The Synthesis of 4-Benzylamino-6-methyl-1*H*-pyrrolo[3,2-*c*]pyridine and 4-Benzylamino-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridine

Eric A. Meade* and Lilia M. Beauchamp

Division of Organic Chemistry, Glaxo Wellcome Co., Research Triangle Park, North Carolina 27709

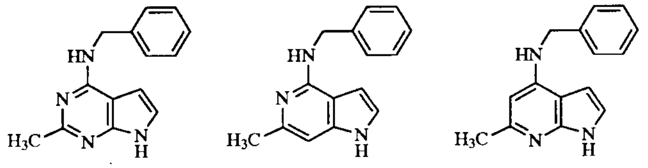
Received September 19, 1995

4-Benzylamino-6-methyl-1*H*-pyrrolo[3,2-*c*]pyridine (**2**) and 4-benzylamino-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (**3**) were synthesized as deaza analogues of the anxiolytic agent 4-benzylamino-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**1**). The 1-deaza analogue (**2**) was prepared *via* a multi-step procedure from a pyrrole precursor, 1-benzyl-2-formylpyrrole (**4**) while the 3-deaza analogue **3** was synthesized from a pyridine precursor, 2-amino-3,6-dimethylpyridine (**12**).

J. Heterocyclic Chem., **33**, 303 (1996).

There is a need to develop agents with better pharmacological profiles than the currently used benzodiazepines to treat severe anxiety disorders. The drawbacks of the benzodiazepines, namely their addictive potential, sedative effects, and alcohol potentiation [1], has led us to search for novel agents with completely different mechanisms of action. 4-Benzylamino-2-methyl-7*H*-pyrrolo[2,3-*d*]pyrimidine (**1**) (Chart I) [2] was found to have excellent anticonflict activity in the Geller conflict test, an *in vivo* test for rapid onset anxiolytics [3]. Although these initial results looked promising, **1** and related benzylaminopyrrolo[2,3-*d*]pyrimidine analogues caused emesis as observed in dogs. To separate the emetic properties from the desired anxiolytic properties we considered modifications of the parent structure using heterocyclic moieties other than the pyrrolo[2,3-*d*]pyrimidine system. By maintaining the peripheral substituents of the lead compound and systematically exchanging the carbon atoms for the *N*-atoms in the pyrimidine moiety, we hoped to find an agent with the desired pharmacological profile.

Chart 1

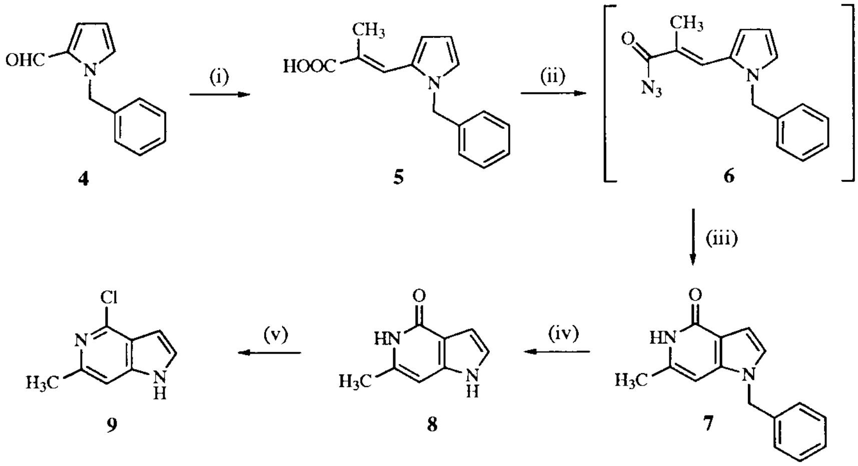


1 **2** **3**

In this manuscript we describe the preparation of two deaza heterocyclic isosteres of **1**; 4-benzylamino-6-methyl-1*H*-pyrrolo[3,2-*c*]pyridine (**2**) and 4-benzylamino-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (**3**) (Chart I). Rasmussen and coworkers [4] recently described the preparations of 1*H*-pyrrolo[3,2-*c*]pyridine and 6-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (**16**) based on modifications of the original routes by Ducrocq [5] and Albert [6], respectively. Our routes to **2** and **3** were similar to the earlier routes, however the difficulty in the addition of the required benzylamino moiety of **2** and **3** led us to some interesting modifications in the latter stages of the syntheses.

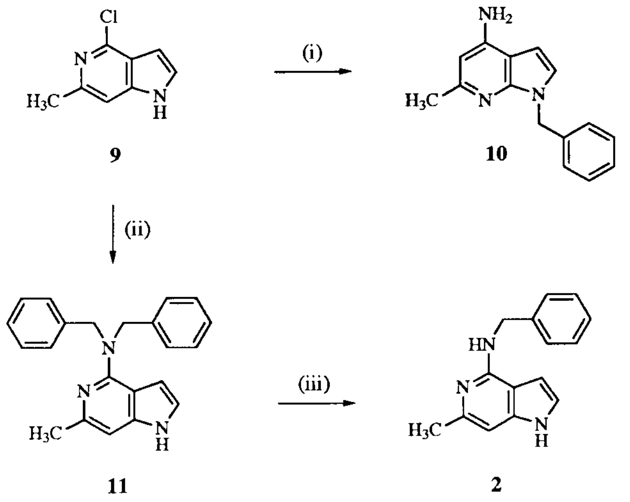
The 1 deaza analogue of **1**, 4-benzylamino-2-methyl-1*H*-pyrrolo[3,2-*c*]pyridine (**2**) was prepared from 1-ben-

