[CONTRIBUTION NO. 970 FROM THE CHEMISTRY LABORATORIES OF INDIANA UNIVERSITY]

# Substitution Reactions of 5,6-Dimethoxybenzothiophene and 5,6-Methylenedioxybenzothiophene[1]

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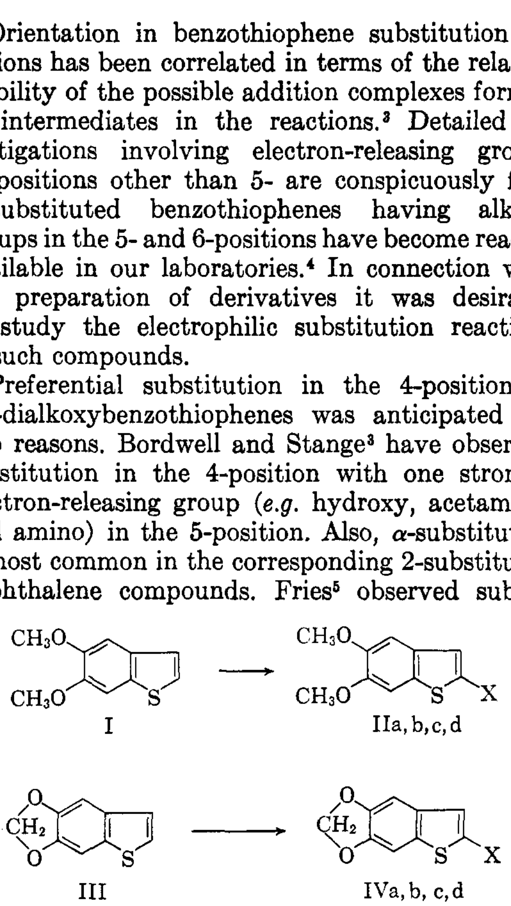
*Received May 23, 1960*

5,6-Dimethoxybenzothiophene and 5,6-methylenedioxybenzothiophene have been subjected to the electrophilic substitution reactions, bromination, acetylation and formylation. Substitution occurs principally at the 2-position in all cases, as shown by conversion of all products to the known 2-carboxylic acid derivatives. This unusual orientation can be rationalized on the basis of relative importance of contributing resonance structures.

Orientation in benzothiophene substitution reactions has been correlated in terms of the relative stability of the possible addition complexes formed as intermediates in the reactions.[3] Detailed investigations involving electron-releasing groups in positions other than 5- are conspicuously few. Disubstituted benzothiophenes having alkoxy groups in the 5- and 6-positions have become readily available in our laboratories.[4] In connection with the preparation of derivatives it was desirable to study the electrophilic substitution reactions of such compounds.

Preferential substitution in the 4-position of 5,6-dialkoxybenzothiophenes was anticipated for two reasons. Bordwell and Stange[3] have observed substitution in the 4-position with one strongly electron-releasing group (*e.g.* hydroxy, acetamido, and amino) in the 5-position. Also, $\alpha$-substitution is most common in the corresponding 2-substituted naphthalene compounds. Fries[5] observed substitution in the 1-position in 2,3-dihydroxynaphthalene while Buu Hoï and Lavit[6] reported a similar result[7] for 2,3-dimethoxynaphthalene.



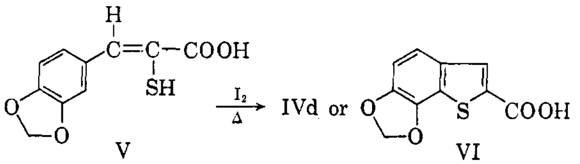
I IIa,b,c,d

III IVa,b,c,d

a. X = —Br, b. X = —CHO, c. X = —COCH$_3$, d. X = —COOH

5,6-Dimethoxybenzothiophene (I) was prepared as previously described.[4] 5,6-Methylenedioxybenzothiophene (III) was prepared in improved yield by a modification of the reported method, involving ring closure of the corresponding $\beta$-(3,4-methylenedioxyphenyl)-$\alpha$-mercaptoacrylic acid (V)[8] and decarboxylation of the resulting carboxylic acid.

