A Synthesis of 5-Carboxamidopyrrolo[3,2-*b*]pyridine

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A four-step synthesis of 5-carboxamidopyrrolo[3,2-*b*]pyridine (**3**) from pyrrolo[3,2-*b*]pyridine (**4**) is described (45% overall yield). The one-step conversion of the *N*-oxide **6** of the pyrrolo[3,2-*b*]pyridine **5** leads to the 5-cyanopyrrolo[3,2-*b*]pyridine **7**. The cyano group is hydrolyzed to afford the title compound **3**, which is the 4-aza analog of the indole backbone in 5-carboxamidotryptamine, a potent agonist of the neurotransmitter, serotonin.

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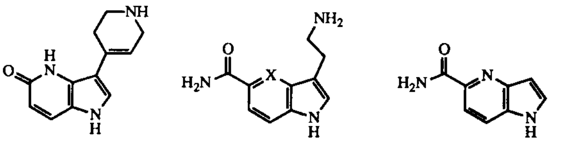
The discovery of the neurotransmitter and vasoconstrictor serotonin [(3-(2-aminoethyl)-5-hydroxyindole), 5-HT] in 1949 [1] was the commencement of a gargantuan research effort to understand the effects of this neurotransmitter and to produce drugs to correct deficiencies of serotonergic neurotransmission. The heterogeneity of the family of serotonin receptors has hampered this study even today, and the search for agents selective for a single subtype of serotonin receptors is seen as integral to drug discovery in this field [2].

Of the many agents which bind to the 5-HT$_1$ subtype of serotonin receptors (*i.e.* 5-HT$_{1A}$, 5-HT$_{1B}$, 5-HT$_{1D}$), 5-carboxamidotryptamine (**1**) seems to be the most potent drug in this class [2]. During the course of our efforts in the area of 5-HT$_1$ agonists, the pyrrolo[3,2-*b*]pyridone CP-93,129 was designed as an agonist selective for the 5-HT$_{1B}$ receptor [3]. This result led us to desire the pyrrolo[3,2-*b*]pyridine analog **2** of 5-carboxamidotryptamine as a potential drug target. This molecule **2** was seen as arising from the application of standard methods of tryptamine synthesis from indoles using, however, 5-carboxamidopyrrolo[3,2-*b*]pyridine (**3**) as the indole-like participant [4]. A survey of the literature did not reveal a route to **3**, since there are very limited reports on the synthesis of functionalized pyrrolo[3,2-*b*]pyridines in the literature [5]. Therefore, in this report we detail the synthesis of 5-carboxamidopyrrolo[3,2-*b*]pyridine (**3**).

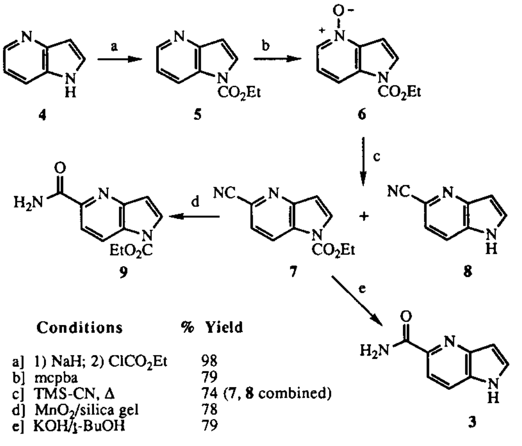
(Structures for manuscript)



CP-93,129 **1** (X=C) **2** (X=N) **3**

Hoping to utilize the one-step conversion of pyridine-*N*-oxides to 2-cyanopyridines developed by Vorbrüggen and Krolikiewicz [6], we envisioned the desired carboxamido functionality arising from the hydrolysis of a nitrile. Protection of the pyrrole portion of pyrrolo[3,2-*b*]pyridine (**4**) [7] was seen as integral to the smooth synthesis of the desired *N*-oxide derivative of **4**. Therefore, treatment of **4** with sodium hydride followed by quenching of the derived anion with ethyl chloroformate afforded the carbamate **5** in almost quantitative yield. Treatment of **5** with *m*-chloroperbenzoic acid in diethyl ether proceeded smoothly to afford the *N*-oxide **6**. While the purified yield of this compound (**6**) was only 79%, tlc of the reaction indicated an almost quantitative conversion, and we believe that the purification of **6** [a silica gel filtration] reduced the actual yield of the oxidation reaction, possibly *via* hydrolysis of the carbamate protecting group. If the oxidation reaction is extracted with a saturated solution of sodium hydrogen carbonate (to remove the *m*-chlorobenzoic acid by-product) a slightly less pure *N*-oxide **6** is isolated, but there appears to be a greater mass return of the desired *N*-oxide. This material can be used in the proceeding step, and while not rigorously investigated, there seemed to be a greater yield of **7** and **8** when crude **6** was used.

