Synthesis of Some Benzofuronaphthyridines and Benzofuronaphthyridine Derivatives

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The new benzofuro[2,3-*b*]naphthyridine ring system was prepared. 2,4-Dichloro-3-(*o*-methoxyphenyl)naphthyridines **3a** and **3b** were obtained by chlorination of hydroxynaphthyridinones **2a** and **2b**. Demethylation followed by cyclization of **3a** and **3b** afforded 11-chlorobenzofuro[2,3-*b*]naphthyridines **4a** and **4b**. Hydrogenolysis of these 11-chlorobenzofuronaphthyridines gave the parent benzofuro[2,3-*b*]naphthyridines **5a** and **5b**. The analog **4b** was also converted to 11-methoxybenzofuro[2,3-*b*][1,8]naphthyridine (**6**).

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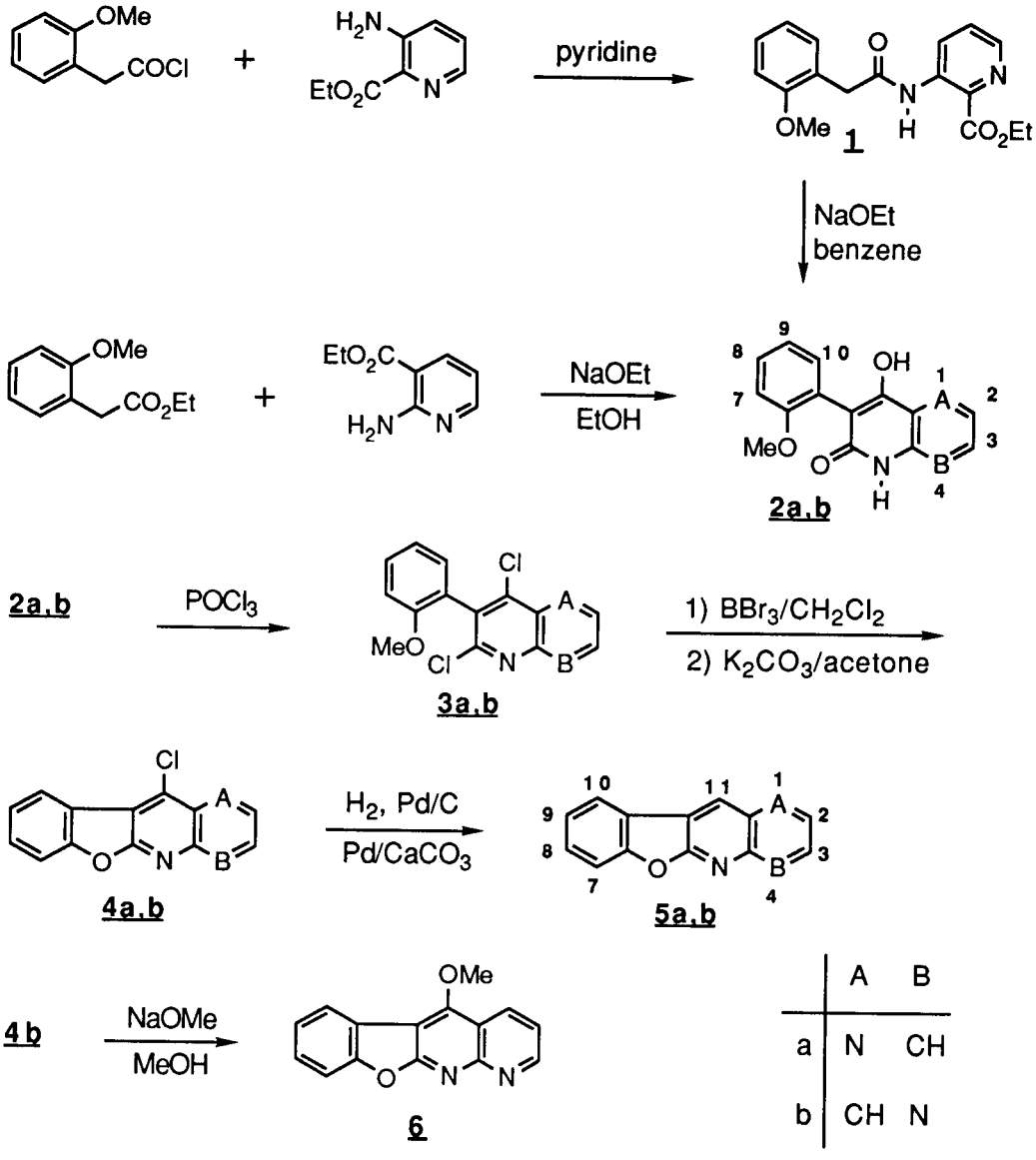
A number of syntheses of naphthyridines have been published [1,2]. Prior to our studies reported herein, the benzo[2,3-*b*]naphthyridine structure had not been reported. In the course of structural elucidation of a new natural product which was isolated in our laboratory, we needed to synthesize this novel ring system. We here

