

L. D. Ruffin and S. B. Bowlus\* (1)

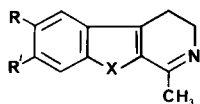
Department of Chemistry, Tougaloo College,  
Tougaloo, Mississippi 39174  
Received July 12, 1982

Synthesis of the title compound, a potential inhibitor of mouse brain monoamine oxidase, is described. The preparation proceeds in eight steps from 1,3-benzodioxole in 1.9% overall yield. The novel hydrogenolysis of an aryl thiocyanate to the aryl methyl sulfide is reported.

*J. Heterocyclic Chem.*, **20**, 461 (1983).

Benzo[*b*]thiophenes are isosteres of the naturally occurring indole nucleus; in many cases, substitution of sulfur for the nitrogen of the natural product gives new materials with novel or improved biochemical or pharmacological properties (2). Bosin (3) has recently evaluated a number of 6- and 7-oxygenated analogs **1** of the alkaloid harmaline (2). Like the parent alkaloid, these compounds exhibit exceptional inhibitory properties toward mouse brain monoamine oxidase (MAO), using tryptamine as substrate. Inasmuch as the methylenedioxyphenyl moiety has been found to lend unusual properties (*e.g.*, metabolic stability) to biologically active materials, it is of interest to test the novel analog **3**, the synthesis of which we now report.

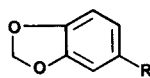
Our method is essentially that of Campaigne *et al.* (4). Thus, 1,3-benzodioxole (4) reacted with the calculated amount of thiocyanogen chloride (5) to provide thiocyanate **5**, which was reduced with sodium bis(methoxyethoxy)aluminum hydride to thiophenol **6**.



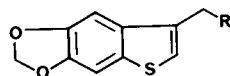
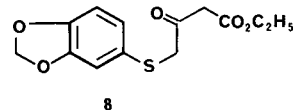
**1** X = S; R and/or R' = H, OH, OCH<sub>3</sub>, OC(CH<sub>3</sub>)<sub>2</sub>O

**2** X = NH; R = H; R' = OCH<sub>3</sub>

**3** X = S; R, R' = OCH<sub>2</sub>O



**4** R = H  
**5** R = SCN  
**6** R = SH  
**7** R = SCH<sub>3</sub>



**9** R = CO<sub>2</sub>C<sub>2</sub>H<sub>5</sub>  
**10** R = CONH<sub>2</sub>  
**11** R = CH<sub>2</sub>NH<sub>2</sub>  
**12** R = CH<sub>2</sub>NHC(=O)CH<sub>3</sub>

An unusual circumstance was noted in this latter reaction. If reduction of **5** were carried out at near-ambient temperatures, **6** was produced as the only observed product (86% yield). Under more forceful conditions (excess reductant, reflux), however, the aryl methyl sulfide **7** was

formed, and was isolated in yields of up to 55%. Such a hydrogenolysis of a thiocyanate is unprecedented to our knowledge, although this reducing agent has been reported (6) to give temperature dependent product distribution.

Thiol **6** was alkylated with a small excess of ethyl 4-chloro-3-oxobutyrates in pyridine. The ketoester **8**, an undistillable oil, was cyclized (polyphosphoric acid) without purification to give benzo[*b*]thiophenylacetic ester **9**. Chromatographically homogeneous **9** was isolated as a low melting (*ca.* 25°), colorless solid by repeated crystallizations at -75° from petroleum ether. In practice, it was more convenient to convert crude **9** to amide **10**, which crystallized nicely from the reaction mixture as it was formed. Yield of the sequence from **6** to **10**, without purification of intermediates, was a modest 39%. The major loss of material appeared to take place in the transformation **8** to **9**. The glpc of crude **9** showed the material to contain up to 30% of an unidentified, less volatile (than **9**) component, which could be recovered as well from the amidation liquors in the preparation of **10**.

