

Benzo[*b*]thiophene Derivatives. XV. Preparation and Electrophilic Substitution of 6-Methoxy-3-methylbenzo[*b*]thiophene (I).

*E. Campaigne, A. Dinner and E. S. Neiss*

The Chemistry Laboratories of Indiana University

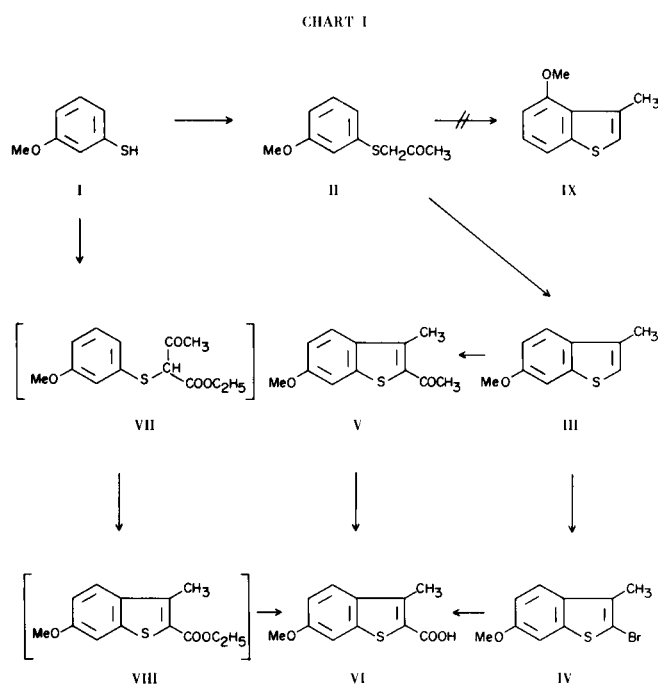
Our interest in benzo[*b*]thiophene derivatives as bioisosteres of analogous biologically active indoles (2) has led us to examine 6-methoxy-3-methylbenzo[*b*]thiophene (III) as a potential intermediate for the preparation of analogs of 6-methoxyindole alkaloids. A convenient source of III is the Tilak (3) cyclization of 3-methoxyphenylthioacetone (II) (see Chart I) but Schuetz and Titus (4) have shown that in some cases such cyclizations will lead to mixtures of the 4- and 6-alkoxy derivatives. It was therefore essential that the product of cyclization of II be unequivocally identified.

Cyclization of II in concentrated sulfuric acid led to a crystalline product in good yield. The 100 MHz NMR spectrum of this compound showed clearly that it was III rather than the isomeric 4-methoxy-3-methylbenzo[*b*]thiophene (IX). It showed clean doublets for H-4 and H-7, and a doublet of doublets for H-5, coupled to H-4,  $J = 8\text{Hz}$  and *meta*-coupled to H-7,  $J = 2\text{Hz}$ . Such a pattern clearly distinguishes it from IX, where the three vicinal aromatic protons would show a more complex coupling pattern. In addition, a fine quartet at  $6.68\delta$ ,  $J = 1\text{Hz}$ , coupled to the methyl group at C-3, is characteristic of H-2 in 3-methylbenzo[*b*]thiophenes (5).

Like the isomeric 5-methoxy-3-methylbenzo[*b*]thiophene, which has been shown to undergo ring bromination readily, even under conditions designed to promote side-chain substitution (6), III was brominated by *N*-bromosuccinimide, with or without added peroxide, to form the ring substituted 6-methoxy-2-bromo-3-methylbenzo[*b*]thiophene (IV) in good yield. Similarly, treatment of III under mild Friedel-Crafts conditions with acetic anhydride produced 6-methoxy-2-acetyl-3-methylbenzo[*b*]thiophene (V). Structures of IV and V were assigned on the basis of the disappearance of the H-2 peak, and conversion of the C-3 methyl doublet to a singlet, shifted appreciably downfield in the case of V by deshielding of the adjacent carbonyl group. Preferential electrophilic substitution at position 2 of compound III is consistent with earlier work in this laboratory (7), which has shown similar results with 6-methoxybenzo[*b*]thiophene and 5,6-methylenedioxybenzo[*b*]thiophene.

