Synthesis and Anticonvulsant Activity of 1-Benzyl-4-alkylamino-1*H*-imidazo[4,5-*c*]pyridines

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Four 3-deaza analogues of the potent anticonvulsant purine, BW A78U, were synthesized and tested for anticonvulsant activity. The imidazo[4,5-*c*]pyridines **9-12** were prepared in two steps from 4-chloro-1*H*-imidazo[4,5-*c*]pyridine (**2**). The compounds were potent anticonvulsant agents against maximal electroshock-induced seizures in rats with i.p. ED_{50} ranging from 2 to 3.5 mg/kg. However, these 3-deazapurines were appreciably more toxic than BW A78U, which precluded their development as potential antiepileptic agents.

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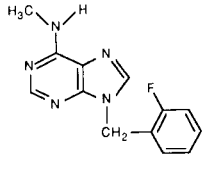
A variety of drugs of diverse chemical structure are used in the treatment of epilepsy [1]. However, many patients fail to experience satisfactory seizure control with them, or they do so at the expense of significant side effects [2,3]. Due to this need for better antiepileptic drugs, a program was initiated to discover and develop improved antiepileptic agents [4-8]. The potent anticonvulsant purine, BW A78U (**1**), emerged from this program [6]. Compared to commonly used anticonvulsants, BW A78U has a unique structure that provides a novel lead for the development of improved agents for use in the treatment of seizure disorders. Modification of the substituents on the purine ring of BW A78U showed that optimum activity was associated with a 9-(2-fluorobenzyl) and 6-alkylamino substitution pattern [7,8]. We have further modified the structure of BW A78U by isosteric replacement of the 3-nitrogen with carbon to give 3-deaza analogues of BW A78U. The synthesis and anticonvulsant activity of these new analogues are reported.



BW A78U 1

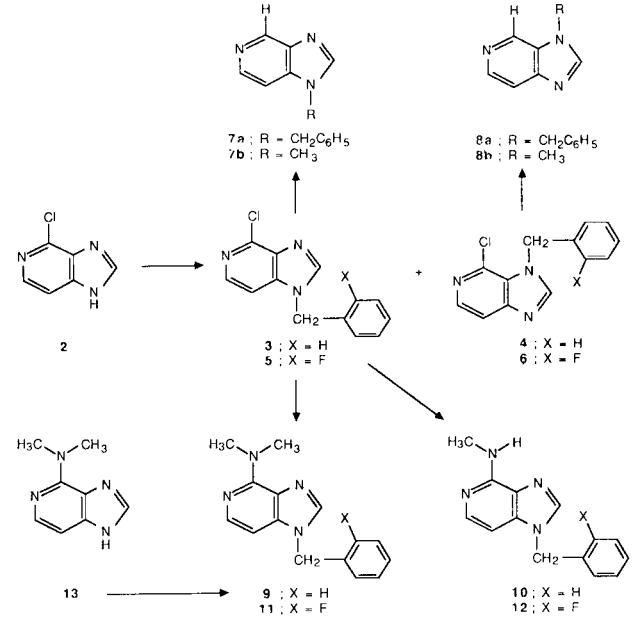
Chemistry.

The 3-deazapurine analogues **9-12** were prepared as outlined in Scheme I. The imidazo[4,5-*c*]pyridine **2** [9] was alkylated with benzyl bromide or 2-fluorobenzyl bromide in the presence of potassium carbonate to give a mixture of the 1-substituted, **3** and **5**, and 3-substituted, **4** and **6**, isomers. These isomers were only minimally resolved by tlc, and the mixture required extensive chromatography by preparative lc and flash chromatography [10] to give pure **3-6**.

