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Reaction of ethyl 3-ethoxycarbonylmethoxyfuro[2,3-*b*]pyridine-2-carboxylates **2a-2d** with sodium ethoxide afforded 3-ethoxy derivatives **3a-3d** which converted to 3-ethoxyfuro[2,3-*b*]pyridines **5a-5d** by hydrolysis and decarboxylation of the ester group. Vilsmeier reaction of **5a** and **5b** gave 2-formyl-3-ethoxy derivatives **6a** and **6b** and 2-formyl-3-chloro derivatives **7a** and **7b**, while **5c** and **5d** did not give any formyl compound. Bromination of 3-ethoxyfuro[2,3-*b*]pyridines with 1 equivalent mole of bromine gave 2-bromo-3-ethoxyfuro[2,3-*b*]pyridines **9a-9d**, whereas reaction with 3 equivalents of bromine yielded 2,2-dibromo-3,3-diethoxy-2,3-dihydrofuro[2,3-*b*]pyridines (**10a** and **10b**) and/or 2-bromo-3,3-diethoxy-2,3-dihydrofuro[2,3-*b*]pyridines **11b**, **11c** and **11d**. Treatment of compounds **5a-5d** with *n*-butyllithium in hexane-tetrahydrofuran at  $-70^{\circ}$  and subsequent addition of *N,N*-dimethylformamide yielded 2-formyl derivatives **6a-6d**.

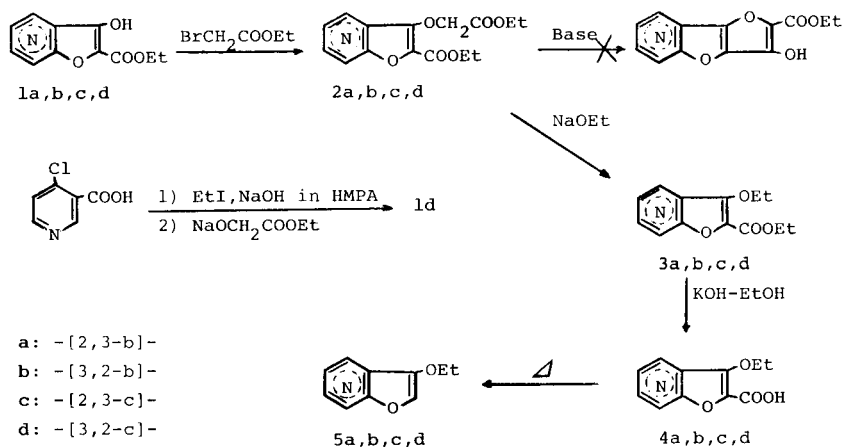
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Recently we reported the syntheses of 2-ethoxycarbonyl-3-hydroxy derivative of furo[2,3-*b*] (1a), furo[3,2-*b*] (1b) and furo[2,3-*c*]pyridine (1c) as the key intermediate for the convenient syntheses of furo[2,3-*b*]-, furo[3,2-*b*]- and furo[2,3-*c*]pyridine, respectively [2,3,4]. It was expected that *O*-alkylation of **1a-1c** with ethyl bromoacetate and the subsequent cyclization with appropriate base would afford furo[3,2-*b*]furo[2,3-*b*]pyridines, new heterocyclic systems. However, several trials [5] to cyclize the 2-ethoxycarbonyl-3-ethoxycarbonyl-methoxy derivative of furo[2,3-*b*] (2a), furo[3,2-*b*] (2b), furo[2,3-*c*] (2c) and furo[3,2-*c*]pyridine (2d) did not give the expected product, but afforded 2-ethoxycarbonyl-3-ethoxy derivatives **3a**, **3b**, **3c** and **3d** with sodium ethoxide in every case. These results are very

interesting and may be caused by the nucleophilic attack of ethoxide anion at 3-position of compounds **2a,b,c,d** which was facilitated by the ethoxycarbonyl group at 2-position.

In this paper we describe the syntheses of 3-ethoxyfuro[2,3-*b*] (5a), -[3,2-*b*] (5b), -[2,3-*c*] (5c) and -[3,2-*c*]pyridine (5d) from compounds **3a-3d**, and their chemical properties. The key intermediate for the synthesis of **5d**, ethyl 3-hydroxyfuro[3,2-*c*]pyridine-2-carboxylate (1d) was prepared from 4-chloronicotinic acid [6] by esterification of the sodium salt with iodoethane in hexamethylphosphoric triamide [7,8] and the subsequent cyclization with sodium ethoxycarbonylmethoxide in 1,2-dimethoxyethane.

*O*-Alkylation of 2-ethoxycarbonyl-3-hydroxy derivatives,



**1a, 1b, 1c** and **1d** with ethyl bromoacetate in acetone gave 3-ethoxycarbonylmethoxy derivatives, **2a, 2b, 2c** and **2d**, which were converted to the 3-ethoxy derivatives, **3a-3d**, by refluxing with sodium ethoxide in toluene in excellent yield. Hydrolysis of the ester group with potassium hy-

dride and the subsequent pyrolytic decarboxylation of the carboxylic acids **4a, 4b, 4c** and **4d** gave the 3-ethoxy compounds, **5a-5d**, in good yield.

In order to compare the electrophilic reactivity, we at first investigated Vilsmeier reaction of compounds **5a-5d**

Table I

Physical Data of Some Derivatives of Furo[2,3-*b*], Furo[3,2-*b*], Furo[2,3-*c*] and Furo[3,2-*c*]pyridine