Scheme 1



(i) methylmalonic acid, aniline, propanol, reflux; (ii) (a) ethyl chloroformate, triethylamine, acetone, 0°C; (b) sodium azide, water, room temperature; (iii) tributylamine, diphenyl ether, 195-198°C; (iv) sodium, liquid ammonia, -78°C; (v) phosphorus oxychloride, 180-185°C

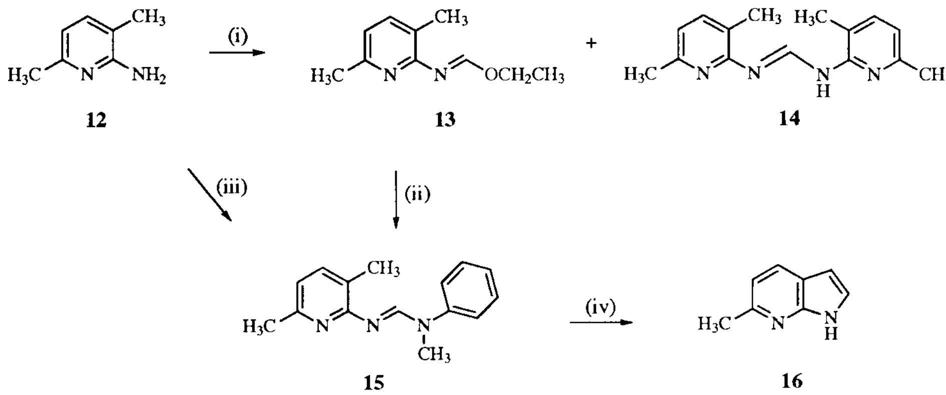
Scheme 2



(i) benzylamine, reflux; (ii) dibenzylamine, 175-185°C; (iii) palladium hydroxide on carbon, H_2

zyl-2-formylpyrrole (**4**) [5] as shown in Scheme 1. The procedure used to prepare 4-chloro-2-methyl-1*H*-pyrrolo[3,2-*c*]pyridine (**9**) was analogous to those used by Ducrocq [5] and later Rasmussen [4] to prepare the desmethyl derivative, 4-chloro-1*H*-pyrrolo[3,2-*c*]pyridine. A Knoevenagel condensation of **4** with methylmalonic acid gave the α,β-unsaturated acid **5** in 47% yield. The *E* stereochemistry of the double bond was determined from NOESY experiments. Activation of the acid moiety *via* its mixed anhydride followed by treatment with sodium azide provided the acyl azide **6**. Heating of the crude acyl azide **6** in diphenyl ether at 180° effected the Curtius rearrangement to provide 1-benzyl-4,5-dihydro-6-methyl-1*H*-4-oxopyrrolo[3,2-*c*]pyridine (**7**) in 70% overall yield from acid **5**. The benzyl protecting group was cleaved with sodium in liquid ammonia to furnish 4,5-dihydro-6-methyl-1*H*-4-oxopyrrolo[3,2-*c*]pyridine (**8**) in 91% yield. Chlorination of the oxo group of **8** at 180° in phosphorus oxychloride proceeded in 83% yield to give 4-chloro-6-methyl-1*H*-pyrrolo[3,2-*c*]pyridine (**9**).

Scheme 3

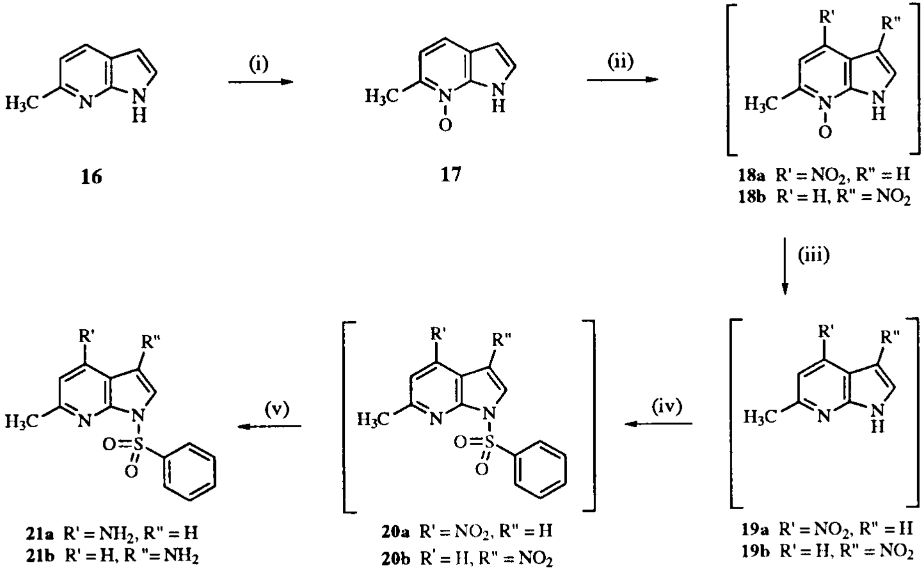


(i) triethylorthoformate, HCl, reflux; (ii) *N*-methylaniline, reflux; (iii) *N*-methylformanilide, phosphorus pentachloride, chloroform, reflux; (iv) sodium hydride, *N*-methylaniline, reflux

