Furopyridines. XXVIII [1]. Reactions of 3-Bromo Derivatives of Furo[2,3-*b*]-, -[3,2-*b*]-, -[2,3-*c*]- and -[3,2-*c*]pyridine and their *N*-Oxides

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Bromination of 3-bromofuro[2,3-*b*]- **1a**, -[3,2-*b*]- **1b** and - [3,2-*c*]pyridine **1d** afforded the 2,3-dibromo derivatives **2a, 2b** and **2d,** while the -[2,3-*c*]- compound **1c** did not give the dibromo derivative. Nitration of **1a-d** gave the 2-nitro-3-bromo compounds **3a-d**. The *N*-oxides **4a-d** of **1a-d** were submitted to the cyanation with trimethylsilyl cyanide to yield the corresponding α-cyanopyridine compound **6a-d**. Chlorination of **4a** and **4d** with phosphorus oxychloride gave mainly the chloropyridine derivatives **7a, 7'a** and **7d**, while **4b** and **4c** gave mainly the chlorofuran derivatives **7"b** and **7"c** accompanying formation of the chloropyridine derivatives **7b**, **7'b** and **7c**. Acetoxylation of **4a** and **4b** with acetic anhydride yielded the acetoxypyridine compounds **8a, 8'a** and **8b**, while **4c** and **4d** gave the acetoxypyridine **8'c, 8'd** and **8"d**, pyridone **8c** and **8d**, acetoxyfuran **8"c** and dibromo compound **9c** and **9'c**.

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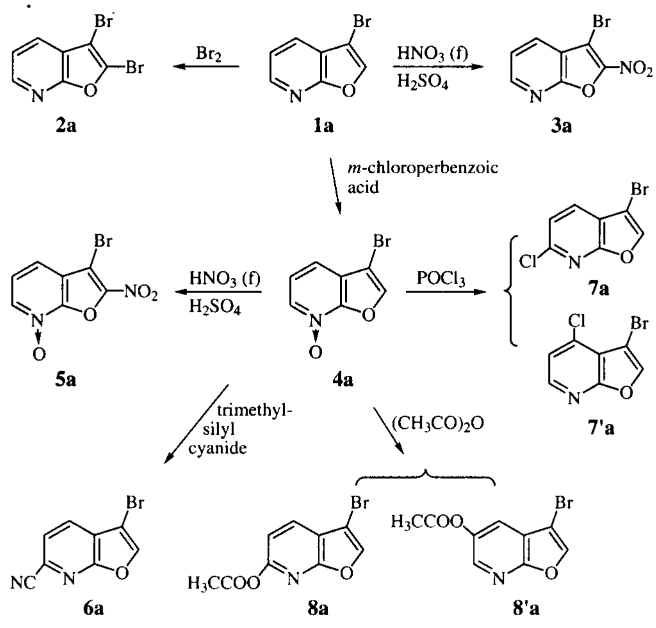
In our continuing studies on the syntheses and reactivity of furopyridines, we recently reported the reactions of 2-methyl, 2-cyano [1] and cyanopyridine derivativees of furo[2,3-*b*]-, -[3,2-*b*]- , -[2,3-*c*]- and -[3,2-*c*]pyridine and their *N*-oxides [2] to see the effects of a functional group at the furan or pyridine ring upon the reactivity of the mono-substitued furopyridines for introduction of the second function. In order to extend the chemistry of furopyridines, we describe in this paper the bromination, nitration of 3-bromofuro[2,3-*b*]- (**1a**), -[3,2-*b*]- (**1b**), -[2,3-*c*]- (**1c**) and -[3,2-*c*]pyridine (**1d**) [3], and cyanation, chlorination and acetoxylation of their *N*-oxides **5a-5d**.

Bromination of compounds **1a, 1b** and **1d** with molecular bromine in carbon tetrachloride afforded 2,3-dibromo derivatives **2a** (96%), **2b** (85%) and **2d** (34%) respectively, while the bromination of **1c** did not give the dibromo compound but recovered the starting compound. The structures of **2a, 2b** and **2d** were determined by the pmr spectrum of each compound, in which the signal of the proton at the 2-position observed in that of **1a, 1b** and **1d** disappeared. The inreactivity of **1c** would be caused by the efficient electron withdrawing effect of the ring nitrogen through the C_{3a}-C3 bond [4] and the electron withdrawing inductive effect of the bromine atom at 3-position. Nitration of **1a-d** with a mixture of fuming nitric acid and sulfuric acid yielded the corresponding 2-nitro compounds **3a-d** (**3a**: 24%, **3b**: 84%, **3c**: 28%, **3d**: 11%), and the structures of these compounds were again determined by their pmr spectra in which no furan proton was observed. *N*-Oxidation of **1a-d** with *m*-chloroperbenzoic acid in dichloromethane gave the *N*-oxide **4a** (38%), **4b** (72%), **4c** (88%) and **4d** (73%) accompanying recovery of the starting compound respectively.

Nitration of **4a-d** gave the 2-nitro-3-bromofuropyridine *N*-oxides **5a-d** in low yields respectively. In the case of **4b**, formation of the deoxygenated compound **3b** was

Scheme 1



accompanyed. The position of the nitro group in each compound was determined again by the pmr spectrum.

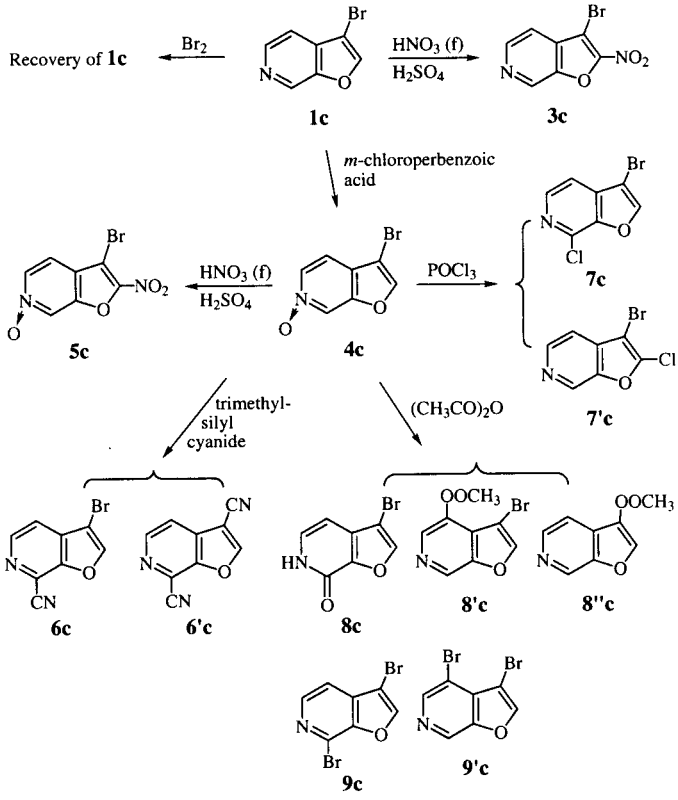
Cyanation of *N*-oxides **4a-d** with trimethylsilyl cyanide afforded the corresponding α-cyanopyridine derivative of furopyridine **6a** (74%), **6b** (84%), **6c** (96%) and **6d** (97%). The position of the cyano group in each compound was determined from the pmr spectrum. Compound **6a** showed two doublets of the pyrdine protons at δ 8.07 and 7.75 (J = 7.9 Hz) and a singlet of the 2-proton at δ 7.98, **6b** exhibited two doublet of the pyridine protons at δ 7.96 and 7.75 (J = 8.5 Hz) and a singlet of the furan proton at δ 8.08, **6c** exhibited two doublets of the pyridine protons at δ 8.65 and 7.78 (J = 5.0 Hz) and a signal of the furan proton as a singlet at δ 7.95, and **6d** showed two doublets of the pyridine protons at