Reduction of **10** with borane-tetrahydrofuran afforded amine **11**, isolated as its hydrochloride salt. Acetylation of **11** gave **12**, Bischler-Napieralski cyclization of which provided the title compound. Both the reduction and cyclization steps gave disappointing yields of their respective products. The products were, however, conveniently isolated as the hydrochloride salts with excellent purity.

## EXPERIMENTAL

Melting points were taken on a Hoover capillary apparatus and are uncorrected. Infrared spectra were recorded as neat liquid films or as mineral oil mulls on a Beckman Accu-Lab 4 instrument. Nuclear magnetic resonance spectra were measured on a Perkin-Elmer R24-B instrument except as noted, using tetramethylsilane as the internal standard.

1,3-Benzodioxole, ethyl 4-chloro-3-oxobutyrates and borane-THF complex were obtained from Aldrich. Sodium bis(methoxyethoxy)aluminum dihydride (Vitride®) was purchased from Sargent-Welch. Pyridine was dried by storage over sodium hydroxide and aromatic solvents were dried by refluxing with, and distillation from, phosphorous pentoxide. All reactions were carried out in an atmosphere of dry nitrogen.

5-Thiocyano-1,3-benzodioxole (5).

Thiocyanogen chloride (0.168 mole), prepared by reaction of lead thiocyanate and chlorine (5), in 600 ml of glacial acetic acid was treated at room temperature with 1,3-benzodioxole (20.5 g, 0.168 mole) in one portion. After one hour, the mixture was filtered, and the filtrate was poured into 3.5 l of ice water. The colorless solid which precipitated was collected, was washed with water and was dried *in vacuo*. There was obtained 24.2 g (80%) of material, mp 32-34°; ir: 2180 cm<sup>-1</sup>; nmr (carbon tetrachloride): 7.1-6.6 (m, 3H), 5.98 (s, 2H).

*Anal.* Calcd. for C<sub>8</sub>H<sub>8</sub>NO<sub>2</sub>S: C, 53.62; H, 2.81; N, 7.82; S, 17.89. Found: C, 53.4; H, 2.7; N, 7.6; S, 17.9.

#### 5-Mercapto-1,3-benzodioxole (6).

To a solution of 5 (17.9 g, 0.1 mole) in 200 ml of benzene, stirred at 5-10°, was added dropwise a solution of Vitride® (29.0 g of a 70% solution, 0.1 mole) in 50 ml of benzene over 30 minutes. After an additional 45 minutes, the solution was poured into water and ice, acidified strongly, and the product was isolated in ether. The ether solution was extracted with 0.5 N sodium hydroxide, the aqueous layer was acidified, and the product was extracted with dichloromethane. Evaporation of the solvent and distillation of the residue afforded 12.4 g (84%) of the product, bp 90-94° (3 mm Hg) [lit (7) bp 91-95° (3 mm Hg)]; ir: 2560 cm<sup>-1</sup>; nmr (carbon tetrachloride): 6.64 (AB q, 2H, J<sub>AB</sub> = 1.5 Hz), 6.59 (s, 1H), 5.90 (s, 2H), 3.30 (s, 1H).

#### 5-Methylthio-1,3-benzodioxole (7).

Thiocyanate 5 (25.2 g, 0.14 mole), dissolved in 100 ml of benzene, was treated with Vitride® (81.3 g of a 70% solution, 0.28 mole) as in the preceding experiment. After stirring for 1 hour at room temperature, the solution was refluxed for 1.5 hours. The cooled mixture was worked up as above. From the organic layer of the base extraction there was obtained 13.5 g (57%) of 7, bp 108-110° (2.5 mm Hg); ir: 2080, 2990, 2900, 2790, 1600, 1470, 1235, 1040, 937, 890, 850, 805 cm<sup>-1</sup>; nmr (carbon tetrachloride): 6.9-6.6 (m, 3H), 5.86 (s, 2H), 2.37 (s, 3H).

*Anal.* Calcd. for C<sub>8</sub>H<sub>8</sub>O<sub>2</sub>S: C, 57.12; H, 4.79; S, 19.06. Found: C, 57.0; H, 4.7; S, 19.1.

