Furopyridines. XIV [1]. Synthesis of 2-Aminoalkyl Derivatives of Furo[2,3-*b*]-, Furo[3,2-*b*]-, Furo[2,3-*c*]- and Furo[3,2-*c*]pyridine

Shunsaku Shiotani

College of Liberal Arts, University of Toyama,
Gofuku 3190, Toyama, Japan

Received March 29, 1993

The preparation of 2-aminomethyl- **3a-d**, 2-acetamidomethyl- **4a-d**, 2-*N*,*N*-dimethylaminomethyl- **5a-d**, 2-(1-hydroxy-2-nitroethyl)- **6a-d**, 2-(1-hydroxyl-2-aminoethyl)- **7a-d** and 2-(1-hydroxy-2-*N*,*N*-dimethylaminoethyl)- **8b-d** derivatives of furo[2,3-*b*]-, furo[3,2-*b*]-, furo[2,3-*c*]- and furo[3,2-*c*]pyridine is described.

J. Heterocyclic Chem., **30**, 1035 (1993).

Furopyridines are of chemical and pharmacological interest because of their similarity to benzofuran, quinoline and isoquinoline which are important moieties in many biologically active compounds. However, there were very few reports on the chemical properties and biological activities of furopyridines [2-7] except from our laboratory. Owing to our interest in the chemistry of furopyridines previously we reported the synthesis of 2-formylfuropyridines [8,9]. With the aim of determining the biological activities, the following 2-aminoalkyl derivatives of furo[2,3-*b*]-, furo[3,2-*b*]-, furo[2,3-*c*]- and furo[3,2-*c*]pyridine were prepared from the corresponding 2-formyl derivatives **1a-d**.

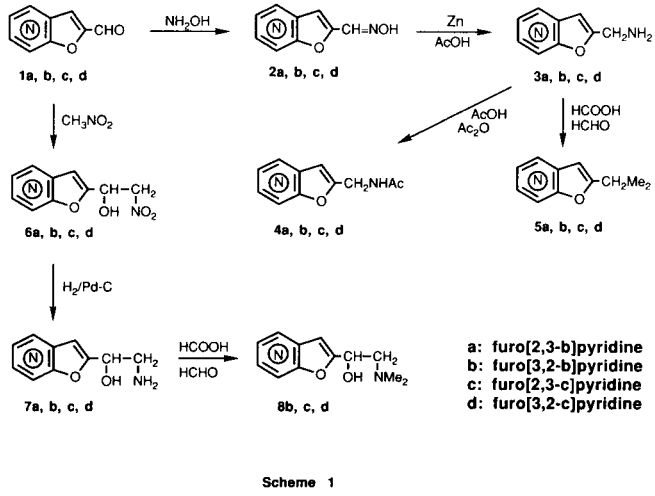
Reduction of the oximes **2a-d** [8,9] of the aldehydes **1a-d** by heating with zinc powder in acetic acid afforded 2-aminomethyl derivatives **3a-d** in almost quantitative yield. The *N*-acetyl derivatives **4a-d** were obtained by heating the aminomethyl compounds with acetic anhydride and acetic acid. The primary amines **2a-d** were converted to the *N*,*N*-dimethyl derivatives **5a-d** by heating with formic acid and formaldehyde.

Condensation of the aldehydes **1a-d** with nitromethane afforded the corresponding nitroethanol compounds **6a-d** in good yield. Catalytic reduction of the nitro group over palladium-charcoal gave the corresponding aminoethanol compounds **7a-d**, which were followed by methylation with formic acid and formaldehyde to give *N*,*N*-dimethylamino derivative **8b-d** [10].

It is worth noting that in the pmr spectrum the β-protons and α-proton of the nitroethanol **6a-d** and the aminoethanol **7a-d** in deuteriochloroform showed an A_2X pattern (J_{AX} = 6.0-6.4 Hz for the nitroethanol **6a-d** and 4.8-5.6 Hz for the aminoethanol **7a-d**), while those protons of these compounds in deuteriomethanol and *N*,*N*-dimethylaminoethanol derivative **8b-d** in deuteriochloroform an ABX pattern (J_{AX} = 4.2-5.6 Hz, J_{BX} = 6.8-8.6 Hz and J_{AB} = 12.4-14.8 Hz for the nitroethanol **6a-d**, J_{AX} = 4.8-5.6 Hz, J_{BX} = 6.0-6.4 Hz and J_{AB} = 12.4-12.8 Hz, for the aminoethanol **7a-d** and J_{AX} = 4.8-5.2 Hz, J_{BX} = 8.8 Hz and J_{AB} = 12.4 Hz for the *N*,*N*-dimethylaminoethanol **8b-d**).

These facts suggest that the dihedral angles between the α-proton and both the β-protons of **6a-d** and **7a-d** in deuteriochloroform are nearly equal (about 60°), while in the latter cases the dihedral angles between the α-proton and each of the β-protons are apparently different. By examination with Dreiding models, it was assumed that in the former conformation the hydroxyl group and the nitro or amino group can link through intramolecular hydrogen-bonding, while in the latter the polar functions are solvated by deuteriomethanol and are far apart. In the case of **8b-d**, the bulky dimethylamino group and the hydroxyl group are far apart even in aprotic deuteriochloroform by their steric repulsion.

The pharmacological effects of these amino compounds will be presented elsewhere in the future.



Scheme 1

EXPERIMENTAL

Melting points were determined by using Yanagimoto micro melting point apparatus. All melting points are uncorrected. The ir spectra were recorded on a JASCO A-102 spectrometer. The pmr spectra were taken on a JEOL JNM-PMX 60 instrument with tetramethylsilane as an internal reference. The mass spectra were obtained by using JEOL JMS-OISG-2 spectrometer.

