; that is, the resonance structure having a positive charge at C-2 is important for compound **2b**.

Refluxing of **2a**, **2b** and **2c** with pyrrolidine gave the corresponding *N*-pyrrolidyl derivative **7a**, **7b** and **7c** in yields of 97%, 67% and 99% respectively. Reaction of **2a**, **2b** and **2c** with sodium phenyl sulfide yielded the corresponding phenylthio compounds **8a**, **8b** and **8c** in yields of 62%, 94% and 71% [9]. Reaction of **2c** with ethyl sodio-cyanoacetate yielded 4-(1-cyano-1-ethoxycarbonyl)methylene-4,5-dihydrofuro[3,2-*c*]pyridine **9** in 46% yield. The reaction of **2a** and **2b** resulted in recovery of the starting chloro compound.

EXPERIMENTAL

All melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. Infrared spectra were recorded on a JASCO FT/IR 7300 spectrometer. The nmr spectra were taken on a JEOL-PMX 60 (60 MHz), a JEOL MAC-FX (90 MHz) or a JEOL JNM FX-A400 (400 MHz) spectrometer in deuteriochloroform with tetramethylsilane as an internal reference. The mass spectra were obtained by using a JEOL JMS-OISG-2 spectrometer. Column chromatography was conducted on silica gel (Chromatography Silica Gel, BW-820MH, Fuji Silysia Chemical Ltd).

General Procedure for Chlorination of Furo[2,3-*b*]-**1a**, -[2,3-*c*]-**1b** and -[3,2-*c*]pyridine *N*-Oxide **1c**.

A mixture of **1** (1.0 g, 7.4 mmoles), phosphorus oxychloride (5.4 ml, 60 mmoles) in chloroform (2 ml) was refluxed for 1.5 hours (in the case of **1b**, reflux was continued for 18 hours to complete the reaction). After being cooled, the mixture was poured into ice-water (20 ml), basified with sodium bicarbonate and extracted with chloroform. Further processing of the residue of the dried (magnesium sulfate) chloroform solution is indicated in a subsequent paragraph.

4-Chloro- **2a** and 6-Chlorofuro[2,3-*b*]pyridine **2'a**.

The residue (950 mg) from **1a** was chromatographed on a silica gel (100 g) column. The first fraction eluted with hexane-ethyl acetate (3:1) yielded 784 mg (69%) of **2a**, the second 57 mg (5%) of **2'a**.

Compound **2a**.

This compound had mp 45-50° (from hexane, colorless crystals) (bp 110-120°/21 mm Hg); ir (potassium bromide): 3129, 3102, 2926, 1595, 1576, 1531, 1382, 1340, 1249, 1140, 1027, 635, 898, 819, 752 cm^{-1}; ^{1}H-nmr: δ 8.24 (d, J = 5.6 Hz, 1H, H-6), 7.74 (d, J = 2.6 Hz, 1H, H-2), 7.26 (d, J = 5.6 Hz, 1H, H-5), 6.88 (d, J = 2.6 Hz, 1H, H-3); ms: m/z (relative intensity) 155 (M^++2, 32), 154 (18), 153 (M^+, 100), 125 (20); hrms: 152.9973. M^+, Calcd. for C_7H_4NOCl: 152.9981.

Compound **2'a**.

This compound had mp 45-48° (ether-hexane, colorless crystals) (bp 110-130°/6 mm Hg); ir (potassium bromide): 3127, 3077, 2925, 1587, 1529, 1436, 1405, 1110, 1016, 922, 822, 735 cm^{-1}; ^{1}H- nmr: δ 7.89 (d, J = 8.2 Hz, 1H, H-4), 7.70 (d, J = 2.6 Hz, 1H, H-2), 7.28 (d, J = 8.2 Hz, 1H, H-5), 6.79 (d, J = 2.6 Hz, 1H, H-3).

Anal. Calcd. for C_7H_4NOCl: C, 54.75; H, 2.63; N, 9.12. Found: C, 54.41; H, 2.72; N, 8.98.

Compound **2'a** (65 mg, 83%) was prepared from 6-chlorofuro[2,3-*b*]pyridine-2-carboxylic acid (**3**) (100 mg) by heating at 250° with copper powder (1.0 g). The ir and ^{1}H-nmr spectra of both samples were identical.