#### Ethyl 4-(3,4-Methylenedioxyphenylthio)-3-oxobutyrate (8).

Following the procedure of Campaigne *et al.* (4), thiophenol 6 (24.9 g, 0.162 mole) was reacted with ethyl 4-chloro-3-oxobutyrate. There was obtained 46 g (quantitative) of a deep red oil, which was used without purification; ir: 2980, 2890, 1720, 1440, 1230, 1030, 925, 883, 848, 800, 745 cm<sup>-1</sup>; nmr (carbon tetrachloride): 6.9-6.5 (m, 3H), 5.91 (s, 2H, OCH<sub>2</sub>O), 4.11 (q, 2H, J = 7 Hz), 3.59 (s, 2H, C(=O)CH<sub>2</sub>C=O), 3.50 (s, 2H, SCH<sub>2</sub>C=O), 1.26 (t, 3H, J = 7 Hz).

#### Ethyl 5,6-Methylenedioxy-3-benzo[b]thienylacetate (9).

To 180 ml of dry toluene was added 3 g of 85% phosphoric acid and 5.1 g of phosphorus pentoxide. The mixture was refluxed with vigorous stirring and Celite (7.5 g) was added. After refluxing for 1 hour, acetoacetate 8 (4.5 g, 16 mmoles) dissolved in 50 ml of toluene was added in one portion. The mixture was refluxed for 1 hour, and was then cooled and was filtered. The filtrate was combined with a boiling toluene wash of the solid residue, and the solution was evaporated. The residue was triturated with cyclohexane, and the solution was evaporated. The residue was triturated with cyclohexane, evaporation of which afforded 3.5 g (83%) of the product; ir: 2980, 2900, 1730, 1463, 1440, 1240, 1160, 1032, 993, 837, 818 cm<sup>-1</sup>; nmr (carbon tetrachloride): 7.0-6.8 (m, 3H), 5.73 (s, 2H, OCH<sub>2</sub>O), 3.99 (q, 2H, J = 6.5 Hz), 3.54 (s, 2H, ArCH<sub>2</sub>C=O), 1.15 (t, 3H, J = 6.5 Hz).

The glpc of this material showed it to contain approximately 30% of a compound less volatile than the product. This component could be removed with considerable loss of 9 by repeated crystallizations from petroleum ether. The chromatographically homogeneous, low melting solid (ca. 25°) thus obtained failed, however, to give a correct analysis.

*Anal.* Calcd. for C<sub>13</sub>H<sub>12</sub>O<sub>4</sub>S: C, 59.08; H, 4.58; S, 12.13. Found: C, 58.1; H, 4.6; S, 12.5.

#### 5,6-Methylenedioxy-3-benzo[b]thienylacetamide (10).

The crude ester 9 (3.59 g, 13.6 mmoles) was dissolved in 100 ml of methanol, and the solution was saturated with ammonia. The tightly

stopped mixture was allowed to stand at room temperature for three days. Filtration of the tan precipitate gave 1.50 g (47%) of 10, mp 235-237°; ir: 3440, 3180, 1675, 1620, 1500, 1380, 1245, 1120, 1075, 1035, 935, 855, 830, 772 cm<sup>-1</sup>; nmr (DMSO-d<sub>6</sub>): 7.49 (s, 1H), 7.32 (s, 2H), 6.9 (s, broad, 2H), 6.07 (s, 2H, OCH<sub>2</sub>O), 3.55 (s, 2H, ArCH<sub>2</sub>C=O).

*Anal.* Calcd. for C<sub>11</sub>H<sub>8</sub>NO<sub>2</sub>S: C, 56.16; H, 3.86; N, 5.95; S, 13.63. Found: C, 56.2; H, 3.9; N, 5.9; S, 13.32.