The assigned structures were confirmed by dechlorination of **3** and **4** to give **7a** and **8a** and through use of ^{1}H-nmr nuclear Overhauser effect (nOe) experiments. The 4-chloro substituent in **3** and **4** was removed by hydrogenolysis with Pd on carbon to give **7a** and **8a**, respectively. The ultraviolet spectra were very similar to the published ultraviolet spectra of **7b** and **8b**, which had been prepared by unequivocal synthetic routes [11]. The structures of **3** and **4** were further substantiated when a ^{1}H-nmr nOe was observed for **3** but not for **4**. When the benzylic methylene signal of **3** was irradiated, the proton at C-7 showed an 11% enhancement of its signal, whereas the C-7 proton of **4** showed no enhancement. The 2-fluoro isomers **5** and **6** had nmr, uv spectra and relative tlc mobility characteristics that were in accord with those for **3** and **4**.

Amination of **3** and **5** with dimethylamine or methylamine at elevated temperatures afforded **9-12**. Compound **9** was also prepared by alkylation of the sodium salt of **13** [12] with benzyl bromide. Compound **13** was prepared

Scheme I



from **2** [9] by reaction with aqueous dimethylamine in ethanol at elevated temperature.

Biological Results and Discussion.

BW A78U (**1**) had potent anticonvulsant activity against maximal electroshock-induced seizures (MES) in Sprague-Dawley male rats with an oral ED_{50} of 2.5 ± 0.4 mg/kg under conditions where phenytoin had an ED_{50} of 20 ± 3 mg/kg. When administered by the i.p. route, **1** was active with an ED_{50} of 1.7 ± 0.4 mg/kg. The four analogues of **1** in which the 3-nitrogen was replaced with carbon were also very active as anticonvulsant agents. The i.p. ED_{50}'s for **9-12** ranged from 2 to 3.5 mg/kg. Compound **12**, which is the most similar analogue to **1**, was very active with an i.p. ED_{50} of 3 mg/kg and an oral ED_{50} of 4 mg/kg. However, these 3-deazapurine analogues were appreciably more toxic than BW A78U. The acute i.p. LD_{50}'s, which were determined in CD-1 male mice, were 65 mg/kg or less, whereas BW A78U had an acute i.p. LD_{50} of approximately 120 mg/kg and an oral LD_{50} >1000 mg/kg [6].

Thus, although 3-deazapurine analogues of BW A78U had potent anticonvulsant activity in an animal model that predicts antiepileptic activity in man, the acute toxicity of the compounds was substantially greater, which precluded them from further consideration as potential antiepileptic agents.

Table 1

Anticonvulsant Activity of 1*H*-imidazo[4,5-*c*]pyridines Against Maximal Electroshock-induced Seizures (MES) [a]

Compound [b]	MES ED_{50}, mg/kg [c], [d], [e] i.p.	p.o.
1	1.7 ± 0.4	2.5 ± 0.4
9	2	N. T.
10	3.5	7
11	2	N. T.
12	3	4

[a] The compounds were tested for their ability to protect Sprague-Dawley male rats against maximal electroshock-induced seizures (MES) as described in ref [5]. The ED_{50} was the dose needed to protect 50% of the animals against the hind-limb extensor component and were calculated using the method of L. C. Miller and M. L. Tainter, *Proc. Soc. Exp. Biol. Med.*, **57**, 261 (1944). [b] Compounds were tested as the hydrochloride salt. [c] The ED_{50} for phenytoin was 10 ± 2 mg/kg i.p. and 20 ± 3 mg/kg p.o. [d] Where ED_{50} values are presented with a standard error a minimum of twelve animals were used per dose level with four doses per compound. The ED_{50} values without standard error were determined using three doses of compound with six animals per point. [e] N. T. = not determined.