Further structure-proof was obtained by relating IV and V to 6-methoxy-3-methylbenzo[*b*]thiophene-2-carboxylic acid (VI), readily obtained by carbonation of the

Grignard derived from IV, or by oxidation of V. This same acid was also obtained, in very poor yield, by condensing I with  $\alpha$ -chloroacetoacetic ester in base, followed by cyclization of the crude product in sulfuric acid and hydrolysis of the resulting ester. The intermediate ethyl  $\alpha$ -(3-methoxyphenylthio)acetoacetate (VII) was an unstable oil, not readily distillable.



### EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are corrected. Infrared spectra were measured on an Infracord Model 137-B Spectrometer in solvents or mulls. The 100 MHz NMR spectra were determined in carbon tetrachloride, on a Varian HA-100 instrument, using tetramethylsilane as internal standard. The following abbreviations are used in reporting the NMR data: s = singlet; d = doublet; dd = double doublet; q = quartet;  $\delta$  values represent centers of resonance.

#### 3-Methoxyphenylthioacetone (II).

A solution of 50.5 g. (0.36 mole) of 3-methoxythiophenol, 14.4 g. (0.36 mole) of sodium hydroxide and 40 ml. of water was stirred and cooled to  $20^\circ$  as 33.3 g. (0.36 mole) of chloroacetone was added dropwise. The addition took about 40 minutes and the

reaction mixture was stirred at room temperature for an additional hour. The mixture was extracted with three 100 ml. portions of ether and the combined ether phase was washed with two 50 ml. portions of water and dried with anhydrous magnesium sulfate. After removal of the ether the residual oil was distilled. The first fraction was collected in the range 94-130°/2 mm. and consisted of residual thiol and some product. The major fraction distilled at 150-151°/2 mm. as a pale yellow liquid which weighed 53.5 g. (76.5%). Gas chromatography of the product showed it to contain about 1% of some impurity. Redistillation of the product gave a chromatographically pure compound which distilled at 133-135°/1 mm.; i.r.  $\lambda$  max (carbon tetrachloride) 3.35 (=C-H), 3.5 (-CH<sub>2</sub>-), 3.55 (CH<sub>3</sub>-), 5.91 (C=O), 14.80  $\mu$  (C-S).

*Anal.* Calcd. for C<sub>10</sub>H<sub>12</sub>O<sub>2</sub>S: C, 61.22; H, 6.16; S, 16.32. Found: C, 60.97; H, 6.19; S, 16.33.

The semicarbazone derivative was prepared by the usual procedure (8) as white platelets which melted at 147-148° after recrystallization from 25% aqueous ethanol.

*Anal.* Calcd. for C<sub>11</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S: N, 16.58. Found: N, 16.35.

#### 6-Methoxy-3-methylbenzo[b]thiophene (II).

When 5.4 g. (0.275 mole) of II was added dropwise with stirring to 81 g. of concentrated sulfuric acid, a deep red color immediately appeared and the reaction mixture became warm. After the addition, which required 5 minutes, the red solution was poured with stirring onto 100 g. of chipped ice. After standing at room temperature overnight, a light tan precipitate was collected and dried to yield 3 g. (61.4%) of product. The compound distilled at 138-140° (1.5 mm.) as a clear liquid with a pleasing, fragrant odor. After two recrystallizations from hexane white crystals were obtained which melted sharply at 35°: i.r.  $\lambda$  max (potassium bromide) 3.24 (=C-H), 3.42, 3.55 (-CH<sub>3</sub>), 8.13  $\mu$  (C-O); u.v.  $\lambda$  max (ethanol), 233 m $\mu$  (log  $\epsilon$  4.53), 266 (3.86), 295 (3.08), 307 m $\mu$  (2.90) (9); NMR  $\delta$  7.36 (d, J<sub>4,5</sub> = 8 Hz, H-4), 7.13 (d, J<sub>5,7</sub> = 2 Hz, H-7), 6.83 (dd, J<sub>4,5</sub> = 8 Hz, J<sub>5,7</sub> = 2 Hz, H-5), 6.68 (q, J = 1 Hz, H-2), 3.66 (s, CH<sub>3</sub>O), 2.26 (d, J = 1 Hz, ArCH<sub>3</sub>).