7-Chloro- **2b**, 2-Chloro- **2'b** and 3-Chlorofuro[2,3-*c*]pyridine **2''b**.

The crude residue (980 mg) from **1b** was chromatographed on a silica gel (100 g) column eluting with chloroform. The first fraction yielded **2b** (340 mg, 30%), the second **2'b** (63 mg, 5.5%) and the third **2''b** (35 mg, 3%).

Compound **2b**.

This compound had mp 63-65° (lit [5] mp 64-65.5°) (from ether-hexane, colorless crystals); ^{1}H-nmr: δ 8.19 (d, J = 5.3 Hz, 1H, H-5), 7.81 (d, J = 2.1 Hz, 1H, H-2), 7.49 (d, J = 5.3 Hz, 1H, H-4), 6.88 (d, J = 2.1 Hz, 1H, H-3).

Compound **2'b**.

This compound had mp 49-53° (from hexane, colorless crystals; this compound is unstable and decomposes by standing at room temperature in the air for 3-4 hours but is stable in solution); ir (potassium bromide): 3118, 3093, 3055, 2926, 1608, 1581, 1536, 1465, 1421, 1261, 1182, 1096, 1029, 927, 836 cm^{-1}; ^{1}H-nmr: δ 8.80 (t, J = 0.9 Hz, 1H, H-7), 8.43 (d, J = 5.3 Hz, 1H, H-5), 7.45 (dd, J = 5.3, 0.9 Hz, 1H, H-4), 6.63 (d, J = 0.9 Hz, 1H, H-3); ms: m/z (relative intensity) 155 (M^++2, 33), 153 (M^+, 100), 131 (13), 127 (11), 125 (31), 118 (13); hrms: 152.9980. M^+, Calcd. for C_7H_4NOCl: 152.9981.

Compound **2''b**.

This compound had mp 91-95° (from acetone-ether, colorless crystals); ir (potassium bromide): 3102, 3044, 2925, 1602, 1537, 1423, 1276, 1179, 1090, 1039, 818 cm^{-1}; ^{1}H-nmr: δ 8.90 (d, J = 0.9 Hz, 1H, H-7), 8.52 (d, J = 5.3 Hz, 1H, H-5), 7.77 (s, 1H, H-2), 7.45 (dd, J = 5.3, 0.9 Hz, 1H, H-4); ms: m/z (relative intensity) 155 (M^++2, 21), 153 (M^+, 76), 131 (29), 119 (21), 90 (23), 69 (100); hrms: 152.9976. M^+, Calcd. for C_7H_4NOCl: 152.9981.

Anal. Calcd. for C_7H_4NOCl: C, 54.75; H, 2.63; N, 9.12. Found: C, 54.96; H, 2.89; N, 8.93.

4-Chloro- **2c**, 6-Chloro- **2'c**, 7-Chlorofuro[3,2-*c*]pyridine **2"c** and 5-(4'-furo[3,2-*c*]pyridyl)furo[3,2-*c*]pyridin-4(5*H*)-one **4**.

The crude product (1.0 g) from **1c** was chromatographed on a silica gel (100 g) column eluting with hexane-ethyl acetate (3:1) to yield 740 mg (65%) of **2c**, 27 mg (2.4%) of **2'c**, 80 mg (7%) of **2"c** and 47 mg (5%) of **4**.

Compound **2c**.

This compound had mp 39-41° and bp 110-125°/20 mm Hg (lit [6] mp 41°, bp 117°/16 mm Hg); ^{1}H-nmr: δ 8.16 (d, J = 5.4 Hz, 1H, H-6), 7.57 (d, J = 2.0 Hz, 1H, H-2), 7.30 (dd, J = 5.4, 0.8 Hz, 1H, H-7), 6.80 (dd, J = 2.0, 0.8 Hz, 1H, H-3).

Compound **2'c**.