EXPERIMENTAL

Melting points were determined with a Thomas Hoover or Mel-Temp capillary melting point apparatus and are uncorrected. The ultra violet spectra were recorded with a Unicam SP 800 spectrophotometer or Cary 118 UV-Vis spectrophotometer. The nmr spectra were recorded using a Varian XL-100-15-FT, a Varian XL-200, a Varian T-60, or a Hitachi Perkin-Elmer R-24 spectrometer. Chemical shift values are reported in parts per million on the δ scale with tetramethylsilane as the internal reference. The nmr spin multiplicities are indicated by the symbols s (singlet), d (doublet), q (quartet), and m (multiplet). Mass spectra (70 eV) were obtained on a Varian CH-5-DF mass spectrometer. Elemental microanalyses were determined by Atlantic Microlabs, Atlanta, GA 30386, and gave combustion values for C, H, and N within 0.4% of theoretical values. Preparative column chromatography was done either using the flash chromatography technique [10] on Silica Gel 60 (40-63 μm, E. Merck No. 9385) or using a Waters Associates Prep LC/System 500 instrument using ethyl acetate/hexane as an eluant. Thin layer chromatography (tlc) was done using Silica Gel (200 μ) MK GF (Whatman) plates eluted with dichloromethane:methanol (9:1) or diethyl ether. Detection of spots was by fluorescence indicator quenching upon exposure of the plates to uv light. Solvents were evaporated by rotary evaporation (Buchler flash evaporator) using a temperature-controlled water bath.

1-Benzyl-4-chloro-1*H*-imidazo[4,5-*c*]pyridine (**3**).

The chromatography fractions from preparation of **4** that were a mixture of **3** and **4** were rechromatographed by flash chromatography on Silica Gel 60. The solvent was evaporated from the combined fractions that contained **3** to give a homogeneous oil, 1.29 g (16%) of **3**. Crystallization of a portion from ethanol-hexane gave 0.212 g of **3**, mp 103.5-104°; tlc, dichloromethane:methanol (95:5), R_f = 0.34; uv (*p*H 7 buffer + 9.5% ethanol): λ max 275 (ε 5500), 267 (ε 7100), 257.5 (ε 7000); λ min 272.5 (ε 5100), 263.5 (ε 6600); nmr (DMSO-d_6): δ 8.66 (s, 1H, H-2), 8.12 (d, 1H, J = 5.6 Hz, H-6), 7.66 (d, 1H, J = 5.6 Hz, H-7), 7.34 (m, 5H, Ar), 5.57 (s, 2H, CH_2); ms: m/e 243 (M^+), 91 ($C_7H_7^+$).

Anal. Calcd. for $C_{13}H_{10}ClN_3$: C, 64.07; H, 4.14; N, 17.24. Found: C, 64.17; H, 4.12; N, 17.01.

3-Benzyl-4-chloro-3*H*-imidazo[4,5-*c*]pyridine (**4**).

A mixture of **2** [9] (5.00 g, 32.6 mmoles), benzyl bromide (4.27 ml, 35.9 mmoles), anhydrous potassium carbonate (4.96 g, 35.9 mmoles), and dimethylformamide (50 ml) was stirred for 20 hours at ambient temperature. The solution was poured into ice-water (400 ml), and the *p*H was adjusted to 5 with acetic acid. The solution was extracted with dichloromethane (2 x 100 ml), the combined extracts were washed with water (2 x 150 ml), and then spin evaporated *in vacuo*. The resultant oil was a mixture of **3** and **4**, which were separated by chromatography on a Water's Prep LC-500 using two silica gel cartridges. The compounds were eluted with hexane:ethyl acetate (1:1). The 3-benzyl isomer **4**, which was the higher R_f component, was obtained pure in several early fractions, but later fractions contained a mixture of **3** and **4**. These later fractions were combined, spin evaporated *in vacuo*, and further purified by flash chromatography on Silica Gel 60. The column was eluted with cyclohexane:ethyl acetate (1:1) to give several fractions of pure **4**. These were combined with pure **4** from the Prep LC-500 column and spin evaporated *in vacuo*. The solids were recrystallized from cyclohexane to give 0.924 g (11%) of **4**, mp 145-146°; tlc, dichloromethane:methanol (95:5), R_f = 0.37; uv (*p*H 7 buffer + 9.5% ethanol): λ max 279 (ε 6600), 249 (ε 3900), 242.5 (ε 4000); λ min 256 (ε 2700), 246.5 (ε 3700), sh 287 (ε 4700); nmr (DMSO-d_6): δ 8.75 (s, 1H, H-2), 8.16 (d, 1H, J = 5.5 Hz, H-6), 7.76 (d, 1H, J = 5.5 Hz, H-7), 7.13 (m, 5H, Ar), 5.80 (s, 2H, CH_2); ms: m/e 243 (M^+), 91 ($C_7H_7^+$).