*Anal.* Calcd. for C<sub>10</sub>H<sub>10</sub>O<sub>2</sub>S: C, 67.40; H, 5.66; S, 17.95. Found: C, 67.27; H, 5.74; S, 18.14.

The picric acid charge transfer complex was prepared as tiny orange needles which melted at 99-100° after recrystallization from ethanol.

*Anal.* Calcd. for C<sub>16</sub>H<sub>13</sub>N<sub>3</sub>O<sub>8</sub>S: S, 7.86. Found: S, 7.81.

#### 2-Bromo-6-Methoxy-3-methylbenzo[b]thiophene (IV).

(a) A mixture of 5 g. (0.0281 mole) of III, 5 g. (0.0281 mole) of *N*-bromosuccinimide, 75 mg. of benzoyl peroxide and 25 ml. of carbon tetrachloride were refluxed for 2.5 hours. The cooled reaction mixture was filtered to remove succinimide and the filtrate was evaporated to leave a red oil, which was then taken up in 25 ml. of dimethylsulfoxide, poured into 250 ml. of water, and cooled in the refrigerator to give 5.6 g. (78%) of a yellow-tan precipitate. After two recrystallizations from methanol white platelets were obtained which melted at 56-57°: i.r. max (potassium bromide) 3.42, 3.55 (-CH<sub>3</sub>), 8.15  $\mu$  (C-O); u.v.  $\lambda$  max (ethanol), 234 m $\mu$  (log  $\epsilon$  4.50), 270 (4.07), 278 (4.05), 295 (3.33), 308 (3.08); NMR  $\delta$  7.29 (d, J<sub>4,5</sub> = 9 Hz, H-4), 7.00 (d, J<sub>5,7</sub> = 2 Hz, H-7), 6.78 (dd, J<sub>4,5</sub> = 8 Hz, J<sub>5,7</sub> = 2 Hz, H-5), 3.72 (s, CH<sub>3</sub>O), 2.24 (s, ArCH<sub>3</sub>).

*Anal.* Calcd. for C<sub>10</sub>H<sub>9</sub>BrOS: C, 46.75; H, 3.53; Br, 31.13; S, 12.45. Found: C, 47.03; H, 3.48; Br, 31.16; S, 12.57.

The picric acid charge transfer complex was prepared as orange needles which melted at 79-80° after recrystallization from ethanol.

*Anal.* Calcd. for C<sub>16</sub>H<sub>12</sub>BrN<sub>3</sub>O<sub>8</sub>S: Br, 16.42; S, 6.59. Found: Br, 16.38; S, 6.36.

(b) A mixture of 5 g. (0.0281 mole) of III, 100 mg. of benzoyl peroxide and 25 ml. of dry benzene was stirred and brought to vigorous reflux and a mixture of 5 g. (0.0281 mole) of *N*-bromosuccinimide and 100 mg. of benzoyl peroxide was added portionwise as fast as the vigorous foaming would allow. The reaction mixture was then allowed to reflux for a further 20 minutes. The cool mixture was filtered to remove succinimide and the solvent was distilled from the filtrate. The residual red oil was dissolved in 25 ml. of dimethylsulfoxide, and worked up as above to yield 5.75 g. (82%) of white platelets which melted at 56-57°, gave the same I.R. spectrum and did not depress the melting point of the product prepared by above procedure (a).

(c) A solution of 5 g. (0.0281 mole) of III and 5 g. (0.0281 mole) of *N*-bromosuccinimide was allowed to reflux in 25 ml. of dry chloroform for 2.5 hours. The cooled mixture was filtered to remove succinimide and the collected crystals were washed with two 10 ml. portions of dry chloroform. After distillation of the chloroform a red oil remained which crystallized upon trituration with methanol and cooling. The solid was collected and recrystallized twice from methanol to yield 6.7 g. (87%) of white crystals, identical in all respects to IV above.