| Compound No.  | Mp °C (Bp °C/mm Hg)     | Solvent                            | Yield (%) | Molecular Formula                                 | Analysis (%) (Calcd./Found) |              |              | IR (cm <sup>-1</sup> )                           | Mass Spectrum (m/e)                                    |
|---------------|-------------------------|------------------------------------|-----------|---|-----------------------------|--------------|--------------|--|--|
|               |                         |                                    |           |   | C                           | H            | N            |  |  |
| <b>2a</b>     | 68-71 (185-190/0.1)     | Ether                              | 78.4      | C <sub>14</sub> H <sub>15</sub> NO <sub>6</sub>   | 57.34<br>57.21              | 5.16<br>5.18 | 4.78<br>4.73 | 1760, 1700, 1600,<br>1580, 1305, 1155            | 293 (M <sup>+</sup> ), 248, 220,<br>192, 190, 174, 162 |
| <b>2b</b>     | 93-94                   | Ether                              | 75        | C <sub>14</sub> H <sub>15</sub> NO <sub>6</sub>   | 57.34<br>57.56              | 5.16<br>5.26 | 4.78<br>4.96 | 1720, 1600, 1560,<br>1400, 1380                  | 293 (M <sup>+</sup> ), 248, 220,<br>192, 190, 174, 162 |
| <b>2c</b>     | 114-116                 | Acetone-<br><i>i</i> -Propyl Ether | 77.8      | C <sub>14</sub> H <sub>15</sub> NO <sub>6</sub>   | 57.34<br>57.40              | 5.16<br>5.17 | 4.78<br>4.96 | 1755, 1710, 1590,<br>1575, 1440, 1220            | 293 (M <sup>+</sup> ), 248, 220,<br>192, 190, 174, 162 |
| <b>2d</b>     | 89-91                   | Ether                              | 79.5      | C <sub>14</sub> H <sub>15</sub> NO <sub>6</sub>   | 57.34<br>57.27              | 5.16<br>5.24 | 4.78<br>4.74 | 1760, 1705, 1590                                 | 293 (M <sup>+</sup> ), 248, 220,<br>192, 190, 174, 162 |
| <b>3a</b>     | 95-97                   | Ether                              | 65        | C <sub>12</sub> H <sub>13</sub> NO <sub>4</sub>   | 61.27<br>60.90              | 5.57<br>5.49 | 5.95<br>5.84 | 1705, 1595, 1410,<br>1295, 1220, 1100            | 235 (M <sup>+</sup> ), 207, 206,<br>179, 162, 161, 105 |
| <b>3b</b>     | 63.5-64.5 (120-130/0.1) | —                                  | 72        | C <sub>12</sub> H <sub>13</sub> NO <sub>4</sub>   | 61.27<br>61.45              | 5.57<br>5.70 | 5.95<br>5.84 | 1700, 1590, 1560,<br>1395                        | 235 (M <sup>+</sup> ), 220, 207,<br>206, 162, 161, 105 |
| <b>3c</b>     | 75-76 (130-135/0.4)     | —                                  | 66        | C <sub>12</sub> H <sub>13</sub> NO <sub>4</sub>   | 61.27<br>60.95              | 5.57<br>5.48 | 5.95<br>5.83 | 1680, 1580, 1560,<br>1430                        | 235 (M <sup>+</sup> ), 220, 207,<br>179, 162, 161, 105 |
| <b>3d</b>     | 103                     | Ether                              | 75        | C <sub>12</sub> H <sub>13</sub> NO <sub>4</sub>   | 61.27<br>61.27              | 5.57<br>5.58 | 5.95<br>6.07 | 1710, 1585                                       | 235 (M <sup>+</sup> ), 207, 179,<br>162, 161, 105      |
| <b>4b</b> HCl | 196-199                 | Acetone-<br>Methanol               | —         | C <sub>10</sub> H <sub>10</sub> ClNO <sub>4</sub> | 49.30<br>49.02              | 4.14<br>4.14 | 5.75<br>5.83 | 3470, 3400, 3150-2350,<br>1690, 1635, 1620, 1600 |  |
| <b>4c</b> HCl | 220-223 dec             | Acetone                            | —         | C <sub>10</sub> H <sub>10</sub> ClNO <sub>4</sub> | 49.30<br>49.06              | 4.14<br>4.12 | 5.75<br>5.91 | 3400, 3100-2300,<br>1705, 1620, 1580             |  |
| <b>5a</b>     | (150-155/18)            | —                                  | 65        | C <sub>9</sub> H <sub>9</sub> NO <sub>2</sub>     | 66.25<br>66.10              | 5.55<br>5.47 | 8.58<br>8.39 | 1660, 1610, 1580,<br>1405, 1205, 1100            | 163 (M <sup>+</sup> ), 135, 106,<br>78                 |
| <b>5b</b>     | (130-140/18)            | —                                  | 58        | C <sub>9</sub> H <sub>9</sub> NO <sub>2</sub>     | 66.25<br>66.09              | 5.55<br>5.62 | 8.58<br>8.83 | 1610, 1595, 1570,<br>1420, 1210, 1080            | 163 (M <sup>+</sup> ), 148, 135,<br>95, 78             |
| <b>5c</b>     | (150-155/20)            | —                                  | 60        | C <sub>9</sub> H <sub>9</sub> NO <sub>2</sub>     | 66.25<br>65.92              | 5.55<br>5.54 | 8.58<br>8.31 | 1610, 1590, 1570,<br>1470, 1420, 1200            | 163 (M <sup>+</sup> ), 135, 106,<br>78                 |
| <b>5d</b>     | 46-49.5 (135-145/15)    | —                                  | 70        | C <sub>9</sub> H <sub>9</sub> NO <sub>2</sub>     | 66.25<br>65.95              | 5.55<br>5.54 | 8.58<br>8.49 | 1605, 1590, 1575,<br>1455, 1340, 1220            | 163 (M <sup>+</sup> ), 135, 106,<br>78                 |
| <b>5b</b> MeI | 241.5-243.5 dec         | Acetone-<br>Methanol               | —         | C <sub>10</sub> H <sub>12</sub> INO <sub>2</sub>  | 39.37<br>39.34              | 3.96<br>4.05 | 4.59<br>4.47 | 1610, 1580, 1495,<br>1435, 1240, 1170            |  |
| <b>5c</b> MeI | 135-137                 | Acetone                            | —         | C <sub>10</sub> H <sub>12</sub> INO <sub>2</sub>  | 39.37<br>39.40              | 3.96<br>4.03 | 4.59<br>4.46 | 1645, 1575, 1475,<br>1370, 1350, 1230            |  |
| <b>6a</b>     | 127-129                 | Acetone                            | —         | C <sub>10</sub> H <sub>9</sub> NO <sub>3</sub>    | 62.82<br>62.81              | 4.74<br>4.67 | 7.33<br>7.31 | 1655, 1600, 1560,<br>1485, 1440, 1410            | 191 (M <sup>+</sup> ), 176, 163,<br>162, 135, 106      |
| <b>6b</b>     | 96-99                   | Ether                              | —         | C <sub>10</sub> H <sub>9</sub> NO <sub>3</sub>    | 62.82<br>63.04              | 4.74<br>4.88 | 7.33<br>7.28 | 1655, 1580, 1555,<br>1485, 1435, 1195            | 191 (M <sup>+</sup> ), 176, 163,<br>162, 135, 119, 106 |
| <b>6c</b>     | 117-118                 | Ether-<br>Acetone                  | —         | C <sub>10</sub> H <sub>9</sub> NO <sub>3</sub>    | 62.82<br>63.06              | 4.74<br>4.82 | 7.33<br>7.43 | 1640, 1590, 1550,<br>1540, 1440, 1430            | 191 (M <sup>+</sup> ), 176, 163,<br>162, 135, 106      |
| <b>6d</b>     | 93-94                   | Ether                              | —         | C <sub>10</sub> H <sub>9</sub> NO <sub>3</sub>    | 62.82<br>62.85              | 4.74<br>4.84 | 7.22<br>7.26 | 1600, 1580, 1290<br>1220                         | 191 (M <sup>+</sup> ), 176, 163,<br>162, 135, 106      |
| <b>7a</b>     | 117-119                 | Ether                              | —         | C <sub>8</sub> H <sub>4</sub> ClNO <sub>2</sub>   | 52.92<br>52.89              | 2.22<br>2.21 | 7.71<br>7.83 | 1680, 1590, 1585,<br>1545, 1320, 1030            | 183, 182, 181, 180,<br>127, 126, 125, 124              |
| <b>7b</b>     | 130-132                 | Ether                              | —         | C <sub>8</sub> H <sub>4</sub> ClNO <sub>2</sub>   | 52.92<br>53.31              | 2.22<br>2.48 | 7.71<br>7.79 | 1660, 1580, 1555,<br>1485, 1435, 1395            | 183, 182, 181, 180,<br>127, 126, 125, 124              |

Table I (continued)

