# Synthesis of the Novel Thieno[4,3,2-*ef*][1,4]benzoxazepine Ring System: 4,5-Dihydro-3-(4-pyridinyl)thieno[4,3,2-*ef*][1,4]benzoxazepine Maleate



John D. Tomer IV [a]* Gregory M. Shutske [a] and Dirk Friedrich [b]

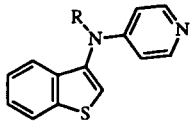
Hoechst Marion Roussel, Inc., Route 202-206, PO Box 6800, Bridgewater, NJ 08807-0800 [a]
and 2110 East Galbraith Road, Cincinnati, OH 45215 [b]

Received November 12, 1996
Revised October 2, 1997

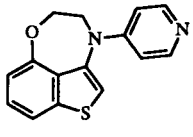
4,5-Dihydro-3-(4-pyridinyl)-thieno[4,3,2-*ef*][1,4]benzoxazepine maleate **2** has been synthesized from 3-amino-4-fluorobenzo[*b*]thiophene by employing an intramolecular nucleophilic aromatic fluoride displacement. In the presence of strong base and heat, **2** rearranges to form the isomeric hemiaminal, 3,4-dihydro-4-methyl-3-(4-pyridinyl)thieno[4,3,2-*de*][1,3]benzoxazine **10**. A proposed mechanism for this rearrangement is discussed.

*J. Heterocyclic Chem.*, **34**, 1769 (1997).

We recently reported the synthesis of a number of 3-(4-pyridinyl)amino-benzo[*b*]thiophenes [1] (**1**), which are selective serotonin re-uptake inhibitors and, as such, may be useful in the treatment of a number of central nervous system disorders, including obsessive compulsive disorder [2]. Within this series of compounds, derivatives having a short alkyl side chain on the aliphatic amine showed particularly promising activity. In an effort to increase potency and selectivity, we restricted the spatial freedom of the side chain by fixing it back onto the aromatic portion of the molecule. The synthesis of this new ring system, **2**, is illustrated in Scheme 1.



**1**

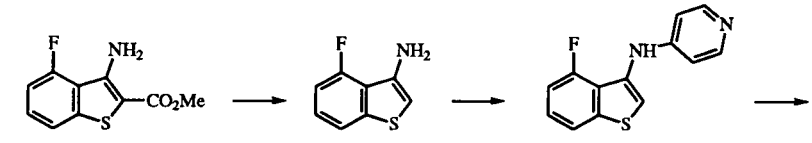


**2**

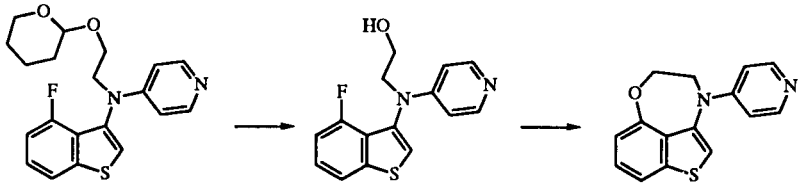
Methyl 3-amino-4-fluoro-1-benzo[*b*]thiophene-2-carboxylate (**3**) was prepared as described by Li, *et al.* [3] and then decarboxylated with piperazine in 1-methyl-2-pyrrolidinone to give amine **4** in good yield. Compound **4** was then reacted with the hydrochloride salt of 4-chloropyridine to yield the 4-pyridinyl derivative, **5**. The use of the hydrochloride salt facilitates the chloride displacement at a reasonable temperature, 130°, in thirty minutes. The introduction of the 2-hydroxyethyl side chain was attempted under a variety of conditions using 2-bromo-ethanol but they all failed to give **7**. Thus, the interfering hydroxyl group of 2-bromoethanol was protected as the tetrahydropyranyl ether and the alkylation of **5** proceeded smoothly using sodium hydride to give **6**. The protecting group was then removed at ambient temperature with excess *p*-toluenesulfonic acid in methanol. Ring closure was also accomplished at ambient temperature with two equivalents of potassium t-butoxide in tetrahydrofuran to give the desired 4,5-dihydro-3-(4-pyridinyl)thieno[4,3,2-*ef*]-[1,4]-benzoxazepine **2**.