#### 6-Methoxy-2-acetyl-3-methylbenzo[b]thiophene (V).

One gram (0.0056 mole) of III and 0.6 g. (0.0059 mole) of acetic anhydride were dissolved in 25 ml. of dry chloroform and 5 ml. of stannic chloride was added with stirring. The green solution was warmed at 60° for 30 minutes, cooled to room temperature and treated with 40 ml. of 10% hydrochloric acid solution. After an additional 10 minutes of boiling, the reaction mixture was cooled and the organic layer was separated and evaporated to dryness to yield 1.1 g. (90%) of white crystals which melted at 72-73° after recrystallization from 80% aqueous ethanol: i.r.  $\lambda$  max (potassium bromide), 3.40, 3.54 (-CH<sub>3</sub>), 6.13 (C-O), 7.32 (CH<sub>3</sub>-C=O), 7.90  $\mu$  (C-O); NMR  $\delta$  7.56 (d, J<sub>4,5</sub> = 8 Hz, H-4), 7.09 (d, J<sub>5,7</sub> = 2 Hz, H-7), 6.89 (dd, J<sub>4,5</sub> = 8 Hz, J<sub>5,7</sub> = 2 Hz, H-5), 3.82 (s, CH<sub>3</sub>O), 2.62 (CH<sub>3</sub>-), 2.46 (s, CH<sub>3</sub>-).

*Anal.* Calcd. for C<sub>12</sub>H<sub>12</sub>O<sub>2</sub>S: C, 65.40; H, 5.49; S, 14.53. Found: C, 65.61; H, 5.49; S, 14.83.

The 2,4-dinitrophenylhydrazine derivative was obtained as orange needles melting at 215-216°. The oxime was obtained as tiny white needles which melted at 164-165° after recrystallization from ethanol; i.r.  $\lambda$  max (potassium bromide), 3.12 (=NOH), 6.15 (C=N), 7.91  $\mu$  (C-O).

*Anal.* Calcd. for C<sub>12</sub>H<sub>13</sub>NO<sub>2</sub>S: N, 5.95; S, 13.61; Found: N, 5.51; S, 13.88.

#### 6-Methoxy-3-methylbenzo[b]thiophene-2-carboxylic acid (VI).

(a) A solution of 2.7 g. (0.0105 mole) of IV and 3 g. of methyl iodide in 10 ml. of dry ether was added dropwise with stirring to a crystal of iodine and 1.8 g. of magnesium turnings suspended in 50 ml. of dry ether. The reaction started without external heating and the mixture was stirred for 3 hours at ambient temperature, concentrated to 25 ml. and poured onto excess powdered dry ice with stirring. The slurry was stirred well and acidified with 10% sulfuric acid solution. The ether layer was separated and the aqueous phase was extracted with two 10 ml. portions of ether. The combined ether layer was washed with water, extracted with three 20 ml. portions of 10% sodium hydroxide, the basic extracts treated with Norit, filtered, and the cooled filtrate acidified by the addition of 20% hydrochloric acid. Collection of the white solid and recrystallization from dilute ethanol gave 1.1 g. (48%) of

white needles which melted at 253-254°: i.r.  $\lambda$  max (potassium bromide), 3.3-4 (OH of carboxylic acid), 5.99 (C=O), 7.95  $\mu$  (C-O); u.v.  $\lambda$  max (ethanol), 239 m $\mu$  (log  $\epsilon$  4.32), 258 (sh) (4.11), 266 (4.19), 296 (sh) (4.18), 305 (4.24), 317 (4.17).

*Anal.* Calcd. for C<sub>11</sub>H<sub>10</sub>O<sub>3</sub>S: C, 59.40; H, 4.54; S, 14.40. Found: C, 59.65; H, 4.63; S, 14.51.

(b) Two grams (0.0091 mole) of V was allowed to reflux for 2 hours with 15 g. of iodine, 75 ml. of dioxane and 200 ml. of 10% sodium hydroxide. The cooled reaction mixture was poured into 250 ml. of water, filtered and the filtrate was acidified by the addition of 10% hydrochloric acid. The excess iodine was reduced by the dropwise addition of 5% sodium bisulfite until the acid solution was a pale yellow color. The yellow precipitate was collected, dissolved in 25 ml. of 10% sodium hydroxide, boiled with Norit and filtered. Acidification of the filtrate yielded 1.3 g. (64%) of white product which melted at 252-253° after recrystallization from ethanol. An additional recrystallization raised the melting point to 253-254°. A mixed melting point determination with the product prepared by procedure (a) above was not depressed, and the I.R. spectrum was identical.