Direct diplacement of the 4-chloro group of **9** proved to be problematic (Scheme 2). Reaction of **9** with benzylamine resulted in the formation of the isomeric 4-amino-1-benzyl-7-methylpyrrolo[2,3-*b*]pyridine (**10**) instead of the desired pyrrolo[3,2-*c*]pyridine **2**. This rearrangement has also been observed in attempts to displace the 4-chloro group of the pyrrolo[3,2-*c*]pyridine ring system with primary amines [7]. The formation of **10** was consistent with rearrangement of the initially formed **2** catalyzed by the primary amine, benzylamine. In order to circumvent this difficulty, the 4-chloro group of **9** was first displaced by dibenzylamine. Secondary amines are known not to effect the heterocyclic rearrangement seen with primary amines, an observation consistent with the rearrangement mechanism proposed by Bisagni [7a]. The crude dibenzylamino intermediate **11** was then hydrogenated using Pearlman's catalyst in the presence of acid to selectively remove one benzyl group to give the target 1-deaza analogue **2** in 26% overall yield from **9**.

The 3-deaza analogue, 4-benzylamino-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (**3**), was prepared from 6-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (**16**) [4] (Scheme 3). This starting material had been previously synthesized by Rasmussen [4] by initial formation of ethyl imidate intermediate **13**. In our hands, the preparation of **13** from 2-amino-3,6-dimethylpyridine (**12**) proved difficult. In small scale experiments (11 g) treatment of **12** with triethylorthoformate provided **13** in 74% yield. The imidate intermediate could then be converted to *N*-(3,6-dimethyl-2-pyridyl)-*N*-methyl-*N*-phenylformamidine (**15**) by heating with *N*-methylaniline. However, upon scaleup (25 g) of the initial imidate forming reaction, a preponderance of

Scheme 4

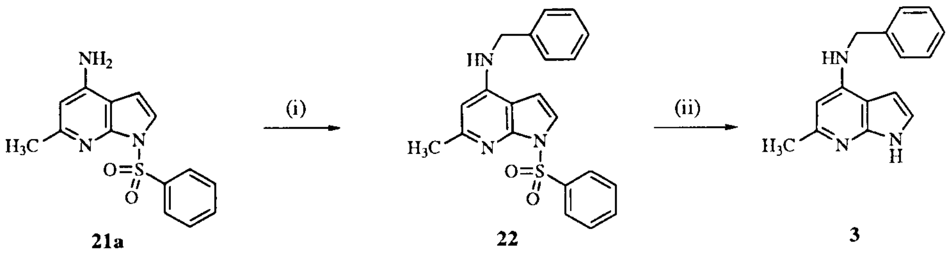


(i) *m*-chloroperbenzoic acid, chloroform, room temperature; (ii) fuming nitric acid, trifluoroacetic acid, 0°C; (iii) phosphorus trichloride, chloroform, reflux; (iv) sodium hydride, benzenesulfonyl chloride, dimethylformamide, room temperature; (v) Raney nickel, H_2, ethanol

a second amidino product **14** was obtained, presumably arising from the condensation of two molecules of **12**. This difficulty was bypassed by reaction of **12** with *N*-methylformanilide [8] and phosphorus pentachloride [9] to provide **15** directly in 87% yield. Pyridine **15** was then cyclized using sodium hydride in *N*-methylaniline as described [3].

The heterocycle **16** was oxidized using *m*-chloroperoxybenzoic acid to afford the *N*-oxide **17** in 47% crude yield (Scheme 4). Nitration of this heterocycle using the same conditions described by Grifantini [10] for the 6-desmethyl derivative, 1*H*-pyrrolo[2,3-*b*]pyridine, resulted in a ~2:3 ratio of the desired 4-nitro derivative **18a** to the undesired 3-nitro derivative **18b**. (In contrast, Grifantini obtained a preponderance of the 4-nitro derivative in the case of the 6-desmethyl analogue.) Since the mixture of nitro isomers **18a** and **18b** was difficult to separate at this stage because of their insolubility in organic solvents, the mixture was carried on in the synthesis. Deoxygenation of the mixture with phosphorus trichloride gave **19a** and **19b**. Partial separation of the isomers could be carried out at this stage. Treatment of the mixture of **19a** and **19b** with sodium hydroxide solution selectively dissolved the 3-nitro isomer **19b** and afforded a precipitate enriched in the desired isomer **19a**. The ratio of **19a** to **19b** in this precipitate was 3:1 as determined by ^{1}H nmr analysis. This mixture was sulfonylated with benzenesulfonyl chloride in 56% yield to afford the protected derivatives **20a** and **20b**. The improved solubility of these analogs eased their handling in further synthetic transformations. The nitro group was reduced with Raney nickel allowing complete separation of the 4-amino isomer **21a** from residual 3-amino isomer **21b** in 78% yield . The benzylamino moiety was introduced *via* reductive amination using benzaldehyde and sodium borohydride to provide 1-benzenesulfonyl-4-benzylamino-6-methylpyrrolo[2,3-*b*]pyridine (**22**) in 80% yield (Scheme 5). Finally, cleavage of the benzenesulfonyl group with potassium hydroxide in

Scheme 5



(i) (a) benzaldehyde, toluene, reflux; (b) sodium borohydride, ethanol, 40-50°C; (ii) potassium hydroxide, methanol, reflux methanol successfully provided the target compound **3** in 71% yield.