| Compound No.  | Mp °C<br>(Bp °C/mm Hg)    | Solvent           | Yield (%) | Molecular Formula   | Analysis (%)<br>(Calcd./Found) |      |       | IR<br>(cm <sup>-1</sup> )                            | Mass Spectrum<br>(m/e)                                 |
|---------------|---------------------------|-------------------|-----------|---|--------------------------------|------|-------|--|--|
|               |                           |                   |           |   | C                              | H    | N     |  |  |
| <b>9a</b>     | 48<br>(110-115/0.2)       | —                 | —         | C <sub>9</sub> H <sub>8</sub> BrNO <sub>2</sub>                 | 44.66                          | 3.33 | 5.79  |  | 243, 241, 215, 213,<br>186, 184, 158, 156              |
|               |                           |                   |           |   | 44.28                          | 3.42 | 5.74  |  |  |
| <b>9b</b>     | 37-39<br>(100/0.1)        | —                 | —         | C <sub>9</sub> H <sub>8</sub> BrNO <sub>2</sub>                 | 44.66                          | 3.33 | 5.79  | 1590, 1550, 1465,<br>1395                            | 243, 241, 215, 213,<br>199, 197, 158, 156              |
|               |                           |                   |           |   | 44.86                          | 3.38 | 5.70  |  |  |
| <b>9d</b>     | 39-44<br>(120-125/0.2)    | —                 | —         | C <sub>9</sub> H <sub>8</sub> BrNO <sub>2</sub>                 | 44.66                          | 3.33 | 5.79  | 1600, 1555, 1440,<br>1345, 1290, 1145                | 243, 241, 215, 213,<br>186, 184, 158, 156              |
|               |                           |                   |           |   | 44.63                          | 3.36 | 5.60  |  |  |
| <b>9a</b> HBr | 80                        | Aceto-<br>nitrile | 70        | C <sub>9</sub> H <sub>8</sub> Br <sub>2</sub> NO <sub>2</sub>   | 33.47                          | 2.81 | 4.34  |  |  |
|               |                           |                   |           |   | 33.67                          | 2.82 | 4.39  |  |  |
| <b>9b</b> HBr | 182-184 dec               | Aceto-<br>nitrile | 72        | C <sub>9</sub> H <sub>8</sub> Br <sub>2</sub> NO <sub>2</sub>   | 33.47                          | 2.81 | 4.39  | 3100-2300, 1625,<br>1600, 1570, 1480                 |  |
|               |                           |                   |           |   | 33.52                          | 2.84 | 4.33  |  |  |
| <b>9c</b> HBr | 163-167 dec               | Aceto-<br>nitrile | 60        | C <sub>9</sub> H <sub>8</sub> Br <sub>2</sub> NO <sub>2</sub>   | 33.47                          | 2.81 | 4.39  | 3100-2400, 1640,<br>1610, 1570, 1450                 |  |
|               |                           |                   |           |   | 33.52                          | 2.97 | 4.46  |  |  |
| <b>9d</b> HBr | 210-210.5 dec             | Aceto-<br>nitrile | 68        | C <sub>9</sub> H <sub>8</sub> Br <sub>2</sub> NO <sub>2</sub>   | 33.47                          | 2.81 | 4.39  | 3050-2400, 1620,<br>1600, 1515, 1430                 |  |
|               |                           |                   |           |   | 33.52                          | 2.74 | 4.59  |  |  |
| <b>10a</b>    | 81-82                     | Ether             | 85        | C <sub>11</sub> H <sub>13</sub> Br <sub>2</sub> NO <sub>3</sub> | 36.00                          | 3.57 | 3.82  | 1600, 1585, 1405,<br>985                             |  |
|               |                           |                   |           |   | 35.76                          | 3.52 | 4.06  |  |  |
| <b>10b</b>    | 98-101<br>(125-135/0.1)   | —                 | 20        | C <sub>11</sub> H <sub>13</sub> Br <sub>2</sub> NO <sub>3</sub> | 36.00                          | 3.57 | 3.82  | 1570, 1425, 1305,<br>1255, 1180                      |  |
|               |                           |                   |           |   | 35.89                          | 3.61 | 3.80  |  |  |
| <b>11b</b>    | 86.5-89<br>(100-110/0.1)  | Ether             | 63        | C <sub>11</sub> H <sub>14</sub> BrNO <sub>3</sub>               | 45.85                          | 4.90 | 4.86  | 1565, 1415, 1315,<br>1255                            |  |
|               |                           |                   |           |   | 45.64                          | 4.89 | 4.61  |  |  |
| <b>11c</b>    | 66-68<br>(135/0.1)        | —                 | 73        | C <sub>11</sub> H <sub>14</sub> BrNO <sub>3</sub>               | 45.85                          | 4.90 | 4.86  | 1600, 1480, 1420,<br>1330, 1270, 1060                |  |
|               |                           |                   |           |   | 45.56                          | 4.86 | 4.63  |  |  |
| <b>11d</b>    | 41-44<br>(110-115/0.08)   | —                 | 85        | C <sub>11</sub> H <sub>14</sub> BrNO <sub>3</sub>               | 45.85                          | 4.90 | 4.86  | 1610, 1585, 1480, 1470,<br>1325, 1265                |  |
|               |                           |                   |           |   | 45.83                          | 4.92 | 4.62  |  |  |
| <b>12a</b>    | 96-99<br>(160-170/0.05)   | —                 | —         | C <sub>10</sub> H <sub>11</sub> NO <sub>3</sub>                 | 62.17                          | 5.74 | 7.25  | 3200, 1625, 1595,<br>1395, 1140, 1020                | 193 (M <sup>+</sup> ), 147, 136,<br>122, 105, 91       |
|               |                           |                   |           |   | 62.36                          | 5.49 | 6.98  |  |  |
| <b>12b</b>    | 115-118<br>(150-160/0.02) | —                 | —         | C <sub>10</sub> H <sub>11</sub> NO <sub>3</sub>                 | 62.17                          | 5.74 | 7.25  | 3230, 1625, 1605,<br>1380, 1145, 1020                | 193 (M <sup>+</sup> ), 147, 105,<br>91                 |
|               |                           |                   |           |   | 62.39                          | 5.78 | 7.10  |  |  |
| <b>12c</b>    | 88-89<br>(150/0.02)       | —                 | —         | C <sub>10</sub> H <sub>11</sub> NO <sub>3</sub>                 | 62.17                          | 5.74 | 7.25  | 3200, 1625, 1605,<br>1430, 1235, 1030                | 193 (M <sup>+</sup> ), 147, 136,<br>122, 105, 91       |
|               |                           |                   |           |   | 61.96                          | 5.70 | 7.12  |  |  |
| <b>13a</b>    | (150-160/0.01)            | —                 | —         | C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>   | 61.53                          | 6.02 | 11.96 | 1635, 1600, 1500,<br>1400, 1125, 1075                | 234 (M <sup>+</sup> ), 206, 190,<br>162, 161, 135, 119 |
|               |                           |                   |           |   | 61.28                          | 5.88 | 12.09 |  |  |
| <b>13b</b>    | (155-160/0.01)            | —                 | —         | C <sub>12</sub> H <sub>14</sub> N <sub>2</sub> O <sub>3</sub>   | 61.53                          | 6.02 | 11.96 | 1640, 1600, 1560,<br>1500, 1400, 1260,<br>1150, 1100 | 234 (M <sup>+</sup> ), 191, 190,<br>162, 161, 135, 119 |
|               |                           |                   |           |   | 61.61                          | 6.11 | 11.89 |  |  |

with phosphoryl chloride and *N,N*-dimethylformamide. The quinoline isosteres gave 3-ethoxy-2-aldehyde **6a** and **6b** and 3-chloro-2-aldehyde **7a** and **7b**, while the isoquinoline isosteres resulted in complete recovery of the starting compound. The parent compounds, furo[2,3-*b*]-, furo[3,2-*b*]-, furo[2,3-*c*]- and furo[3,2-*c*]pyridine also did not give any reaction product. These results indicate that the electron density of the furan ring of the parent compounds and isoquinoline isosteres which would exist in ammonium salts in the reaction medium would be much lowered and the Vilsmeier reagent, a weaker electrophile, can not react, and in the cases of 3-ethoxy derivatives of the quinoline isosteres, the electron-donating effect of the ethoxy group at 3-position overcomes the electron-withdrawing

effect of the pyridinium ring. The 3-chloro-2-aldehydes, **7a** and **7b**, would be formed by the nucleophilic substitution of the ethoxy group with chloride anion which was facilitated by the formyl group at 2-position.

Secondly, the stabilities for the acidic hydrolysis of the ethoxy group in quinoline and isoquinoline isosteres were examined. The hydrolysis of **5a**, **5b**, **5c** and **5d** with hydrochloric acid were followed by <sup>1</sup>H nmr technique. Compound **5a** was hydrolyzed very easily with diluted hydrochloric acid even at 25° and was converted completely to furo[2,3-*b*]pyridin-3(2*H*)-one (**8a**) in about 2 hours. Compounds **5b**, **5c** and **5d** were not hydrolyzed at room temperature, but at 70° compound **5b** was converted to **8b** in 95% after 3 days, compound **5c** to **8c** in about 30% after 5

Table II

<sup>1</sup>H NMR Data of Some Derivatives of Furo[2,3-*b*], Furo[3,2-*b*], Furo[2,3-*c*] and Furo[3,2-*c*]pyridine [a]