Scheme 1



report the synthesis of benzofuro[2,3-*b*][1,5]naphthyridine (**5a**), benzofuro[2,3-*b*][1,8]naphthyridine (**5b**) and some of their derivatives.

The title compounds were prepared by sequences described in Scheme 1. *o*-Methoxyphenylacetyl chloride was reacted with ethyl 3-aminopicolinate in pyridine to give in good yield amido-ester **1**. Cyclization of **1** with sodium ethoxide gave 4-hydroxy-3-(*o*-methoxyphenyl)-1,5-naphthyridin-2(1*H*)-one (**2a**). 4-Hydroxy-3-(*o*-methoxyphenyl)-1,8-naphthyridin-2(1*H*)-one (**2b**) was obtained directly from the reaction of ethyl *o*-methoxyphenylacetate and ethyl 2-aminonicotinate [3]. Under the same conditions, however, the cyclocondensation between ethyl *o*-methoxyphenylacetate and ethyl 3-aminopicolinate was unsuccessful.

Hydroxynaphthyridinones **2a** and **2b** were converted to the corresponding dichloronaphthyridines **3a** and **3b** by reaction with phosphoryl chloride. Demethylation of **3a** and **3b** with boron tribromide, followed by treatment with potassium carbonate in refluxing acetone, gave excellent yields of 11-chlorobenzofuro[2,3-*b*]naphthyridines **4a** and **4b**. Linear benzofuro[2,3-*b*]naphthyridine **4a** or **4b** was the only product in the cyclization, no angular isomer was detected. Assignment of the structures **4a** and **4b** was supported by their uv spectra, which were similar to linear benzofuro[2,3-*b*]quinoline, not to angular benzofuro[3,2-*c*]-quinoline [4]. Furthermore, this result can be explained by the fact that the halogen in the 2-position of 2,4-dihalo-1,X-naphthyridines undergoes nucleophilic substitution more readily than the halogen at position 4 [1b]. Demethylation of **3a** and **3b** gave the corresponding 2,4-dichloro-3-(*o*-hydroxyphenyl)naphthyridines, in which the chlorine in position 2 underwent intramolecular nucleophilic substitution of phenol preferentially.

Hydrogenolysis of 11-chlorobenzofuronaphthyridines **4a** and **4b** over palladium on calcium carbonate and palladium on carbon provided the parents benzofuro[2,3-*b*]-[1,5]naphthyridine (**5a**) and benzofuro[2,3-*b*][1,8]naphthyridine (**5b**) respectively. 11-Methoxybenzofuro[2,3-*b*][1,8]-naphthyridine (**6**) was synthesized from **4b** by reaction with sodium methoxide in methanol.

In summary, the novel benzofuro[2,3-*b*]naphthyridine ring system and some of their derivatives have been synthesized by a convenient route and their structures were proved *via* elemental analyses and spectral data.

EXPERIMENTAL

Melting points were taken on a Buchi melting point apparatus and are uncorrected. The ir spectra were obtained using a Perkin-Elmer 1420 infrared spectrometer. The uv spectra were determined with UV Hewlett Packard 8452A instrument. The ^{1}H nmr spectra were measured with Varian EM-390, Bruker AC 200 instrument (tetramethylsilane as the internal reference). The high resolution mass spectra were recorded on an AEI MS 50 spectrometer operating at 70 eV. Elemental analyses were performed at the Institute of Organic Chemistry and Biochemistry, University of Bonn.

Preparation of Amido-ester **1**.