Anal. Calcd. for $C_{13}H_{10}ClN_3$: C, 64.07; H, 4.14; N, 17.24. Found: C, 63.86; H, 4.11; N, 17.22.

4-Chloro-1-(2-fluorobenzyl)-1*H*-imidazo[4,5-*c*]pyridine (**5**).

The chromatography fractions from the preparation of **6** that contained **5** contaminated with a few percent of **6** were spin evaporated *in vacuo* to give 9.82 g (44%) of white solid. A 2.43 g sample was recrystallized twice from cyclohexane-ethyl acetate to give 1.12 g of pure **5**, mp 108-110°; tlc, diethyl ether, R_f = 0.27; uv (*p*H 7 buffer + 9.5% ethanol): λ max 274 (ε 5200), 267 (ε 7500), 257.5 (ε 7400); λ min 272.5 (ε 4900),

263.5 (ε 6900); nmr (DMSO-d_6): δ 8.59 (s, 1H, H-2), 8.14 (d, 1H, J = 5.6 Hz, H-6), 7.64 (d, 1H, J = 5.5 Hz, H-7), 7.12-7.46 (m, 4H, Ar), 5.64 (s, 2H, CH_2).

Anal. Calcd. for $C_{13}H_9ClFN_3$: C, 59.66; H, 3.47; N, 16.06. Found: C, 59.63; H, 3.49; N, 16.10.

4-Chloro-3-(2-fluorobenzyl)-3*H*-imidazo[4,5-*c*]pyridine (**6**).

A mixture of **2** [9] (13.0 g, 84.9 mmoles), 2-fluorobenzyl bromide (10 ml, 82.7 mmoles), anhydrous potassium carbonate (14.1 g, 102 mmoles), and dimethylsulfoxide (100 ml) was stirred at ambient temperature for 18 hours. The solution was poured into ice-water (400 ml) and extracted with dichloromethane (4 x 100 ml). The combined extracts were washed with water (6 x 50 ml), 1 *N* sodium hydroxide (2 x 50 ml), water (50 ml), filtered through glass wool, and spin evaporated *in vacuo*. The solid residue was dissolved in dichloromethane (100 ml) and applied to a column (23 cm x 18 cm) of Silica Gel 60 wetted with ether. The column was eluted with ether and forty-four 200-ml fractions were collected. The fractions containing only **6**, the higher R_f component, were combined and spin evaporated *in vacuo* to give 2.36 g (10%) of **6** that was one spot on tlc. Two recrystallizations from cyclohexane-ethyl acetate gave an analytical sample of **6**, 1.37 g (6%), mp 152-154°; tlc, diethyl ether, R_f = 0.37; uv (*p*H 7 buffer + 9.5% ethanol): λ max 279 (ε 7100), 249.5 (ε 4300), 242.5 (ε 4300); λ min 256.5 (ε 3100), 246.5 (ε 4000), sh 287.5 (ε 5000); nmr (DMSO-d_6): δ 8.69 (s, 1H, H-2), 8.16 (d, 1H, J = 5.5 Hz, H-6), 7.76 (d, 1H, J = 5.5 Hz, H-7), 6.67-7.44 (m, 4H, Ar), 5.86 (s, 2H, CH_2).

Anal. Calcd. for $C_{13}H_9ClFN_3$: C, 59.66; H, 3.47; N, 16.06. Found: C, 59.70; H, 3.50; N, 16.14.

1-Benzyl-1*H*-imidazo[4,5-*c*]pyridine (**7a**).