An interesting rearrangement was discovered during initial attempts at the intramolecular fluoride displacement. When ring closure was performed with excess sodium hydride in 1-methyl-2-pyrrolidinone at 100°, an

Scheme 1

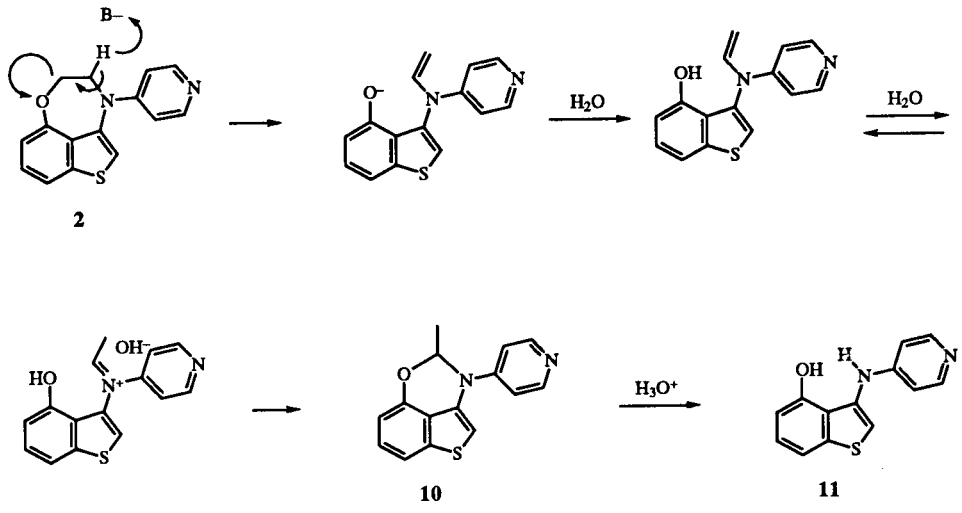


**3** **4** **5**

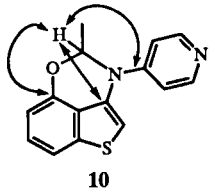


**6** **7** **2**

Scheme 2



additional product was isolated having the same molecular weight as **2**. The proton nmr spectrum in deuteriochloroform suggested a structure in which the 2-carbon bridge had rearranged to give hemiaminal **10** (Scheme 2) and this structure was confirmed by the appropriate $^3J_{CH}$ correlations (Figure 1) and NOE relationships (Figure 2).

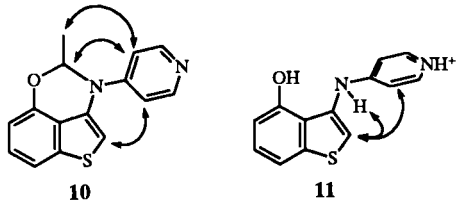


**10**

Figure 1. Important $^3J_{CH}$ correlations for **10** (established by HMBC).

In the presence of strong base, compound **2** apparently undergoes proton abstraction at the methylene group alpha to the nitrogen, and then beta-elimination yields a phenoxide anion which could, upon protonation, attack the resulting enamine to give **10**. This rearrangement would be similar to the ring contraction of 3-dialkylamino-2-phenyl-2,3-dihydro-4*H*-benzopyran-4-ones that is observed under basic conditions to give 2-benzyl-2-dialkylamino-3(2*H*)-benzofuranones [4]. That **10** was derived from **2** was further supported by subjecting **2** to excess sodium hydride in 1-methyl-2-pyrrolidinone at 100° to give material identical to **10**. Compound **10** was somewhat unstable and could not be obtained analytically pure but additional proof of structure was obtained by its rapid hydrolysis in 5% hydrochloric acid to yield exclusively a compound whose spectral and analytical data were consistent with 4-hydroxy-3-(4-pyridinylamino)-benzo[*b*]thiophene **11**. The structure of **11** was also confirmed by the appropriate NOE relationships (see Figure 2) and by $^{15}N$ HMQC, which established the presence of a secondary amine (see experimental).