| Compound No. | H-2      | H-4                       | H-5                       | H-6                       | H-7                        | Others   |
|--------------|----------|---------------------------|---------------------------|---------------------------|----------------------------|--|
| <b>2a</b>    | —        | 8.15 (dd)<br>J = 1.9, 8.0 | 7.24 (dd)<br>J = 4.8, 8.0 | 8.42 (dd)<br>J = 1.9, 4.8 | —                          | 5.00 (s, 2H, —CH <sub>2</sub> COOEt)<br>4.38 (q, J = 7.2, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>4.17 (q, J = 7.2, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.37 (t, J = 7.2, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.20 (t, J = 7.2, 3H, —OCH <sub>2</sub> CH <sub>3</sub> ) |
| <b>2b</b>    | —        | —                         | 8.45 (dd)<br>J = 1.4, 4.6 | 7.24 (dd)<br>J = 4.6, 8.4 | 7.71 (dd)<br>J = 1.4, 8.4  | 5.43 (s, 2H, —CH <sub>2</sub> COOEt)<br>4.42 (q, J = 7.0, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>4.18 (q, J = 7.0, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.41 (t, J = 7.0, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.23 (t, J = 7.0, 3H, —OCH <sub>2</sub> CH <sub>3</sub> ) |
| <b>2c</b>    | —        | 7.64 (dd)<br>J = 0.8, 5.0 | 8.40 (d)<br>J = 5.0       | —                         | 8.82 (d)<br>J = 0.8        | 4.98 (s, 2H, —CH <sub>2</sub> COOEt)<br>4.42 (q, J = 7.0, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>4.18 (q, J = 7.0, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.43 (t, J = 7.0, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.24 (t, J = 7.0, 3H, —OCH <sub>2</sub> CH <sub>3</sub> ) |
| <b>2d</b>    | —        | 9.05 (d)<br>J = 0.9       | —                         | 8.53 (d)<br>J = 5.8       | 7.35 (dd)<br>J = 0.9, 5.8  | 5.04 (s, 2H, —CH <sub>2</sub> COOEt)<br>4.40 (q, J = 7.0, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>4.20 (q, J = 7.0, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.40 (t, J = 7.0, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.23 (t, J = 7.0, 3H, —OCH <sub>2</sub> CH <sub>3</sub> ) |
| <b>3a</b>    | —        | 8.01 (dd)<br>J = 1.9, 7.6 | 7.19 (dd)<br>J = 4.8, 7.6 | 8.44 (dd)<br>J = 1.9, 4.8 | —                          | 4.52 (q, J = 6.8, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>4.41 (q, J = 6.8, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.47 (t, J = 6.8, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.43 (t, J = 6.8, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )   |
| <b>3b</b>    | —        | —                         | 8.48 (dd)<br>J = 1.4, 4.4 | 7.24 (dd)<br>J = 4.4, 8.4 | 7.68 (dd)<br>J = 1.4, 8.4  | 4.88 (q, J = 6.8, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>4.40 (q, J = 6.8, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.48 (t, J = 6.8, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.23 (t, J = 6.8, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )   |
| <b>3c</b>    | —        | 7.62 (dd)<br>J = 0.8, 5.2 | 8.43 (d)<br>J = 5.2       | —                         | 8.88 (d)<br>J = 0.8        | 4.49 (q, J = 6.8, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>4.45 (q, J = 6.8, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.47 (t, J = 6.8, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.43 (t, J = 6.8, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )   |
| <b>3d</b>    | —        | 8.95 (d)                  | —                         | 8.46 (d)                  | 7.30 (dd)                  | 4.50 (q, J = 6.8, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>4.37 (q, J = 6.8, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.46 (t, J = 6.8, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.20 (t, J = 6.8, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )   |
| <b>5a</b>    | 7.20 (s) | 7.89 (dd)<br>J = 1.6, 7.4 | 7.12 (dd)<br>J = 4.8, 7.4 | 8.27 (dd)<br>J = 1.6, 4.8 | —                          | 4.00 (q, J = 6.8, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.44 (t, J = 6.8, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )   |
| <b>5b</b>    | 7.35 (s) | —                         | 8.40 (dd)<br>J = 1.2, 4.4 | 7.08 (dd)<br>J = 4.4, 7.8 | 7.53 (dd)<br>J = 1.2, 7.8  | 4.12 (q, J = 6.6, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.48 (t, J = 6.6, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )   |
| <b>5c</b>    | 7.24 (s) | 7.62 (dd)<br>J = 0.8, 5.0 | 8.32 (d)<br>J = 5.0       | —                         | 8.70 (d)<br>J = 0.8        | 4.03 (q, J = 6.8, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.46 (t, J = 6.8, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )   |
| <b>5d</b>    | 7.13 (s) | 8.84 (d)<br>J = 0.8       | —                         | 8.38 (d)<br>J = 5.8       | 7.20 (dd)<br>J = 0.8, 5.8  | 3.99 (q, J = 6.8, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.43 (t, J = 6.8, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )   |
| <b>6a</b>    | —        | 8.12 (dd)<br>J = 1.6, 7.6 | 7.24 (dd)<br>J = 4.4, 7.6 | 8.47 (dd)<br>J = 1.6, 4.4 | —                          | 9.88 (s, 1H, —CHO)<br>4.58 (q, J = 6.6, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.42 (t, J = 6.6, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )   |
| <b>6b</b>    | —        | —                         | 8.40 (dd)<br>J = 1.3, 4.4 | 7.33 (dd)<br>J = 4.4, 8.2 | 7.74 (dd)<br>J = 1.34, 8.2 | 9.89 (s, 1H, —CHO)<br>4.98 (q, J = 6.8, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.51 (t, J = 6.8, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )   |
| <b>6c</b>    | —        | 7.64 (dd)<br>J = 1.0, 5.2 | 8.44 (d)<br>J = 5.2       | —                         | 8.89 (d)<br>J = 1.0        | 9.99 (s, 1H, —CHO)<br>4.58 (q, J = 6.8, 2H, —OCH <sub>2</sub> CH <sub>3</sub> )<br>1.54 (t, J = 6.8, 3H, —OCH <sub>2</sub> CH <sub>3</sub> )   |

Table II (continued)