The two deaza analogues of **1** were evaluated for their anxiolytic potential in the Geller conflict assay. In contrast to the excellent activity of **1**, compounds **2** and **3** were found to have no anxiolytic activity in this screen at concentrations up to 25 mg/kg p.o. A number of explanations for the inactivity of these analogues are possible, including poor interaction at the relevant receptor since the Geller conflict test is an *in vivo* assay. Further testing of closely related analogues may clarify this phenomena.

EXPERIMENTAL

General Methods.

Melting points were determined in open glass capillaries by use of a Thomas-Hoover apparatus, and are uncorrected. The ^1H nmr spectra were recorded at 300 MHz with a Varian XL-300 spectrometer or at 200 MHz with a Gemini 200 spectrometer. Chemical ionization ms were recorded with a platform mass spectrometer (Fisons Instrument) operated in a APcI (Atmospheric pressure chemical ionization) mode. Infrared spectra were taken with a Mattson FTIR. Evaporations were performed under diminished pressure in a Buchi rotatory evaporator at 40° under water aspirator pressure unless otherwise indicated. Analysis (tlc) was performed on precoated glass plates (0.25 mm) with Silica Gel $60F_{254}$ (E. Merck, Darmstad). Flash column chromatography was performed with Silica Gel 60 (230-400 mesh, E. Merck, Darmstad). Elemental analyses were determined by Atlantic Microlab (Atlanta, GA).

(*E*)-1-Methyl-2-[2-(1-benzylpyrrolo)]acrylic Acid (**5**).

A solution of 1-benzyl-2-formylpyrrole (**4**) [5] in anhydrous propanol (5 ml) was added in one portion to a refluxing solution of methylmalonic acid (4.15 g, 34.4 mmoles) and aniline (3.11 g, 33.4 mmoles) in anhydrous propanol (10 ml). After heating the solution at reflux for 2 hours the reaction mixture was poured into ice water (60 ml), and a purple-colored precipitate was collected by filtration. The filtrate was extracted with dichloromethane (1 x 50 ml). The dichloromethane layer was dried by filtration through phase separator paper and then was combined with the purple-colored precipitate. The volume of the resulting solution was reduced to 20 ml by distillation at atmospheric pressure, and the mixture was purified by column chromatography on silica gel eluting with dichloromethane/hexanes, 1:1, then 4:1, and finally with dichloromethane/ethyl acetate, 4:1 to give a brown solid. The solid was recrystallized from toluene to furnish 3.81 g (47%) of **5**, as a pink-colored crystalline solid: mp 157-159°; ^1H nmr (300 MHz, dimethyl sulfoxide-d_6): δ 7.73 (s, 1H, ArC*H*), 7.35-7.06 (m, 5H, phenyl H), 6.90 (t, J = 1.6 Hz, 1H, pyrrole H), 6.69 (m, 1H, pyrrole H), 6.34 (t, J = 2.9 Hz, 1H, pyrrole H), 5.22 (s, 2H, PhCH_2), 2.13 (s, 3H, CH_3).

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.80. Found: C, 74.50; H, 6.28; N, 5.74.

1-Benzyl-4,5-dihydro-6-methyl-4-oxopyrrolo[3,2-*c*]pyridine (**7**).

A solution of ethyl chloroformate (13.7 ml, 140 mmoles) in anhydrous acetone (50 ml) was added dropwise to a solution of **5** (17.22 g, 71.4 mmoles) and triethylamine (11.9 ml, 85.8 mmoles) in anhydrous acetone (60 ml) at 0° under a nitrogen atmosphere. The resulting yellow suspension was allowed to stir at 0° for 2 hours. A solution of sodium azide in water (36 ml) was then added dropwise to the chilled reaction mixture (maintained <10°), and the resulting mixture was stirred at room temperature for 2 hours. The mixture was poured onto crushed ice (100 ml) and extracted with benzene (2 x 70 ml). The benzene layers were combined, evaporated to 70 ml, and then dried over sodium sulfate.

The benzene solution of the crude acyl azide **6** was added dropwise to a solution of tributylamine (20.4 ml, 111 mmoles) and diphenyl ether (70 ml) that was maintained at 175-185° over the course of 1 hour. After the addition was complete the reaction mixture was heated at 195-198° for 45 minutes and then cooled to room temperature. Ether (100 ml) was added, and the solution was allowed to stand at room temperature overnight to effect crystallization. A yellow crystalline solid was collected by filtration and washed with ether to give 11.89 g (70%) of **7**, mp 219-221°; ^1H nmr (300 MHz, dimethyl sulfoxide-d_6): δ 10.75 (s, 1H, 5-NH), 7.40-7.09 (m, 6H, phenyl H, 2-H), 6.45 (d, J = 3.1 Hz, 1H, 3-H) 6.29 (s, 1H, 7-H), 5.25 (s, 2H, phenyl CH_2), 2.14 (s, 3H, 6-CH_3).

Anal. Calcd. for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92, N, 11.76. Found: C, 75.71; H, 5.94; N, 11.80.

4,5-Dihydro-6-methyl-4-oxo-1*H*-pyrrolo[3,2-*c*]pyridine (**8**).