A mixture of ethyl 3-aminopicolinate (1.50 g, 9.03 mmoles) and *o*-methoxyphenylacetyl chloride (2.70 g, 14.62 mmoles) in pyridine (3 ml) was heated under reflux for 30 minutes. The mixture was cooled, diluted with water and extracted with chloroform. The organic layer was washed with water, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluant: ethyl acetate/petroleum ether 2/1) to give 2.13 g of **1** (75%), which was recrystallized from ethanol as colorless tablets, mp 102°; ir (potassium bromide): 1710 and 1685 (C=O), 3250 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.38 (t, 3H, CH_3CH_2), 3.76 (s, 2H, CH_2CO), 3.82 (s, 3H, OCH_3), 4.41 (q, 2H, OCH_2), 6.87-7.49 (m, 5H, H_3 and phenyl protons), 8.38 (dd, 1H, H_4, J = 4.2, 1.8 Hz), 9.10 (dd, 1H, H_2, J = 8.2, 1.8 Hz), 10.94 (s, 1H, NH); ms: m/z 314.1262 (3.07%, molecular ion, Calcd. for $C_{17}H_{18}N_2O_4$ 314.1262), 241 (22.5), 193 (32.0), 148 (98.0), 121 (71.5), 91 (100).

Anal. Calcd. for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 64.88; H, 5.96; N, 8.55.

4-Hydroxy-3-(*o*-methoxyphenyl)-1,5-naphthyridin-2(1*H*)-one (**2a**).

A mixture of **1** (3.21 g, 10.6 mmoles) and sodium ethoxide (prepared from 1.0 g of sodium metal and absolute ethanol) in dry benzene (22 ml) was refluxed for 5 hours. The cooled reaction mixture was treated with water. The aqueous layer was acidified with acetic acid to yield a precipitate, which was collected and recrystallized from acetic acid/ethanol to give 2.0 g of **2a** (73%), as a colorless powder, mp 287°; ir (potassium bromide): 1630 (C=O), 3400 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform and deuteriotrifluoroacetic acid): δ 3.92 (s, 3H, OCH_3), 7.14-7.70 (m, 4H, phenyl protons), 8.23 (dd, 1H, H_3, J = 7.5, 5.0 Hz), 8.63 (d, 1H, H_4, J = 7.5 Hz), 8.98 (d, 1H, H_2, J = 5.0 Hz); ms: m/z 268.0876 (26.0%, molecular ion, Calcd. for $C_{15}H_{12}N_2O_3$, 268.0845), 251 (14.5), 237 (62.0), 175 (41.5), 93 (33.0), 43 (40.0), 36 (100).

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.01; H, 4.41; N, 10.25.

4-Hydroxy-3-(*o*-methoxyphenyl)-1,8-naphthyridin-2(1*H*)-one (**2b**).

To a solution of freshly prepared sodium ethoxide (0.28 g of sodium metal and 4 ml of absolute ethanol, 12 mmoles) was added ethyl *o*-methoxyphenylacetate (3.0 g, 15 mmoles) and 2-aminonicotinate (1.0 g, 6.0 mmoles). The mixture was refluxed for 2 hours. After cooling, the precipitate was collected and dissolved in water. The aqueous solution was acidified with acetic acid to give crude product. Recrystallization from acetic acid/ethanol gave 1.1 g of **2b** (68%), as a colorless powder, mp 293°; ir (potassium bromide): 1630 (C=O), 3400 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform and deuteriotrifluoroacetic acid): δ 3.89 (s, 3H, OCH_3), 7.12-7.67 (m, 4H, phenyl protons), 7.83 (dd, 1H, H_2, J = 8.0, 6.0 Hz), 8.83 (dd, 1H, H_1, J = 6.0, 1.6 Hz), 9.12 (dd, 1H, H_3, J = 8.0, 1.6 Hz); ms: m/z 268.0848 (62.62%, molecular ion, Calcd. for $C_{15}H_{12}N_2O_3$, 268.0845), 251 (38.0), 237 (100).

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.27; H, 4.50; N, 10.31.

General Procedure for the Chlorination of **2** to **3**.

A mixture of **2a** (2.0 g) or **2b** (1.9 g) and excess phosphoryl chloride was refluxed for 6 hours. After removal of excess phosphoryl chloride, the cooled reaction mixture was treated with water and aqueous ammonia, and extracted with chloroform. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by silica gel chromatography (eluant: ethyl acetate/petroleum ether 1/1) to give 1.8 g of **3a** (79%) or 1.8 g of **3b** (83%), respectively.