General Procedure for the Preparation of 2-Aminomethylfuropyridines **3a**, **3b**, **3c** and **3d**.

To a solution of oxime **2** (2.12 g, 13.1 mmoles) in acetic acid (30 ml) was added zinc powder (20 g, 300 mmoles) portionwise during 10 minutes. After stirring at room temperature for 2 hours, the acetic acid solution was separated and evaporated *in vacuo* to leave a viscous syrup. The residue was dissolved in water (100 ml), made strongly alkaline to dissolve the zinc hydroxide, and extracted with chloroform. The chloroform solution was dried over magnesium sulfate and evaporated under reduced pressure to leave an oily residue. The oily aminomethyl compound **3** was converted to the hydrochloride and purified by recrystallization from methanol-acetone to afford the pure sample of the hydrochlorides of **3a,b,c** and **d** in a yield of 85, 90, 95 and 85% respectively.

2-Aminomethylfuro[2,3-*b*]pyridine Hydrochloride **3a-HCl**.

This compound has mp 228-231° (from methanol-acetone).

Anal. Calcd. for $C_8H_8N_2O$·HCl: C, 52.04; H, 4.91; N, 15.17. Found: C, 52.02; H, 4.91; N, 15.02.

The free base from the hydrochloride was a colorless oil of bp 110-120° (bath temperature) (0.1 mm Hg); ir (liquid film): 3600-2500 (broad), 3060, 3020, 2920, 2850, 1580, 1400, 1335, 1300, 1270, 1240, 1220, 1160, 1140, 1110, 940, 810, 770 cm^{-1}; pmr (deuteriochloroform): δ 8.16 (dd, J = 1.6, 5.8 Hz, 1H, H-6), 7.76 (dd, J = 1.6, 7.4 Hz, 1H, H-4), 7.08 (dd, J = 5.8, 7.4 Hz, 1H, H-5), 6.46 (t, J = 0.8 Hz, 1H, H-3), 3.93 (d, J = 0.8 Hz, 2H, H-α), 1.85 (s, 2H, NH_2); ms: m/z 148.0637 (M^+, Calcd. for $C_8H_8N_2O$: 148.0636).

Anal. Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.45; H, 5.66; N, 18.59.

2-Aminomethylfuro[3,2-*b*]pyridine Dihydrochloride **3b-2HCl**.

This compound had mp 240-243° dec (from methanol-acetone).

Anal. Calcd. for $C_8H_8N_2O$·2HCl: C, 43.46; H, 4.56; N, 12.67. Found: C, 43.39; H, 4.57; N, 12.55.

The free base was a colorless oil of bp 100-110° (bath temperature) (0.1 mm Hg); ir (liquid film): 3600-2500 (broad), 2920, 2850, 1610, 1590, 1560, 1475, 1410, 1285, 1240, 1175, 1150, 1105, 940, 810, 790 cm^{-1}; pmr (deuteriochloroform): δ 8.54 (dd, J = 1.2, 4.6 Hz, 1H, H-5), 7.65 (ddd, J = 0.8, 1.2, 8.2 Hz, 1H, H-7), 7.11 (dd, J = 4.6, 8.2 Hz, 1H, H-6), 6.73 (q, J = 0.8 Hz, 1H, H-3), 4.00 (d, J = 0.8 Hz, 2H, H-α), 2.27 (s, 2H, NH_2); ms: m/z 148.0635 (M^+, Calcd. for $C_8H_8N_2O$: 148.0636).

2-Aminomethylfuro[2,3-*c*]pyridine Dihydrochloride **3c-2HCl**.

This compound had mp 268-270° (from methanol-acetone).

Anal. Calcd. for $C_8H_8N_2O$·2HCl: C, 43.46; H, 4.56; N, 12.67. Found: C, 43.46; H, 4.54; N, 12.28.

The free base was a colorless oil of bp 120-130° (bath temperature) (0.1 mm Hg); ir (liquid film): 3360, 3290, 3090, 2910, 2840, 1610, 1590, 1470, 1425, 1355, 1330, 1280, 1260, 1230, 1190, 1135, 1095, 1030, 955, 920, 900, 880, 840 cm^{-1}; pmr (deuteriochloroform): δ 8.69 (dd, J = 0.8, 1.0 Hz, 1H, H-7), 8.27 (d, J = 5.2 Hz, 1H, H-5), 7.31 (dd, J = 1.0, 5.2 Hz, 1H, H-4), 6.44 (q, J = 0.8 Hz, 1H, H-3), 3.87 (d, J = 0.8 Hz, 2H, H-α), 1.77 (s, 2H, NH_2); ms: m/z 148.0662 (M^+, Calcd. for $C_8H_8N_2O$: 148.0636).

2-Aminomethylfuro[3,2-*c*]pyridine Dihydrochloride **3d-2HCl**.

This compound had mp 256-257° (from methanol-acetone).

Anal. Calcd. for $C_8H_8N_2O$·2HCl: C, 43.46; H, 4.56; N, 12.67. Found: C, 43.66; H, 4.54; N, 12.54.

The free base was a colorless oil of bp 120-130° (bath temperature) (0.1 mm Hg); ir (liquid film): 3600-2700 (broad), 3050, 2820, 1600, 1575, 1460, 1435, 1320, 1260, 1190, 1165, 1150, 1130, 1020, 940, 890, 815, 760 cm^{-1}; pmr (deuteriochloroform): δ 8.70 (d, J = 0.8 Hz, 1H, H-4), 8.32 (d, J = 5.6 Hz, 1H, H-6), 7.26 (dt, J = 0.8, 5.6 Hz, 1H, H-7), 6.50 (q, J = 0.8 Hz, 1H, H-3), 3.94 (d, J = 0.8 Hz, 2H, H-α), 2.89 (s, 2H, NH_2); ms: m/z 148.0636 (M^+, Calcd. for $C_8H_8N_2O$: 148.0636).