#### 3-(2-Aminoethyl)-5,6-methylenedioxybenzo[b]thiophene (11) Hydrochloride.

Reduction of acetamide 10 (2.35 g, 10 mmoles) with excess borane-tetrahydrofuran as described by Campaigne *et al.* (4) afforded 1.24 g (48%) of 11, isolated as the hydrochloride, mp 271-273°; ir: 3000 (broad), 1600, 1555, 1515, 1505, 1250, 1043, 940, 870, 820, 760 cm<sup>-1</sup>; nmr (DMSO-d<sub>6</sub>): 8.45 (s, broad, 3H), 7.46 (s, 1H), 7.38 (s, 1H), 7.35 (s, 1H), 6.09 (s, 2H), 3.16 (s, broad, 4H).

*Anal.* Calcd. for C<sub>11</sub>H<sub>11</sub>NO<sub>2</sub>S·HCl: C, 51.26; H, 4.69; Cl, 13.76; N, 5.43; S, 12.44. Found: C, 51.3; H, 4.8; Cl, 13.9; N, 5.4; S, 12.4.

#### 3-(2-Acetylaminoethyl)-5,6-methylenedioxybenzo[b]thiophene (12).

Amine 11 (3.7 g, 14.4 mmoles) was dissolved in acetic anhydride by gently heating, and the solution was allowed to stand for two days. The solution was poured into 300 ml of water, and after stirring for several hours, the mixture was neutralized with solid sodium hydroxide. The solid which precipitated was collected and dried to afford 3.29 g (87%) of 12, mp 134-137°; ir: 3290, 1645, 1567, 1250, 1050, 1040, 940, 860, 845, 828 cm<sup>-1</sup>; nmr (DMSO-d<sub>6</sub>): 7.41 (s, 1H), 7.35 (s, 1H), 7.25 (s, 1H), 6.10 (s, 2H, OCH<sub>2</sub>O), 3.7-3.1 (m, 3H, ring CH<sub>2</sub> plus NH), 3.1-2.8 (m, 2H, ring CH<sub>2</sub>), 1.81 (s, 3H, acetyl).

*Anal.* Calcd. for C<sub>13</sub>H<sub>13</sub>NO<sub>2</sub>S: C, 59.30; H, 4.98; N, 5.32; S, 12.18. Found: C, 59.1; H, 4.8; N, 5.3; S, 12.3.

#### 3,4-Dihydro-1-methyl-6,7-methylenedioxybenzothieno[2,3-c]pyridine (3) Hydrochloride.

Acetamide 12 (1 g) was cyclized by the procedure of Campaigne *et al.* (4). The crude, free amine from three such experiments was dissolved in hot 4 N hydrochloric acid. The hot solution was filtered with charcoal, the cooled filtrate was basified to pH 9, and the pure amine was isolated in ether. After brief drying (potassium carbonate), the solution was treated with dry hydrogen chloride gas. There precipitated 0.56 g (17%) of 3 hydrochloride monohydrate, mp 257-261° dec; ir: 3500, 3410, 1630, 1590, 1515, 1480, 1340, 1295, 1240, 1027, 927, 870 cm<sup>-1</sup>; nmr (deuterium oxide): 90 MHz 7.43 (s, 1H), 7.32 (s, 1H), 6.16 (s, 2H, OCH<sub>2</sub>O), 3.99 (t, 2H, J = 9 Hz, ring CH<sub>2</sub>), 3.25 (t, 2H, J = 9 Hz, ring CH<sub>2</sub>), 2.69 (s, 3H).

*Anal.* Calcd. for C<sub>13</sub>H<sub>11</sub>NO<sub>2</sub>S·HCl·H<sub>2</sub>O: C, 52.08; H, 4.71; Cl, 11.83; N, 4.67; S, 10.70. Found: C, 52.1; H, 4.6; Cl, 12.1; N, 4.5; S, 10.5.

#### Acknowledgement.

This work was supported by a MARC grant from the National Institutes of Health. Funds for the purchase of the nmr spectrometer were provided by grants from the National Science Foundation and the DuPont Company. We thank T. R. Bosin (Indiana University) for helpful discussions, and D. Fritz and G. Babbitt (Diamond Shamrock Corp.) for microanalyses and the nmr spectrum of 3, respectively.

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