Scheme 1 - Synthesis of 5-Carboxamidopyrrolo[3,2-b]pyridine



Conditions	% Yield
a] 1) NaH; 2) ClCO$_2$Et	98
b] mcpba	79
c] TMS-CN, Δ	74 (**7**, **8** combined)
d] MnO$_2$/silica gel	78
e] KOH/t-BuOH	79

Reaction of the *N*-oxide **6** with a large excess of trimethylsilyl cyanide afforded conversion of the *N*-oxide **6** to the 5-cyanopyrrolo[3,2-*b*]pyridines, **7** (42%) and **8** (32%), in a combined yield of 74%. The somewhat vigorous conditions of this reaction led to a partial removal of our carbamate protecting group giving rise to **8**. When **7** was subjected to hydrolysis (potassium hydroxide refluxing *t*-butyl alcohol) [8], a 79% yield of the desired 5-carboxamidopyrrolo[3,2-*b*]pyridine was isolated. The mixture of **7** and **8** can also be used directly in this hydrolysis (potassium hydroxide refluxing *t*-butyl alcohol) resulting in a similar yield of the desired carboxamide **3**, indicating that the hydrolysis of the nitrile in **8** occurred with the same efficiency as the hydrolysis of the nitrile in **7**.

An alternate, milder hydrolysis was explored which did not remove the carbamate protecting group in **7**. This involved the use of specially prepared manganese dioxide on silica gel in the presence of a trace of water in a refluxing benzene [9]. While the reaction time needed to achieve a 78% yield of the protected carboxamide **9** was lengthy, the reaction conditions preserved the ethyl carbamate and produced little side reactions, since returned starting material **7** was the only other compound seen by tlc in this reaction. Since our future plans for the synthesis of serotonergic agents involved **3** rather than **9**, no effort was made to improve or hasten the formation of **9**.

The synthesis and pharmacology of the serotonergic analogs arising from **3** is presently under study, and the results of this research will be reported in an appropriate forum shortly.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover open capillary melting point apparatus and are uncorrected. Infrared spectra were obtained from a Perkin Elmer IR-283B Infrared Spectrophotometer, and nmr spectra were recorded on either a Bruker AM-300 (300 MHz), Varian XL300 (300 MHz), or Varian XL250 (250 MHz) spectrometer. The nmr data are reported in parts per million (δ) and are referenced to the deuterium lock signal from the sample solvent. Low resolution mass spectra were obtained on a Finnigan 4310 instrument; high resolution mass spectra (EI and FAB) were obtained on a Kratos Concept IS instrument. Elemental analyses were performed at Schwarzkopf Microanalytical Laboratory, Woodside, NY.

Commercial reagents (Aldrich Chemical Co.) were utilized without further purification, including Aldrich anhydrous solvents. Diethyl ether was dried *via* distillation over sodium hydride. Chromatography refers to column chromatography performed using 32-63 μm silica gel (approximately 50 g silica gel per gram of material to be chromatographed) and executed under nitrogen pressure (flash chromatography) conditions. Room temperature refers to 20-25°.

5-Carboxamidopyrrolo[3,2-*b*]pyridine (**3**).

To a stirred solution of **7** (1.00 g, 4.65 mmoles) in *t*-butyl alcohol was added finely crushed potassium hydroxide (5.0 g). The resulting reaction mixture was heated at reflux under nitrogen for 1.5 hours. The reaction solution was then evaporated under reduced pressure, and the residual solid was dissolved in an aqueous solution of 10% hydrochloric acid (5 ml). The *p*H of this mixture was adjusted to a *p*H <5 using concentrated hydrochloric acid (approximately 5 ml). The resulting aqueous mixture was extracted with ethyl acetate (4 x 10 ml). The ethyl acetate extracts were combined, dried (magnesium sulfate), and evaporated under reduced pressure to afford 0.59 g (79%) of **3** as a white powder, mp 189.0-192.0°; R_f = 0.3 in ethyl acetate; ir (potassium bromide): 3470, 1720, 1680, 1660, 1640 cm^{-1}; ^1H nmr (DMSO-d_6): δ 11.6 (br m, 1H, NH indole), 8.03 (br s, 1H, NH amide), 7.92-7.85 (m, 2H), 7.79 (t, 1H, J = 3.0 Hz), 7.42 (br s, 1H, NH amide), 6.64 (dd, 1H, J = 2.2, 2.3 Hz); ^{13}C nmr (DMSO-d_6): δ 167.3, 145.0, 143.8, 131.2, 129.9, 118.9, 114.8, 102.0; ms: (70 eV, electron impact) m/z 161 (M^+), 149, 143, 104; hrms Calcd. for $C_8H_7N_3O$: 161.0590, Found: 161.0593.