Preparation of 2-Acetamidomethylfuropyridines **4a**, **4b**, **4c** and **4d**.

General Procedure.

A mixture of compound **3** (900 mg, 6.1 mmoles), acetic acid (5 ml) and acetic anhydride (5 ml) was heated on a water bath for 2 hours. After evaporation of the excess acetic anhydride and acetic acid under reduced pressure, the viscous residue was treated with water, basified with 10% sodium hydroxide solution and extracted with chloroform. The dried (magnesium sulfate) chloroform solution was evaporated under reduced pressure to give a colorless solid mass of **4**.

2-Acetamidomethylfuro[2,3-*b*]pyridine **4a**.

The crude residue was recrystallized from acetone-ether to give 1.05 g (90%) of pure **4a** of mp 128.5-130.5°; ir (potassium bromide): 3280, 3110, 3050, 2980, 2910, 2810, 1625, 1585, 1545, 1395, 1340, 1320, 1270, 1240, 1170, 1140, 1090, 1010, 930, 825, 785, 770 cm^{-1}; pmr (deuteriochloroform): δ 8.16 (dd, J = 1.6, 4.8 Hz, 1H, H-6), 7.75 (dd, J = 1.6, 7.4 Hz, 1H, H-4), 7.10 (dd, J = 4.8, 7.4 Hz, 1H, H-5), 6.55 (t, J = 0.8 Hz, 1H, H-3), 4.56 (dd, J = 0.8, 5.8 Hz, 2H, H-α, changed to a doublet of J = 0.8 Hz by addition of deuterium oxide), 2.02 (s, 3H, -COCH_3), 7.70 (broad one peak, 1H, N*H*, disappeared by addition of deuterium oxide).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.24; H, 5.33; N, 24.62.

2-Acetamidomethylfuro[3,2-*b*]pyridine **4b**.

The crude product was purified by recrystallization from acetoneether to give 1.0 g (86%) of **4b**, mp 114.5-115.5°; ir (potassium bromide): 3280, 3070, 2920, 2820, 1640, 1600, 1550, 1400, 1370, 1285, 1260, 1210, 1165, 1140, 1085, 1020, 935, 790 cm^{-1}; pmr (deuteriochloroform): δ 8.42 (dd, J = 1.4, 4.4 Hz, 1H, H-5), 7.63 (ddd, J = 0.8, 1.4, 8.0 Hz, 1H, H-7), 7.10 (dd, J = 4.4, 8.0 Hz, 1H, H-6), 6.74 (q, J = 0.8 Hz, 1H, H-3), 4.57 (dd, J = 0.8, 5.4 Hz, 2H, H-α, changed to a doublet of J = 0.8 Hz by addition of deuterium oxide), 2.02 (s, 3H, -COCH_3), 6.64 (broad one peak, 1H, N*H*, disappeared by addition of deuterium oxide).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.25; H, 5.28; N, 14.70.

2-Acetamidomethylfuro[2,3-*c*]pyridine **4c**.

The crude product was recrystallized from methanol-ether to give 0.95 g (80%) of **4c**, mp 81-83°; ir (potassium bromide): 3600-2600 (broad), 3080, 2880, 1635, 1570, 1540, 1460, 1415, 1365, 1310, 1250, 1230, 1180, 1140, 1110, 1025, 945, 845, 815 cm^{-1}; pmr (deuteriochloroform): δ 8.65 (dd, J = 0.8, 1.0 Hz, 1H, H-7), 8.26 (d, J = 5.2 Hz, 1H, H-5), 7.36 (dd, J = 1.0, 5.2 Hz, 1H, H-4), 6.56 (q, J = 0.8 Hz, 1H, H-3), 4.56 (dd, J = 0.8, 5.4 Hz, 2H, H-α, changed to a doublet of J = 0.8 Hz by addition of deuterium oxide), 2.02 (s, 3H, -COCH_3), 8.20 (broad one peak, disappeared by addition of deuterium oxide); ms: m/z 190.0764 (M^+, Calcd. for $C_{10}H_{10}N_2O_2$: 190.0742).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.18; H, 5.53; N, 15.09.

2-Acetamidomethylfuro[3,2-*c*]pyridine **4d**.

The crude residue was recrystallized from acetone-ether to give 1.0 g (86%) of **4d**, mp 92-94°; ir (potassium bromide): 3200, 3020, 2925, 2840, 1655, 1570, 1450, 1420, 1360, 1295, 1255, 1150, 1110, 1020, 940, 890, 820, 760 cm^{-1}; pmr (deuteriochloroform): δ 8.65 (d, J = 0.8 Hz, 1H, H-4), 8.29 (d, J = 5.6 Hz, 1H, H-6), 7.23 (dt, J = 0.8, 5.6 Hz, 1H, H-7), 6.54 (q, J = 0.8 Hz, 1H, H-3), 4.52 (dd, J = 0.8, 5.6 Hz, 1H, H-α, changed to a doublet of J = 0.8 Hz by addition of deuterium oxide), 2.01 (s, 3H, $-COCH_3$), 7.57 (broad one peak, disappeared by addition of deuterium oxide).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.38; H, 5.40; N, 14.33.

Preparation of 2-*N*,*N*-Dimethylaminomethylfuropyridines **5a**, **5b**, **5c** and **5d**.

General Procedure.

A mixture of **3** (200 mg, 1.35 mmoles), formic acid (2 ml) and formalin (2 ml) was heated on a water bath for 30 minutes. After cooling, the mixture was diluted with water (20 ml), basified with 10% sodium hydroxide, extracted with chloroform and dried over magnesium sulfate. The chloroform solution was evaporated under reduced pressure to afford a slightly brown syrup. Further processing of the residue from **3a**, **3b**, **3c** and **3d** is indicated in the subsequent paragraph.

