

2-Amino-3-(6-methoxybenzo[*b*]thien-3-yl)propanoic Acid (I)

Richard L. Titus and Carolyn F. Titus

Departments of Chemistry, University of Nevada, Las Vegas, Nevada 89154  
and The University of Toledo, Toledo, Ohio 43606

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2-Amino-3-(6-methoxybenzo[*b*]thien-3-yl)propanoic acid (VIII) is structurally related to tryptophan, an essential amino acid, indole-3-propionic acid, a plant growth regulator, and serotonin, a vasoconstrictor, and would be expected to exhibit physiological activity. For a review of the physiological activities of benzo[*b*]thiophene derivatives see the article by Campaigne, *et al.* (2). Chapman, *et al.*, have prepared a number of pharmacologically active benzo[*b*]thiophene derivatives (3,4,5).

Preparation of 3-chloromethyl-6-methoxybenzo[*b*]thiophene (V), the chloro compound necessary for this amino acid synthesis, was based on the procedures of Tilak, *et al.* (6) and Schuetz, *et al.* (7). 3-Methoxythiophenol was alkylated with ethyl bromopyruvate to obtain the sulfide, ethyl 3-(3-methoxyphenylthio)-2-oxopropanoate (I). Cyclization of I by refluxing in chlorobenzene with polyphosphoric acid yielded largely ethyl 6-methoxybenzo[*b*]thiophene-3-carboxylate (IIa) accompanied by a small amount of the 4-methoxy isomer (IIb), (Scheme I). Reduction of IIa with lithium aluminum hydride yielded 3-hydroxymethyl-6-methoxybenzo[*b*]thiophene (IV) which was converted to 3-chloromethyl-6-methoxybenzo[*b*]thiophene (V). The chloride V was reacted both with ethyl acetamidocyanoacetate and also with diethyl acet-

amidomalonate in the presence of sodium ethoxide. Hydrolysis of the intermediates thus obtained yielded the desired amino acid VIII, (Scheme II).

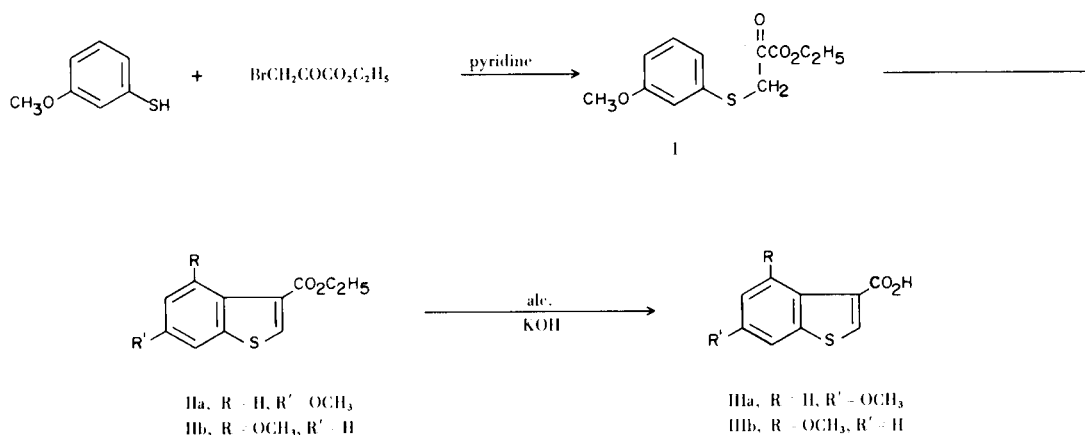
## EXPERIMENTAL

Melting points were taken on a hot stage and are uncorrected. Boiling points are uncorrected. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan and Galbraith Laboratories, Inc., Knoxville, Tennessee. Infrared spectra were obtained using a Beckman IR-20A spectrometer; nmr spectra were obtained using a Perkin-Elmer R-12 spectrometer; mass spectra at 70 eV using a direct solids probe were obtained with a Perkin-Elmer RMS-4 spectrometer.