(c) Sodium 3-methoxythiophenolate was prepared by adding 70 g. (0.5 mole) of I to a solution of 20 g. (0.5 mole) of sodium hydroxide in 60 ml. of water. The water was evaporated on the steam bath under reduced pressure and the residue was dried. To the residue was added 500 ml. of dry benzene and the suspension was heated to boiling on the steam bath as 83 g. (0.5 mole) of ethyl  $\alpha$ -chloroacetate was added with stirring. Steam bath heating was not used after initiation of the addition as the reaction was exothermic. The addition required 3 hours and the yellow suspension was refluxed with stirring for an additional 2.5 hours. The suspension was cooled to room temperature, extracted with two 250 ml. portions of water and dried with anhydrous magnesium sulfate. After removal of the solvent under reduced pressure, 131 g. of a brown oil remained. Attempts to distill this oil produced tars. The crude product was, therefore, added with stirring to 131 ml. of concentrated sulfuric acid contained in a one liter 3-necked round-bottomed flask immersed in an ice-salt bath and fitted with a dropping funnel, thermometer and stirrer. During the addition, the temperature in the reaction flask was maintained at 0°. After the 2 hour addition, the mixture was maintained at 0° for an additional hour with stirring and 250 g. of ice and 250 ml. of water were added, with external cooling. The aqueous phase

was decanted and extracted with two 250 ml. portions of ether. The yellow-orange tarry residue was dissolved with a boiling mixture of ethanol and benzene which was combined with the ether extracts. A dark tarry mass was left after evaporation of the mixed solvents. This residue was treated with 500 ml. of 10% potassium hydroxide and boiled in the presence of Norit for 2 hours. The hot alkaline solution was filtered and the dark filtrate was acidified with excess 10% hydrochloric acid to yield a tan precipitate, which was collected and recrystallized twice from aqueous ethanol to yield 6.1 g. (5.5%) of an acid which melted at 250-251°. Two further recrystallizations raised the melting point to 253-254°, and the product had identical infrared absorption characteristics to VI, above.

#### REFERENCES

- (1) Contribution No. 1775, supported by Public Health Service Research Grant GM-10366 to Indiana University. For paper number XIV in this series, see E. Campaigne and D. R. Knapp, *J. Heterocyclic Chem.*, **7**, 107 (1970). Taken in part from the Ph.D. thesis of ESN, Indiana University, 1964.
- (2) *cf.*, E. Campaigne, E. S. Neiss, C. C. Pfeiffer and R. A. Beck, *J. Med. Chem.*, **11**, 1049 (1968).
- (3) *cf.*, M. K. Bhattacharjie, R. B. Mitra, B. D. Tilak and M. R. VanKiteswaran, *Tetrahedron*, **10**, 215 (1960).
- (4) R. D. Schuetz and R. L. Titus, *J. Heterocyclic Chem.*, **4**, 465 (1967).
- (5) E. Campaigne and A. Dinner, *J. Pharm. Sci.*, **58**, 892 (1969).
- (6a) E. S. Neiss, Ph.D. thesis, Indiana University, 1964; (b) I. Brown, Ph.D. thesis, University of Glasgow, 1962; (c) S. T. Reid, Ph.D. thesis, University of Glasgow, 1960.
- (7) E. Campaigne and W. E. Kreighbaum, *J. Org. Chem.*, **26**, 363 (1961).
- (8) "The Systematic Identification of Organic Compounds," R. L. Shriner, R. C. Fuson and D. Y. Curtin, 4th Ed., John Wiley and Sons, New York, 1956, p. 218.
- (9) The U.V. values for 6-ethoxybenzo[*b*]thiophene are 230 (4.55), 264 (3.94), 294 (3.09), 306 (3.11); M. R. Padhye and S. R. Desai, *Trans. Faraday Soc.*, **49**, 1386 (1953).

Received February 9, 1970

Bloomington, Indiana 47401