This compound had mp 65-68° (from hexane, colorless crystals); ir (potassium bromide): 3130, 3118, 3105, 2924, 1606, 1575, 1533, 1451, 1396, 1307, 1275, 1262, 1121, 1048, 1019, 918, 839 cm^{-1}; ^{1}H-nmr: δ 8.63 (s, 1H, H-4), 7.68 (d, J = 2.2 Hz, 1H, H-2), 7.45 (d, J = 0.8 Hz, 1H, H-6), 6.80 (dd, J = 2.2, 0.8 Hz, 1H, H-3); ms: m/z (relative intensity) 155 (M^++2, 32), 153 (M^+, 100), 118 (60), 63 (41); hrms: 152.9988. M^+, Calcd. for C_7H_4NOCl: 152.9981.

Compound **2"c**.

This compound had bp 115-120°/20 mm Hg (colorless oil); ir (neat): 3153, 3103, 3092, 3055, 2961, 2927, 1615, 1588, 1447, 1418, 1327, 1261, 1172, 1020, 877, 746 cm^{-1}; ^{1}H-nmr: δ 8.63 (s, 1H, H-4), 8.28 (s, 1H, H-6), 7.53 (d, J = 2.2 Hz, 1H, H-2), 6.72 (d, J = 2.2 Hz, 1H, H-3); ms: m/z (relative intensity) 155 (M^++2, 33), 154 (15), 153 (M^+, 100), 118 (30), 90 (26), 63 (55); hrms: 152.9980. M^+, Calcd. for C_7H_4NOCl: 152.9981.

Compound **4**.

This compound had mp 234-237° (from methanol-acetone, colorless crystals) (lit [3] mp 233-235°); ^{1}H-nmr: δ 8.47 (d, J = 5.6 Hz, 1H, H-6'), 7.69 (d, J = 2.0 Hz, 1H, H-2), 7.68 (d, J = 8.0 Hz, 1H, H-6), 7.58 (d, J = 2.0 Hz, 1H, H-2'), 7.56 (dd, J = 5.6, 1.2 Hz, 1H, H-7'), 7.05 (dd, J = 2.0, 1.2 Hz, 1H, H-3'), 6.81 (dd, J = 2.0, 0.8 Hz, 1H, H-3), 6.72 (dd, J = 8.0, 0.8 Hz, 1H, H-7).

General Procedure for the Preparation of 4-Methoxyfuro[2,3-*b*]- **5a**, 7-Methoxyfuro[2,3-*c*]- **5b** and 4-Methoxyfuro[3,2-*c*]pyridine **5c** and 2-Methoxy-7-chloro-2,3-dihydrofuro[2,3-*c*]pyridine **6**.

A solution of **2** (75 mg, 0.5 mmole) and sodium methoxide prepared from 125 mg (5.4 mmole) of sodium in methanol (3.0 ml) was refluxed for 20 hours for **2a** (for 45 hours for **2b** and for 70 hours for **2c** to complete the reaction). After evaporation of the solvent, the residue was treated with water and chloroform. The chloroform layer was dried (magnesium sulfate) and evaporated to leave a colorless oil which was distilled to give pure samples of **5a** (73 mg, 82%) and **5c** (45 mg, 62%). In the case of product from **2b**, the crude residue (70 mg) was chromatographed on a silica gel (7 g) column eluting with hexane-ethyl acetate (3:1) to give **5b** (36 mg, 49%), **6** (9 mg, 13%) and recovery of the starting chloro compound **2b** (10 mg, 13%).

Compound **5a**.

This compound was a colorless oil of bp 120-140° (bath temperature)/20 mm Hg, and solidified on standing in a refrigerator: mp 54-59°; ir (potassium bromide): 3137, 3105, 3029, 2984, 2949, 1592, 1498, 1353, 1330, 1290, 1149, 1106, 1075, 1026, 901, 780, 759 cm^{-1}; ^{1}H-nmr: δ 8.21 (d, J = 5.9 Hz, 1H, H-6), 7.56 (d, J = 2.6 Hz, 1H, H-2), 6.83 (d, J = 2.6 Hz, 1H, H-3), 6.69 (d, J = 5.9 Hz, 1H, H-5), 4.00 (s, 3H, -OMe); ms: m/z (relative intensity) 149 (M^+, 100), 134 (23), 120 (11), 106 (37), 91 (13); hrms: 149.0477. M^+, Calcd. for $C_8H_7NO_2$: 149.0476.

Anal. Calcd. for $C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.24; H, 4.97; N, 9.33.

Compound **5b**.