A mixture of **3** (0.100 g, 0.410 mmole), 5% palladium on carbon (0.100 g), sodium acetate trihydrate (0.056 g, 0.410 mmole), and methanol (50 ml) was shaken in the presence of hydrogen at 2-3 atmospheres for 18 hours. The catalyst was removed by filtration through Celite, and the filtrate was spin evaporated *in vacuo*. The residue was partitioned between ethyl acetate:water (40 ml:20 ml), and the phases were separated. The organic phase was spin evaporated *in vacuo* to a clear oil that crystallized to give 0.057 g (66%) of crude **7a**. One recrystallization from hexane-acetone gave the analytical sample, 0.028 g (33%), mp 133-136°; tlc, dichloromethane:methanol (19:1), R_f = 0.37; uv (0.1 *N* hydrochloric acid + 9.5% ethanol): λ max 263.5 (ε 5760); λ min 234 (ε 2700), sh 252 (ε 4970); (*p*H 7 buffer + 9.5% ethanol): λ max 270.5 (ε 3890), 263.5 (ε 5430), 252.5 (ε 5800); λ min 269 (ε 3830), 261 (ε 5290), 227.5 (ε 2690); (0.1 *N* sodium hydroxide + 9.5% ethanol): λ max 252.5 (ε 5990), 263.5 (ε 5580), 270.5 (ε 4000); λ min 269 (ε 3920), 261.5 (ε 5410), 227 (ε 2850); nmr (DMSO-d_6): δ 8.94 (s, 1H, H-4), 8.55 (s, 1H, H-2), 8.29 (d, 1H, J = 5.7 Hz, H-6), 7.59 (d, 1H, J = 5.7 Hz, H-7), 7.32 (m, 5H, Ar), 5.53 (s, 2H, CH_2); ms: m/e 210 (MH^+), 91 ($C_7H_7^+$).

Anal. Calcd. for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.61; H, 5.31; N, 20.04.

3-Benzyl-1*H*-imidazo[4,5-*c*]pyridine (**8a**).

A mixture of **4** (0.100 g, 0.410 mmole), 5% palladium on carbon (0.100 g), sodium acetate trihydrate (0.056 g, 0.410 mmole), and methanol (50 ml) was shaken in the presence of hydrogen at 2-3 atmospheres for 4.5 hours. The catalyst was removed by filtration through Celite, and the filtrate was spin evaporated *in vacuo* to give a white solid residue. The residue was extracted with boiling ethyl acetate (25 ml), the mixture was filtered, and the filtrate was reduced to dryness to give 0.048 g (56%) of crude **8a**. One recrystallization from hexane-acetone gave an analytical sample 0.015 g (17%), mp 112-114°; tlc, dichloromethane:methanol (19:1), R_f = 0.40; uv (0.1 *N* hydrochloric acid + 9.5% ethanol): λ max 285.5 (ε 8200), 254.5 (ε 5500); λ min 265 (ε 3660), 227.5 (ε 2280); (*p*H 7 buffer + 9.5% ethanol): λ max 283 (ε 5000), 275.5 (ε 6780), 250 (ε 5580); λ min 258.5 (ε 4330), 228 (ε 3460); (0.1 *N* sodium hydroxide + 9.5% ethanol): λ max 275.5 (ε 6670), 250 (ε 5300), 283 (ε 4770); λ min 258 (ε 4070), 228 (ε 3200), sh 269 (ε 5850), sh 245 (ε 5130); nmr (DMSO-d_6): δ 8.88 (s, 1H, H-4), 8.62 (s, 1H, H-2), 8.29 (s, 1H, J = 5.7 Hz, H-6), 7.65 (s, 1H, J = 5.7 Hz, H-7), 7.35 (m, 5H, Ar), 5.59 (s, 2H, CH_2); ms: m/e 210 (MH^+), 91 ($C_7H_7^+$).

Anal. Calcd. for $C_{13}H_{11}N_3$: C, 74.62; H, 5.30; N, 20.08. Found: C, 74.48; H, 5.34; N, 20.04.

1-Benzyl-4-dimethylamino-1*H*-imidazo[4,5-*c*]pyridine (**9**).