δ 8.68 and 7.70 (J = 5.8 Hz) and a singlet of the furan proton at δ 7.87.

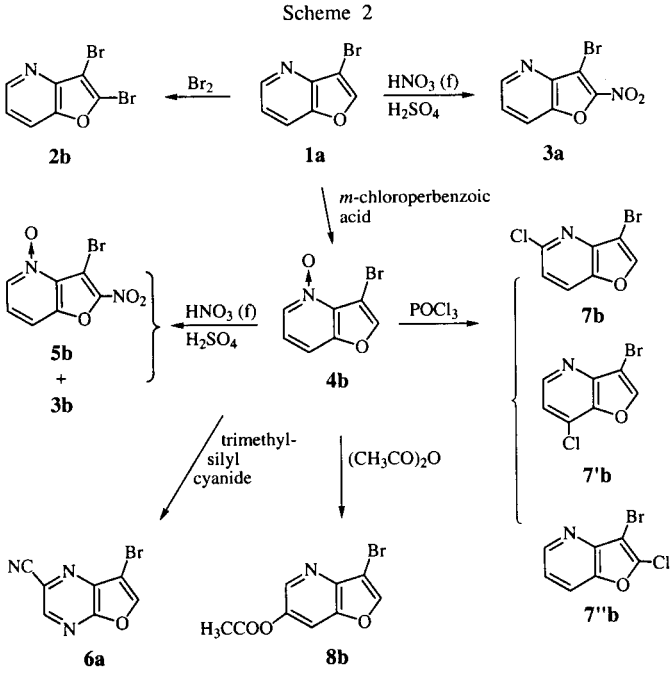
Chlorination of **1a-d** with phosphorus oxychloride yielded somewhat complex results. Compound **4a** gave the 3-bromo-6-chloro **7a** (23%) and the 3-bromo-4-chloro compound **7'a** (38%), **4b** gave the 3-bromo-5-chloro **7b** (11%), the 3-bromo-7-chloro **7'b** (20%) and the 3-bromo-2-chloro compound **7"b** (36%), **4c** gave the 3-bromo-7-chloro **7c** (6%) and the 3-bromo-2-chloro compound **7'c** (36%), and **4d** gave the 3-bromo-4-chloro compound **7d**(92%). In the pmr spectrum, **7a** showed two doublets of the pyridine protons at δ 7.87 and 7.37 (J = 8.2 Hz) and a singlet of the furan proton at δ 7.75, **7'a** showed two doublets of the pyridine protons at δ 8.25 and 7.28 (J = 5.3 Hz) and a singlet of the furan proton at δ 7.77. Compounds **7b** and **7'b** exhibited two doublets of the pyridine protons at δ 7.69 and 7.25 (J = 8.6 Hz) and at δ 8.55 and 7.36 (J = 5.2 Hz) and a singlet of the furan proton at δ 7.85 and at δ 7.97 respectively; compound **7"b** exhibited signals of the three pyridine protons at δ 8.54 (dd, J = 1.2, 5.0 Hz), 7.66 (dd, J = 1.2, 8.5 Hz) and 7.22 (dd, J = 5.0, 8.5 Hz). From these spectral data, the positions of the chlorine atom in these compounds were determined.

Acetoxylation of the *N*-oxides **4a-d** by refluxing with acetic anhydride also yielded complex results: compound **4a** gave the 6-acetoxy-3-bromo **8a** (33%) and the 5-acetoxy-3-bromo derivative **8'a** (18%), **4b** gave the 6-acetoxy-3-bromo compound **8b** (33%), **4c** gave the 3-bromofuro[2,3-*c*]pyridin-7(6*H*)-one **8c** (10%), the 4-acetoxy-3-bromo **8'c** (3%), the 3-acetoxy **8"c** (6%), the 3,7-dibromo **9c** (3%) and the 3,4-dibromo derivative **9'c** (2%), and **4d** gave 3-bromofuro[3,2-*c*]pyridin-4(5H)-one **8d** (73%), the 6-acetoxy-3-bromo **8'd** (3%) and the 7-acetoxy-3-bromo derivative **8"d** (3%).