This compound was a colorless oil, bp 110-125° (bath temperature)/40 mm Hg; ir (neat): 3121, 3037, 3005, 2952, 1618, 1579, 1477, 1419, 1354, 1192, 1110, 1033, 970, 882, 814 cm^{-1}; ^{1}H-nmr: 7.93 (d, J = 5.6 Hz, 1H, H-5), 7.71 (d, J = 2.1 Hz, 1H, H-2), 7.16 (d, J = 5.6 Hz, 1H, H-4), 6.77 (d, J = 2.1 Hz, 1H, H-3), 4.14 (s, 3H, -OMe); ms: m/z (relative intensity) 149 (M^+, 100), 148 (92), 120 (40), 119 (80), 91 (33); hrms: 149.0474. M^+, Calcd. for $C_8H_7NO_2$: 149.0476.

Anal. Calcd. for $C_8H_7NO_2$: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.21; H, 4.73; N, 9.34.

Compound **6**.

This compound had mp 56-59° (from ether-hexane, colorless crystals); ir (potassium bromide): 2999, 2976, 2935, 2843, 1601, 1570, 1462, 1426, 1366, 1206, 1101, 1065, 1019, 1000, 944, 886, 823 cm^{-1}; ^{1}H-nmr: δ 7.98 (d, J = 4.7 Hz, 1H, H-5), 7.12 (ddd, J = 4.7, 1.2, 0.9 Hz, 1H, H-4), 5.77 (dd, J = 6.2, 2.6 Hz, 1H, H-2), 3.58 (s, 3H, -OMe), 3.44 (ddd, J = 17.6, 6.2, 1.2 Hz, 1H, H-3), 3.10 (ddd, J = 17.6, 2.6, 0.9 Hz, 1H, H-3'); ^{13}C-nmr: δ 151.5 (s, C-7a), 141.9 (d, C-5), 136.6 (s, C-7), 132.8 (s, C-3a), 119.5 (d, C-4), 107.6 (d, C-2), 56.4 (q, -OMe), 37.1 (t, C-3); ms: m/z (relative intensity) 187 (M^++2, 30), 185 (M^+, 100), 149 (89), 106 (46), 78 (46), 63 (35); hrms: 185.0243. M^+, Calcd. for $C_8H_8NO_2Cl$: 185.0243.

Anal. Calcd. for $C_8H_8NO_2Cl$: C, 51.77; H, 4.34; N, 7.55. Found: C, 52.18; H, 4.65; N, 7.14.

Compound **5c**.

This compound was a colorless oil of bp 115-125° (bath temperature)/40 mm Hg; ir (neat): 3097, 2925, 2854, 1600, 1473, 1357, 1278, 1142, 1091, 1018, 779 cm^{-1}; ^{1}H-nmr: δ 7.88 (d, J = 5.8 Hz, 1H, H-6), 7.42 (d, J = 2.2 Hz, 1H, H-2), 6.96 (dd, J = 5.8, 0.8 Hz, 1H, H-7), 6.71 (dd, J = 2.2, 0.8 Hz, 1H, H-3); ms: m/z (relative intensity) 149 (M^+, 36), 95 (36), 83 (42), 71 (56), 57 (100); hrms: 149.0483. M^+, Calcd. for $C_8H_7NO_2$: 149.0476.

General Procedure for the Preparation of 4-(1-Pyrrolidyl)furo[2,3-*b*]- **7a**, 7-(1-Pyrrolidyl)furo[2,3-*c*]- **7b** and 4-(1-Pyrrolidyl)furo[3,2-*c*]pyridine **7c**.

A solution of **2** (70 mg, 0.46 mmole) in dry pyrrolidine (1 ml) was refluxed for 4.5 hours. After evaporation of the excess pyrrolidine, the residual syrup was dissolved in chloroform. The chloroform solution was washed with water, dried over magnesium sulfate, and evaporated to leave a semi-solid, which was purified by chromatography on a silica gel (1.5 g) column eluting with chloroform to give 83 mg (97%) of **7a**, 57 mg (67%) of **7b** and 85 mg (99%) of **7c**.

Compound **7a**.