A. Dimethylamination of **3**.

A solution of **3** (2.21 g, 9.07 mmoles) and 2.2 *M* dimethylamine in ethanol (205 ml, 454 mmoles) was heated in a stainless steel reaction vessel at 145° for 30 hours. The cooled reaction mixture was spin evaporated *in vacuo*, the residual solid was triturated with water, and then collected by suction filtration. Recrystallization from cyclohexane (charcoal) gave 1.87 g (81%) of **9**, mp 121.5-122°; tlc, dichloromethane:-methanol (9:1), R_f = 0.48; uv (0.1 *N* hydrochloric acid + 10% ethanol): λ max 274 (ε 14200); λ min 240 (ε 1800); (*p*H 7 buffer + 10% ethanol): λ max 280 (ε 13600); λ min 240 (ε 1700); (0.1 *N* sodium hydroxide + 10% ethanol): λ max 285 (ε 14800); λ min 242 (ε 2100); nmr (DMSO-d_6): δ 8.23 (s, 1H, H-2), 7.75 (d, 1H, J = 6 Hz, H-6), 7.29 (m, 5H, Ar), 6.76 (d, 1H, J = 6 Hz, H-7), 5.41 (s, 2H, CH_2), 3.37 (s, 6H, NMe_2); ms: m/e 252 (M^+), 237 ($M-CH_3$)$^+$, 223 (M-29)$^+$, 208 ($M-NMe_2$)$^+$.

Anal. Calcd. for $C_{15}H_{16}N_4$: C, 71.40; H, 6.39; N, 22.20. Found: C, 71.30; H, 6.42; N, 22.30.

B. Alkylation of **13**.

To a stirred dispersion of pentane-washed sodium hydride (60.2% dispersion in mineral oil) (1.49 g, 37.2 mmoles) in dry dimethylformamide (50 ml) was added **13** [12] (5.50 g, 33.9 mmoles). The mixture was stirred at ambient temperature for 15 minutes, and then benzyl bromide (6.37 g, 37.2 mmoles) was added. The solution was stirred at ambient temperature for 15 hours, when additional benzyl bromide (1.0 g, 5.8 mmoles) was added. The solution was spin evaporated *in vacuo* after an additional 15 hours. The residual syrup was partitioned between water (150 ml) and ethyl acetate-dichloromethane (300 ml), and the layers were separated. The aqueous layer was extracted with ethyl acetate (50 ml) and with dichloromethane (50 ml). The nonaqueous solutions were combined, washed with water (100 ml), dried, and spin evaporated *in vacuo*. The residual solids were dissolved in dichloromethane and added to Silica Gel 60. The mixture was spin evaporated *in vacuo*, and the solids were introduced onto a column of Silica Gel 60 wetted with ethyl acetate. The column was eluted with ethyl acetate, and the fractions that contained product were combined and spin evaporated *in vacuo*. The residue was dissolved in ether and diluted with ethereal hydrogen chloride to afford a white solid. The solvent was decanted from the solid, which was recrystallized from ethyl acetate-ethanol to give 3.59 g (36%) of **9** hydrochloride, mp 235-239°; tlc, dichloromethane:methanol (10:1), R_f = 0.57; uv (0.1 *N* hydrochloric acid + 10% ethanol): λ max 274 (ε 13000); λ min 240 (ε 1700); (*p*H 7 buffer + 10% ethanol): λ max 280 (ε12600); λ min 240 (ε 1500); (0.1 *N* sodium hydroxide + 10% ethanol): λ max 285 (ε 13600); λ min 242 (ε 1700); nmr (DMSO-d_6): δ 12.9 (broad s, 1H, NH^+), 8.65 (s, 1H, H-2), 7.69 (d, 1H, J = 7.1 Hz, H-6), 7.32 (m, 5H, Ar), 7.23 (d, 1H, J = 7.1 Hz, H-7), 5.58 (s, 2H, CH_2), 3.29 (s, 6H, NMe_2).

Anal. Calcd. for $C_{15}H_{16}N_4 \cdot HCl$: C, 62.38; H, 5.94; N, 19.40. Found: C, 62.29; H, 6.03; N, 19.12.

1-Benzyl-4-methylamino-1*H*-imidazo[4,5-*c*]pyridine Hydrochloride (**10**).