All the compounds were tested and, in contrast to **1**, were found inactive *in vitro* as serotonin re-uptake inhibitors.



**10** **11**

Figure 2. Important NOE relationships for **10** and **11**-hydrochloride (established by NOESY.)

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra of **2**, **4-7** and of **11** were taken on a Varian Gemini-200 at 200 MHz for $^1H$ and 50 MHz for $^{13}C$, spectral assignments for these compounds were made on the basis of APT and HETCOR experiments and by consideration of $J_{HF}$ and $J_{CF}$ where appropriate. Nuclear magnetic resonance spectra of **10** and **11**-hydrochloride were taken on a Varian Unity-400 at 400 MHz for $^1H$ and 100 MHz for $^{13}C$; spectral assignments for these compounds were made on the basis of HMQC, HMBC, and NOESY experiments. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectra were determined in the electron impact mode by direct insertion at 70 eV with a Finnigan 4000 GC-MS equipped with an INCOS data system. E. Merck 230-400 mesh silica gel and Aldrich 60-100 mesh florisil were used for flash chromatography. Elemental analyses were performed by Robertson Microlit Laboratories, Madison, NJ.

3-Amino 4-fluorobenzo[*b*]thiophene (**4**).

To a solution of **3** (13.3 g, 0.059 mole) [3] in 1-methyl-2-pyrrolidinone (86 ml) was added piperazine (25.33 g, 0.294

mole) and the reaction was heated at 130° overnight. The reaction was poured into ice and the resulting aqueous phase was extracted with ethyl acetate. The organic extract was washed twice with water, dried over magnesium sulfate, filtered over a column of florisil (ethyl acetate), and then concentrated under reduced pressure to yield 8.33 g (84%) of **4**. An analytical sample was obtained by recrystallization from heptane, mp 61-63°; tlc $R_f$, ethyl acetate/heptane (1:20), 0.20; $^1H$ nmr (dimethyl-$d_6$ sulfoxide): δ 5.10 (s, 2H, $NH_2$), 6.25 (s, 1H, $C_2$-H), 7.05 (dd, J = 11.7, 8 Hz, 1H, $C_5$-H), 7.30 (ddd, J = 8.3, 8, 4 Hz, 1H, $C_6$-H), 7.62 (d, J = 8.3 Hz, 1H, $C_7$-H); $^{13}C$ nmr (dimethyl-$d_6$ sulfoxide): δ 96.0 ($C_2$), 108.8 (d, $^2J_{CF}$ = 19.8 Hz, $C_5$), 119.2 (d, $^4J_{CF}$ = 3.8 Hz, $C_7$), 121.4 (d, $^2J_{CF}$ = 15.1 Hz, $C_{3a}$), 125.1 (d, $^3J_{CF}$ = 7.7 Hz, $C_6$), 139.2 (d, $^3J_{CF}$ = 3.6 Hz, $C_3$), 141.5 (d, $^3J_{CF}$ = 6.4 Hz, $C_{7a}$), 157.8 (d, $^1J_{CF}$ = 246.9 Hz, $C_4$); ms: m/z 167 ($M^+$).

*Anal.* Calcd. for $C_8H_6FNS$: C, 57.47; H, 3.62; N, 8.38. Found: C, 57.29; H, 3.53; N, 8.23.

4-Fluoro-3-(4-pyridinylamino)benzo[*b*]thiophene Maleate (**5**).