This compound had mp 85-87° (from ether-hexane, colorless crystals); ir (potassium bromide): 3127, 3078, 3031, 2967, 2952, 2927, 2857, 1597, 1562, 1509, 1484, 1462, 1417, 1308, 1165, 1123, 908, 824 cm^{-1}; ^{1}H-nmr: δ 7.94 (d, J = 5.9 Hz, 1H, H-6), 7.42 (d, J = 2.6 Hz, 1H, H-2), 6.87 (d, J = 2.6 Hz, 1H, H-3), 6.18

(d, J = 5.9 Hz, 1H, H-5), 3.60 (m, 4H, 2 x N-CH_2-), 2.06 (m, 4H, -CH_2CH_2-).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.44; H, 6.55; N, 14.97.

Compound **7b**.

This compound had mp 57-59° (from ether-hexane, colorless crystals); ir (potassium bromide): 3106, 3077, 3039, 3008, 2975, 2922, 2866, 1607, 1564, 1532, 1479, 1458, 1436, 1200, 1173, 1039, 924, 825, 797 cm^{-1}; ^{1}H-nmr: δ 7.89 (d, J = 5.6 Hz, 1H, H-5), 7.58 (d, J = 2.1 Hz, 1H, H-2), 6.76 (d, J = 5.6 HZ, 1H, H-4), 6.66 (d, J = 2.1 Hz, 1H, H-3), 3.84 (m, 4H, 2 x N-CH_2-), 1.99 (m, 4H, -CH_2CH_2-).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 69.94; H, 6.21; N, 15.04.

Compound **7c**.

This compound had mp 83-86° (from ether-hexane, colorless crystals); ir (potassium bromide): 3092, 3036, 2964, 2867, 1600, 1575, 1498, 1478, 1459, 1305, 1206, 1053, 1038, 864, 775, 748 cm^{-1}; ^{1}H-nmr: δ 7.98 (d, J = 5.9 Hz, 1H, H-6), 7.45 (d, J = 2.3 Hz, 1H, H-2), 6.88 (dd, J = 2.3, 0.9 Hz, 1H, H-3), 6.75 (dd, J = 5.9, 0.9 Hz, 1H, H-7), 3.74 (m, 4H, 2 x N-CH_2-), 2.02 (m, 4H, -CH_2CH_2-).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.27; H, 6.37; N, 14.82.

General Procedure for the Preparation of 4-Phenylthiofuro-[2,3-*b*]- **8a**, 7-Phenylthiofuro[2,3-*c*]- **8b** and 4-Phenylthiofuro-[3,2-*c*]pyridine **8c**.

A mixture of sodium phenyl sulfide (prepared from thiophenol (0.6 g, 5.45 mmoles) and sodium hydride (210 mg of 60% dispersion in mineral oil, 5.3 mmoles), compound **2** (88 mg, 0.57 mmole) and methanol (0.5 ml) in tetrahydrofuran (15 ml) was stirred and refluxed for 45 hours. After evaporation of the solvent, the residual solid mass was treated with water and ether. The ethereal layer was washed with 5% sodium hydroxide solution and dried over magnesium sulfate. The residue of the ethereal solution was chromatographed on a silica gel (20 g) column eluting with hexane-ethyl acetate to give 81 mg (62%) of **8a** from **2a**, 122 mg (94%) of **8b** from **2b** and 92 mg (71%) of **8c** from **2c**.

Compound **8a**.

This compound was a colorless oil of bp 130-140° (bath temperature)/0.1 mm Hg; ir (neat): 3147, 3118, 3059, 3016, 1579, 1529, 1477, 1462, 1382, 1338, 1246, 1138, 1036, 932, 898, 819, 749 cm^{-1}; ^{1}H-nmr: δ 8.08 (d, J = 5.3 Hz, 1H, H-6), 7.64 (d, J = 2.3 Hz, 1H, H-2), 7.52-7.39 (m, 5H, -Ph), 6.74 (d, J = 5.3 Hz, 1H, H- 5), 6.62 (d, J = 2.3 Hz, 1H, H-3).

Anal. Calcd. for $C_{13}H_9NOS$: C, 68.70; H, 3.99; N, 6.16. Found: C, 68.85; H, 4.11; N, 6.07.

Compound **8b**.