2-*N*,*N*-Dimethylaminomethylfuro[2,3-*b*]pyridine **5a**.

The residue from **3a** was distilled to yield 200 mg (84%) of **5a** as a colorless oil of bp 100° (bath temperature) (0.4 mm Hg); ir (liquid film): 3120, 3060, 3020, 2980, 2945, 2860, 2830, 2780, 1585, 1470, 1455, 1410, 1365, 1335, 1325, 1280, 1255, 1240, 1180, 1145, 1110, 1100, 1040, 1025, 940, 850, 815, 770 cm^{-1}; pmr (deuteriochloroform): δ 8.23 (dd, J = 1.8, 4.8 Hz, 1H, H-6), 7.81 (dd, J = 1.8, 7.6 Hz, 1H, H-4), 7.13 (dd, J = 4.8, 7.6 Hz, 1H, H-5), 6.23 (t, J = 0.8 Hz, 1H, H-3), 3.63 (d, J = 0.8 Hz, 2H, H-α), 2.32 (s, 6H, NMe_2).

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 67.77; H, 6.86; N, 15.50.

2-*N*,*N*-Dimethylaminomethylfuro[3,2-*b*]pyridine **5b**.

The crude product from **3b** was distilled to give 200 mg (84%) of **5b** as a colorless oil of bp 100-105° (bath temperature) (0.5 mm Hg); ir (liquid film): 3050, 3010, 2970, 2940, 2850, 2810, 2760, 1600, 1560, 1450, 1410, 1360, 1300, 1260, 1230, 1170, 1140, 1095, 1040, 1020, 930, 845, 810, 785 cm^{-1}; pmr (deuteriochloroform): δ 8.45 (dd, J = 1.4, 4.4 Hz, 1H, H-5), 7.67 (ddd, J = 0.8, 1.4, 7.8 Hz, 1H, H-7), 7.10 (dd, J = 4.4, 7.8 Hz, 1H, H-6), 6.78 (q, J = 0.8 Hz, 1H, H-3), 3.66 (d, J = 0.8 Hz, 2H, H-α), 2.34 (s, 6H, NMe_2); ms: m/z 176.0953 (M^+, Calcd. for $C_{10}H_{12}N_2O$: 176.0949).

The hydrochloride had mp 246-249° (from methanol-acetone).

Anal. Calcd. for $C_{10}H_{12}N_2O \cdot 2HCl$: C, 48.21; H, 5.66; N, 11.24. Found: C, 48.00; H, 5.62; N, 11.40.

2-*N*,*N*-Dimethylaminomethylfuro[2,3-*c*]pyridine **5c**.

The residue from **3c** was distilled to give 210 mg (88%) of **5c** as a colorless oil, bp 110-120° (bath temperature) (0.5 mm Hg); ir (liquid film): 3050, 2970, 2950, 2870, 2830, 2780, 1600, 1450, 1420, 1360, 1260, 1180, 1130, 1095, 1025, 950, 935, 880, 825 cm^{-1}; pmr (deuteriochloroform): δ 8.77 (dd, J = 0.8, 1.0 Hz, 1H, H-7), 8.33 (d, J = 5.2 Hz, 1H, H-5), 7.43 (dd, J = 1.0, 5.2 Hz, 1H, H-4), 6.60 (q, J = 0.8 Hz, 1H, H-3), 3.65 (d, J = 0.8 Hz, 2H, H-α), 2.33 (s, 6H, NMe_2); ms: m/z 176.0957 (M^+, Calcd. for $C_{10}H_{12}N_2$: 176.0947).

2-*N*,*N*-Dimethylaminomethylfuro[3,2-*c*]pyridine **5d**.

The crude product from **3d** was distilled to give 215 mg (90%) of **5d** as a colorless oil, bp 110-120° (bath temperature) (0.5 mm Hg); ir (liquid film): 3100, 3040, 2980, 2950, 2860, 2830, 2775, 1600, 1570, 1455, 1430, 1360, 1325, 1260, 1160, 1135, 1020, 925, 880, 810, 760 cm^{-1}; pmr (deuteriochloroform): δ 8.84 (d, J = 0.8 Hz, 1H, H-4), 8.45 (d, J = 5.6 Hz, 1H, H-6), 7.40 (dt, J = 0.8, 5.6 Hz, 1H, H-7), 6.67 (q, J = 0.8 Hz, 1H, H-3), 3.66 (d, J = 0.8 Hz, 2H, H-α), 2.33 (s, 6H, NMe_2); ms: m/z 176.0955 (M^+, Calcd. for $C_{10}H_{12}N_2O$: 176.0947).

Preparation of 2-(1-Hydroxy-2-nitroethyl)furopyridines **6a**, **6b**, **6c** and **6d**.

General Procedure.

To a solution of **1** (750 mg, 5.1 mmoles) and nitromethane (520 mg, 8.52 mmoles) in absolute methanol (40 ml) was added a solution of sodium methoxide (280 mg, 5.2 mmoles) in methanol (5 ml) by syringe under a nitrogen atmosphere and stirring at -15°. The mixture was stirred at -15° for 2.5 hours and at room temperature for 0.5 hour, treated with water (10 ml), acidified with acetic acid, basified with sodium bicarbonate and evaporated under reduced pressure to remove the methanol. The residue was diluted with water (20 ml), extracted with ethyl acetate and dried over magnesium sulfate. The solvent was evaporated and the solid residue was recrystallized to give a pure sample of **6**.

2-(1-Hydroxy-2-nitroethyl)furo[2,3-*b*]pyridine **6a**.