| Compound No.      | H-2      | H-4                       | H-5                       | H-6                       | H-7                       | Others  |
|-------------------|----------|---------------------------|---------------------------|---------------------------|---------------------------|---|
| <b>6d</b>         | —        | 9.12 (d)<br>J = 0.8       | —                         | 8.61 (d)<br>J = 6.0       | 7.41 (dd)<br>J = 0.6, 6.0 | 9.92 (s, 1H, -CHO)<br>4.66 (q, J = 7.0, 2H, -OCH <sub>2</sub> CH <sub>3</sub> )<br>1.58 (t, J = 7.0, 3H, -OCH <sub>2</sub> CH <sub>3</sub> )  |
| <b>7a</b>         | —        | 8.13 (dd)<br>J = 1.8, 7.6 | 7.41 (dd)<br>J = 4.6, 7.6 | 8.58 (dd)<br>J = 1.8, 4.6 | —                         | 10.03 (s, 1H, -CHO)   |
| <b>7b</b>         | —        | —                         | 8.67 (dd)<br>J = 1.3, 4.4 | 7.42 (dd)<br>J = 4.4, 8.0 | 7.84 (dd)<br>J = 1.3, 8.0 | 10.10 (s, 1H, -CHO)   |
| <b>9a</b>         | —        | 7.85 (dd)<br>J = 1.7, 7.6 | 7.16 (dd)<br>J = 4.8, 7.6 | 8.23 (dd)<br>J = 1.7, 4.8 | —                         | 4.28 (q, J = 7.2, 2H, -OCH <sub>2</sub> CH <sub>3</sub> )<br>1.41 (t, J = 7.2, 3H, -OCH <sub>2</sub> CH <sub>3</sub> )  |
| <b>9b</b>         | —        | —                         | 8.43 (dd)<br>J = 1.2, 4.6 | 7.11 (dd)<br>J = 4.6, 8.3 | 7.57 (dd)<br>J = 1.2, 8.3 | 4.60 (q, J = 7.0, 2H, -OCH <sub>2</sub> CH <sub>3</sub> )<br>1.43 (t, J = 7.0, 3H, -OCH <sub>2</sub> CH <sub>3</sub> )  |
| <b>9c</b>         | —        | 7.38 (dd)<br>J = 0.8, 5.0 | 8.27 (d)<br>J = 5.0       | —                         | 8.62 (d)<br>J = 0.8       | 4.24 (q, J = 7.0, 2H, -OCH <sub>2</sub> CH <sub>3</sub> )<br>1.40 (t, J = 7.0, 3H, -OCH <sub>2</sub> CH <sub>3</sub> )  |
| <b>9c</b> HBr [b] | —        | 8.11 (d)<br>J = 6.0       | 8.47 (d)<br>J = 6.0       | —                         | 8.99 (s)                  | 4.40 (q, J = 7.0, 2H, -OCH <sub>2</sub> CH <sub>3</sub> )<br>1.40 (t, J = 7.0, 3H, -OCH <sub>2</sub> CH <sub>3</sub> )  |
| <b>10a</b>        | —        | 7.79 (dd)<br>J = 1.8, 7.2 | 7.06 (dd)<br>J = 5.0, 7.2 | 8.22 (dd)<br>J = 1.8, 5.0 | —                         | 3.32-4.13 (m, 4H, 2x -OCH <sub>2</sub> CH <sub>3</sub> ) [c]<br>1.25 (t, J = 7.2, 6H, 2x -OCH <sub>2</sub> CH <sub>3</sub> )  |
| <b>10b</b>        | —        | —                         | 8.16 (t)<br>J = 3.0       | 7.07 (d, 2H)<br>J = 3.0   | —                         | 3.40-4.19 (m, 4H, 2x -OCH <sub>2</sub> CH <sub>3</sub> ) [c]<br>1.21 (t, J = 7.6, 6H, 2x -OCH <sub>2</sub> CH <sub>3</sub> )  |
| <b>11b</b>        | 6.50 (s) | —                         | 8.27 (t)<br>J = 3.0       | 7.17 (d, 2H)<br>J = 3.0   | —                         | 3.23-3.95 (m, 4H, 2x -OCH <sub>2</sub> CH <sub>3</sub> ) [c]<br>1.34 (t, J = 6.8, 3H, -OCH <sub>2</sub> CH <sub>3</sub> )<br>1.03 (t, J = 6.8, 3H, -OCH <sub>2</sub> CH <sub>3</sub> )              |
| <b>11c</b>        | 6.45 (s) | 7.27 (dd)<br>J = 0.8, 4.6 | 8.30 (d)<br>J = 4.6       | —                         | 8.27 (d)<br>J = 0.8       | 2.97-3.85 (m, 4H, 2x -OCH <sub>2</sub> CH <sub>3</sub> ) [c]<br>1.62 (t, J = 6.6, 3H, -OCH <sub>2</sub> CH <sub>3</sub> )<br>1.07 (t, J = 6.6, 3H, -OCH <sub>2</sub> CH <sub>3</sub> )              |
| <b>11d</b>        | 6.51 (s) | 8.56 (d)<br>J = 0.8       | —                         | 8.47 (d)<br>J = 5.6       | 6.88 (dd)<br>J = 0.8, 5.6 | 3.05-3.92 (m, 4H, 2x -OCH <sub>2</sub> CH <sub>3</sub> ) [c]<br>1.30 (t, J = 7.0, 3H, -OCH <sub>2</sub> CH <sub>3</sub> )<br>1.08 (t, J = 7.0, 3H, -OCH <sub>2</sub> CH <sub>3</sub> )              |
| <b>12a</b>        | —        | 7.85 (dd)<br>J = 1.8, 7.5 | 7.12 (dd)<br>J = 4.8, 7.5 | 8.21 (dd)<br>J = 1.8, 4.8 | —                         | 4.24 (s, 2H, -CH <sub>2</sub> OH)<br>4.22 (q, J = 7.0, 2H, -OCH <sub>2</sub> CH <sub>3</sub> )<br>1.40 (t, J = 7.0, 3H, -OCH <sub>2</sub> CH <sub>3</sub> )   |
| <b>12b</b>        | —        | —                         | 8.40 (dd)<br>J = 1.2, 4.4 | 7.08 (dd)<br>J = 4.4, 8.2 | 7.56 (dd)<br>J = 1.2, 8.2 | 4.75 (s, 2H, -CH <sub>2</sub> OH)<br>4.52 (q, J = 7.0, 2H, -OCH <sub>2</sub> CH <sub>3</sub> )<br>2.60 (broad s, 1H, OH)<br>1.37 (t, J = 7.0, 3H, -OCH <sub>2</sub> CH <sub>3</sub> )               |
| <b>12c</b>        | —        | 7.42 (dd)<br>J = 1.0, 5.2 | 8.28 (d)<br>J = 5.2       | —                         | 8.66 (d)<br>J = 1.0       | 4.74 (s, 2H, -CH <sub>2</sub> CH <sub>3</sub> )<br>4.20 (q, J = 7.0, 2H, -OCH <sub>2</sub> CH <sub>3</sub> )<br>2.70 (broad s, 1H, OH)<br>1.36 (t, J = 7.0, 3H, -OCH <sub>2</sub> CH <sub>3</sub> ) |
| <b>13a</b>        | —        | 8.05 (dd)<br>J = 1.8, 8.0 | 7.25 (dd)<br>J = 4.5, 8.0 | 8.42 (dd)<br>J = 1.8, 4.5 | —                         | 4.36 (q, J = 7.0, 2H, -OCH <sub>2</sub> CH <sub>3</sub> )<br>3.16 (s, 6H, NMe <sub>2</sub> )<br>1.33 (t, J = 7.0, 3H, -OCH <sub>2</sub> CH <sub>3</sub> )   |
| <b>13b</b>        | —        | —                         | 8.51 (dd)<br>J = 1.3, 4.8 | 7.23 (dd)<br>J = 1.3, 8.2 | 7.70 (dd)<br>J = 4.8, 8.2 | 4.74 (q, J = 6.8, 2H, -OCH <sub>2</sub> CH <sub>3</sub> )<br>3.13 (s, 6H, NMe <sub>2</sub> )<br>1.44 (t, J = 6.8, 3H, -OCH <sub>2</sub> CH <sub>3</sub> )   |

[a] Spectra were taken in deuteriochloroform. Chemical shifts ( $\delta$  values) are in parts per million from tetramethylsilane. Coupling constants (J) are in Hz. [b] Taken in deuterioacetonitrile. [c] These signals can be analyzed as the overlapped signals of four quartets centered at 3.95, 3.81, 3.64 and 3.50 ppm (J = 7.2 Hz) for **10a**, 3.98, 3.85, 3.73 and 3.69 (J = 7.6 Hz) for **10b**, 3.76, 3.75, 3.56 and 3.40 (J = 6.8 Hz) for **11b**, 3.66, 3.53, 3.28 and 3.14 (J = 6.6 Hz) for **11c**, and 3.72, 3.70, 3.37 and 3.22 (J = 7.0 Hz) for **11d**. The multiplicity may be caused by the steric crowdedness around the ethoxy groups at 3-position due to the bromine atom(s) at 2-position.

days, and compound **5d** to **8d** in 95% after 5 hours. Thus, these results indicated that the 3-ethoxy compounds **5a,b,c,d** possess some enol-ether character, and the order is : **5a** >> **5d** > **5b** > **5c**.

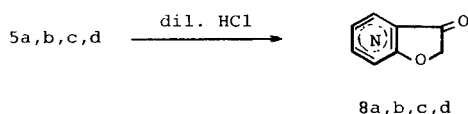
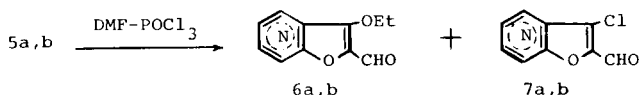


Chart 2

Bromination of the 3-ethoxyfuropyridines with 1 equivalent mole of molecular bromine in chloroform gave 2-bromo-3-ethoxyfuropyridines **9a, 9b, 9c** and **9d** in good yield, respectively. The hydrobromide of these four compounds and the free base of the quinoline isosteres are stable but the free base of the isoquinoline isosteres are unstable, particularly compound **9c** was decolorized and polymerized at room temperature in a few minutes. In the case of **5a**, the nmr spectrum of the reaction mixture in deuteriochloroform at lower temperature exhibited the signals of the addition product (a mixture of *cis*- and *trans*-2,3-dibromo-3-ethoxy-2,3-dihydrofuro[2,3-*b*]pyridine, (**9'a**) ( $\delta$  1.26 (t,  $J = 7.2$  Hz, *ca.* 3/2H, 1/2  $x$  -CH<sub>2</sub>-CH<sub>3</sub>), 1.48 (t,  $J = 7.2$  Hz, *ca.* 3/2H, 1/2  $x$  -CH<sub>2</sub>-CH<sub>3</sub>), 3.49-4.50 (complex m, 2H, -CH<sub>2</sub>-CH<sub>3</sub>, the multiplicity may be caused by

the steric crowding of the ethoxy group at 3-position due to the two bromine atoms at 2- and 3-position), 6.57 (s, 1H, 2-H), 7.20 (dd,  $J = 4.8, 5.6$  Hz, 1H, 5-H), 8.12 (dd,  $J = 5.6, 1.5$  Hz, 1H, 4-H), 8.59 (dd,  $J = 4.8, 1.5$  Hz, 1H, 6-H)). The reaction mixture slowly precipitated crystalline solid at 40-50° and the nmr spectrum of the solid in deuteriomethanol showed the signals of hydrobromide of 2-bromo-3-ethoxyfuro[2,3-*b*]pyridine. This fact suggests that bromination of the 3-ethoxyfuropyridines proceeds by the addition and the subsequent elimination process as in the cases of the parent compounds [9], not by the simple substitution. Bromination with 3 equivalent moles of molecular bromine in chloroform (commercial reagent grade containing ethanol (*ca.* 1%)) gave somewhat complex results. Compound **5a** afforded 2,2-dibromo-3,3-diethoxy-2,3-dihydrofuro[2,3-*b*]pyridine (**10a**) in 80% yield, and **5b** a mixture of 2,2-bromo-3,3-diethoxy-2,3-dihydrofuro[3,2-*b*]pyridine (**10b**), 2-bromo-3,3-diethoxy-2,3-dihydrofuro[3,2-*b*]pyridine (**11b**) and **9b**. While, isoquinoline isosteres, **5c** and **5d**, yielded 2-bromo-3,3-diethoxy-2,3-dihydro derivatives, **11c** and **11d**, in fairly good yield. Because it was difficult to determine the position of the bromine and ethoxy groups in compound **10a** by common spectroscopic methods, the final structure was confirmed by single crystal X-ray analysis (Figure 1). The structures of **11b**, **11c** and **11d** were estimated by elemental analyses, <sup>1</sup>H nmr spectra and mass spectral data, and by the fact that the compounds **11b**, and **11d** were converted to compounds **9b** and **9d**, respectively, by refluxing with *p*-toluenesulfonic acid in benzene. It can be speculated that the compounds **10a** and **10b** were formed by addition of another bromine molecule to the 2-bromo-3-ethoxy derivatives and the subsequent substitution of the bromine atom