Scheme 3

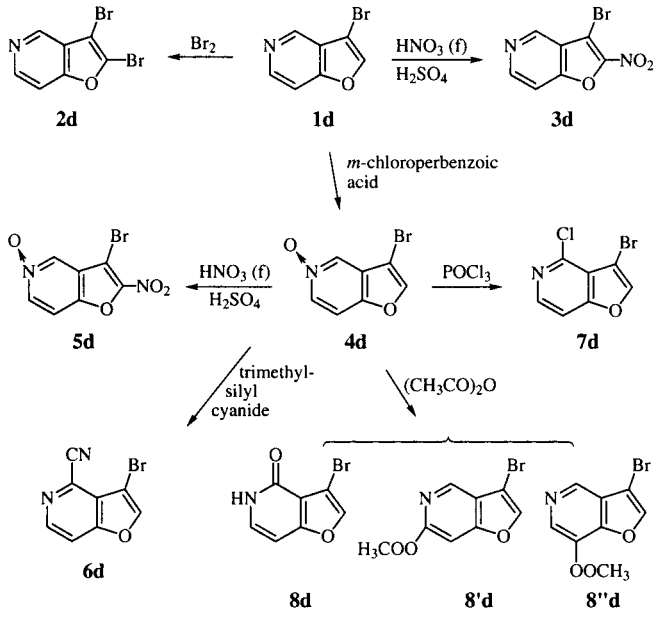


Scheme 2



The elemental analyses of compounds **8a, 8'a, 8b, 8'c, 8'd** and **8"d** indicated the molecular formula of each compound to be $C_9H_6NO_3Br$. The pmr spectra of these compounds exhibited a singlet for the methyl protons of an acetyl group at δ 2.37 (**8a**), 2.37 (**8'a**), 2.37 (**8b**), 2.44 (**8'c**), 2.38 (**8'd**) and 2.43 (**8"d**), respectively. Compound **8a** showed two doublets of the pyridine protons at δ 7.98 and 7.11 (J = 8.2 Hz) and a singlet of the furan proton at δ 7.45. Compound **8'a** showed two doublets of the pyridine protons at δ 8.16 and 7.71 (J = 2.6 Hz; the small coupling constant corresponds to the *meta* coupling between H-6 and H-4) and a singlet of thre furan proton at δ 7.79. Compound **8b** exhibited two doublets of the pyridine protons at δ 8.46 and 7.68 (J = 2.0 Hz, the small coupling constant corresponds to the *meta* coupling between H-5 and H-7) and a singlet of the furan proton at δ 7.92. Compound **8'c** exhibited two singlets of the pyridine protons at δ 8.23 and 8.28 and a singlet of the furan proton at δ 7.74. Compound **8'd** showed two singlets of the pyridine proton at δ 8.62 and 7.23 and a singlet of the furan proton at δ 7.68. Compound **8"d** showed two singlets of the pyridine protons at δ 8.77 and 8.40 and a singlet of the furan proton

Scheme 4



at δ 7.68. These pmr spectral data confirmed the position of the acetoxy group in each compound.

The elemental analysis of compound **8c** and **8d** indicated both the compounds to have the molecular formula $C_7H_4NO_2Br$. The ir spectra showed an absorption of the carbonyl group at 1657 and 1665 cm^{-1}, respectively, suggesting the presence of an amide group. The pmr spectrum of **8c** showed two doublet of the pyridine protons at δ 7.29 and 6.54 (J = 6.5 Hz) and a singlet of the furan proton at δ 7.81; **8d** two doublets of the pyridine protons at δ 7.32 and 6.59 (J = 7.3 Hz) and a singlet of the furan proton at δ 7.52. Compound **8"c** was identified as 3-acetoxyf uro [2, 3-*c*] pyridine [5] by comparion of the ir and pmr spectra. The elemental analysis of **9c** and **9'c** indicated the molecular formula of these compounds to be $C_7H_3NOBr_2$. The pmr spectrum of **9c** exhibited two doublets of the pyridine protons at δ 8.30 and 7.49 (J = 5.3 Hz) and a singlet of the furan proton at δ 7.85; **9'c** showed two singlets of the pyridine protons at δ 8.83 and 8.55 and a singlet of the furan proton at δ 7.83.

Formation of compounds having the second substituent at the pyridine carbons **6a**, **6b**, **6c**, **6d**, **7a**, **7'a**, **7b**, **7'b**, **7"b, 7c, 7'c, 7d**, **8a, 8'a, 8b, 8'c, 8'd** and **8"d**, and furopyridones **8c** and **8d** is interpreted by the well known mechanism for cyanation, chlorination and acetoxylation of the *N*-oxides of pyridine, quinoline and isoquinoline [6], and formation of compounds substituted at the furan ring **7"b, 7'c** would be understood by the mechanism postulated for the formation of the furan-chlorinated products from furo [3,2-*b*] pyridine *N*-oxide [7] 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 [5]. 3-Acetoxy **8"c**, 3,7-dibromo- 9**c** and 3,4-dibromofuro[2,3-*c*] pyridine **9'c** would be formed through the Meisenheimer-type substitution of 3-bromo derivative with acetate ion, 3-bromo-7-acetoxy and 3-bromo-4-acetoxy derivative with bromide ion.

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 pmr spectra were taken on 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 Silisia Chemical Ltd).

General Procedure for the Bromination of 3-Bromofuro[2,3-*b*]- **1a,** -[3,2-*b*]- **1b,** -[2,3-*c*] **1c** and -[3,2-*c*]pyridine **1d**.

To a solution of **1** (100 mg, 0.51 mmole) in carbon tetrachloride (3 ml) was added a solution of bromine (400 mg, 2.5 mmoles) in carbon tetrachloride (1 ml) at -15° with stirring. After being stirred at room temperature for 22 hours, the mixture was evaporated under reduced pressure to leave a light brown semi-solid. The residue was treated with water, basified with sodium bicarbonate and extracted with chlororform. The chloroform solution was dried (magnesium sulfate) and evaporated. The further processing of the residue is indicated in a subsequent paragraph. In the case of **1c,** the residue (99 mg) of the chloroform solution was found to be complete recovery of the starting **1c**.

2,3-Dibromofuro[2,3-*b*]pyridine **2a**.

The residue (170 mg) from **1a** was recrystallized from ether-hexane to give colorless crystals (135 mg, 96%) of mp 85-87°; ir (potassium bromide): 3063, 2926, 1600, 1590, 1536, 1394, 1321, 1245, 1211, 1133, 1100, 993, 885, 797, 767 cm^{-1}; pmr: δ 8.33 (dd, J = 1.5, 4.7 Hz, 1H, H-6), 7.82 (dd, J = 1.5, 7.6 Hz, 1H, H-4), 7.31 (dd, J = 4.7, 7.6 Hz, 1H, H-5).

Anal. Calcd. for $C_7H_3NOBr_2$: C, 30.36; H, 1.09; N, 5.06. Found: C, 30.26; H, 1.09; N, 4.99.

2,3-Dibromofuro[3,2-*b*]pyridine **2b**.

The residue (180 mg) from **1b** was chromatographed on a silica gel (30 g) column eluting with chloroform to give 10 mg (10%) of the starting **1b** and 120 mg (85%) of **2b** as colorless crystals of mp 63-65°; ir (potassium bromide): 3092, 3043, 1604, 1574, 1561, 1543, 1403, 1337, 1278, 1254, 1205, 1124, 1099, 1011, 998, 807, 785, 765 cm^{-1}; pmr: δ 8.58 (dd, J = 1.2, 4.7 Hz, 1H, H-5), 7.73 (dd, J = 1.2, 8.5 Hz, 1H, H-7), 7.26 (dd, J = 4.7, 8.5 Hz, 1H, H-6).

Anal. Calcd. for $C_7H_3NOBr_2$: C, 30.36; H, 1.09; N, 5.06. Found: C, 30.48; H, 1.20; N, 4.73.

2,3-Dibromofuro[3,2-*c*]pyridine **2d**.

The residue (150 mg) from **1d** was chromatographed on a silica gel (30 g) column to give 9 mg (9%) of the starting **1d** and 48 mg (34%) of **2d** as colorless crystals of mp 110-113°; ir (potassium bromide): 3065, 1605, 1579, 1538, 1449, 1436, 1317, 1271, 1227, 1097, 1026, 1001, 880, 810 cm^{-1}; pmr: δ 8.81 (s, 1H, H-4), 8.56 (d, J = 5.9 Hz, 1H, H-6), 7.40 (d, J = 5.9 Hz, 1H, H-7).