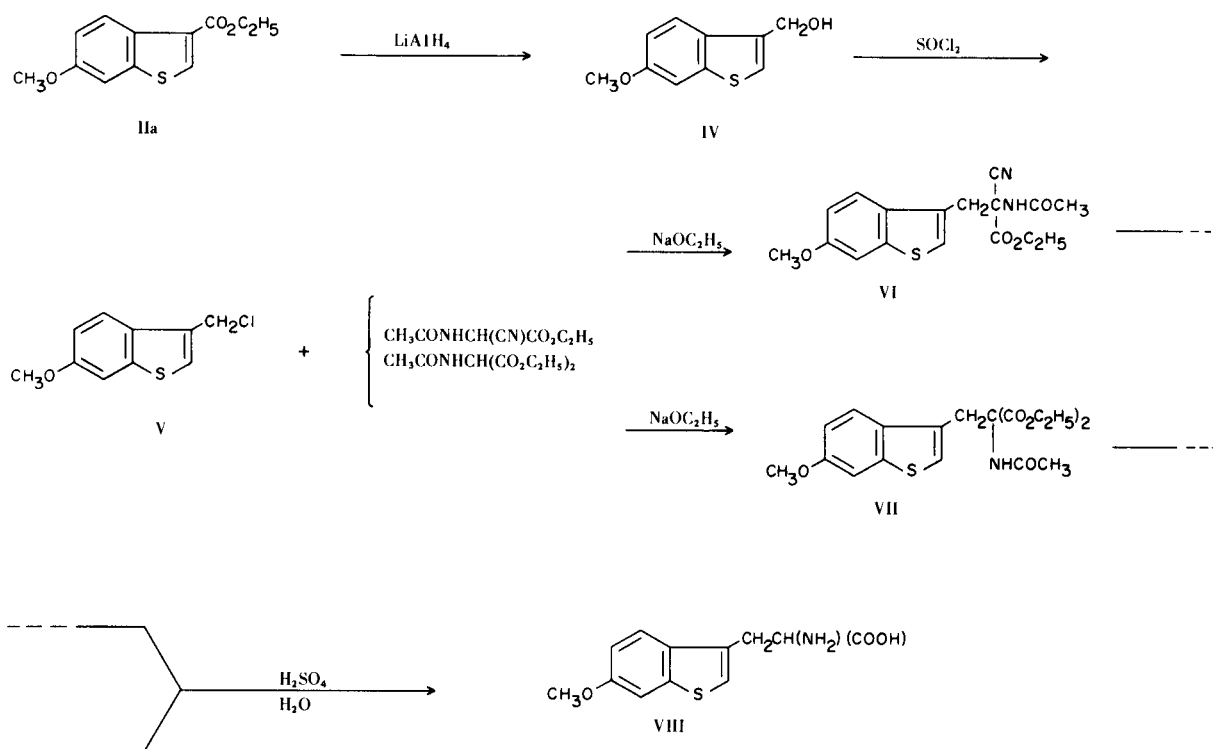
Ethyl 3-(3-Methoxyphenylthio)-2-oxopropanoate (I).

A cooled, magnetically stirred solution of 7.18 g. (0.0512 mole) of 3-methoxythiophenol (8) in 36 ml. of pyridine was treated dropwise with 10.0 g. (0.0512 mole) of ethyl bromopyruvate then allowed to stand for 15 minutes, and finally treated, with cooling and stirring, with 72 ml. of dilute hydrochloric acid. The oil which formed was separated and the aqueous layer was extracted with diethyl ether. The combined oil and extracts were washed with dilute hydrochloric acid and water, then dried with anhydrous magnesium sulfate. Removal of solvent and fractionation of the residue yielded I, 7.22 g. (55.5%) of yellow product, b.p. 140° (0.12 mm.) -170° (0.25 mm.) (d), with most distilling at 150°.