Anal. Calcd. for $C_8H_7N_3O$: C, 59.62; H, 4.38; N, 26.07. Found: C, 59.80; H, 4.43; N, 25.74.

Ethyl Pyrrolo[3,2-*b*]pyridine-1-carboxylic Acid (**5**).

To a stirred solution of **4** [7] (19.88 g, 0.168 mole) in anhydrous tetrahydrofuran (250 ml) at 0° was added sodium hydride (60% in oil, 7.41 g, 0.185 mole, 1.1 equivalents), and the resulting effervescing mixture was stirred at 0° under nitrogen until all effervescence ceased (30 minutes). Then ethyl chloroformate (17.7 ml, 0.185 mole, 1.1 equivalents) was added dropwise slowly at 0°, and the resulting reaction mixture was stirred at room temperature under nitrogen for 16 hours. The resulting reaction mixture was evaporated under reduced pressure, and the residue was partitioned between a saturated solution of sodium hydrogen carbonate (100 ml) and ether (100 ml). The ether layer was removed, and the remaining aqueous layer was extracted with ether (2 x 100 ml). All ether extracts were combined, dried (magnesium sulfate), and evaporated under reduced pressure. The residual yellow oil (37 g) was passed through a silica gel filter (approximately 1 kg) followed by hexanes (2 ℓ, to remove oil from sodium hydride dispersion) and then ether (4 ℓ). The ether eluet was evaporated under reduced pressure to afford 31.30 g (98%) of **5** as an oil which crystallized upon cooling to afford a white solid, mp 43.5-44.5°; ir (potassium bromide): 1745 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.51 (dd, 1H, J = 4.8, 1.4 Hz), 8.37 (br d, 1H, J = 7.9 Hz), 7.83 (d, 1H, J = 3.8 Hz), 7.21 (dd, 1H, J = 8.3, 4.8 Hz), 6.78 (d, 1H, J = 3.9 Hz), 4.49 (q, 2H, J = 7.1 Hz), 1.46 (t, 3H, J = 7.1 Hz); ^{13}C nmr (deuteriochloroform): δ 150.5, 148.8, 145.8, 128.6, 122.2, 118.9, 109.0, 63.7, 14.3; ms: (70 eV, electron impact) m/z 190 (M^+), 145, 131, 118, 91.

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.00; H, 5.22; N, 14.49.

Ethyl Pyrrolo[3,2-*b*]pyridine-1-carboxylic Acid *N*-Oxide (**6**).

To a stirred solution of **5** (4.13 g, 21.7 mmoles) in anhydrous ether (60 ml) was added *m*-chloroperbenzoic acid (60%, 10.84 g, 37.7 mmoles, 1.7 equivalents) as a solid portionwise. The resulting reaction solution was stirred at room temperature under nitrogen for 24 hours. The resulting reaction mixture was evaporated under reduced pressure, the residue was redissolved in ethyl acetate (25 ml). This solution was passed through a silica gel filter (approximately 250 g) followed first by ethyl acetate (2 ℓ) and then by 10% absolute methanol in ethyl acetate (2.5 ℓ). The latter filtrate (2.5 ℓ) was evaporated under reduced pressure to afford 3.54 g (79%) of **6** as a white solid, mp 114.0-117.0°; ir (potassium bromide): 1745, 1600 cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.18 (d, 1H, J = 6.7 Hz), 8.04 (d, 1H, J = 8.6 Hz), 7.74 (d, 1H, J = 4.0 Hz), 7.15 (dd, 1H, J = 8.2, 6.2 Hz), 7.05 (d, 1H, J = 3.8 Hz), 4.49 (q, 2H, J = 7.0 Hz), 1.45 (t, 3H, J = 7.3 Hz); ^1H nmr (acetone-d_6): δ 8.13 (d, 1H, J = 6.3 Hz), 7.96 (d, 1H, J = 8.5 Hz), 7.85

(d, 1H, J = 3.9 Hz), 7.29 (dd, 1H, J = 8.5, 6.3 Hz), 6.93 (d, 1H, J = 3.9 Hz), 4.53 (q, 2H, J = 7.1 Hz), 1.46 (t, 3H, J = 7.1 Hz); ^{13}C nmr (acetone-d_6): δ 150.6, 139.6, 134.1, 132.8, 128.6, 121.5, 113.0, 102.5, 65.0, 14.3; ms: (fast atom bombardment) m/z 207 (MH$^+$).

Anal. Calcd. for $C_{10}H_{10}N_2O_3$: C, 58.25; H, 4.89; N, 13.59. Found: C, 57.86; H, 5.05; N, 13.38.