A mixture of **3** (2.70 g, 11.0 mmoles), ethanol (70 ml), and the solution prepared from water (70 ml), sodium hydroxide (5.50 g, 137 mmoles), and methylamine hydrochloride (10.0 g, 148 mmoles) was heated in a stainless steel reaction vessel at 130° for 72 hours. The cooled reaction mixture was spin evaporated *in vacuo*. The white solids were dispersed in water (100 ml) and collected by suction filtration. The solids were dissolved in ethanol and diluted with concentrated hydrochloric acid. The resultant mixture was spin evaporated *in vacuo*, and the solids were recrystallized from ethyl acetate-ethanol to give 0.99 g (32%) of **10**, mp 244-250°; tlc, dichloromethane:methanol (10:1); uv (0.1 *N* hydrochloric acid + 10% ethanol): λ max 269 (ε 13600); λ min 236 (ε 1500); (*p*H 7 buffer + 10% ethanol): λ max 271 (ε 13200); λ min 236 (ε 1600); (0.1 *N* sodium hydrox-

ide + 10% ethanol): λ max 275 (ε 13400); λ min 236 (ε 1500); nmr (DMSO-d_6): δ 13.1 (broad s, 1H, NH^+), 9.10 (broad q, 1H, NH), 8.62 (s, 1H, H-2), 7.68 (d, 1H, J = 7.0 Hz, H-6), 7.35 (m, 5H, Ar), 7.21 (d, 1H, J = 7.0 Hz, H-7), 5.58 (s, 2H, CH_2), 3.11 (d, 3H, J = 5.0 Hz, CH_3).

Anal. Calcd. for $C_{14}H_{14}N_4$·HCl: C, 61.20; H, 5.50; N, 20.39. Found: C, 61.08; H, 5.50; N, 20.28.

4-Dimethylamino-1-(2-fluorobenzyl)-1*H*-imidazo[4,5-*c*]pyridine Hydrochloride (**11**).

A solution of **5** (7.30 g, 27.9 mmoles), ethanol (120 ml), and 40% aqueous dimethylamine (120 ml) was heated in a stainless steel reaction vessel at 134° for 115 hours. The cooled reaction mixture was spin evaporated *in vacuo*. The white solids were dispersed in water (120 ml) and collected by suction filtration to give 6.56 g (87%) of **11**, mp 123-125°. Recrystallization of 0.50 g from cyclohexane gave 0.23 g of analytically pure **11**, mp 125-126°; tlc, dichloromethane:methanol (10:1); uv (0.1 *N* hydrochloric acid + 10% ethanol): λ max 272 (ε 14100); λ min 239 (ε 1400); (*p*H 7 buffer + 10% ethanol): λ max 278 (ε 13700); λ min 240 (ε 1900); (0.1 *N* sodium hydroxide + 10% ethanol): λ max 284 (ε 14600); λ min 242 (ε 1900); nmr (DMSO-d_6): δ 8.18 (s, 1H, H-2), 7.77 (d, 1H, J = 5.4 Hz, H-6), 7.0-7.5 (m, 4H, Ar), 6.76 (d, 1H, J = 5.4 Hz, H-7), 5.47 (s, 2H, CH_2), 3.38 (s, 6H, $N(CH_3)_2$).

Anal. Calcd. for $C_{15}H_{15}FN_4$: C, 66.65; H, 5.59; N, 20.73. Found: C, 66.60; H, 5.57; N, 20.84.

The hydrochloride of **11** was prepared by dissolution of 6.06 g of **11** in ethanol-ether. The solution was diluted with concentrated hydrochloric acid (10 ml) and spin evaporated *in vacuo*. The white solids were recrystallized from ethyl acetate-ethanol to give 4.55 g (66%) of **11** hydrochloride, mp 258-261°; tlc, dichloromethane:methanol (10:1); uv (0.1 *N* hydrochloric acid + 10% ethanol): λ max 272 (ε 14200); λ min 239 (ε 1600); (*p*H 7 buffer + 10% ethanol): λ max 280 (ε 13600); λ min 240 (ε 1800); (0.1 *N* sodium hydroxide + 10% ethanol): λ max 284 (ε 14500); λ min 242 (ε 2500); nmr (DMSO-d_6): δ 13.0 (broad s, 1H, NH^+), 8.58 (s, 1H, H-2), 7.74 (d, 1H, J = 7.0 Hz, H-6), 7.1-7.6 (m, 4H, Ar), 7.24 (d, 1H, J = 7.1 Hz, H-7), 5.68 (s, 2H, CH_2), 3.61 (s, 6H, $N(CH_3)_2$).