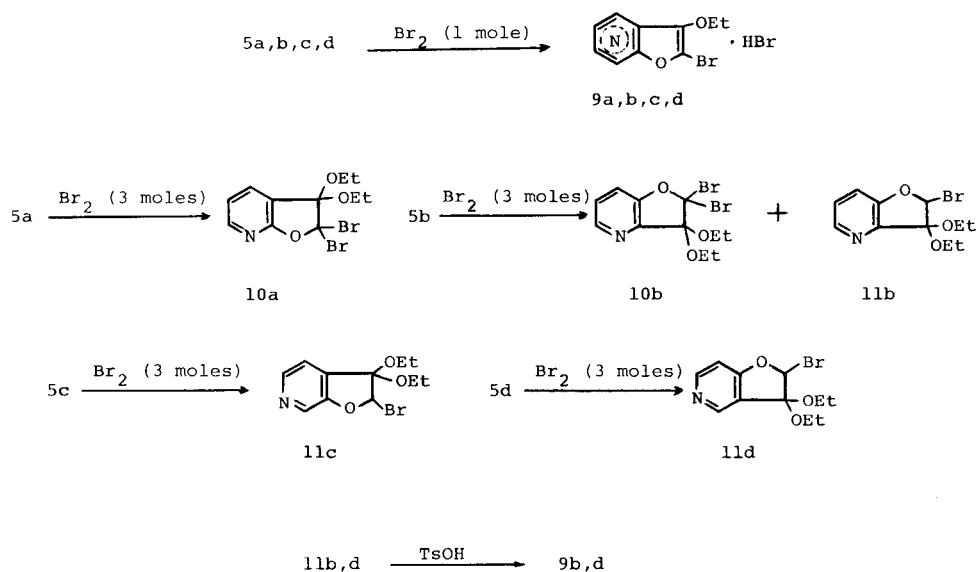


Chart 3

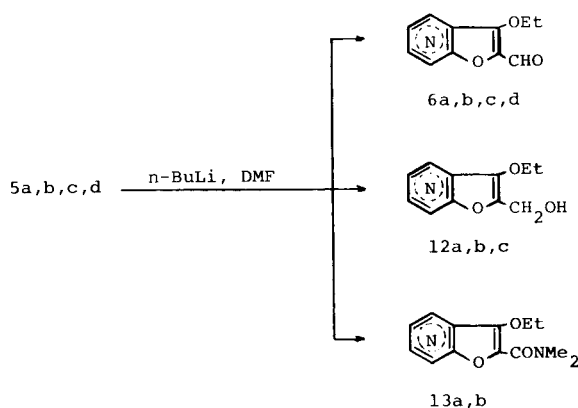
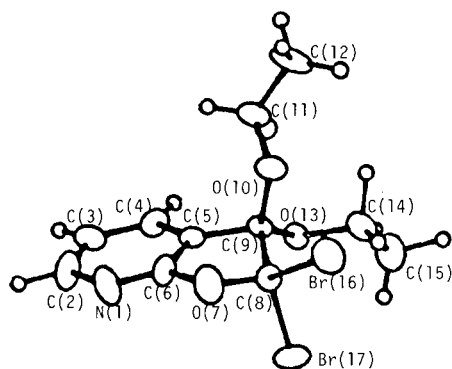


Chart 4

at 3-position with ethoxide anion, and **11b**, **11c** and **11d** were formed by substitution of the bromine atom at 3-position of 2,3-dibromo-3-ethoxy derivatives, the intermediate addition product, with ethoxide anion. This speculation may be supported by the fact that the bromination of these 3-ethoxyfuropyridines with 3 equivalent moles of bromine in absolute chloroform afforded 2-bromo-3-ethoxy compounds, as the main product, respectively.

Figure 1. ORTEP drawing of compound **10a**.

The 3-ethoxyfuropyridines, **5a**, **5b**, **5c** and **5d**, were treated with *n*-butyllithium in hexane (molar ratio: BuLi: **5a**, **5b**, **5c** or **5d** = 1.1-1.2) in tetrahydrofuran at  $-70^\circ$  to give the 2-lithio intermediate *in situ*, and subsequently reacted with *N,N*-dimethylformamide to afford 2-formyl derivatives **6a**, **6b**, **6c** and **6d**, 2-hydroxymethyl derivatives **12a**, **12b** and **12c**, and 2-dimethylaminocarbonyl compounds, **13a** and **13b**, respectively, accompanying recovery of the starting compounds [10].

Table III

Atomic Parameters and Equivalent Isotropic Thermal Parameters for Nonhydrogen Atoms in Compound **10a**  
(Estimated standard deviations are in parentheses)

| Atom   | X         | Y           | Z          | Beq     |
|--------|-----------|-------------|------------|---------|
| N(1)   | 1.390(1)  | 0.1984(6)   | 0.2676(6)  | 3.5(4)  |
| C(2)   | 1.498(2)  | 0.2609(7)   | 0.2162(8)  | 4.3(5)  |
| C(3)   | 1.520(2)  | 0.2499(7)   | 0.1114(7)  | 3.4(4)  |
| C(4)   | 1.424(1)  | 0.1740(6)   | 0.0609(7)  | 2.7(4)  |
| C(5)   | 1.321(1)  | 0.1122(6)   | 0.1154(6)  | 2.1(3)  |
| C(6)   | 1.310(1)  | 0.1324(6)   | 0.2188(8)  | 2.8(4)  |
| O(7)   | 1.197(1)  | 0.0667(5)   | 0.2648(5)  | 3.6(3)  |
| C(8)   | 1.091(1)  | 0.0215(6)   | 0.1913(5)  | 2.0(3)  |
| C(9)   | 1.209(1)  | 0.0223(5)   | 0.0934(5)  | 1.7(3)  |
| O(10)  | 1.3079(8) | -0.0667(4)  | 0.0937(5)  | 2.6(3)  |
| C(11)  | 1.448(1)  | -0.0710(7)  | 0.0181(8)  | 3.6(5)  |
| C(12)  | 1.484(2)  | -0.1779(7)  | -0.001(1)  | 4.8(6)  |
| O(13)  | 1.1160(8) | 0.0360(4)   | 0.0061(4)  | 2.0(2)  |
| C(14)  | 1.007(1)  | -0.0442(8)  | -0.0249(7) | 3.2(4)  |
| C(15)  | 0.890(2)  | -0.0042(7)  | -0.1076(8) | 4.4(5)  |
| Br(16) | 1.0244(2) | -0.10940(8) | 0.23993(9) | 1.88(5) |
| Br(17) | 0.8820(1) | 0.10316(8)  | 0.17155(9) | 3.92(5) |