The crude residue was purified by recrystallization from methanol-ether to afford 950 mg (90%) of **6a**, mp 117-119° (pale yellow needles); ir (potassium bromide): 3500-2400 (broad), 1590, 1550, 1410, 1380, 1365, 1335, 1315, 1280, 1260, 1230, 1200, 1180, 1150, 1090, 960, 895, 820, 765 cm^{-1}; pmr (deuteriochloroform): δ 8.16 (dd, J = 1.8, 4.8 Hz, 1H, H-6), 7.85 (dd, J = 1.8, 7.6 Hz, 1H, H-4), 7.14 (dd, J = 4.8, 7.6 Hz, 1H, H-5), 6.80 (d, J = 0.8 Hz, 1H, H-3), 6.43 (br s, 1H, -O*H*), 5.70 (dt, J = 0.8, 6.0 Hz, 1H, H-α), 4.87 (d, J = 6.0 Hz, 2H, H-β); pmr (deuteriomethanol): δ 8.23 (dd, J = 1.8, 4.8 Hz, 1H, H-6), 8.04 (dd, J = 1.8, 7.6 Hz, 1H, H-4), 7.30 (dd, J = 4.8, 7.6 Hz, 1H, H-5), 5.58 (ddd, J = 0.8, 4.2, 8.2 Hz, 1H, H-α), 5.00 (dd, J = 4.2, 12.8 Hz, 1H, H-β_1), 4.76 (dd, J = 8.2, 12.8 Hz, 1H, H-β_2).

Anal. Calcd. for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 52.20; H, 3.91; N, 13.49.

2-(1-Hydroxy-2-nitroethyl)furo[3,2-*b*]pyridines **6b**.

Recrystallization of the crude product from methanol yielded 900 mg (85%) of pure **6b**, mp 141-142° (pale yellow sandy crystals); ir (potassium bromide): 3500-2400 (broad), 1560, 1414, 1370, 1330, 1270, 1235, 1210, 1170, 1150, 1095, 960, 890, 820, 805, 770 cm^{-1}; pmr (deuteriochloroform): δ 8.47 (dd, J = 1.0, 4.8 Hz, 1H, H-5), 7.84 (dt, J = 1.0, 8.4 Hz, 1H, H-7), 7.27 (dd, J = 4.8, 8.4 Hz, 1H, H-6), 7.01 (t, J = 1.0 Hz, 1H, H-3), 6.50 (br s, 1H, -O*H*), 5.64 (dt, J = 1.0, 6.4 Hz, 1H, H-α), 4.87 (d, J = 6.4 Hz, 2H, H-β); pmr (deuteriomethanol): δ 8.46 (dd, J = 1.0, 4.8 Hz, 1H, H-5), 7.95 (dt, J = 1.0, 8.4 Hz, 1H, H-7), 7.34 (dd, J = 4.8, 8.4 Hz, 1H, H-6), 7.02 (t, J = 1.0 Hz, 1H, H-3), 5.64 (ddd, J = 1.0, 4.4, 8.6 Hz, 1H, H-α), 5.03 (dd, J = 4.4, 13.4 Hz, 1H, H-β_1), 4.82 (dd, J = 8.6, 13.4 Hz, 1H, H-β_2).

Anal. Calcd. for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 52.26; H, 3.97; N, 13.39.

2-(1-Hydroxy-2-nitroethyl)furo[2,3-*c*]pyridine **6c**.

The crude product was recrystallized from methanol-ether to give 900 mg (85%) of pure **6c**, mp 127-129° (pale yellow sandy crystals); ir (potassium bromide): 3600-2300 (broad), 1580, 1530, 1465, 1410, 1370, 1325, 1260, 1180, 1100, 1035, 955, 895, 820, 780 cm^{-1}; pmr (deuteriochloroform): δ 8.79 (t, J = 1.0 Hz, 1H, H-7), 8.38 (d, J = 4.8 Hz, 1H, H-5), 7.51 (dd, J = 1.0, 4.8 Hz, 1H, H-4), 7.23 (br s, 1H, -O*H*), 6.86 (t, J = 1.0 Hz, 1H, H-3), 5.66 (dt, J = 1.0, 6.0 Hz, 1H, H-α), 4.84 (d, J = 6.0 Hz, 2H, H-β); pmr (deuteriomethanol): δ 8.75 (t, J = 1.0 Hz, 1H, H-7), 8.33 (d, J = 5.2 Hz, 1H, H-5), 7.57 (dd, J = 1.0, 5.2 Hz, 1H, H-4), 5.62 (ddd, J = 1.0, 5.6, 6.8 Hz, 1H, H-α), 4.95 (dd, J = 6.8, 14.8 Hz, 1H, H-β_1), 4.72 (dd, J = 5.6, 14.8 Hz, 1H, H-β_2).

Anal. Calcd. for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 52.04; H, 3.91; N, 13.68.

2-(1-Hydroxy-2-nitroethyl)furo[3,2-*c*]pyridine **6d**.

The crude product was purified by recrystallization from methanol-ether to afford 920 mg (87%) of **6d**, mp 123-125° (pale yellow sandy crystals); ir (potassium bromide): 3300-2200 (broad), 1540, 1425, 1360, 1320, 1260, 1195, 1160, 1140, 1090, 1030, 955, 940, 890, 760 cm^{-1}; pmr (deuteriochloroform): δ 8.88 (d, J = 0.8 Hz, 1H, H-4), 8.49 (d, J = 5.2 Hz, 1H, H-6), 7.42 (dt, J = 0.8, 5.2 Hz, 1H, H-7), 7.25 (br s, 1H, -O*H*), 6.89 (t, J = 0.8 Hz, 1H, H-3), 5.67 (dt, J = 0.8, 6.0 Hz, 1H, H-α), 4.84 (d, J = 6.0 Hz, 2H, H-β); pmr (deuteriomethanol): δ 8.80 (d, J = 0.8 Hz, 1H, H-4), 8.37 (d, J = 5.8 Hz, 1H, H-6), 7.55 (dt, J = 0.8, 5.8 Hz, 1H, H-7), 6.98 (t, J = 0.8 Hz, 1H, H-3), 5.58 (ddd, J = 0.8, 4.4, 8.0 Hz, 1H, H-α), 4.98 (dd, J = 4.4, 12.4 Hz, 1H, H-β_1), 4.76 (dd, J = 8.0, 12.4 Hz, 1H, H-β_2).