Sodium (2.17 g, 94.4 mmoles) was added in small portions to a chilled (external dry ice-2-propanol bath) suspension of **7** (4.50 g, 18.9 mmoles) in liquid ammonia over the course of 10 minutes. The resulting dark blue suspension was stirred for 1.5 hours and then ammonium chloride (4.34 g, 81 mmoles) was added. The ammonia was then allowed to evaporate, and the resulting concentrate was treated with water (40 ml). The *p*H of the resulting mixture was adjusted to 8 by the addition of concentrated hydrochloric acid. The resulting suspension was filtered to yield 2.58 g (91%) of **8** as an off-white solid, mp >250°; ^1H nmr (300 MHz, dimethyl sulfoxide-d_6): δ 11.18 (s, 1H, N*H*), 10.62 (s, 1H, N*H*), 6.94 (d, J = 2.4 Hz, 1H, 2-H), 6.38 (d, J = 2.1 Hz, 1H, 3-H), 6.11 (s, 1H, 7-H), 2.15 (s, 3H, 6-CH_3); ms: m/z 149 $(M+1)^+$.

Anal. Calcd. for $C_8H_8N_2O{\bullet}0.1H_2O$: C, 64.07; H, 5.51; N, 18.68. Found: C, 63.78; H, 5.45; N, 18.65.

4-Chloro-2-methyl-1*H*-pyrrolo[3,2-*c*]pyridine (**9**).

A suspension of **8** (1.48 g, 10 mmoles) in phosphorus oxychloride (10 ml) in a sealed tube was heated *via* external oil bath at 180-185° for 6 hours. The reaction mixture was evaporated, and the resulting concentrate was treated with crushed ice (20 ml). Solid sodium bicarbonate and then 5 *N* sodium hydroxide solution was added to adjust the aqueous mixture to *p*H = 6. A gray-colored precipitate was collected by filtration to provide 1.38 g (83%) of **9**, mp 217-220°; ms: (CI) *m/z* = 167 (M + 1, 100%); ^1H nmr (300 MHz, dimethyl sulfoxide-d_6): δ 11.69 (s, 1H, N*H*-1), 7.44 (t, J = 2.6 Hz, 1H, 2-H), 7.22 (s, 1H, 7-H), 6.45 (m, 1H, 3-H), 2.46 (s, 3H, CH_3-6); ms: m/z 167 $(M+1)^+$.

Anal. Calcd. for $C_8H_7N_2Cl{\bullet}0.1H_2O$: C, 57.06; H, 4.31; N, 16.63; Cl, 21.05. Found: C, 56.93; H, 4.27; N, 16.56; Cl, 20.85.

4-Amino-1-benzyl-6-methylpyrrolo[2,3-*b*]pyridine (**10**).

A solution of **9** (0.152 g, 0.91 mmole) in benzylamine (1.8 ml) was heated at reflux under a nitrogen atmosphere for 2.5 hours. The excess benzylamine was removed by distillation *in vacuo* (0.08 mm Hg). The resultant concentrate was purified by column chromatography on silica gel eluting with ethyl acetate to yield **10** as yellow crystals, 0.131 g (59%), mp 108-111°; ^{1}H nmr (300 MHz, dimethyl sulfoxide-d$_6$): δ 7.35-7.10 (m, 5H phenyl H), 7.02 (d, J = 3.4 Hz, 1H, 2-H), 6.40 (d, 1H, J = 3.5 Hz, 1H, 3-H), 6.06 (m, 3H, 7-H, N*H*$_2$), 5.29 (s, 2H, PhC*H*$_2$), 2.29 (s, 3H, 6-C*H*$_3$); ms: m/z 238.1 (M+1)$^+$; uv: (*p*H 1): λ max 277 nm (ε 9500), λ max 296 nm (ε 9900); (*p*H 7): λ max 276 nm (ε 9400), λ max 293 nm (ε 9500); (*p*H 13): λ max 276 nm (ε 9000), λ max 288 nm (ε 9000).

Anal. Calcd. for $C_{15}H_{15}N_3{\bullet}0.3H_2O$: C, 73.68; H, 6.51; N, 17.19. Found: C, 73.86; H, 6.48; N, 17.00.

4-Benzylamino-2-methyl-1*H*-pyrrolo[3,2-*c*]pyridine (**2**).

A mixture of **9** (1.071 g, 6.43 mmoles) in dibenzylamine (8 ml) was heated at 175-185° under a nitrogen atmosphere for 4 hours. Upon cooling, precipitated dibenzylamine hydrochloride was removed by filtration. The concentrate was distilled *in vacuo* (0.05 mm Hg) to remove the excess dibenzylamine. The stillpot residue was purified by column chromatography on silica gel eluting with dichloromethane, then dichloromethane/methanol, 98:2, and finally with dichloromethane-/methanol/triethylamine, 94:5:1 to yield 1.78 g of 4-dibenzylamino-2-methyl-1*H*-pyrrolo[3,2-*c*]pyridine (**11**) as a brown foam which was not further purified; ms: m/z 328.1 (M+1)$^+$.