To a solution of **4** (8.33 g, 0.050 mole) in 1-methyl-2-pyrrolidinone (75 ml) was added 4-chloropyridine hydrochloride (9.71 g, 0.065 mole). The reaction mixture was placed in a 130° preheated oil bath with stirring for 30 minutes. After cooling, the mixture was poured into a saturated sodium bicarbonate solution. The solution was extracted with ethyl acetate, then the organic layer was washed with a minimum of water, dried over magnesium sulfate, and evaporated The residue was flash chromatographed (methanol/ethyl acetate, 1:19) to obtain a tan solid. The solid was decolorized in methanol with "Darco" activated carbon and then evaporated and triturated with diethyl ether/pentane (1:1) to obtain 6.21 g (51%) of **5** as an off-white solid. An analytical sample was obtained by precipitating the maleate salt from methanol/diethyl ether, mp 148-149°; tlc $R_f$, triethylamine/ethyl acetate (1:20), 0.22; $^1H$ nmr (dimethyl-$d_6$ sulfoxide): δ 6.05 (s, 2H, maleic acid), 6.93 (d, J = 6.7 Hz, 2H, β-pyridine), 7.25 (dd, J = 11, 8 Hz, 1H, $C_5$-H), 7.48 (ddd, J = 8.3, 8, 4 Hz, 1H, $C_6$-H), 7.90 (d, 1H, J = 8.3 Hz, $C_7$-H), 7.95 (s, 1H, $C_2$-H), 8.28 (d, J = 6.7 Hz, 2H, α-pyridine), 10.4 (broad s, 1H, NH); $^{13}C$ nmr (dimethyl-$d_6$ sulfoxide): δ 108.6 ($C_{3'5'}$), 110.7 (d, $^2J_{CF}$ = 19.1 Hz, $C_5$), 119.9 ($^4J_{CF}$ = 19.1 Hz, $C_7$), 122.8 (d, $^2J_{CF}$ = 14.9 Hz, $C_{3a}$), 123.7 ($C_2$), 126.6 (d, $^3J_{CF}$ = 7.6 Hz, $C_6$), 126.9 (d, $^3J_{CF}$ = 2.9 Hz, $C_3$), 135.7 (maleic acid), 141.1 ($C_{2'6'}$), 141.4 (d, $^3J_{CF}$ = 5.3 Hz, $C_{7a}$), 156.4 (d, $^1J_{CF}$ = 249 Hz, $C_4$), 157.9 ($C_{4'}$), 167.2 (maleic acid); ms: m/z 244 ($M^+$).

*Anal.* Calcd. for $C_{13}H_9FN_2S \cdot C_4H_4O_4$: C, 56.66; H, 3.64; N, 7.77. Found: C, 56.59; H, 3.64; N, 7.68.

4-Fluoro-3-[(2-((2-tetrahydropyranyl)oxy)ethyl)(4-pyridinyl)amino]benzo[*b*]thiophene (**6**).

To a mixture of sodium hydride (0.36 g, 0.009 mole) in dimethylformamide was slowly added a solution of **5** (2.0 g, 0.008 mole) in dimethylformamide. The reaction was stirred at room temperature for 15 minutes, after which a solution of 2-bromoethoxytetrahydropyran (1.88 g, 0.009 mole) in dimethylformamide was added. The reaction was stirred at 80° for thirty minutes and cooled. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed twice with water, dried over magnesium sulfate, and evaporated. The residue was flash chromatographed (ethyl acetate; then methanol/ethyl acetate; 1:19) to afford 3.01 g of **6** which was used without further purification.

4-Fluoro-3-[(2-hydroxyethyl)(4-pyridinyl)amino]benzo[*b*]thiophene hydrochloride (**7**).