Anal. Calcd. for $C_9H_8N_2O_4$: C, 51.93; H, 3.87; N, 13.46. Found: C, 52.09; H, 3.88; N, 13.23.

Preparation of 2-(1-Hydroxy-2-aminoethyl)furopyridines **7a**, **7b**, **7c** and **7d**.

General Procedure.

A mixture of compound **6** (300 mg, 1.44 mmoles) and palladium-charcoal (5%, 500 mg) in methanol (30 ml) was stirred in a hydrogen atmosphere at room temperature. After the uptake of hydrogen (95-100 ml, 10-14 hours) had ceased, the catalyst was filtered off and the filtrate evaporated under reduced pressure. The residual syrup was converted to the oxalate for **7b**, **7c** and **7d** and the hydrochloride for **7a**, which were recrystallized from the appropriate solvent to give the pure sample.

2-(1-Hydroxy-2-aminoethyl)furo[2,3-*b*]pyridine **7a**.

The crude **7a**-**HCl** was recrystallized from methanol-acetone to give 250 mg (80%) of the pure sample, mp 180-183°.

Anal. Calcd. for $C_9H_{10}N_2O_2$·HCl: C, 50.36; H, 5.17; N, 13.05. Found: C, 50.47; H, 5.10; N, 13.02.

The free base **7a** from the hydrochloride was recrystallized from methanol-ether to give colorless needles of mp 103.5-105.5°; ir (potassium bromide): 3600-2400 (broad), 3060, 3010, 2920, 2820, 1575, 1470, 1435, 1390, 1335, 1295, 1265, 1240, 1210, 1185, 1170, 1140, 1110, 1050, 1020, 960, 935, 820, 770, 745 cm^{-1}; pmr (deuteriochloroform): δ 8.17 (dd, J = 1.6, 4.8 Hz, 1H, H-6), 7.79 (dd, J = 1.6, 7.6 Hz, 1H, H-4), 7.11 (dd, J = 4.8, 7.6 Hz, 1H, H-5), 6.61 (d, J = 0.8 Hz, 1H, H-3), 4.81 (dt, J = 0.8, 5.6 Hz, 1H, H-α), 3.10 (d, J = 5.6 Hz, 2H, H-β), 2.83 (s, 3H, -O*H* and -NH_2); pmr (deuteriomethanol): δ 8.17 (dd, J = 1.6, 4.6 Hz, 1H, H-6), 8.01 (dd, J = 1.6, 7.6 Hz, 1H, H-4), 7.25 (dd, J = 4.6, 7.2 Hz, 1H, H-5), 6.78 (d, J = 0.8 Hz, 1H, H-3), 4.80 (ddd, J = 0.8, 5.6, 6.4 Hz, 1H, H-α), 3.10 (dd, J = 5.6, 12.8 Hz, 1H, H-β_1), 2.95 (dd, J = 6.4, 12.8 Hz, 1H, H-β_2).

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.81; H, 5.62; N, 15.43.

2-(1-Hydroxy-2-aminoethyl)furo[3,2-*b*]pyridine **7b**.

The crude oxalate of **7b** was recrystallized from methanol to give 380 mg (84%) of pure sample, mp 191-193° dec.

Anal. Calcd. for $C_9H_{10}N_2O_2 \cdot 1.5C_2H_2O_4$: C, 46.01; H, 4.18; N, 8.94. Found: C, 46.01; H, 4.33; N, 8.74.

The free base **7b** from the oxalate was a colorless viscous oil which showed a single spot on thin-layer chromatography on silica gel (R_f 0.33 (chloroform-methanol (9:1))), and was characterized by the following data; ir (liquid film): 3600-2400 (broad), 2930, 2860, 1590, 1475, 1410, 1330, 1260, 1230, 1220, 1160, 1130, 1090, 950, 935, 810, 790 cm^{-1}; pmr (deuteriochloroform): δ 8.43 (dd, J = 1.8, 5.0 Hz, 1H, H-5), 7.68 (ddd, J = 0.8, 1.8, 8.6 Hz, 1H, H-7), 7.13 (dd, J = 5.0, 8.6 Hz, 1H, H-6), 6.88 (t, J = 0.8 Hz, 1H, H-3), 4.86 (dt, J = 0.8, 5.4 Hz, 1H, H-α), 3.12 (d, J = 5.4 Hz, 2H, H-β), 2.95 (s, 3H, -O*H* and -NH_2); pmr (deuteriomethanol): δ 8.42 (dd, J = 1.6, 4.8 Hz, 1H, H-5), 7.87 (ddd, J = 0.8, 1.6, 8.4 Hz, 1H, H-7), 7.27 (dd, J = 4.8, 8.4 Hz, 1H, H-6), 6.89 (t, J = 0.8 Hz, 1H, H-3), 4.85 (ddd, J = 0.8, 5.6, 6.4 Hz, 1H, H-α), 3.15 (dd, J = 5.6, 12.8 Hz, 1H, H-β_1), 2.97 (dd, J = 6.4, 12.8 Hz, 1H, H-β_2); ms: m/z 178.07521 (M^+, Calcd. for $C_9H_{10}N_2O_2$: 178.07416).

2-(1-Hydroxy-2-aminoethyl)furo[2,3-*c*]pyridine **7c**.