A mixture of the foam **11** and 20% palladium hydroxide on carbon (0.40 g) in ethanol (50 ml) was shaken at 50 psi on a Parr hydrogenation apparatus at room temperature for 2 days. Glacial acetic acid (2 ml) was added to the reaction mixture and the mixture was again hydrogenated at 50 psi for 4 more days. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to dryness. The concentrate was suspended in water (5 ml), and then 5 *N* sodium hydroxide solution was added to adjust the *p*H of the solution to 10. The resulting suspension was extracted with chloroform (3 x 25 ml). The chloroform layers were combined, dried by filtration through phase separator paper, and then evaporated to a pink foam. The foam was purified by column chromatography on silica gel eluting with dichloromethane, then dichloromethane/methanol, 98:2, and finally, with dichloromethane/methanol/triethylamine, 94:5:1 to give a pink foam. An attempt to prepare the hydrochloride of **2** (in order to obtain a solid) was made by treatment of **2** with ethereal hydrochloric acid. A gum resulted which could not be induced to crystallize, therefore the mixture was evaporated. The free base was liberated by suspending the concentrate in 5 *N* sodium hydroxide (10 ml) and extracting the resulting suspension with dichloromethane (3 x 20 ml). The dichloromethane layers were combined and evaporated to a gum. The gum was purified by column chromatography on silica gel eluting with dichloromethane and then with dichloromethane/methanol/triethylamine, 97:2:1 to give 0.389 g (25% from **9**) of **2** as a pink foam; ^{1}H nmr (300 MHz, dimethyl sulfoxide-d$_6$): δ 10.90 (s, 1H, 1-N*H*), 7.36-7.15 (m, 5H, phenyl H), 6.98 (t, J = 2.6 Hz, 1H, 2-H), 6.95 (m, 1H, 4-N*H*), 6.56 (s, 1H), 6.42 (s, 1H) 4.66 (d, J = 6.0 Hz, 2H, PhC*H*$_2$), 2.25 (s, 3H, 6-C*H*$_3$); ms: m/z 238.0 (M+1)$^+$; uv: (*p*H 1): λ max 275 nm (ε 10,700), λ max 295 (ε 10,300); (*p*H 7): λ max 275 (ε 10,800), λ max 295 (ε 10,400); (*p*H 11): λ max 279 (ε 12,800).

Anal. Calcd. for $C_{15}H_{15}N_3{\bullet}0.3H_2O$: C, 74.23; H, 6.48; N, 17.31. Found: C, 74.50; H, 6.54; N, 17.31.

N-(3,6-Dimethyl-2-pyridyl)-*N*-methyl-*N*-phenylformamidine (**15**).

A suspension of phosphorus pentachloride (46.50 g, 220 mmoles) in chloroform (300 ml) was treated consecutively with a solution of *N*-methylformanilide [8] (25.00 g, 185 mmoles) in chloroform (50 ml) and then with a solution of 2-amino-3,6-dimethylpyridine (**12**) (24.93 g, 185 mmoles) [6], dropwise, at 3°. After the additions the resulting mixture was heated at reflux for 3 hours. The solution was cooled to room temperature and then slowly poured with stirring into an ice/water chilled 2.5 *N* sodium hydroxide solution (150 ml). As the reaction mixture was added to the basic solution, additional 5 *N* sodium hydroxide solution was added to maintain the *p*H of the resulting mixture >11. The resulting organic layer was separated, dried over potassium carbonate, and evaporated to a red liquid. The crude product was purified by column chromatography on silica gel eluting with chloroform to furnish 38.53 g (87%) of **15** as a pale yellow oil. The ^{1}H nmr spectrum of **15** was in good agreement with the spectrum reported by Rasmussen [4].

2-Methyl-1*H*-pyrrolo[2,3-*b*]pyridine *N*-Oxide (**17**).

A solution of **16** [4] (1.50 g, 11.3 mmoles) in dichloromethane (20 ml) was added to a suspension of *m*-chloroperoxybenzoic acid (50-60% reagent, 7.80 g, 23 mmoles) in dichloromethane (30 ml), dropwise over the course of 1 hour at 0°. After the addition was complete the suspension was allowed to stir at room temperature for 20 hours. The suspension was filtered to remove the solids, and the resulting filtrate was evaporated to dryness. The concentrate was taken up in potassium carbonate (30 ml) and chloroform (50 ml) to give an emulsion. The emulsion was filtered to remove a small amount of precipitate which was washed with additional chloroform (50 ml). The filtrate's layers were separated and the chloroform layer was dried over magnesium sulfate and evaporated to give 0.78 g (47%) of crude **17**. An analytical sample of **17** was purified by column chromatography on silica gel eluting with dichloromethane/ethyl acetate, 4:1 then dichloromethane/methanol, 95:5 to give 0.24 g (14%) of **17** as a beige-colored solid, mp 213-217°; ^{1}H nmr (300 MHz, dimethyl sulfoxide-d$_6$): δ 12.26 (s, 1 H, N*H*-1), 7.51 (d, J = 7.8 Hz, 1 H, pyridine H), 7.32 (t, J = 2.7 Hz, 1 H, H-2), 7.08 (t, J = 8.1 Hz, 1 H, pyridine H), 6.49 (dd, J = 1.9 Hz, J = 3.2 Hz, 1 H, H-3), 2.48 (s, 3 H, C*H*$_3$-2); ms: m/z 149.1 (M+1)$^+$.

Anal. Calcd. for $C_8H_8N_2O{\bullet}0.1H_2O$: C, 64.07; H, 5.51; N, 18.68. Found: C, 63.86; H, 5.49; N, 18.53.

6-Methyl-4-nitro-1*H*-pyrrolo[2,3-*b*]pyridine *N*-Oxide (**18a**).