2,4-Dichloro-3-(*o*-methoxyphenyl)-1,5-naphthyridine (**3a**).

This compound was obtained as colorless needles (ethanol), mp 123°; ^{1}H nmr (deuteriochloroform): δ 3.81 (s, 3H, OCH_3), 7.07-7.66 (m, 4H, phenyl protons), 7.78 (dd, 1H, H_3, J = 8.2, 4.2 Hz), 8.47 (dd, 1H, H_4, J = 8.2, 1.9 Hz), 9.13 (dd, 1H, H_2, J = 4.2, 1.9 Hz); ms: m/z 304.0169 (100%, molecular ion, Calcd. for $C_{15}H_{10}Cl_2N_2O$ 304.0168), 269 (87.0), 254 (91.0).

Anal. Calcd. for $C_{15}H_{10}Cl_2N_2O$: C, 59.04; H, 3.30; N, 9.18. Found: C, 58.86; H, 3.27; N, 9.05.

2,4-Dichloro-3-(*o*-methoxyphenyl)-1,8-naphthyridine (**3b**).

This compound was obtained as colorless needles (ethanol), mp 118°; ^{1}H nmr (deuteriochloroform): δ 3.78 (s, 3H, OCH_3), 7.03-7.63 (m, 4H, phenyl protons), 7.65 (dd, 1H, H_2, J = 8.4, 4.2 Hz), 8.65 (dd, 1H, H_1, J = 8.4, 2.0 Hz), 9.19 (dd, 1H, H_3, J = 4.2, 2.0 Hz); ms: m/z 304.0151 (77.03%, molecular ion, Calcd. for $C_{15}H_{10}Cl_2N_2O$ 304.0168), 269 (100), 254 (45.0).

Anal. Calcd. for $C_{15}H_{10}Cl_2N_2O$: C, 59.04; H, 3.30; N, 9.18. Found: C, 58.83; H, 3.31; N, 9.01.

General Procedure for the Preparation of 11-Chlorobenzofuro-[2,3-*b*]naphthyridines **4a** and **4b**.

To a well stirred solution of **3a** (1.31 g) or **3b** (1.89 g) in dry dichloromethane was added dropwise excess boron tribromide in dichloromethane at −78°. The mixture was stirred at room temperature for two hours, then treated with water and extracted with ethyl acetate. The organic layer was dried over anhydrous magnesium sulfate and concentrated *in vacuo* to dryness. The residue was dissolved in acetone, potassium carbonate was added and the mixture was refluxed at 60-70° for 3-4 hours. After removal of solvent, the residue was treated with water and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified on a silica gel column (eluant: acetone/chloroform 1/8) to yield 1.01 g of **4a** (93%) or 1.50 g of **4b** (95%), respectively.

11-Chlorobenzofuro[2,3-*b*][1,5]naphthyridine (**4a**).

This compound was obtained as colorless needles (ethanol), mp 225°; uv (dichloromethane): λ max 220 (log ε 4.72), 230 (3.91), 250 (4.37), 258 (4.82), 274 (3.50), 314 (3.86), 320 (4.21), 336 (4.09); ^{1}H nmr (deuteriochloroform): δ 7.40-7.68 (m, 3H, H_7, H_8 and H_9), 7.71 (dd, 1H, H_3, J = 8.4, 4.2 Hz), 8.40 (m, 1H, H_{10}), 8.42 (dd, 1H, H_4, J = 8.4, 1.8 Hz), 9.06 (dd, 1H, H_2, J = 4.2, 1.8 Hz); ms: m/z 254.0220 (100%, molecular ion, Calcd. for $C_{14}H_7ClN_2O$, 254.0245), 219 (4.5), 191 (10.0), 164 (18.0).

Anal. Calcd. for $C_{14}H_7ClN_2O$: C, 66.03; H, 2.77; N, 11.00. Found: C, 65.73; H, 2.70; N, 10.99.

11-Chlorobenzofuro[2,3-*b*][1,8]naphthyridine (**4b**).