Anal. Calcd. for $C_7H_3NOBr_2$: C, 30.36; H, 1.09; N, 5.06. Found: C, 30.34; H, 1.09; N, 5.04.

General Procedure for the Nitration of 3-Bromofuro[2,3-*b*]- **1a,** -[3,2-*b*]- **1b**, -[2,3-*c*]- **1c** and -[3,2-*c*]pyridine **1d**.

To a mixture of **1** (50 mg, 0.25 mmoles) in sulfuric acid (1 ml) was added a mixture of fuming nitric acid (d. 1.50, 0.5 ml) and sulfuric acid (0.1 ml) with stirring at 0-5°. After being stirred at room temperature for 10 minutes, the mixture was treated with ice-water, basified with sodium bicarbonate and extracted with chloroform. The chloroform extract was dried over magnesium sulfate and evaporated to leave a yellow-brown solid. The solid residue was recrystallized from ether to give pure sample of 2-nitro-3-bromofuropyridine **3a** (15 mg, 26%), **3b** (51 mg, 84%), **3c** (17 mg, 28%) and **3d** (7 mg, 11%).

2-Nitro-3-bromofuro[2,3-*b*]pyridine **3a**.

This compound had mp 140-141.5° (yellow crystals); ir (potassium bromide): 3058, 1600, 1589, 1548, 1514, 1404, 1359, 1318, 1304, 1246, 1120, 1026, 875, 811, 774 cm^{-1}; pmr: δ 8.70 (dd, J = 1.8, 5.0 Hz, 1H, H-6), 8.16 (dd, J = 1.8, 7.9 Hz, 1H, H-4), 7.54 (dd, J = 5.0, 7.9 Hz, 1H, H-5).

Anal. Calcd. for $C_7H_3N_2O_3Br$: C, 34.60; H, 1.24; N, 11.53. Found: C, 34.77; H, 1.30; N, 11.53.

2-Nitro-3-bromofuro[3,2-*b*]pyridine **3b**.

This compound had mp 166-169° (slightly yellow crystals); ir (potassium bromide): 3067, 1597, 1556, 1515, 1406, 1360, 1289, 1219, 1182, 1037, 931, 869, 854, 805, 773, 744 cm^{-1}; pmr: δ 8.87 (dd, J = 1.2, 4.7 Hz, 1H, H-5), 8.01 (dd, J = 1.2, 8.5 Hz, 1H, H-7), 7.64 (dd, J = 4.7, 8.5 Hz, 1H, H-6).

Anal. Calcd. for $C_7H_3N_2O_3Br$: C, 34.60; H, 1.24; N, 11.53. Found: C, 34.73; H, 1.31; N, 11.47.

2-Nitro-3-bromofuro[2,3-*c*]pyridine **3c**.

This compound had mp 94-97° (slightly yellow crystals); ir (potassium bormide): 3084, 3029, 1601, 1556, 1519, 1421, 1345, 1278, 1252, 1175, 1157, 1044, 1015, 920, 866, 843, 835, 782, 745 cm^{-1}; pmr: δ 9.11 (d, J = 0.9 Hz, 1H, H-7), 8.74 (d, J = 5.3 Hz, 1H, H-5), 7.70 (dd, J = 0.9, 5.3 Hz, 1H, H-4).

Anal. Calcd. for $C_7H_3N_2O_3Br$: C, 34.60; H, 1.24; N, 11.53. Found: C, 34.73; H, 1.29; N, 11.32.

2-Nitro-3-bromofuro[3,2-*c*]pyridine **3d**.

This compound had mp 93-95° (slightly yellow crystals); ir (potassium bromide): 3067, 1609, 1549, 1509, 1358, 1322, 1281, 1253, 1194, 1159, 1031, 873, 822 cm^{-1}; pmr: δ 9.11 (s, 1H, H-4), 8.85 (d, J = 5.9 Hz, 1H, H-6), 7.59 (d, J = 5.9 Hz, 1H, H-7).

Anal. Calcd. for $C_7H_3N_2O_3Br$: C, 34.60; H, 1.24; N, 11.53. Found: C, 34.79; H, 1.45; N, 11.15.

General Procedure for the *N*-Oxidation of 3-Bromofuro[2,3-*b*]- **1a,** -[3,2-*b*]- **1b**, -[2,3-*c*]- **1c** and -[3,2-*c*] pyridine **1d**.

A mixture of **1** (600 mg, 3 mmoles) and *m*-chloroperbenzoic acid (1.12 g, purity 70%, 4.5 mmoles) in dichloromethane (20 ml) was stirred at room temperature for 43 hours for **1a,** 47 hours for **1b**, 41 hours for **1c** and 24 hours for **1d**. The mixture was filtered slowly through a sintered glass filter with an alumina (70 g) pad, and the filtrate was evaporated. The residual crystalline mass was recrystallized from ether-acetone to give the pure sample of each *N*-oxide (yield; **4a**: 38%, **4b**: 72%, **4c**: 88%, **4d**: 73%).

Compound **4a** had mp 168-171° (colorless crystals); ir (potassium bromide) : 3097, 3048, 1600, 1531, 1462, 1447, 1326, 1243, 1211, 1100, 1046, 923, 855, 793 cm^{-1}; pmr: δ 8.31 (d, J = 6.0 Hz, 1H, H-6), 7.82 (s, 1H, H-2), 7.53 (d, J = 8.0 Hz, 1H, H-4), 7.28 (dd, J = 6.0, 8.0 Hz, 1H, H-5).

Anal. Calcd. for $C_7H_4NO_2Br$: C, 39.28; H, 1.88; N, 6.54. Found: C, 39.35; H, 1.98; N, 6.56.

Compound **4b** had mp 183-186° (colorless crystals); ir (potassium bromide): 3108, 3078, 3055, 3026, 1613, 1568, 1528, 1458, 1429, 1356, 1302, 1256, 1212, 1156, 1099, 1064, 1040, 1000, 837, 783, 725, 702 cm^{-1}; pmr: δ 8.19 (d, J = 6.5 Hz, 1H, H-5), 7.73 (s, 1H, H-2), 7.44 (d, J = 8.5 Hz, 1H, H-7), 7.19 (dd, J = 6.5, 8.5 Hz, 1H, H-6).

Anal. Calcd. for $C_7H_4NO_2Br$: C, 39.28; H, 1.88; N, 6.54. Found: C, 39.28; H, 1.86; N, 6.25.