Anal. Calcd. for $C_{15}H_{15}FN_4$·HCl: C, 58.72; H, 5.26; N, 18.26. Found: C, 59.08; H, 5.33; N, 18.35.

1-(2-Fluorobenzyl)-4-methylamino-1*H*-imidazo[4,5-*c*]pyridine Hydrochloride (**12**).

A solution of **5** (5.90 g, 22.5 mmoles), ethanol (100 ml), and the solution prepared from water (100 ml), sodium hydroxide (11.0 g, 275 mmoles), and methylamine hydrochloride (20.0 g, 296 mmoles) was heated in a stainless steel reaction vessel at 130° for 72 hours. The cooled reaction mixture was spin evaporated *in vacuo*. The white solids were dispersed in water (100 ml), collected by suction filtration, and thoroughly washed with water (200 ml) to give 5.10 g (86%) of **12**, mp 164-165° that was one spot on tlc. The material was dissolved in ethanol, diluted with concentrated hydrochloric acid (10 ml), and spin evaporated *in vacuo*. The solids were recrystallized from ethyl acetate-ethanol to give 4.35 g (66%) of **12**, mp 283-286°; tlc, dichloromethane:methanol (10:1); uv (0.1 *N* hydrochloric acid + 10% ethanol): λ max 269 (ε 13800); λ min 234 (ε 1200); (*p*H 7 buffer + 10% ethanol): λ max 269 (ε 14000); λ min 234 (ε 1600); (0.1 *N* sodium hydroxide + 10% ethanol): λ max 274 (ε 12300); λ min 236 (ε 1100); nmr (DMSO-d_6): δ 13.1 (br s, 1H, NH^+), 9.06 (br q, 1H, NH), 8.54 (s, 1H, H-2), 7.70 (d, 1H, J = 7.0 Hz, H-6), 7.1-7.5 (m, 4H, Ar), 7.18 (d, 1H, J = 7.0 Hz, H-7), 5.65 (s, 2H, CH_2), 3.10 (d, 3H, J = 5.0 Hz, CH_3).

Anal. Calcd. for $C_{14}H_{13}FN_4$·HCl: C, 57.43; H, 4.82; N, 19.14. Found: C, 57.40; H, 4.90; N, 19.14.

4-(Dimethylamino)-1*H*-imidazo[4,5-*c*]pyridine (**13**).

A mixture of **2** [9] (10.0 g, 65.1 mmoles) and dimethylamine (37.4 g, 0.830 mole) in 60% aqueous ethanol was heated at 125° for 18 hours in a glass-lined stainless steel reaction vessel. The volatiles were removed under reduced pressure. The residue was taken up into 50% aqueous ethanol and then treated with Rexyn 201 (OH) ion-exchange resin. After stirring for 72 hours, the resin was removed, and the filtrate was evaporated to dryness under reduced pressure. The residue was chromatographed on Silica Gel 60 (40-63 μm, E. Merck 9385) using methanol:methylene chloride (2:8) to give 5.83 g (55%) of **13**. A portion (0.228 g) of the material was recrystallized from ethyl acetate-cyclohexane to give the analytically pure product, mp 162-165° (lit mp >250° for HCl salt [12]); uv (*p*H 7 buffer + 10% ethanol): λ max 272 (ε 11400); λ min 234 (ε 1450); nmr (DMSO-d_6): δ 11.5 (br s, 1H, NH), 8.06 (s, 1H, H-2), 7.75 (d, 1H, J = 5.6 Hz, H-6), 6.78 (d, 1H, J = 5.6 Hz, H-7), 3.38 (s, 6H, $N(CH_3)_2$).

Anal. Calcd. for $C_8H_{10}N_4$: C, 59.24; H, 6.21; N, 34.54. Found: C, 59.13; H, 6.29; N, 34.56.

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