Fuming nitric acid (17.7 ml) was added dropwise to a solution of **17** (5.22 g, 35.2 mmoles) in trifluoroacetic acid (41 ml) at 0°. After the addition was complete the reaction mixture was poured onto crushed ice (120 ml). The resulting suspension was neutralized with 5 *N* sodium hydroxide solution. A yellow precipitate was recovered by filtration to provide 4.86 g (71%) of a mixture of **18a** and **18b**. The solid mixture was very insoluble in organic solvents. This property prevented the separation of **18a** and **18b** by either recrystallization or column chromatography. Integration of the peaks corresponding to the pyrrolic H's in the 300 MHz ^{1}H nmr spectrum gives a ratio for **18a**:**18b** of 37:63. The spectrum of **18a** was: ^{1}H nmr (300 MHz, dimethyl sulfoxide-d$_6$): δ 13.08 (s, 1H, 1-N*H*), 8.18 (s, 1H, 5-H), 7.69 (t, 1H, 2-H), 6.97 (m, 1H, 3-H), 2.56 (s, 3H, 6-C*H*$_3$). The spectrum of **18b** was: ^{1}H nmr (300 MHz, dimethyl sulfoxide-d$_6$): δ 8.63 (s, 1H, 2-H), 7.90 (d, J = 8.1 Hz, 1H, pyridine H), 7.43 (d, J = 8.1 Hz, pyridine H), 2.52 (s, 3H, 6-C*H*$_3$).

6-Methyl-4-nitro-1*H*-pyrrolo[2,3-*b*]pyridine (**19a**).

Phosphorus trichloride (6.6 ml, 75.6 mmoles) was added to an ice-water chilled suspension of the mixture of **18a** and **18b** (4.86 g, 25.2 mmoles) in chloroform (75 ml). The resulting suspension was heated at reflux for 2 hours and then evaporated. The concentrate was treated with crushed ice (30 ml), and the resulting mixture's *p*H was adjusted to *p*H >11 by the addition of 5 *N* sodium hydroxide solution. A yellow precipitate was collected by filtration to yield 2.03 g (46%). Integration of the peaks corresponding to the pyrrolic H's in the 300 MHz ^{1}H nmr spectrum of this yellow precipitate gave a ratio for **19a**:**19b** of 3:1; The spectrum of **19a** was: ^{1}H nmr (300 MHz, dimethyl sulfoxide-d$_6$): δ 12.39 (s, 1H, 1-N*H*), 7.79 (m, 2H, 2-H, 5-H), 6.89 (d, J = 3.2 Hz, 1H, 3-H), 2.65 (s, 3H, 6-C*H*$_3$).

1-Benzenesulfonyl-6-methyl-4-nitropyrrolo[2,3-*b*]pyridine (**20a**).

A suspension of the solid enriched in **19a** (1.84 g, 10.4 mmoles) in anhydrous dimethylformamide (18 ml) was treated with sodium hydride (60% mineral oil dispersion, 0.50 g, 12.5 mmoles) and stirred at 25° for 30 minutes under a nitrogen atmosphere. Benzenesulfonyl chloride (1.5 ml, 11.8 mmoles) was added dropwise, and the resulting suspension was stirred at room temperature for 3 days. The reaction mixture was evaporated, and the resulting concentrate was taken up in water (20 ml). The mixture was extracted with chloroform (3 x 50 ml). The chloroform layers were combined, dried over magnesium sulfate, and evaporated to a gummy solid. This solid was purified by column chromatography on silica gel eluting with dichloromethane/hexane, 1:1 then dichloromethane, and finally with dichloromethane/methanol, 95:5 to yield 1.86 g (56%). Integration of the peaks corresponding to the pyrrolic H's in the 300 MHz ^{1}H nmr spectrum of this yellow precipitate gave a ratio for **20a**:**20b** of 9:1; ^{1}H nmr (200 MHz, dimethyl sulfoxide-d$_6$): δ 8.23 (m, 3H, *o*-phenyl H, 2-H), 8.03 (s, 1H, 5-H), 7.82-7.63 (m, 3H, phenyl H), 7.22 (d, J = 4.1 Hz, 1H, 3-H), 2.73 (s, 3H, 6-C*H*$_3$).

1-Benzenesulfonyl-4-amino-6-methylpyrrolo[2,3-*b*]pyridine (**21a**).

A mixture of solid enriched in **20a** (1.76 g, 5.5.mmoles) and Raney nickel (1.40 g) in ethanol (70 ml) was hydrogenated at 50 psi for 4 hours. The catalyst was removed by filtration and the filtrate was evaporated to a gum. The gum was purified by column chromatography on silica gel eluting with dichloromethane to afford 1.24 g (78%) of **21a** as a foam; ^{1}H nmr (300 MHz, dimethyl sulfoxide-d$_6$): δ 8.07 (d, J = 7.3 Hz, 2H, phenyl H), 7.69-7.55 (m, 3H, phenyl H), 7.38 (d, J = 4.2 Hz, 1H, 2-H), 6.76 (d, J = 3.9 Hz, 1H, 3-H), 6.39 (s, 2H, 4-N*H*$_2$), 6.15 (s, 1H, 5-H), 2.28 (s, 3H, 6-C*H*$_3$); ms: m/z 288.0 (M+1)$^+$.

Anal. Calcd. for $C_{14}H_{13}N_3O_2S{\bullet}0.3H_2O$: C, 57.44; H, 4.56; N, 14.35; S, 10.95. Found: C, 57.54; H, 4.57; N, 14.29; S, 10.90.

1-Benzenesulfonyl-4-benzylamino-6-methylpyrrolo[2,3-*b*]pyridine (**22**).