Ethyl 5-Cyanopyrrolo[3,2-*b*]pyridine-1-carboxylic Acid (**7**) and 5-Cyanopyrrolo[3,2-*b*]pyridine (**8**).

To a stirred mixture of **6** (4.76 g, 23.1 mmoles) in triethylamine (50 ml) was added dropwise trimethylsilyl cyanide (**CAUTION: HIGHLY TOXIC**) (20.0 ml, 150 mmoles, 6.5 equivalents), and the resulting reaction mixture was heated at reflux under nitrogen for 16 hours. The resulting amber-colored reaction solution was cooled to 0°, and a saturated solution of sodium hydrogen carbonate (60 ml) was added dropwise cautiously. The resulting aqueous mixture was extracted with ethyl acetate (3 x 100 ml), and the combined extracts were dried (magnesium sulfate), and evaporated under reduced pressure. The residual solid (4.9 g) was chromatographed using silica gel (approximately 250 g) and elution first with ethyl acetate/hexanes [1:3] to afford 2.10 g (42%) of **7** as an off-white solid, mp 139.0-141.0°; ir (potassium bromide): 2235, 1750 cm^{-1}; ^{1}H nmr (acetone-d_6): δ 8.50 (d, 1H, J = 8.5 Hz), 8.16 (d, 1H, J = 2.2 Hz), 7.81 (d, 1H, J = 8.5 Hz), 6.86 (d, 1H, J = 2.3 Hz), 4.56 (q, 2H, J = 7.1 Hz), 1.48 (t, 3H, J = 7.1 Hz); ^{13}C nmr (acetone-d_6): δ 150.6, 150.4, 133.0, 130.5, 129.4, 124.3, 123.6, 118.7, 108.7, 65.1, 14.3; ms: (fast atom bombardment) m/z 216 (MH$^+$).

Anal. Calcd. for $C_{11}H_9N_3O_2$: C, 61.39; H, 4.22; N, 19.53. Found: C, 61.08; H, 4.06; N, 19.60.

Further elution using ethyl acetate afforded 1.07 g (32%) of **8** as an off-white solid, mp 230-234°; ir (potassium bromide): 2225, 1625 cm^{-1}; ^{1}H nmr (acetone-d_6): δ 11.0 (br m, 1H, NH), 8.00 (d, 1H, J = 8.4 Hz), 7.88 (t, 1H, J = 2.9 Hz), 7.59 (d, 1H, J = 8.4 Hz), 6.71 (br t, 1H); ^{13}C nmr (acetone-d_6): δ 148.3, 133.0, 130.7, 126.5, 121.5, 119.7, 119.7, 103.6; ms: (70 eV, electron impact) m/z 143 (M$^+$), 129, 116; hrms Calcd. for $C_8H_5N_3$: 143.0485, Found: 143.0473.

Anal. Calcd. for $C_8H_5N_3 \cdot 1/8H_2O$: C, 66.09; H, 3.64; N, 28.90. Found: C, 66.30; H, 3.44; N, 28.72.

Ethyl 5-Carboxamidopyrrolo[3,2-*b*]pyridine-1-carboxylic Acid (**9**).

A mixture of **7** (0.200 g, 0.93 mmole) and manganese dioxide on silica gel [9] (2 g) in benzene (5 ml) and water (5 drops) was heated at reflux under nitrogen for 5 days. Methanol (50 ml) was added to the reaction mixture [to free product from manganese dioxide on silica gel], and the resulting mixture was filtered through celite, and the filtered solids washed generously with methanol. The combined filtrates were evaporated under reduced pressure, and the residual solid (0.250 g) was chromatographed using silica gel (approximately 25 g) and elution with hexanes in ethyl acetate [1:2] to afford 0.170 g (78%) of **9** as a white solid, mp 210.0-213.0° (with effervescence); ir (potassium bromide): 3420, 1755, 1715 cm^{-1}; ^{1}H nmr (DMSO-d_6): δ 8.48 (d, 1H, J = 8.6 Hz), 8.14 (d, 1H, J = 3.8 Hz), 8.11 (br s, 1H, NH), 8.06 (d, 1H, J = 8.6 Hz), 7.62 (br s, 1H, NH), 6.91 (d, 1H, J = 3.9 Hz), 4.49 (q, 2H, J = 7.1 Hz), 1.42 (t, 3H, J = 7.1 Hz); ^{13}C nmr (DMSO-d_6): δ 166.3, 149.9, 147.1, 146.6, 131.1, 129.5, 122.6, 117.7, 108.3, 64.1, 14.1; ms: (70 eV, electron impact) m/z 233 (M$^+$), 190, 162, 144, 118.

Anal. Calcd. for $C_{11}H_{11}N_3O_3$: C, 56.65; H, 4.75; N, 18.02. Found: C, 56.66; H, 4.68; N, 17.93.

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