This compound had mp 49-51° (from ether-hexane, colorless crystals); ir (potassium bromide): 3139, 3112, 3087, 3054, 3022, 1592, 1566, 1442, 1281, 1266, 1169, 1129, 1034, 1023, 961, 868, 824, 744 cm^{-1}; ^{1}H-nmr: δ 8.24 (d, J = 5.3 Hz, 1H, H-5), 7.68 (d, J = 2.3 Hz, 1H, H-2), 7.64-7.32 (complex m, 6H, H-4 and -Ph), 6.77 (d, J = 2.3 Hz, 1H, H-3).

Anal. Calcd. for $C_{13}H_9NOS$: C, 68.70; H, 3.99; N, 6.16. Found: C, 68.81; H, 4.15; N, 6.11.

Compound **8c**.

This compound had bp 140-150° (bath temperature)/0.1 mm Hg (colorless oil); ir (neat): 3148, 3119, 3053, 1596, 1566, 1432, 1413, 1325, 1269, 1127, 1025, 935, 810, 778, 744 cm^{-1}; ^{1}H-nmr: δ 8.31 (d, J = 5.9 Hz, 1H, H-6), 7.63-7.25 (complex m, 5H, -Ph), 7.51 (d, J = 2.3 Hz, 1H, H-2), 7.25 (dd, J = 5.9, 0.9 Hz, 1H, H-7), 6.39 (dd, J = 2.3, 0.9 Hz, 1H, H-3).

Anal. Calcd. for $C_{13}H_9NOS$: C, 68.70; H, 3.99; N, 6.16. Found: C, 68.75; H, 4.16; N, 6.05.

4-(1-Cyano-1-ethoxycarbonyl)methylenefuro[3,2-*c*]pyridine **9**.

To a suspension of sodium hydride (555 mg, 60% in mineral oil, 13.8 mmoles, washed with hexane) in *N,N*-dimethylformamide (1 ml) was added ethyl cyanoacetate (1.48 g, 13.2 mmoles) with stirring. After being stirred for 30 minutes at room temperature, to this mixture was added a solution of **2c** (200 mg, 1.3 mmoles) in *N,N*-dimethylformamide (2.5 ml), and the mixture was stirred at 120° for 25 hours. After being cooled, the reaction mixture was diluted with water, acidified with hydrochloric acid and extracted with ethyl acetate. The organic extract was washed with brine, dried over magnesium sulfate and evaporated to yield 185 mg of yellow solid mass. The residue was recrystallized from acetone-ether to give 135 mg (46%) of **9**, mp 175-177°; ir (potassium bromide): 3200-2750 (broad), 3126, 3003, 2961, 2201, 1638, 1601, 1542, 1423, 1353, 1297, 1239, 1184, 1098, 1031, 923, 870, 772 cm^{-1}; ^{1}H-nmr: δ 7.70 (dd, J = 2.0, 0.8 Hz, 1H, H-3), 7.55 (d, J = 2.0 Hz, 1H, H-2), 7.42 (d, J = 6.6 Hz, 1H, H-6), 6.96 (dd, J = 6.6, 0.8 Hz, 1H, H-4), 4.23 (q, J = 6.0 Hz, 2H, -O$CH_2$$CH_3$), 1.32 (t, J = 6.0 Hz, 3H, -O$CH_2$$CH_3$).

Anal. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found: C, 62.85; H, 4.47; N, 12.15.

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[9] The reaction of 7-chlorofuro[3,2-*b*]pyridine [2] with sodium phenyl sulfide under the same condition yielded 7-phenylthio derivative in 56% yield as colorless crystals of mp 110-111° (from ether-hexane); ir (potassium bromide): 3136, 3096, 3064, 3021, 1590, 1551, 1439, 1379, 1352, 1172, 1127, 1020, 827, 812, 799, 756, 748 cm^{-1}; ^{1}H-nmr: δ 8.29 (d, J = 5.0 Hz, 1H, H-5), 7.83 (d, J = 2.1 Hz, 1H, H-2), 7.62-7.37 (complex m, 5H, -Ph), 6.97 (d, J = 2.1 Hz, 1H, H-3), 6.63 (d, J = 5.0 Hz, 1H, H-6).

Anal. Calcd. for $C_{13}H_9NOS$: C, 68.70; H, 3.99; N, 6.16. Found: C, 68.63; H, 4.21; N, 6.01.