Compound **4c** had mp 190-193° (colorless crystals); ir (potassium bromide): 3103, 3040, 1623, 1533, 1479, 1461, 1441, 1303, 1259, 1204, 1152, 1125, 1059, 1000, 957, 834, 813 cm^{-1}; pmr: 6 8.60 (d, J = 1.2 Hz, 1H, H-7), 8.22 (dd, J = 1.2, 6.7 Hz, 1H, H-5), 7.82 (s, 1H, H-2), 7.42 (d, J = 6.7 Hz, 1H, H-4).

Anal. Calcd. for $C_7H_4NO_2Br$: C, 39.28; H, 1.88; N, 6.54. Found: C, 39.24; H, 1.95; N, 6.45.

Compound **4d** had mp 180-183° (colorless crystals); ir (potassium bromide): 3151, 3090, 3028, 1588, 1533, 1442, 1322, 1264, 1193, 1161, 1124, 1084, 1065, 1006, 931, 866, 823, 797, 763 cm^{-1}; pmr: δ 8.52 (d, J = 1.8 Hz, 1H, H-4), 8.24 (dd, J = 1.8, 7.3 Hz, 1H, H- 6), 7.79 (s, 1H, H-2), 7.43 (d, J = 7.3 Hz, 1H, H-7).

Anal. Calcd. for $C_7H_4NO_2Br$: C, 39.28; H, 1.88; N, 6.54. Found: C, 39.38; H, 1.90; N, 6.33.

General Procedure for the Nitration of *N*-Oxides **4a-d**.

To a mixture of **4** (54 mg, 0.25 mmoles) in sulfuric acid (0.5 ml) was added a mixture of fuming nitric acid (d. 1.50, 0.5 ml) and sulfuric acid (0.1 ml) at 0-5°. After being stirred for 20 minutes at room temperature, the reaction mixture was diluted with ice water, basified with sodium bicarbonate, and extracted with chloroform. The chloroform solution was dried (magnesium sulfate) and evaporated. The crystalline residues from **4a**, **4c** and **4d** were recrystallized from ether-acetone to give the pure sample of **5a** (10 mg, 19%), **5c** (16 mg, 25%) and **5d** (21 mg, 18%). The residue from **4b** was chromatographed on an alumina (1 g) column to afford 30 mg (51%) of **5b** and 3 mg (5%) of **3b**.

Compound **5a** had mp 213-215° (yellow crystals); ir (potassium bromide): 3107, 3066, 3025, 1561, 1518, 1456, 1377, 1364, 1318, 1263, 1214, 1002, 876, 854, 802, 721 cm^{-1}; pmr: δ 8. 5 2 (dd, J = 1.2, 6.2 Hz, 1H, H-6), 7.67 (dd, J = 1.2, 8.2 Hz, 1H, H-4), 7.45 (dd, J = 6.2, 8.2 Hz, 1H, H-5).

Anal. Calcd. for $C_7H_3N_2O_4Br$: C, 32.46; H, 1.17; N, 10.82. Found: C, 32.49; H, 1.19; N, 10.66.

Compound **5b** had mp 231-234° (yellow crystals); ir (potassium bromide): 3112, 3086, 1608, 1546, 1508, 1456, 1429, 1356, 1283, 1255, 1164, 1073, 1034, 911, 804, 732 cm^{-1}; pmr: δ 8.44 (dd, J = 0.7, 5.6 Hz, 1H, H-5), 7.91 (dd, J = 0.7, 8.8 Hz, 1H, H-7), 7.69 (dd, J = 5.6, 8.8 Hz, 1H, H-6).

Anal. Calcd. for $C_7H_3N_2O_4Br$: C, 32.46; H, 1.17; N, 10.82. Found: C, 32.49; H, 1.19; N, 10.66.

Compound **5c** had mp 158-161° (yellow crystals); ir (potassium bromide): 3114, 3029, 1635, 1557, 1515, 1476, 1443, 1361, 1294, 1255, 1176, 1128, 1036, 970, 910, 852, 807 cm^{-1}; pmr: δ 8.66 (d, J = 1.5 Hz, 1H, H-7), 8.28 (dd, J = 1.5, 7.0 Hz, 1H, H-5), 7.62 (d, J = 7.0 Hz, 1H, H-4)

Anal. Calcd. for $C_7H_3N_2O_4Br$: C, 32.46; H, 1.17; N, 10.82. Found: C, 32.50; H, 1.27; N, 10.48.

Compound **5d** had mp 146-149° (yellow crystals); ir (potassium bromide): 3113, 3033, 3013, 1556, 1524, 1439, 1352, 1249, 1233, 1200, 1181, 1025, 867, 825, 774 cm^{-1}; pmr: δ 8.64 (d, J = 1.8, Hz, 1H, H-4), 8.40 (dd, J = 1.8, 6.7 Hz, H-6), 7.58 (d, J = 6.7 Hz, 1H, H-7).

Anal. Calcd. for $C_7H_3N_2O_4Br$: C, 32.46; H, 1.17; N, 10.82. Found: C, 32.59; H, 1.17; N, 10.69.

General Procedure for the Cyanation of 3-Bromofuro[2,3-*b*]- **4a**, -[3,2-*b*]- **4b**, -[2,3-*c*]- **4c** and -[3,2-*c*] pyridine *N*-Oxide **4d**.

To a solution of **4** (50 mg, 0.23 mmole) in acetonitrile (4 ml) was added triethylamine (0.05 ml, 0.35 mmole) and trimethylsilyl cyanide (0.08 ml, 0.58 mmole) by syringe under nitrogen atmosphere with stirring at room temperature. Then, the mixture was refluxed and stirred for 45 hours for **4a**, 24 hours for **4b**, 2 hours for **4c** and 1.5 hours for **4d**. After being cooled, the reaction mixture was evaporated and treated with water and chloroform. The chloroform layer was dried (magnesium sulfate) and evaporated. The crystalline residues from **4a** and **4b** were recrystallized from ether-acetone to give pure **6a** (28 mg, 74%) and **6b** (43 mg, 84%), those from **4c** and **4d** were recystallinezed from ether to give **6c** (52 mg, 96%) and **6d** (54 mg, 97%).

Compound **6d** was identified as 3-bromo-4-cyanofuro[3,2-*c*] pyridine by mixed melting point test and comparison of the ir and pmr spectra with the those of the sample prepared from 4-cyanofuro[3,2-*c*]pyridine in our laboratory [2].

3-Bromo-6-cyanofuro[2,3-*b*]pyridine **6a**.

This compound had mp 203-205° (colorless crystals); ir (potassium bromide) : 3139, 3123, 3084, 3066, 2238 , 1636 , 1599 , 1583, 1530, 1393, 1347, 1278, 1218, 1152, 1139, 1130, 986, 938, 856, 820, 776 cm^{-1}; pmr: δ 8.07 (d, J = 7.9 Hz, 1H, H-4), 7.98 (s, 1H, H-2), 7.75 (d, J = 7.9 Hz, 1H, H-5).