To a solution of **6** (3.01 g, 0.008 mole) in methanol was added *p*-toluenesulfonic acid (1.39 g, 0.008 mole). The reaction mixture was stirred at room temperature for one hour and then additional *p*-toluenesulfonic acid (0.50 g) was added portionwise over 3.5 hours. The reaction mixture was concentrated and the residue was distributed between diethyl ether and saturated sodium bicarbonate solution. The precipitates were collected and washed first with water and then with diethyl ether to obtain 0.55 g of product. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated to afford an additional 1.15 g of product, giving a combined yield of 74% of **7**. The hydrochloride was formed in a mixture of methanol and ethereal hydrogen chloride and then the resulting solution was concentrated under reduced pressure. After the residue was triturated with diethyl ether, recrystallization from methanol/diethyl ether afforded white crystals, mp 249° dec; tlc $R_f$, triethylamine/ethyl acetate (1:20), 0.16; $^1H$ nmr (dimethyl-$d_6$ sulfoxide): δ 3.73-3.83 (m, 3H), 4.23-4.37 (m, 1H), 6.9 (broad s, 2H, β-pyridine), 7.12 (dd, J = 10, 8 Hz, $C_5$-H), 7.48 (ddd, J = 8, 8, 4 Hz, 1H, $C_6$-H), 7.95 (dd, J = 8, 2 Hz, 1H, $C_7$-H), 8.18 (s, 1H, $C_2$-H), 8.22 (d, J = 7 Hz, 2H, α-pyridine); $^{13}C$ nmr (dimethyl-$d_6$ sulfoxide): δ 53.9 (C-N), 57.3 (C-O), 108.2 ($C_{3'5'}$), 110.4 (d, $^2J_{CF}$ = 19.3 Hz, $C_5$), 119.6 (d, $^4J_{CF}$ = 4.2 Hz, $C_7$), 121.7 (d, $^2J_{CF}$ = 15.0 Hz, $C_{3a}$), 126.3 (d, $^3J_{CF}$ = 7.6 Hz, $C_6$), 127.1 ($C_2$), 131.1 (d, $^3J_{CF}$ = 2.9 Hz, $C_3$), 139.4 ($C_{2'6'}$), 141.5 (d, $^3J_{CF}$ = 5.2 Hz, $C_{7a}$), 155.8 (d, $^1J_{CF}$ = 248 Hz, $C_4$), 158.3 ($C_{4'}$); ms: m/z 288 ($M^+$).

*Anal.* Calcd. for $C_{15}H_{13}N_2FOS \cdot HCl$: C, 55.47; H, 4.34; N, 8.62. Found: C, 55.53; H, 4.13; N, 8.45.

4,5-Dihydro-3-(4-pyridinyl)thieno[4,3,2-*ef*][1,4]benzoxazepine Maleate (**2**).

To a solution of **7** (1.8 g, 0.00625 mole) in dry tetrahydrofuran (45 ml) was added potassium t-butoxide (0.70 g, 0.00625 mole). The reaction mixture was stirred at room temperature for one hour. Additional base (0.70 g) was added and stirring was continued for 2.25 hours. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate, and evaporated. The residue was flash chromatographed (triethylamine/ethyl acetate, 1:19) to afford 1.9 g of **2** as a clear oil. The maleate salt was formed in methanol and isolated by evaporation. The residue was triturated with diethyl ether to afford 1.63 g (68%) of **2** as an off-white solid, mp 169° dec; tlc $R_f$, triethylamine/ethyl acetate (1:20), 0.16; $^1H$ nmr (dimethyl-$d_6$ sulfoxide): δ 4.35 (t, J = 5.3 Hz, $CH_2$-N), 4.56 (t, J = 5.0 Hz, $CH_2$-O), 6.06 (s, 2H, maleic acid), 6.98 (d, J = 6.7 Hz, 1H, $C_7$-H), 7.37 (t, J = 7.3 Hz, 1H, $C_8$-H), 7.45 (d, J = 6.7 Hz, 2H, β-pyridine), 7.71 (d, J = 7.3 Hz, 1H, $C_9$-H), 7.82 (s, 1H, $C_2$-H), 8.40 (d, J = 6.7 Hz, 2H, α-pyridine); $^{13}C$ nmr (dimethyl-$d_6$ sulfoxide): δ 50.7 ($C_4$), 70.6 ($C_5$), 109.8 ($C_{3'5'}$), 114.0 ($C_7$), 117.2 ($C_9$), 117.9 ($C_2$), 125.5 ($C_{9b}$), 126.5 ($C_8$), 132.6 ($C_{2a}$), 135.3 (maleic acid), 140.1 ($C_{9a}$), 141.8 ($C_{2'6'}$), 153.7 ($C_{6a}$), 156.6 ($C_{4'}$), 167.2 (maleic acid); ms: m/z 268 ($M^+$).