The crude oxalate of **7c** was purified by recrystallization from methanol to yield 450 mg (85%) of the pure sample, mp 178-180° dec.

Anal. Calcd. for $C_9H_{10}N_2O_2 \cdot 2C_2H_2O_4 \cdot 1/2H_2O$: C, 42.51; H, 4.12; N, 7.63. Found: C, 42.90; H, 4.44; N, 7.33.

The free base **7c** from the oxalate was a crystalline solid which was recrystallized from chloroform to give the analytical sample of mp 127.5-130.5°; ir (potassium bromide): 3600-2400 (broad), 3180, 2980, 2920, 2870, 1600, 1580, 1460, 1425, 1330, 1315, 1255, 1180, 1095, 1025, 970, 950, 890, 830 cm^{-1}; pmr (deuteriochloroform): δ 8.78 (dd, J = 0.8, 1.2 Hz, 1H, H-7), 8.37 (d, J = 5.4 Hz, 1H, H-5), 7.48 (dd, J = 1.2, 5.4 Hz, 1H, H-4), 6.74 (t, J = 0.8 Hz, 1H, H-3), 4.88 (dt, J = 0.8, 4.8 Hz, 1H, H-α), 3.16 (d, J = 4.8 Hz, 2H, H-β), 2.85 (s, 3H, -O*H* and -NH_2); pmr (deuteriomethanol): δ 8.73 (dd, J = 0.8, 1.2 Hz, 1H, H-7), 8.30 (d, J = 5.4 Hz, 1H, H-5), 7.58 (dd, J = 1.2, 5.4 Hz, 1H, H-4), 6.81 (t, J = 0.8 Hz, 1H, H-3), 4.87 (ddd, J = 0.8, 4.8, 6.0 Hz, 1H, H-α), 3.13 (dd, J = 4.8, 12.4 Hz, 1H, H-β_1), 3.00 (dd, J = 6.0, 12.4 Hz, 1H, H-β_2).

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.26; H, 5.71; N, 15.37.

2-(1-Hydroxy-2-aminoethyl)furo[3,2-*c*]pyridine **7d**.

The crude oxalate was recrystallized to give 360 mg (80%) of **7d**-oxalate, mp 174-176° dec.

Anal. Calcd. for $C_9H_{10}N_2O_2 \cdot 1.5C_2H_2O_4$: C, 46.01; H, 4.18; N, 8.94. Found: C, 45.98; H, 4.33; N, 8.54.

The free base **7d** from the oxalate was a crystalline solid which was recrystallized from chloroform to give the pure sample, mp 130-132°; ir (potassium bromide): 3550-2350 (broad), 3300, 3250, 2960, 2840, 1600, 1585, 1565, 1490, 1480, 1455, 1445, 1420, 1340, 1260, 1190, 1145, 1130, 1100, 1040, 935, 880, 825, 805, 760 cm^{-1}; pmr (deuteriochloroform): δ 8.75 (d, J = 0.8 Hz, 1H, H-4), 8.36 (d, J = 5.8 Hz, 1H, H-6), 7.32 (dt, J = 0.8, 5.8 Hz, 1H, H-7), 6.70

(t, J = 0.8 Hz, 1H, H-3), 4.82 (dt, J = 0.8, 5.6 Hz, 1H, H-α), 3.13 (d, J = 5.6 Hz, 2H, H-β), 2.80 (s, 3H, -O*H* and -NH_2); pmr (deuteriomethanol): δ 8.78 (d, J = 0.8 Hz, 1H, H-4), 8.36 (d, J = 5.6 Hz, 1H, H-6), 7.51 (dt, J = 0.8, 5.6 Hz, 1H, H-7), 6.86 (t, J = 0.8 Hz, 1H, H-3), 4.83 (ddd, J = 0.8, 5.2, 6.4 Hz, 1H, H-α), 3.15 (dd, J = 5.2, 12.8 Hz, 1H, H-β_1), 2.97 (dd, J = 6.4, 12.8 Hz, 1H, H-β_2).

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.58; H, 5.53; N, 15.51.

Preparation of 2-(1-Hydroxy-2-*N*,*N*-dimethylaminoethyl)furopyridines **8b**, **8c** and **8d**.

General Procedure.

A mixture of compound **7** (100 mg, 0.56 mmole), formic acid (1 ml) and formalin (30%, 1 ml) was heated on a water bath for 1 hour. After evaporation of the excess formic acid and formalin under reduced pressure, the residual syrup was dissolved in water (2 ml), made alkaline with potassium carbonate, extracted with chloroform and dried (magnesium sulfate). The syrupy residue of the chloroform solution was converted to the oxalate and recrystallized from the appropriate solvent.

2-(1-Hydroxy-2-*N*,*N*-dimethylaminoethyl)furo[3,2-*b*]pyridine **8b**.

The crude oxalate was recrystallized from methanol-acetone to yield 174 mg (80%) of the pure sample of mp 137-139° dec.

Anal. Calcd. for $C_{11}H_{14}N_2O_2 \cdot 2C_2H_2O_4$: C, 46.64; H, 4.70; N, 7.25. Found: C, 46.86; H, 4.74; N, 7.01.

The free base from the oxalate was a crystalline solid which was recrystallized from ether to give the pure sample of **8b**, mp 82-85°; ir (potassium bromide): 3400-2400 (broad), 3050, 2950, 2860, 1590, 1460, 1440, 1405, 1355, 1325, 1260, 1210, 1165, 1130, 1110, 1090, 1015, 890, 855, 815, 790 cm^{-1}; pmr (deuteriochloroform): δ 8.46 (dd, J = 1.4, 4.8 Hz, 1H, H-5), 7.67 (dt, J = 1.4, 8.2 Hz, 1H, H-7), 7.13 (dd, J = 4.8, 8.2 Hz, 1H, H-6), 6.88 (dd, J = 0.8, 1.4 Hz, 1H, H-3), 4.87 (ddd, J = 0.8, 4.8, 8.8 Hz, H-α), 3.20 (br s, 1H, -O*H*), 2.90 (dd, J = 8.8, 12.4 Hz, 1H, H-β_1), 2.60 (dd, J = 4.8, 12.4 Hz, 1H, H-β_2), 2.36 (s, 6H, 2 x NCH_3); ms: m/z 206.1050 (M^+, Calcd. for $C_{11}H_{14}N_2O_2$: 206.10544).