Anal. Calcd. for $C_8H_3N_2OBr$: C, 43.08; H, 1.36; N, 12.56. Found: C, 43.16; H, 1.41; N, 12.49.

3-Bromo-5-cyanofuro[3,2-*b*]pyridine **6b**.

This compound had mp 182-184° (colorless crystals); ir (potassium bromide): 3131, 3086, 3072, 3056, 2238, 1603, 1538, 1441, 1321, 1303, 1278, 1209, 1157, 1140, 1114, 1072, 903, 831, 793 cm^{-1}; pmr: δ 8.08 (s, 1H, H-2), 7.96 (d, J = 8.5 Hz, 1H, H-7), 7.75 (d, J = 8.5 Hz, 1H, H-6).

Anal. Calcd. for $C_8H_3N_2OBr$: C, 43.08; H, 1.36; N, 12.56. Found: C, 43.04; H, 1.50; N, 12.68.

3-Bromo-7-cyanofuro[2,3-*c*]pyridine **6c**.

This compound had mp 177-179° (colorless crystals); ir (potassium bromide); 3150, 3055, 3010, 2990, 2242, 1605, 1535, 1422, 1333, 1266, 1242, 1174, 1098, 1058, 910, 863, 828 cm^{-1}; pmr: δ 8.65 (d, J = 5.0 Hz, 1H, H-5), 7.95 (s, 1H, H-2), 7.78 (d, J = 5.0 Hz, 1H, H-4).

Anal. Calcd. for $C_8H_3N_2OBr$: C, 43.08; H, 1.36; N, 12.56. Found: C, 43.24; H, 1.48; N, 12.45.

General Procedure for the Chlorination of 3-Bromofuro[2,3-*b*]- **4a**, -[3,2-*b*]- **4b**, -[2,3-*c*]- **4c** and -[3,2-*c*] pyridine *N*-Oxide **4d**.

A mixture of 4 (100 mg, 0.47 mmoles) and phosphorus oxychloride (1 ml) in chloroform (1 ml) was refluxed for 1 hour for compound **4a** and **4d**, and 4 hours for **4b** and **4c**. 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.

6-Chloro- **7a** and 4-Chloro-3-bromofuro[2,3-*b*]pyridine **7'a**.

The residue from **4a** was chromatographed on a silica gel (7 g) column. The first fraction eluted with hexane-chloroform (6:4) yielded 25 mg (23%) of **7a**, and the second 41 mg (38%) of **7'a**.

Compound **7a**.

This compound had mp 83-85° (from hexane-ether, colorless crystals); ir (potassium bromide): 3149, 3089, 3074, 1595, 1579, 1568, 1537, 1435, 1422, 1392, 1329, 1270, 1117, 1085, 984, 903, 823, 791, 766 cm^{-1}; pmr: δ 7.87 (d, J = 8.2 Hz, 1H, H-4), 7.75 (s, 1H, H-2), 7.37 (d, J = 8.2 Hz, 1H, H-5).

Anal. Calcd. for $C_7H_3NOBrCl$: C, 36.17; H, 1.30; N, 6.03. Found: C, 36.21; H, 1.35; N, 5.97.

Compound **7'a**.

This compound had mp 81.5-83° (from hexane-ether, colorless crystals); ir (potassium bromide): 3111, 3013, 1591, 2575, 1566, 1365, 1350, 1315, 1.246, 1166, 1109, 1074, 982, 937, 822 cm^{-1}; pmr: δ 8.25 (d, J = 5.3 Hz, 1H, H-6), 7.77 (s, 1H, H-2), 7.18 (d, J = 5.3 Hz, 1H, H-5).

Anal. Calcd. for $C_7H_3NOBrCl$: C, 36.17; H, 1.30; N, 6.03. Found: C, 35.96; H, 1.26; N, 5.90.

5-Chloro- **7b**, 7-Chloro- **7'b** and 2-Chloro-3-bromofuro[3,2-*b*]-pyridine **7''b**.

The residue from **4b** was chromatographed on a silica gel (10 g) column. The first fraction eluted with hexane-ethyl acetate (9:1) yielded 50 mg of a mixture of **7b** and **7'b**, the second 39 mg (36%) of **7''b**. The mixture of **7b** and **7'b** was chromatographed on a silica gel (6 g) column eluting with hexane-chloroform (6:4) to give 12 mg (11%) of **7b** and 22 mg (20%) of **7'b**.

Compound **7b**.

This compopund had mp 73-76° (from hexane-ether, colorless crystals); ir (potassium bromide): 3150, 3088, 3058, 1601, 1566, 1412, 1399, 1306, 1278, 1182, 1169, 1126, 1088, 1011, 885, 828, 813, 776, 702 cm^{-1}; pmr: δ 7.85 (s, 1H, H-2), 7.69 (d, J = 8.5 Hz, 1H, H-7), 7.25 (d, J = 8.6 Hz, 1H, H-6).

Anal. Calcd. for $C_7H_3NOBrCl$: C, 36.17; H, 1.30; N, 6.03. Found: C, 36.05; H, 1.28; N, 5.97.

Compound **7'b**.

This compound had mp 95-98° (from hexane-ether, colorless crystals); ir (potassium bromide): 3154, 3056, 3011, 1603, 1558, 1543, 1382, 1342, 1301, 1244, 1153, 1091, 1072, 1041, 880, 840, 808 cm^{-1}; pmr: δ 8.55 (J = 5.2 Hz, 1H, H-5), 7.97 (s, 1H, H-2), 7.36 (d, J = 5.2 Hz, 1H, H-6).

Anal. Calcd. for $C_7H_3NOBrCl$: C, 36.17; H, 1.30; N, 6.03. Found: C, 36.14; H, 1.27; N, 5.93.

Compound **7''b**.

This compound had mp 102-104.5° (hexane ether, colorless crystals); ir (potassium bromide): 3071, 3028, 1601, 1579, 1545, 1469, 1424, 1268, 1182, 1174, 1134, 1034, 1007, 903, 817 cm^{-1}; pmr: δ 8.54 (dd, J = 1.2, 5.0 Hz, 1H, H-5), 7.65 (dd, J = 1.2, 8.5 Hz, 1H, H-7), 7.22 (dd, J = 5.0, 8.5 Hz, 1H, H-6).

Anal. Calcd. for $C_7H_3NOBrCl$: C, 35.80; H, 1.57; N, 6.03. Found: C, 36.17; H, 1.30; N, 6.03.

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

The residue from **4c** was recrystallized from hexane-ether to give **7'c** (32 mg). The residue of the mother liquor was chromatographed on a silica gel (10 g) column eluting with chloroform to give **7c** (5.5 mg, 6%) and **7'c** (7 mg), the total yield of **7'c** was 39 mg, 36%).

Compound **7c**.