*Anal.* Calcd. for $C_{15}H_{12}N_2OS \cdot C_4H_4O_4$: C, 59.37; H, 4.20; N, 7.29. Found: C, 59.31; H, 4.17; N, 7.22.

3,4-Dihydro-4-methyl-3-(4-pyridinyl)thieno[4,3,2-*de*][1,3]benzoxazine (**10**).

To a solution of **7** (0.1 g, 0.00035 mole) in 1-methyl-2-pyrrolidinone added sodium hydride (0.02 g, 0.00050 mole, 60% in

mineral oil) and the reaction mixture was stirred at 100° for one hour. The reaction was cooled, distributed between water and dichloromethane, and the organic phase was washed with water. After drying with magnesium sulfate and concentrating under reduced pressure, the residue was flash chromatographed (triethylamine/ethyl acetate, 1:100) to yield **2** and a higher $R_f$ component whose spectral data were consistent with **10**; tlc $R_f$ methanol/ethyl acetate (1:20), 0.40; $^1H$ nmr (acid-free deuteriochloroform): δ 1.55 (d, J = 6 Hz, 3H, $CH_3$), 6.10 (q, J = 6 Hz, 1H, $C_4$-H), 6.83 (dd, 1H, J = 7.5, 0.5 Hz, $C_6$-H), 6.86 (s, 1H, $C_2$-H), 7.15 (m, 2H, β-pyridine), 7.35 (dd, J = 8, 7.5 Hz, 1H, $C_7$-H), 7.44 (dd, J = 7.5, 0.5 Hz, 1H, $C_8$-H), 8.43 (m, 2H, α-pyridine); $^{13}C$ nmr (deuteriochloroform): δ 19.0 ($CH_3$), 84.5 ($C_4$), 104.7 ($C_2$), 109.0 ($C_6$), 111.4 ($C_{3',5'}$), 115.7 ($C_8$), 122.2 ($C_{8b}$), 127.2 ($C_7$), 127.4 ($C_{2a}$), 137.8 ($C_{8a}$), 148.4 ($C_{5a}$), 150.6 ($C_{4'}$), 151.0 ($C_{2',6'}$); ms: m/z 268 ($M^+$). Compound **10** proved to be somewhat unstable and was not purified further.

Reaction of **2** with Sodium Hydride.

To a solution of **2** (0.55 g, 0.00205 mole) in 1-methyl-2-pyrrolidinone was added sodium hydride (0.32 g, 0.008 mole, 60% in mineral oil) and the reaction mixture was stirred at 100° for one hour. An additional 4 equivalents of sodium hydride were added and the reaction was complete within 30 minutes. The reaction was cooled, distributed between water and ethyl acetate, and the organic phase was washed with water. After drying with sodium sulfate and concentration, the resulting solid was adhered to silica gel (methanol) and flash chromatographed (methanol/ethyl acetate, 1:50; then methanol/ethyl acetate, 1:5). After concentration, the solid was triturated in methanol to yield 0.17 g (31%) of product identical by nmr and ms to **10**, which was used in the following reaction without further purification.

4-Hydroxy-3-(4-pyridinylamino)benzo[*b*]thiophene (**11**).