Table IV

Bond Length ( $\text{\AA}$ ) and Bond Angle ( $^\circ$ ) in Compound **10a**  
(Estimated standard deviations are in parentheses)

| Bond      | Length  | Bond        | Length   |
|-----------|---------|-------------|----------|
| N(1)-C(2) | 1.35(2) | C(8)-C(9)   | 1.59(1)  |
| N(1)-C(6) | 1.26(2) | C(8)-Br(16) | 1.940(9) |
| C(2)-C(3) | 1.43(2) | C(8)-Br(17) | 1.931(9) |
| C(3)-C(4) | 1.42(2) | C(9)-O(10)  | 1.40(1)  |
| C(4)-C(5) | 1.35(1) | C(9)-O(13)  | 1.38(1)  |
| C(5)-C(6) | 1.42(1) | O(10)-C(11) | 1.47(1)  |
| C(5)-C(9) | 1.50(1) | C(11)-C(12) | 1.48(2)  |
| C(6)-O(7) | 1.37(1) | O(13)-C(14) | 1.42(1)  |
| O(7)-C(8) | 1.41(1) | C(14)-C(15) | 1.51(2)  |

| Bond           | Angle    | Bond               | Angle    |
|----------------|----------|--------------------|----------|
| C(2)-N(1)-C(6) | 116.9(8) | C(9)-C(8)-Br(16)   | 115.5(3) |
| N(1)-C(2)-C(3) | 120.8(7) | C(9)-C(8)-Br(17)   | 109.8(3) |
| C(2)-C(3)-C(4) | 119.2(7) | Br(16)-C(8)-Br(17) | 110.3(2) |
| C(3)-C(4)-C(5) | 117.8(6) | C(5)-C(9)-C(8)     | 98.7(5)  |
| C(4)-C(5)-C(6) | 116.8(6) | C(5)-C(9)-O(10)    | 112.7(5) |
| C(4)-C(5)-C(9) | 134.8(5) | C(5)-C(9)-O(13)    | 110.3(5) |
| C(6)-C(5)-C(9) | 108.4(6) | C(8)-C(9)-O(10)    | 106.5(5) |
| N(1)-C(6)-C(5) | 128.3(6) | C(8)-C(9)-O(13)    | 115.4(5) |

|                  |          |                   |          |
|------------------|----------|-------------------|----------|
| N(1)-C(6)-O(7)   | 120.7(6) | O(10)-C(9)-O(13)  | 112.5(4) |
| C(5)-C(6)-O(7)   | 110.9(5) | C(9)-O(10)-C(11)  | 114.1(6) |
| C(6)-O(7)-C(8)   | 107.8(6) | O(10)-C(11)-C(12) | 106.8(6) |
| O(7)-C(8)-C(9)   | 105.7(5) | C(9)-O(13)-C(14)  | 116.4(6) |
| O(7)-C(8)-Br(16) | 107.2(3) | O(13)-C(14)-C(15) | 106.4(6) |
| O(7)-C(8)-Br(17) | 107.9(3) |                   |          |

### EXPERIMENTAL

The melting points were determined on a micro melting point apparatus (Yanagimoto) and are uncorrected. The ir spectra were taken with a JASCO A-102 spectrometer. The  $^1\text{H}$  nmr spectra were recorded on a JOEL JNM-PMX-60 instrument using tetramethylsilane as a internal standard. Mass spectra were obtained with a ESCO EMD-05B instrument.

#### Ethyl 3-Hydroxyfuro[3,2-*c*]pyridine-2-carboxylate (**1d**).

To a solution of 4-chloronicotinic acid [5] (4.3 g, 27.3 mmoles) in 70 ml of hexamethylphosphoric triamide was added a solution of sodium hydroxide (1.7 g, 42.5 mmoles) in 8 ml of water with stirring and cooling with ice bath. Then, iodoethane (17.2 g, 110 mmoles) was added to the mixture during 1 hour, and stirred at room temperature for another hour. After dilution with 250 ml of water, the mixture was extracted with ether (50 ml x 4). The combined ethereal extracts were washed with water, dried (magnesium sulfate) and evaporated to give 4.1 g (81%) of the crude ester as a light brown syrup, which was used for the next step without any purification (the ester was resinified by heating near 100° (0.5 mm Hg)).

To a suspension of sodium hydride (2.3 g of 60% dispersion in mineral oil, 57.5 mmoles) in 50 ml of 1,2-dimethoxyethane was added ethyl glycolate (6.5 g, 62.5 mmoles) in 10 ml of 1,2-dimethoxyethane during 15 minutes with ice-cooling and stirring, to this mixture was added ethyl 4-chloronicotinate (4.1 g, 22.1 mmoles) in 15 ml of 1,2-dimethoxyethane over a period of 30 minutes. The mixture was stirred and heated at 60° for 7 hours. After evaporation of the solvent *in vacuo*, the residue was treated with 100 ml of water, washed with benzene and acidified with acetic acid. The crystalline solid precipitated was filtered and recrystallized from ethanol to give 2.1 g (46%) of compound **1d**, mp 167-171° (yellow prisms); ir (potassium bromide):  $\text{cm}^{-1}$  3100-2300 (broad, OH), 1685, 1610, 1585, 1480, 1420, 1380, 1360, 1320, 1210, 1185, 1130, 1030, 1020, 920, 880,  $^1\text{H}$  nmr (deuteriochloroform):  $\delta$  9.00 (d, J = 1.0 Hz, 1H, H-4), 8.56 (d, J = 5.8 Hz, 1H, H-6), 7.34 (dd, J = 1.0, 5.8 Hz, 1H, H-7), 6.45 (broad s, 1H, OH), 4.48 (q, J = 7.0 Hz, 2H,  $-\text{CH}_2\text{CH}_3$ ), 1.46 (t, J = 7.0 Hz, 3H,  $-\text{CH}_2\text{CH}_3$ ).

*Anal.* Calcd. for  $\text{C}_{10}\text{H}_9\text{NO}_4$ : C, 57.97; H, 4.38; N, 6.76. Found: C, 58.13; H, 4.47; N, 6.56.

#### Ethyl 3-Ethoxycarbonylmethoxyfuro[2,3-*b*] (**2a**), -[3,2-*b*] (**2b**), -[2,3-*c*] (**2c**) and -[3,2-*c*]pyridine-2-carboxylate (**2d**).

##### General Procedure.

A solution of ethyl 3-hydroxyfuro[2,3-*b*] (**1**) (3.0 g, 14.5 mmoles), ethyl bromoacetate (2.6 g, 15.5 mmoles) and potassium carbonate (20 g, 145 mmoles) in 200 ml of dry acetone was stirred and refluxed for 4-6 hours. After cooling, the insoluble in organic materials were filtered off and the filtrate was evaporated *in vacuo*. The residual mass was treated with water and extracted with chloroform. The chloroform extract was dried (magnesium sulfate) and evaporated to give crude 3-ethoxycarbonyl-methoxy compounds **2a,b,c** and **d**. Recrystallization from ether or acetone-isopropyl ether gave pure samples. Compounds thus obtained are listed in Table I.

#### Ethyl 3-Ethoxyfuro[2,3-*b*] (**3a**), -[3,2-*b*] (**3b**), -[2,3-*c*] (**3c**) and -[3,2-*c*]pyridine-2-carboxylate (**3d**).

##### General Procedure.

To a suspension of sodium ethoxide prepared from sodium (0.14 g, 6.1

mmoles) and absolute ethanol in 100 ml of dry toluene was added a solution of ethyl 3-ethoxycarbonylmethoxyfuro[2,3-*b*] (**2**) (1.0 g, 3.4 mmoles) in 50 ml of toluene during 15 minutes under reflux and stirring. After refluxing and stirring for further 2 hours, the reaction mixture was cooled, washed with water, dried (magnesium sulfate) and evaporated to give crude 3-ethoxy-2-ethoxycarbonyl compounds **3a,b,c** and **d** which were purified by recrystallization from ether or vacuum distillation. The compounds obtained by this procedure are listed in Table I.

#### 3-Ethoxyfuro[2,3-*b*] (**5a**), -[3,2-*b*] (**5b**), -[2,3-*c*] (**5c**) and -[3,2-*c*]pyridine (**5d**).

##### General Procedure.

A mixture of ethyl 3-ethoxyfuro[2,3-*b*] (**3**) (1.1 g, 4.9 mmoles), potassium hydroxide (1.2 g, 21.4 mmoles) and 5 ml of water in 25 ml of ethanol was refluxed for 1 hour. After evaporation of the solvent, the residual solid was dissolved in 5 ml of water, acidified with acetic acid. The aqueous solution was evaporated to dryness and the solid residue was used for the next step without isolation of the carboxylic acid **4**. The solid residue was mixed with copper powder (15 g) in a 5 ml flask equipped with an air condenser, and then heated to pyrolyze using a soft flame. The distillate was distilled *in vacuo* to give 3-ethoxyfuro[2,3-*b*] (**5a**), **5b**, **5c** or **5d**. In the cases of compound **3b** and **3c**, the aqueous alkaline solution was acidified with hydrochloric acid and cooled in a refrigerator to precipitate the hydrochloride of **4b** and **4c**. The 3-ethoxy compounds thus obtained are listed in Table I.