This Compound had mp 100-102° (from hexane-ether, colorless crystals); ir (potassium bromide): 3070, 3025, 1601, 1541, 1459, 1412, 1324, 1258, 1204, 1155, 1088, 882, 824, 748 cm^{-1}; pmr: δ 8.31 (d, J = 5.9 Hz, 1H, H-5), 7.72 (s, 1H, H-2), 7.33 (d, J = 5.9 Hz); ms: m/z (relative intensity) 235 (M^++4, 24), 233 (M^++2, 100), 231 (M^+, 76), 198 (15), 186 (17), 126 (13), 124 (46); hrms: 230.9026. M^+, Calcd. for $C_7H_3NOBrCl$: 230.9086.

Anal. Calcd. for $C_7H_3NOBrCl$: C, 36.17; H, 1.30; N, 6.03. Found: C, 36.06; H, 1.54; N, 5.88.

Compound **7'c**.

This compound had mp 92-95° (hexane-ether, colorless crystals); ir (potassium bromide): 3072, 3028, 1601, 1545, 1469, 1268, 1175, 1134, 1034, 1007, (03, 817 cm^{-1}; pmr: δ 8.82 (s, 1H, H-7), 8.53 (d, J = 5.3 Hz, 1H, H-5), 7.44 (d, J = 5.3 Hz, 1H, H-4).

Anal. Calcd. for $C_7H_3NOBrCl$: C, 36.17; H, 1.30; N, 6.03. Found: C, 36.02; H, 1.33; N, 5.82.

4-Chloro-3-bromofuro[3,2-*c*]pyridine **7d**.

The residue from **4d** was recrystallized from acetone-ether to give 99 mg (92%) of pure **7d**, mp 139-141° (colorless crystals); ir (potassium bromide): 3123, 3044, 1599, 1568, 1552, 1535, 1430, 1306, 1286, 1262, 1175, 1.085, 1058, 984, 935, 817 cm^{-1}; pmr: δ 8.31 (d, J = 5.8 Hz, 1H, H-6), 7.73 (s, 1H, H-2), 7.44 (d, J = 5.8 Hz, 1H, H-7).

Anal. Calcd. for $C_7H_3NOBrCl$: C, 36.17; H, 1.30; N, 6.03. Found: C, 36.17; H, 1.35; N, 5.90.

General Procedure for the Acetoxylation of 3-Bromofuro[2,3-*b*]- **4a**, -[3,2-*b*]- **4b**, -[2,3-*c*]- **4c** and -[3,2-*c*]pyridine *N*-Oxide **4d**.

A mixture of **4** (304 mg, 1.4 mmoles) in acetic anhydride (2.5 ml) was refluxed for 1 hour. After being cooled, the excess acetic anhydride was evaporated under reduced pressure. The syrupy residue was treated with water, 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.

6-Acetoxy- **8a** and 5-Acetoxy-3-bromofuro[2,3-*b*]pyridine **8'a**.

The residue from **4a** was chromatographed on a silica gel (30 g) column. The first. fraction eluted with chloroform yielded 122 mg (33%) of **8a**, the second 67 mg (18%) of **8'a**.

Compound **8a**.

This compound had mp 65-67° (from hexane-ether, colorless crystals); ir (potassium bromide): 3163, 3146, 3124, 3049, 2929, 2857, 1750, 1596, 1502, 1465, 1396, 1373, 1342, 1287, 1242, 1198, 1146, 1086, 1018, 990, 898, 822, 763 cm^{-1}; pmr: δ 7.98 (d, J = 8.2 Hz, 1H, H-4), 7.45 (s, 1H, H-2), 7.11 (d, J = 8.2 Hz, 1H, H-5),2.37 (s, 3H, -$COCH_3$)

Anal. Calcd. for $C_9H_6NO_3Br$: C, 42.22; H, 2.36; N, 5.47. Found: C,42.58; H, 2.41; N, 5.45.

Compound **8'a**.

This compound had mp 63-66° (from hexane-ether, colorless crystals); ir (potassium bromide): 3163, 3140, 3089, 2925, 2855, 1771, 1606, 1501. 1470, 1388, 1289, 1241, 1199, 1172, 1102, 1019, 936, 906, 870, 800, 769 cm^{-1}; pmr: δ 8.16 (d, J = 2.6 Hz, 1H, H- 6), 7.79 (s, 1H, H-2), 7.71 (d, J = 2.6 Hz, 1H, H-4), 2.37 (s, 3H, -$COCH_3$).

Anal. Calcd. for $C_9H_6NO_3Br$: C, 42.22; H, 2.36; N, 5.47. Found: C, 42.24; H, 2.37; N, 5.49.

6-Acetoxy-3-bromofuro[3,2-*b*]pyridine **8b**.

The residue from **4b** was chromatographed on a silica gel (25 g) column eluting with hexane-ethyl acetate (8:2) to give 120 mg (33%) of **8b**.

Compound **8b** had mp 102.5-104° (from hexane-ether, colorless crystals); ir (potassium bromide): 3101, 3044, 1768, 1540, 1489, 1389, 1372, 1287, 1197, 1172, 1117, 1070, 1002, 922, 889, 847, 791, 767 cm^{-1}; pmr: δ 8.46 (d, J = 2.1 Hz, 1H, H-5), 7.92 (s, 1H, H- 2), 7.68 (d, J = 2.1 Hz, 1H, H-7), 2.37 (s, 3H, -$COCH_3$).

Anal. Calcd. for $C_9H_6NO_3Br$: C, 42.22; H, 2.36; N, 5.47. Found: C, 42.19; H, 2.35; N, .5.46.

3-Bromofuro[2,3-*c*]pyridin-7(6*H*)-one **8c**, 4-Acetoxy-3-bromo- **8'c**, 3-Acetoxy- **8"c**, 3,7-Dibromo- **9c** and 3,4-Dibromofuro-[2,3-*c*]pyridine **9'c**.

The residue from **4c** was chromatographed on a silica gel (30 g) column eluting with hexane-ethyl acetate (8:2) to yield 18 mg (3%) of **9c**, 12 mg (2%) of **9'c**, 19 mg (3%) of **8'c**, 23 mg (6%) of **8"c** and 30 mg (10%) of **8c**.

Compound **8c** had mp 227-230° (from acetone-ether, ccolorless crystals0; ir (potassium bromide): 3147, 3103, 2981, 2900, 2852. 1657, 1608, 1561, 1485, 1432, 1271, 1223, 1097, 1060, 992, 953, 901, 788, 765 cm^{-1}; pmr: δ 7.81 (s, 1H, H-2), 7.28 (d, J = 6.7 Hz, 1H, H-5), 6.54 (d, J = 6.7 Hz, 1H, H-4).

Anal. Calcd. for $C_7H_4NO_2Br$; C, 39.28; H, 1.88; N, 6.54. Found: C, 39.26; H, 1.96; N, 6.47.