This compound was obtained as colorless needles (ethanol), mp 229°; uv (dichloromethane): λ max 222 (4.65), 230 (3.94), 246 (4.35), 256 (4.85), 270 (3.65), 310 (3.97), 324 (4.10), 340 (3.84); ^{1}H nmr: δ 7.38-7.71 (m, 4H, H_2, H_7, H_8 and H_9), 8.37 (m, 1H, H_{10}), 8.76 (dd, 1H, H_1, J = 8.2, 2.0 Hz), 9.19 (dd, 1H, H_3, J = 4.2, 2.0 Hz); ms: m/z 254.0246 (100%, molecular ion, Calcd.. for $C_{14}H_7ClN_2O$, 254.0245), 219 (8.0), 191 (9.1), 164 (14.5), 105 (38.0).

Anal. Calcd. for $C_{14}H_7ClN_2O$: C, 66.03; H, 2.77; N, 11.00. Found: C, 65.86; H, 2.67; N, 10.84.

General Procedure for the Preparation of Benzofuro[2,3-*b*]naphthyridines **5a** and **5b**.

A mixture of **4a** (200 mg) or **4b** (200 mg), palladium on calcium carbonate (5%, 120 mg), a small quantity of palladium on carbon (10%) and potassium hydroxide (100 mg) in methanol (40 ml) was hydrogenated at 3.5 bar of hydrogen for 1 hour. The catalyst was filtered off and the solvent was evaporated under reduced pressure. The residue was treated with water and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluant: ethyl acetate/petroleum ether 3/1) to give 110 mg of **5a** (64%) or 120 mg of **5b** (69%), respectively.

Benzofuro[2,3-*b*][1,5]naphthyridine (**5a**).

This compound was obtained as colorless tablets (ethanol), mp 205°; ^{1}H nmr (deuteriochloroform): δ 7.36-7.65 (m, 3H, H_7, H_8 and H_9), 7.68 (dd, 1H, H_3, J = 8.7, 4.2 Hz), 8.08 (m, 1H, H_{10}), 8.44 (dd, 1H, H_4, J = 8.7, 1.8 Hz), 8.87 (s, 1H, H_{11}), 9.0 (dd, 1H, H_2, J = 4.2, 1.8 Hz); ms: m/z 220.0600 (100%, molecular ion, Calcd. for $C_{14}H_8N_2O$, 220.0635), 193 (5.0), 164 (14.5), 138 (5.5).

Anal. Calcd. for $C_{14}H_8N_2O$: C, 76.35; H, 3.66; N, 12.72. Found: C, 76.17; H, 3.74; N, 12.51.

Benzofuro[2,3-*b*][1,8]naphthyridine (**5b**).

This compound was obtained as colorless tablets (ethanol), mp 211°; ^{1}H nmr (deuteriochloroform): δ 7.36-7.76 (m, 4H, H_2, H_7, H_8 and H_9), 8.07 (m, 1H, H_{10}), 8.42 (dd, 1H, H_1, J = 8.2, 2.0 Hz), 8.71 (s, 1H, H_{11}), 9.18 (dd, 1H, H_3, J = 4.2, 2.0 Hz); ms: m/z 220.0642 (100%, molecular ion, Calcd. for $C_{14}H_8N_2O$, 220.0635), 193 (5.0), 164 (20.0), 138 (12.0), 110 (42.5).

Anal. Calcd. for $C_{14}H_8N_2O$: C, 76.35; H, 3.66; N, 12.72. Found: C, 76.08; H, 3.74; N, 12.47.

11-Methoxybenzofuro[2,3-*b*][1,8]naphthyridine (**6**).

A mixture of **5b** (250 mg) and sodium methoxide (prepared from 120 mg of sodium metal) in methanol (12 ml) was refluxed for 3 hours. After removal of solvent, the residue was treated with water and extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed on silica gel (eluant: acetone/chloroform 1/10) to give 200 mg of **6** (81%), as a colorless powder (cyclohexane), mp 164°; ^{1}H nmr (deuteriochloroform): δ 4.41 (s, 3H, OCH_3), 7.41-7.80 (m, 4H, H_2, H_7, H_8 and H_9), 8.16 (m, 1H, H_{10}), 8.64 (dd, 1H, H_1, J = 8.1, 1.9 Hz), 9.02 (dd, 1H, H_3, J = 4.3, 1.9 Hz); ms: m/z 250.0732 (100%, molecular ion, Calcd. for $C_{15}H_{10}N_2O_2$, 250.0739), 220 (53.0), 192 (5.0).

Anal. Calcd. for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.19. Found: C, 71.67; H, 3.97; N, 11.09.

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