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.09; H, 6.76; N, 13.37.

2-(1-Hydroxy-2-*N*,*N*-dimethylaminoethyl)furo[2,3-*c*]pyridine **8c**.

The crude oxalate was recrystallized from methanol-acetone to give 170 mg (78%) of the pure sample, mp 176-178° dec.

Anal. Calcd. for $C_{11}H_{14}N_2O_2 \cdot 2C_2H_2O_4$: C, 46.64; H, 4.70; N, 7.25. Found: C, 46.39; H, 4.73; N, 6.95.

The free base **8c** from the oxalate was a colorless viscous oil which gave a single spot in thin-layer chromatography on a silica gel plate (R_f 0.45 (chloroform-methanol (9:1))), and was characterized by the following data; ir (liquid film): 3600-2400 (broad), 2970, 2940, 2850, 2820, 2770, 1600, 1540, 1460, 1425, 1355, 1310, 1260, 1180, 1150, 1095, 1030, 955, 890, 830, 750 cm^{-1}; pmr (deuteriochloroform): δ 8.80 (dd, J = 0.8, 1.2 Hz, 1H, H-7), 8.37 (d, J = 5.4 Hz, 1H, H-5), 7.48 (dd, J = 1.2, 5.4 Hz, 1H, H-4), 6.74 (t, J = 0.8 Hz, 1H, H-3), 4.90 (ddd, J = 0.8, 5.2, 8.8 Hz, 1H, H-α), 2.86 (dd, J = 8.8. 12.4 Hz, 1H, H-β_1), 2.66 (dd, J = 5.2, 12.4 Hz, 1H, H-β_2), 2.37 (s, 6H, 2 x NCH_3), 2.38 (br s, 1H, -O*H*); ms: m/z 206.1040 (M^+, Calcd. for $C_{11}H_{14}N_2O_2$: 206.10544).

2-(1-Hydroxy-2-*N*,*N*-dimethylaminoethyl)furo[3,2-*c*]pyridine **8d**.

The crude oxalate was recrystallized from methanol to give 180 mg (83%) of the pure sample of mp 187-188.5° dec.

Anal. Calcd. for $C_{11}H_{14}N_2O_2 \cdot 2C_2H_2O_4$: C, 46.64; H, 4.70; N, 7.25. Found: C, 46.62; H, 4.74; N, 7.01.

The free base **8d** from the oxalate was a colorless viscous oil which gave a single spot in thin-layer chromatography on a silica gel plate (R_f 0.43 (chloroform-methanol (9:1))), and was characterized by the following data; ir (liquid film): 3600-2500 (broad), 2980, 2940, 2850, 2820, 2770, 1605, 1575, 1455, 1435, 1320, 1260, 1170, 1155, 1130, 1095, 1040, 1025, 950, 930, 890, 855, 815, 760 cm^{-1}; pmr (deuteriochloroform): δ 8.84 (d, J = 0.8 Hz, 1H, H-4), 8.46 (d, J = 5.8 Hz, 1H, H-6), 7.37 (dt, J = 0.8, 5.8 Hz, 1H, H-7), 6.74 (t, J = 0.8 Hz, 1H, H-3), 4.88 (ddd, J = 0.8, 5.2, 8.8 Hz, 1H, H-α), 3.63 (br s, 1H, -O*H*), 2.85 (dd, J = 8.8, 12.4 Hz, 1H, H-β_1), 2.62 (dd, J = 5.2, 12.4 Hz, 1H, H-β_2), 2.35 (s, 6H, 2 x NCH_3); ms: m/z 206.1031 (M^+, Calcd. for $C_{11}H_{14}N_2O_2$: 206.1054).

REFERENCES AND NOTES

[1] Part **XIII**: S. Shiotani, *J. Heterocyclic Chem.*, **30, 1025 (1993).**

[2] J. W. McFarland, R. P. Wollermann, W. C. Sadler and G. N. Coleman, *J. Heterocyclic Chem.*, **8**, 735 (1971).

[3] J. W. McFarland, W. A. Essary, L. Cilenti, W. Cozart and P. E. McFarland, *J. Heterocyclic Chem.*, **12**, 705 (1975).

[4] N. Desideri, F. Manna and M. L. Stein, *J. Heterocyclic Chem.*, **25**, 333 (1988).

[5] A. P. VanSickle and H. Rapoport, *J. Org. Chem.*, **55**, 895 (1990).

[6] A. R. J. Castaigne, Romanian Patent 63,529 (1978), Centre d'Etudes pour l'Industrie Pharmaceutique; *Chem. Abstr.*, **92**, 41917x (1980).

[7] Centre d'Etudes pour l'Industrie Pharmaceutique, German Offen. 2,659,104 (1977); *Chem. Abstr.*, **87**, 157197p (1977).

[8] H. Morita and S. Shiotani, *J. Heterocyclic Chem.*, **23**, 1465 (1986).

[9] H. Morita and S. Shiotani, *J. Heterocyclic Chem.*, **24**, 373 (1987).

[10] Several trials to obtain the *N*,*N*-dimethylamino derivative **8a** by methylation of **7a** with formic acid and formaldehyde gave only a mixture of compounds from which no single compound could be isolated.