Compound **8'c** had mp 102-104° (from hexane-ether, colorless crystals); ir (potassium bromide): 3145, 3102, 2926, 2853, 1760, 1704, 1593, 1255, 1372, 1279, 1255, 1226, 1206, 1107, 1048, 1021, 951, 899, 822 cm^{-1}; pmr: δ 8.23 (s, IH, H-7), 8.28 (s, 1H, H-5), 7.74 (s, 1H, H-2), 2.44 (s, 3H, -$COCH_3$).

Anal. Calcd. for $C_9H_6NO_3Br$: C, 42.22; H, 2.36; N, 5.47. Found: C, 42.31; H, 2.30; N, 5.47.

Compound **8"c** had mp 56-59° (from hexane, colorless crystals; literature [5], mp 59-62°), which was identified by the mixed melting point test with the authentic sample and by comparison of the ir and pmr spectra.

Compound **9c** had inp 92-95° (from hexane-ether, colorless crystals); ir (potassium bromide): 3145, 3132, 3085, 1598, 1562, 1525, 1460, 1438, 1405, 1281, 1262, 1200, 1155, 1088, 1055, 870, 829, 811 cm^{-1}; pmr: δ 8.30 (d, J = 5.3 Hz, 1H, H-5), 7.85 (s, 1H, H-2), 7.49 (d, J = 5.3 Hz, 1H, H-4); ms: m/z (relative intensity) 279 (M^++4, 48), 277 (M^++2, 100), 275 (M^+, 51), 198 (67), 196 (68), 170 (11), 168 (12).

Anal. Calcd. for $C_7H_3NOBr_2$: C, 30.36; H, 1.09; N, 5.06. Found: C, 30.41; H, 1.12; N, 5.01.

Compound **9'c** had mp 101-104° (from hexane-ether, colorless crystals); ir (potassium bromide): 3091, 3028, 1591, 1529, 1464, 1403, 1314, 1262, 1231, 1159, 1118, 1089, 907, 882, 819, 749 cm^{-1}; pmr: δ 8.83 (s, 1H, H-7), 8.55 (s, 1H, H-5) 7.83 (s, 1H, H-2); ms: m/z (relative intensity) 279 (M^++4, 49), 277 (M^++2, 100), 275 (M^+, 51), 198 (22), 196 (20), 170 (28), 168 (28), 143 (20), 141 (25).

Anal. Calcd. for $C_7H_3NOBr_2$: C, 30.36; H, 1.09; N, 5.06. Found: C, 30.38; H, 1.15; N, 4.96.

3-Bromofuro[3,2-*c*]pyridin-4(5*H*)-one **8d**, 6-Acetoxy- **8'd** and 7-Acetoxy-3-bromofuro[3,2-*c*]pyridine **8"d**.

The residue from **4d** was chromatographed on a silica gel (30 g) column eluting with chloroform-methanol (99:3) to yield 9.5 mg (3%) of **8'd**, 13 mg (3%) of **8"d** and 222 mg (73%) of **8d**.

Compound **8d**.

This compound had mp 225-227° (from acetone, colorless crystals); ir (potassium bromide): 3053, 1665, 1605, 1579, 1538, 1449, 1436, 1272, 1097, 1001, 881, 811 cm^{-1}; pmr: δ 7.52 (s, 1H, H- 2), 7.32 (d, J = 7.3 Hz, 1H, H-0), 6.59 (d, J = 7.3 Hz, 1H, H-7).

Anal. Calcd. for $C_7H_4NO_2Br$: C, 39.28; H, 1.88; N, 6.54. Found: C, 39.32; H, 1.92; N, 6.54.

Compound **8'd**.

This compound had mp 86-88° (from hexane-ether, colorless crystals); 3130, 3052, 2924, 2853, 1767, 1612, 1588, 1455, 1371, 1268, 1209, 1175, 1110, 1063, 1015, 987, 953, 930, 895, 848, 834 cm^{-1}; pmr: δ 8.62 (s, 1H, H-4), 7.68 (s, 1H, H-2), 7.23 (s, 1H, H-7), 2.78 (s, 3H, $-COCH_3$); ms: m/z (relative intensity) 257 (M^++2, 7), 255 (M^+, 4), 21.6 (5), 215 (54), 214 (5), 213 (59), 187 (2), 185 (2), 131 (7), 129 (7), 106 (17); hrms: 254.9546. 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, 42.51; H, 2.41; N, 5.22.

Compound **8"d**.

This compound had mp 72-75° (from hexane-ether, colorless crystals); ir (potassium bromide): 3148, 2924, 2852, 1778, 1621, 1457, 1429, 1373, 1318, 1274, 1213, 1173, 1075, 1010, 940, 891, 856 cm^{-1}; pmr: δ 8.77 (s, 1H, H-4), 8.40 (s, 1H, H-6), 7.68 (s, 1H, H-2), 2.43 (s, 3H, $-COCH_3$); ms: m/z (relative intensity) 257 (M^++2, 4), 255 (M^+, 4), 2116 (7), 215 (75), 214 (8), 213 (76), 187 (21), 185 (22), 106 (29); hrms: 254.9552. 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, 42.55; H, 2.48; N, 5.17.

REFERENCES AND NOTES

[1] Part **XXVII**, S. Yamaguchi, M. Kurosaki, K. Orito, H. Yokoyama, Y. Hirai and S. Shiotani, *J. Heterocyclic Chem.*, **35**, 1237 1998.

[2] Part **XXVI**, S. Yamaguchi, H, Saitoh, M. Kurosaki, H. Yokoyama, Y. Hirai and S. Shiotani, *J. Heterocyclic Chem.*, **35**, 000 (1998).

[3] S. Shiotani, H. Morita, M Inoue, T. Ishida, Y. Iitaka and A. Itai, *J. Heterocyclic Chem.*, **21**, 725 (1984).

[4a] S. Shiotani, *J. Heterocyclic Chem.*, **30**, 1025 (1993); [b] S. Shiotani, M. Tsuno, N. Tanaka, M. Tsuiki and M. Itoh, *J. Heterocyclic Chem.*, **32**, 129 (1995).

[5] S. Shiotani and K. Taniguchi, *J. Heterocyclic Chem.*, **33**, 647 (1996).

[6a] R. A. Abramovitch and G. M. Singer, *Chem. Heterocyclic Compd.*, **14**, Suppl. **1**, 1 (1974); [b] R. A. Abramovitch and B. M. Smith, *Chem. Heterocyclic Compd.*, **14**, Suppl. **2**, 1 (1974); [c] S. Oae and R. Ogino, *Heterocycles,*, **6**, 583 (1976).

[7] S. Shiotani, K. Taniguchi, *J. Heterocyclic Chem.*, **34**, 925 (1997).