SCHEME I



## SCHEME II



## Ethyl 6-Methoxybenzo[b]thiophene-3-carboxylate (IIa).

A 12.6 g. (0.0497 mole) quantity of I dissolved in 113 ml. of chlorobenzene was refluxed ten hours with polyphosphoric acid (48.6 g., 0.171 mole of phosphorus pentoxide in 24 ml. of 85% phosphoric acid). The chlorobenzene was decanted. The residue was refluxed one half hour with 113 ml. of benzene, which was decanted. The combined aromatic solutions were washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride and dried with anhydrous magnesium sulfate. Removal of the solvents and distillation of the residue gave 7.69 g. of crude crystalline product, b.p. range 110-152° (0.03 mm.). Fractional crystallization of the crude product from methanol with decolorization gave a yellow oil and 3.71 g. (32%) of white crystals of IIa, m.p. 66-67°;  $\text{ir } \nu_{\text{max}}$  (potassium bromide)  $\text{cm}^{-1}$ : 1715 (C=O), 1230 (C-O);  $\text{nmr } \delta$  (deuteriochloroform): 8.49 (1H, doublet,  $J = 8.6$  Hz, C<sub>4</sub>-H), 8.22 (1H, singlet, C<sub>2</sub>-H), 7.34 (1H, doublet,  $J = 2.2$  Hz, C<sub>7</sub>-H), 7.12 (1H, quartet,  $J = 8.6, 2.2$  Hz, C<sub>5</sub>-H), 4.41 (2H, quartet,  $J = 7.1$  Hz, O-CH<sub>2</sub>-), 3.89 (3H, singlet, OCH<sub>3</sub>), 1.43 (3H, triplet,  $J = 7.1$  Hz, CH<sub>2</sub>CH<sub>3</sub>).

*Anal.* Calcd. for C<sub>12</sub>H<sub>12</sub>O<sub>3</sub>S: C, 60.99; H, 5.12; S, 13.57. Found: C, 61.06; H, 5.23; S, 13.66.

## 4-Methoxybenzo[b]thiophene-3-carboxylic Acid (IIIb).

Some of the oil (consisting mostly of IIa and IIb) remaining from fractional crystallization of IIa was further purified by gas chromatography (two passes, 10' x 1/4" SE-30 column, temperature programmed at 8°/min. from 100-225°). The oil (impure IIb) thus obtained was saponified by refluxing with alcoholic potassium hydroxide. The crude acid was sublimed, then purified by preparative scale thin layer chromatography on silica gel using acetone as developer. The band of adsorbent containing the product was eluted with acetone. The residue obtained by

evaporation of the acetone was boiled with aqueous sodium carbonate. Filtration and acidification of the filtrate yielded IIIb (12 gm.) which was sublimed at 90-140° (0.04 mm.), then recrystallized from water, m.p. 124.5-126°;  $\text{ir } \nu_{\text{max}}$  (potassium bromide)  $\text{cm}^{-1}$ : 3100 (COOH), 1720 (C=O), 1380 (COOH), 1260 (COOH), 1030 (OCH<sub>3</sub>), 880 (COOH); mass spectrum  $m/e$ : 208 (M<sup>+</sup>) 100%, 209 (M + 1) (11.6), 210 (M + 2) (5.7), 193 (13), 162 (8), 161 (16), 135 (8), 121 (29).

*Anal.* Calcd. for C<sub>10</sub>H<sub>8</sub>O<sub>3</sub>S: C, 57.68; H, 3.87. Found: C, 57.78; H, 3.96.

## 6-Methoxybenzo[b]thiophene-3-carboxylic Acid (IIIa).

Compound IIa (0.50 g., 0.0021 mole) was saponified by refluxing in alcoholic potassium hydroxide. Recrystallization of the product from methanol-water with decolorization gave IIIa, m.p. 219.5-220.5°;  $\text{ir } \nu_{\text{max}}$  (potassium bromide)  $\text{cm}^{-1}$ : 3200-2400 (COOH), 1690 (C=O), 1260 (COOH), 1060 (OCH<sub>3</sub>), 900 (COOH); mass spectrum  $m/e$ : 208 (M<sup>+</sup>) 100%, 209 (M + 1) (13), 210 (M + 2) (5.5), 193 (47), 165 (16), 109 (7).

*Anal.* Calcd. for C<sub>10</sub>H<sub>8</sub>O<sub>3</sub>S: C, 57.68; H, 3.87; S, 15.40. Found: C, 57.55; H, 3.90; S, 15.36.

A sample of the acid was converted to the amide which after recrystallization from ethanol-water (1:1) melted at 202.5-203.5°.

*Anal.* Calcd. for C<sub>10</sub>H<sub>9</sub>NO<sub>2</sub>S: C, 57.96; H, 4.38; N, 6.76; S, 15.48. Found: C, 57.76; H, 4.34; N, 6.85; S, 15.55.

Desulfurization of IIIa with Raney nickel (9) gave an acid melting at 53-53.5°. The literature melting point of 2-(4-methoxyphenyl)propanoic acid is 57° (10). Oxidation of the desulfurized acid with alkaline permanganate gave *p*-anisic acid whose infrared spectrum was identical with that of authentic *p*-anisic acid.