A solution of **21a** (1.12 g, 3.9 mmoles) and benzaldehyde (2 ml, 19.6 mmoles) in toluene (20 ml) was heated at reflux removing water using a Dean-Stark apparatus for 6 hours. The reaction mixture was evaporated to a yellow solid which was used without further purification. Sodium borohydride (0.59 g, 15.6 mmoles) was added in small portions over the course of 40 minutes to a solution of the above Schiff's base in ethanol (15 ml) heated at 40-50°. After the addition was complete the suspension was heated at 65-70° for an additional 2 hours and then evaporated to dryness. The concentrate was taken up in 0.1 *N* sodium hydroxide solution and the resulting suspension was extracted with dichloromethane (2 x 30 ml). The dichloromethane layers were combined, dried over magnesium sulfate, and then evaporated to a yellow solid. The solid was suspended in methanol and collected by filtration to yield 1.18 g (80%) of **22** as an off-white solid, mp 193-196.5°; ^{1}H nmr (300 MHz, dimethyl sulfoxide-d$_6$): δ 8.08 (d, J = 7.1 Hz, 2H, phenyl H), 7.69 (m, 10H, phenyl H, 4-N*H*, 2-H), 6.88 (d, J = 4.2 Hz, 1H, 3-H), 6.13 (s, 1H, 5-H), 4.40 (d, J = 6.0 Hz, 2H, PhC*H*$_2$), 2.27 (s, 3H, C*H*$_3$-6); ms: m/z 378.0 (M+1)$^+$.

Anal. Calcd. for $C_{21}H_{19}N_3O_2S{\bullet}0.3H_2O$: C, 65.88; H, 5.16; N, 10.98; S, 8.37. Found: C, 65.97; H, 5.15; N, 10.92; S, 8.29.

4-Benzylamino-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (**3**).

A suspension of **22** (1.11 g, 2.9 mmoles) and potassium hydroxide (0.74 g, 13.2 mmoles) in methanol (10 ml) was heated at reflux under a nitrogen atmosphere for 4 hours and then evaporated. The concentrate was taken up in water (10 ml), and this suspension was extracted with ethyl acetate (2 x 30 ml). The ethyl acetate layers were combined, dried over magnesium sulfate, and then evaporated to a solid. The solid was recrystallized from methanol to provide 0.492 g (71%) of **3** as a beige crystalline solid, mp 203-204.5°; ^{1}H nmr (300 MHz, dimethyl sulfoxide-d$_6$): δ 10.91 (s, 1H, 1-N*H*), 7.35-7.17 (m, 5H, phenyl H), 7.02 (t, J = 6.3 Hz, 1H, 4-N*H*), 6.94 (d, J = 3.2 Hz, 1H, 2-H), 6.49 (d, J = 3.2 Hz, 1H, 3-H), 5.92 (s, 1H, 5-H), 4.42 (d, J = 6.3 Hz, 2H, PhC*H*$_2$), 2.23 (s, 3H, 6-C*H*$_3$); ms: m/z 238.0 (M+1)$^+$; uv: (*p*H 1) λ max 277 nm (ε 11,400), λ max 302 nm (ε 19,600); (*p*H 7): λ max 277 nm (ε 11,700), λ max 301 nm (ε 18,600); (*p*H 11): λ max 279 nm (ε 15,000), λ max 291 nm (ε 17,300).

Anal. Calcd. for $C_{15}H_{15}N_3$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.83; H, 6.36; N, 17.76.

Acknowledgement.

Our thanks to the nmr staff of the Division of Bioanalytical Sciences for help with structural elucidation; to K. Nanry and G. Pollard of the Division of pharmacology for behavioral testing.

REFERENCES AND NOTES

* To whom correspondence should be addressed.

[1] R. Baldessarini, The Pharmacological Basis of Therapeutics, 8th Ed, A. G. Gilman, T. W. Rall, A. S. Nies, P. Taylor, eds, Pergamon Press, New York, 1990, p 383.

[2] R. A. West and L. M. Beauchamp, *J. Org. Chem.*, **26**, 3809 (1961).

[3a] I. Geller and J. Seifter, *Psychopharmacologia*, **1**, 482 (1960); [b] G. T. Pollard, K. P. Nanry, and J. L. Howard, *Eur. J. Pharmacology*, **221**, 297 (1992).

[4] I. Mahadevan and M. Rasmussen, *J. Heterocyclic Chem.*, **29**, 359 (1992).

[5] C. Ducrocq, E. Bisagni, J. M. Lhoste, J. Mispelter, and J. Defaye, *Tetrahedron*, **32**, 773 (1976).

[6] A. Albert and R. E. Willette, *J. Chem. Soc.*, 4063 (1964).

[7a] E. Bisagni, M. Legraverend, and J. M. Lhoste, *J. Org. Chem.*, **47**, 1500 (1982); [b] A. F. Casy, R. J. Needle, and C. Upton, *J. Chem. Res. (S)*, 4 (1986).

[8] L. F. Fieser and J. E. Jones, Organic Syntheses, Coll. Vol **3**, E. C. Horning, ed, Wiley and Sons, Inc, New York, 1955, p 590.

[9] H. G. Mandel and A. G. Hill, *J. Org. Chem.*, **76**, 3978 (1954).

[10] I. Antonini, F. Claudi, G. Cristalli, P. Franchetti, M. Grifantini, and S. Martelli, *J. Med. Chem.*, **25**, 1258 (1982).