#### Vilsmeier Reaction of Compound **5a**, **5b**, **5c** and **5d**.

##### General Procedure.

To a solution of compound **5** (270 mg, 1.66 mmoles) in 1 ml of *N,N*-dimethylformamide was added a mixture of phosphoryl chloride (0.5 g) and *N,N*-dimethylformamide (0.5 g) at room temperature. The mixture was heated on a water bath for 1 hour, diluted with water, basified with sodium hydrogen carbonate and extracted with ether. The ethereal extract was washed with water and dried (magnesium sulfate). In the cases of **5c** and **5d**, the residue of the ethereal solution was identical with the starting compound **5c** or **5d** (identified by comparison of the ir spectra). The residue of the ethereal solution obtained from **5a** or **5b** was chromatographed on a silica gel (Merck silica gel 60, 20 g) with chloroform. In the case of **5a**, the first fraction gave 3-chloro-2-formyl derivative **7a** (43% yield) and the second fraction 3-ethoxy-2-formyl derivative **6a** (22% yield). In the case of **5b**, the first fraction gave the 3-ethoxy-2-formyl **6b** (30% yield) and the second fraction 3-chloro-2-formyl derivative **7b** (35% yield).

#### Acidic Hydrolysis of Compound **5a**, **5b**, **5c** and **5d**.

These experiments were carried out with 90 mg samples of **5a**, **5b**, **5c** and **5d**, dissolved in 1.0 ml of 15% deuterium chloride in deuterium oxide. The hydrolysis was carried out in an external thermostat at 25° and at 70°. The ratio of hydrolysis was determined by integration over the hydrogen signals of the ethoxy group of **5a**, **5b**, **5c** and **5d**, and those of the ethanol formed. After the hydrolysis ceased, the products were isolated and identified. Compound **8a**, **8b** and **8c** were identified by comparison of the ir spectrum with that of the authentic sample [2,3,4] respectively, compound **8d** was isolated as the hydrochloride salt (prepared by evaporation of the solution used for the hydrolysis and recrystallization of the resultant crystalline solid from methanol-acetone). Compound **8d** HCl had mp 261-263°, ir (potassium bromide):  $\text{cm}^{-1}$  3200-2400 (broad, OH), 1630, 1455, 1430, 1375, 1210, 1055, 805.

*Anal.* Calcd. for  $\text{C}_7\text{H}_9\text{ClNO}_2$ : C, 49.00; H, 3.52; N, 8.16. Found: C, 49.26; H, 3.55; N, 8.15.

#### Bromination of Compound **5a**, **5b**, **5c** and **5d**.

##### (A) With 1 Equivalent Mole of Bromine in Absolute Chloroform.

##### General Procedure.

To a solution of 3-ethoxy compound **5a**, **5b**, **5c** or **5d** (163 mg, 1.0



mmole) in 7 ml of absolute chloroform (the commercial chloroform containing ethanol as a stabilizer was treated with sulfuric acid, phosphorus pentoxide and potassium carbonate and distilled to remove the ethanol [11]) was added bromine (170 mg, 1.06 mmoles) in 2 ml of absolute chloroform at room temperature with stirring during 5-10 minutes. The yellow to orange yellow mixture was stirred at room temperature for 3 to 5 hours (in the cases of **5b**, **5c** and **5d**, almost immediately after the addition of bromine, colorless crystals began to deposit). After evaporation of the solvent *in vacuo*, the crystalline product (in the case of **5a**, the syrupy residue was warmed at 40-50° to solidify the syrup) was recrystallized from acetonitrile to give the hydrobromide of 2-bromo-3-ethoxy compound. The free bases, except **5c**, were obtained by treatment of the aqueous solution of the salt with sodium hydroxide, extraction with chloroform and evaporation of the solvent. The compounds thus obtained are listed in Table I.

#### (B) With 3 Equivalent Moles of Bromine in Commercial Chloroform.

##### General Procedure.

To a solution of compound **5a**, **5b**, **5c** or **5d** (163 mg, 1.0 mmole) in 10 ml of chloroform (commercial grade) was added bromine (500 mg, 3.1 mmoles) in 5 ml of chloroform with cooling and stirring during 10 minutes. The red-orange solution was stirred at room temperature for 2 hours. After evaporation of the solvent and the excess of the bromine, the residual mass was dissolved in 20 ml of methanol, made alkaline with sodium hydroxide, stirred for 15 minutes, and evaporated the solvent. The residue was treated with water, extracted with chloroform and dried (magnesium sulfate). From the residue of the chloroform extract compounds produced were isolated by chromatograph on a silica gel column (Merck silica gel 60) with chloroform and purified by recrystallization or vacuum distillation. Compound **5a** yielded **10a**, **5b** gave **10b** and **11b**, **5c** gave **11c**, and **5d** gave **11d**, respectively, which are listed in Table I.

##### Conversion of Compound **11b** and **11d** to **9b** and **9d**.

A mixture of **11b** or **11d** (66 mg, 0.23 mmole) and *p*-toluenesulfonic acid (100 mg, 0.53 mmole) in 5 ml of benzene was refluxed for 3 hours. After cooling, the mixture was washed with 5 ml of 5% sodium hydroxide solution, and dried (magnesium sulfate). Evaporation of the solvent yielded 50 mg of syrup which was purified by distillation and identified with **9b** and **9d**, respectively, by comparison of the ir spectra.

Formylation of **5a**, **5b**, **5c** and **5d** with Butyllithium and *N,N*-Dimethylformamide.

##### General Procedure.

A solution of 3-ethoxyfuropyridine (305 mg, 1.87 mmoles) in 8 ml of dry tetrahydrofuran was stirred under a nitrogen atmosphere and cooled at -70°. To this solution was added a solution of *n*-butyllithium in hexane (0.9 ml, 15%, 2.11 mmoles) dropwise by syringe over a period of 10 minutes at -70°. After stirring at this temperature for 20-30 minutes, the mixture was treated with *N,N*-dimethylformamide (190 mg, 2.6 mmoles). The reaction mixture was stirred for 15 hours after removal of the cooling bath. Then, the mixture was treated with 1 ml of water, evaporated the solvent and extracted with dichloromethane. The extract was washed with water, dried (magnesium sulfate) and evaporated to give a syrupy residue from which compounds **6**, **12**, **13** and **5** were isolated by high-performance liquid chromatography carried out on a column (250 mm x 8 i.d.) of Chemopak, Nucleosil 100-7 (Chemco Co. Ltd., Osaka) with a hexane-ethyl acetate (1:1) system. By this procedure, compound **5a** gave 2-formyl derivative **6a** (40% yield), 2-hydroxymethyl derivative **12a** (20%) and 2-dimethylaminocarbonyl derivative **13a** (2%), **5b** gave **6b** (18%), **12b** (18%) and **13b** (2%), **5c** afforded **6c** (33%), **12c** (8%) and a trace amount of **13c**, and **5d** afforded **6d** (47%) and a trace amount of **12d** and accompanying recovery of the starting material in 30%, 54%, 50% and 45%, respectively. Compounds obtained by this procedure are listed in Table I.

#### X-Ray Structural Determination of **10a**.

A single crystal of **10a** (C<sub>11</sub>H<sub>13</sub>Br<sub>2</sub>NO<sub>3</sub>) was recrystallized by slow evaporation of a ethereal solution at room temperature. Cell parameters were measured on a Rigaku automatic four-circle diffractometer with a graphite-monochromated CuK $\alpha$  radiation ( $\lambda = 1.5405 \text{ \AA}$ ) and refined by least-squares method. The crystallographic data are as follows:  $M_r = 367.038$ , orthorhombic, space group P2<sub>1</sub>2<sub>1</sub>2<sub>1</sub>,  $a = 7.5040$ ,  $b = 13.4060$ ,  $c = 13.5030 \text{ \AA}$ ,  $D_x = 1.7948 \text{ g/cm}^3$ ,  $V = 1358.38 \text{ \AA}^3$ ,  $z = 4$ . By means of the omega-2 theta scanning mode, a total of 1353 independent reflections were collected. Numerical calculations for the structure determination and refinement were carried out using UNICS and AUTO library of Crystallographic Research Center, Institute for Protein Research of Osaka University. The structure of **10a** was solved by the direct method using MULTAN 78 program [12]. The structure was refined by a block-diagonal least-squares procedure, minimizing the quantity  $\sum w (|F_o| - |F_c|)^2$  with weights  $w$  equal to  $1/\sigma(F_o)^2$ . The final R value was 0.0823. The final atomic parameters of the non-hydrogen atoms, bond lengths and bond angles are listed in Table III.

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*Anal.* Calcd. for C<sub>10</sub>H<sub>9</sub>NO<sub>4</sub>: C, 57.97; H, 4.38; N, 6.76. Found: C, 57.91; H, 4.57; N, 6.88.
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