A solution of **10** (0.17 g, 0.00063 mole) in methanol/5% hydrochloric acid (8 ml of 1:1) was stirred for 15 minutes. A precipitate that formed was filtered off (0.063 g) and shown to be **11** hydrochloride (36%), mp 246° dec; $^1H$ nmr (dimethyl-$d_6$ sulfoxide): δ 6.79 (dd, J = 8, 0.5 Hz, 1H, $C_5$-H), 6.94 (broad s, 2H, β-pyridine), 7.23 (dd, J = 8, 8 Hz, 1H, $C_6$-H), 7.44 (dd, J = 8, 0.5 Hz, 1H, $C_7$-H), 7.64 (s, 1H, $C_2$-H), 8.22 (d, J = 7.5 Hz, 2H, α-pyridine); 10.18 (s, 1H, OH), 10.34 (s 1H, NH), 13.69 (s, 1H, pyridine NH); $^{13}C$ nmr (HMQC and HMBC, dimethyl-$d_6$ sulfoxide): δ 108.5 ($C_{3',5'}$), 109.5 ($C_5$), 114.0 ($C_7$), 119.5 ($C_2$), 123.0 ($C_{3a}$), 126.5 ($C_6$), 128.5 ($C_3$), 140.0 ($C_{2'6'}$), 140.5 ($C_{7a}$), 153.0 ($C_4$), 158.0 ($C_{4'}$); $^{15}N$ nmr (HMQC, dimethyl-$d_6$ sulfoxide): δ 110 (Ar-NH-Ar, $^1J_{NH}$ = 95 Hz), $C_5H_4NH^+$ not detected due to exchange broadening; ms: m/z 242 ($M^+$).

The filtrate from above was concentrated and the resulting solids were stirred vigorously for one hour in ethyl acetate/aqueous sodium bicarbonate (1:1). The solids were collected, washed with water and then with ethyl acetate to yield 0.056 g (30%) of analytically pure **11** as an off white solid, mp 253° dec; tlc $R_f$, methanol/ethyl acetate (1:33), 0.18; $^1H$ nmr (dimethyl-$d_6$ sulfoxide): δ 5.60 (broad s, 2H, OH, NH), 6.75 (d, J = 6.7 Hz, 1H, $C_5$-H), 7.00 (d, J = 6.0 Hz, 2H, β-pyridine), 7.20 (m, 2H, $C_2$-H and $C_6$-H), 7.30 (d, J = 7.0 Hz, 1H, $C_7$-H), 8.22 (d, J = 6.0 Hz, 2H, α-pyridine); $^{13}C$ nmr (dimethyl-$d_6$ sulfoxide): δ 105.5 ($C_2$), 109.3 ($C_{3'5'}$), 109.3 ($C_5$), 113.7 ($C_7$), 122.4 ($C_{3a}$), 126.1 ($C_6$), 132.8 ($C_3$), 139.6 ($C_{7a}$), 149.6 ($C_{2'6'}$), 150.1 ($C_4$), 153.6 ($C_{4'}$); ms: m/z 242 ($M^+$).

*Anal.* Calcd. for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.28; H, 4.26; N, 11.16.

Acknowledgment.

The authors wish to thank Anastasia Linville, Sandra H. Anselmo and Jason Karns for help with 200 MHz nmr data.

REFERENCES AND NOTES

[1] R. C. Effland, J. T. Klein, L. L. Martin, G. M. Shutske, K. J. Kapples, and J. D. Tomer IV, US Patent 5,328,920 (1994); *Chem. Abstr.*, **123**, 83210a (1995).

[2] J. Zohar, R. C. Zohar-Kadouch, and S. Kindler, *Drugs*, **43**, 210 (1992).

[3] Z. Li, Y. Lin, and C. Chi, *Heterocycles*, **34**, 1729 (1992).

[4a] T. Patonay, G. Litkei, and R. Bognar, *Acta Chim. Acad. Sci. Hung.*, **108**, 135 (1981); [b] E. Patonay-Peli, G. Litker, and T. Patonay, *Synthesis*, 511 (1990).