## 3-Hydroxymethyl-6-methoxybenzo[b]thiophene (IV).

The ester IIa was reduced by adding a solution of IIa (10.24 g., 0.0432 mole) in 60 ml. of absolute diethyl ether to a stirred slurry of lithium aluminum hydride (5.00 g., 0.131 mole) in 70 ml. of absolute diethyl ether at room temperature. After addition was complete the mixture was stirred for one hour then refluxed one hour. The reaction mixture was hydrolyzed by adding dropwise to the stirred mixture, 5 ml. of water, then 5 ml. of 15% aqueous sodium hydroxide, and finally 15 ml. of water. The mixture was filtered and the ether solution was heated to remove the solvent. The solid residue IV (7.26 g., 86%) melted at 71-72° after recrystallization from benzene-hexane;  $\nu$  max (potassium bromide)  $\text{cm}^{-1}$ : 3380 (OH), 1240 (OCH<sub>3</sub>), 1050 (COH); nmr  $\delta$  (deuteriochloroform): 7.75 (1H, doublet, J = 8.9 Hz, C<sub>4</sub>-H), 7.35 (1H, doublet, J = 2.3 Hz, C<sub>7</sub>-H), 7.22 (1H, triplet, J = 0.9 Hz, C<sub>2</sub>-H), 7.03 (1H, quartet, J = 8.9, 2.3 Hz, C<sub>5</sub>-H), 4.87 (2H, singlet, -CH<sub>2</sub>-), 3.87 (3H, singlet, OCH<sub>3</sub>), 1.67 (1H, singlet, OH).

Anal. Calcd. for C<sub>10</sub>H<sub>10</sub>O<sub>2</sub>S: C, 61.83; H, 5.16; S, 16.51. Found: C, 61.71; H, 5.12; S, 16.77.

### 3-Chloromethyl-6-methoxybenzo[b]thiophene (V).

A mixture of 3 g. (0.0155 mole) of IV, three drops of pyridine and 20 ml. of benzene was treated dropwise with a solution of 3 ml. of thionyl chloride in 5 ml. of benzene then heated to 40-45° for 10 minutes. The benzene and excess thionyl chloride were removed under reduced pressure. An additional 10 ml. of benzene was added and then removed under reduced pressure. The red oil V which remained contained a small amount of pyridine hydrochloride and was used without further purification.

### 2-Amino-3-(6-methoxybenzo[b]thien-3-yl)propanoic Acid (VIII).

#### A. Using Ethyl Acetamidocyanoacetate.

Ethyl acetamidocyanoacetate (2.64 g., 0.0155 mole) was dissolved, with stirring, in sodium ethoxide prepared from 0.4 g. (0.0175 g.-atom) of sodium and 30 ml. of absolute ethanol. When all the ester had dissolved, a solution of crude V, prepared from 0.0155 mole of IV, in 40 ml. of absolute ethanol was added. The mixture was stirred for four hours, then filtered. The filtrate was taken to dryness and the residue was recrystallized from 20 ml. of benzene to give 3.51 g. (66%) of yellow crystals of ethyl 2-cyano-2-acetamido-3-(6-methoxybenzo[b]thien-3-yl)propanoate (VI), m.p. 133-133.5°;  $\nu$  max (potassium bromide)  $\text{cm}^{-1}$ : 3350 (NH), 1730 (COO), 1690 (CON); nmr  $\delta$  (deuteriochloroform): 7.60 (1H, doublet, J = 8.6 Hz, C<sub>4</sub>'-H), 7.30 (1H, doublet, J = 2.5 Hz, C<sub>7</sub>'-H), 7.22 (1H, multiplet, C<sub>2</sub>'-H), 6.99 (1H, quartet, J = 8.6, 2.5 Hz, C<sub>5</sub>'-H), 6.47 (1H, singlet, broad, NH), 4.14 (2H, quartet, J = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.84 (3H, singlet, OCH<sub>3</sub>), 3.73, 3.68 (2H, both singlets, CH<sub>2</sub>), 1.99 (3H, singlet, COCH<sub>3</sub>), 1.18 (3H, triplet, J = 7.2 Hz, CH<sub>2</sub>CH<sub>3</sub>).

Anal. Calcd. for C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>S: C, 58.94; H, 5.24; N, 8.09; S, 9.26. Found: C, 58.74; H, 5.32; N, 7.96; S, 9.00.

A 1.48 g. (0.0043 mole) quantity of VI was hydrolyzed by refluxing for 18 hours with 15 ml. of water and 2 ml. of concentrated sulfuric acid. Excess saturated aqueous barium hydroxide was added and the mixture was filtered. The filtrate was treated with carbon dioxide, boiled and then filtered. The water was removed from the filtrate with a rotary evaporator yielding 1.07 g. (83%) of VIII. Two recrystallizations from water with decolorization gave pure VIII, m.p. 244.5-246° dec.;  $\nu$  max (potassium bromide)  $\text{cm}^{-1}$ : 3060 (broad) (NH<sub>3</sub><sup>+</sup>), 1600 (COO<sup>-</sup>), 1390 (COO<sup>-</sup>); nmr  $\delta$  (deuterium oxide; acidic): 7.60 (1H, doublet, J = 9.0 Hz, C<sub>4</sub>'-H), 7.40 (1H, doublet, J = 2.3 Hz, C<sub>7</sub>'-H), 7.26 (1H, singlet, C<sub>2</sub>'-H), 6.96 (1H, quartet, J = 9.0, 2.3 Hz, C<sub>5</sub>'-H), 4.34 (1H, quartet, J = 7.8, 6.0 Hz, CH<sub>2</sub>CH), 3.79 (3H, singlet,

OCH<sub>3</sub>), 3.40 (1H, doublet, J = 6.0 Hz, CH<sub>2</sub>), 3.38 (1H, doublet, J = 7.8 Hz, CH<sub>2</sub>).

Anal. Calcd. for C<sub>12</sub>H<sub>13</sub>NO<sub>3</sub>S: C, 57.35; H, 5.21; N, 5.58; S, 12.76. Found: C, 57.17; H, 5.19; N, 5.43; S, 12.60.

#### B. Using Diethyl Acetamidomalonate.

A solution of crude V, obtained from 1.41 g. (0.0073 mole) of IV as previously described, in 20 ml. of absolute ethanol was reacted with the solution obtained from 0.167 g. (0.0073 g.-atom) of sodium in 17 ml. of absolute ethanol, and 1.58 g. (0.0073 mole) of diethyl acetamidomalonate in the manner previously described for ethyl acetamidocyanoacetate. The reaction mixture was allowed to stand overnight, then filtered through Celite. The filtrate was concentrated on a rotary evaporator and 25 ml. of acetone was added to the syrupy residue. The precipitate which was formed was removed by filtration and the filtrate was concentrated to yield a yellow oil which crystallized on standing. The entire crude product was chromatographed on a 1" x 7" alumina column. A total of 58 ten-ml. fractions was collected. The eluting solvent for fractions 1-16 was benzene; for fractions 17-42, chloroform; for the remaining fractions, ethyl acetate. The product was contained in fractions 38-46, which were combined and evaporated. Recrystallization of the residue from benzene-ligroin (1:3) gave 0.3 g. (11%) of white prisms of ethyl 2-carboethoxy-2-acetamido-3-(6-methoxybenzo[b]thien-3-yl)propanoate (VIII), m.p. 133-134°;  $\nu$  max (potassium bromide)  $\text{cm}^{-1}$ : 3420 (NH), 1750 (COO), 1650 (CON); nmr  $\delta$  (deuteriochloroform): 7.56 (1H, doublet, J = 8.8 Hz, C<sub>4</sub>'-H), 7.32 (1H, doublet, J = 2.4 Hz, C<sub>7</sub>'-H), 6.94 (1H, quartet, J = 8.8, 2.4 Hz, C<sub>5</sub>'-H), 6.85 (1H, singlet, C<sub>2</sub>'-H), 6.63 (1H, singlet, broad, NH), 4.23 (2H, quartet, J = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.90 (2H, singlet, CH<sub>2</sub>), 3.84 (3H, singlet, OCH<sub>3</sub>), 1.95 (3H, singlet, COCH<sub>3</sub>), 1.28 (3H, triplet, J = 7.2 Hz, OCH<sub>2</sub>CH<sub>3</sub>).

Anal. Calcd. for C<sub>19</sub>H<sub>23</sub>NO<sub>6</sub>S: C, 58.00; H, 5.89; N, 3.56; S, 8.15. Found: C, 58.26; H, 6.01; N, 3.41; S, 8.21.

Sulfuric acid hydrolysis of VII in the same manner as that used for VI yielded amino acid VIII identical with that prepared from VI.

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