The structure of III was assigned on the basis of analogy of synthesis of I and on the following supplementary evidence. Ring closure of V, followed by desulfurization of the product with Raney nickel, according to the method of Papa, Schwenk, and Whitman,[9] gave an acid which melted at the same temperature as $\beta$-(3,4-methylenedioxyphenyl)propionic acid, prepared by Lorenz[10] and Schwenk and Papa.[11] Desulfurization, however, only confirmed the nature of the ring system and it was necessary to use other means to determine whether the ring closure occurred so as to form IVd or 6,7-methylenedioxybenzothiophene-2-carboxylic (VI).



V VI

As the structures of I and IId have been established,[4] ultraviolet spectra were obtained for I, III, IId, and IVd (Table I). The similarity between I and III, and IId and IVd is evident from the correspondence of the $\lambda_{max}$ in each pair with slight bathochromic shifts due to the presence of an additional ring in III and IVd. The similarity in the spectra of IId and IVd, which differ markedly in shape from the spectrum of a benzothiophene-2-carboxylic acid having alkoxy groups in different

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(1) Taken from a portion of a thesis to be submitted by W.E.K. in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Indiana University. Presented before the Organic Division at the 137th meeting of the American Chemical Society, Cleveland, Ohio, April, 1960.

(2) White Laboratories Fellow in Chemistry, 1957–1958. Schering Fellow, 1958–1959. Lubrizol Fellow, 1959–1960.

(3) F. G. Bordwell and Hugo Stange, *J. Am. Chem. Soc.*, **77**, 5939 (1955).

(4) E. Campaigne and R. E. Cline, *J. Org. Chem.*, **21**, 39 (1956).

(5) Th. Zincke and K. Fries, *Ann.*, **334**, 342 (1904).

(6) Ng. Ph. Buu Hoï and D. Lavit, *J. Org. Chem.*, **21**, 21 (1956).

(7) Acetylation was believed to attack the 6-position but the proof of structure was lacking.

(8) R. Andreasch, *Monatsh.*, **39**, 419 (1918).

(9) D. Papa, E. Schwenk, and B. Whitman, *J. Org. Chem.*, **7**, 587 (1942).

(10) C. Lorenz, *Ber.*, **13**, 758 (1880).

(11) E. Schwenk and D. Papa, *J. Org. Chem.*, **10**, 232 (1945).

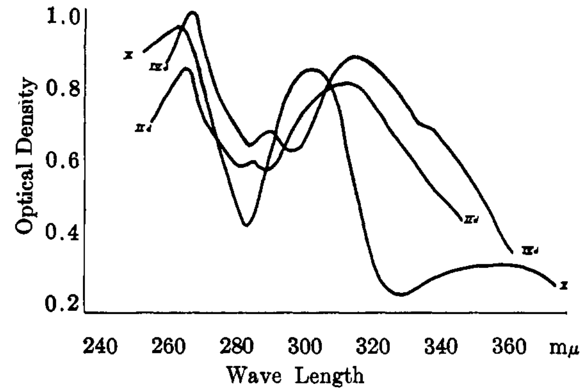


Fig. 1. Ultraviolet spectra of the dialkoxybenzothiophene-2-carboxylic acids

positions (X) is shown in Fig. 1. It is therefore probable that a 6,7-isomer would also have a different ultraviolet absorption. The synthesis of 4,5-dimethoxybenzothiophene-2-carboxylic acid (X) from 2,3-dimethoxybenzaldehyde is unequivocal, as the ring closure can occur in only one way.

I and III were each subjected to three common substitution reactions. Yields were relatively low in the case of formylation, as no special effort was made to discover the conditions for maximum yield in that reaction. The possibility that significant amounts of other isomers were produced but not detected because of solubility differences is not likely, since both brominations and acetylations occurred in good yield with formation of single isomers, and low yields are frequently obtained in formylations unless the position is highly activated.[12]

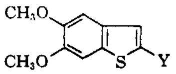
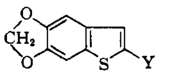
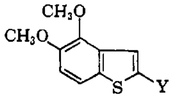
Monobromination of I and III occurred in the 2-position to produce IIa and IVa, as was shown by conversion *via* Grignard carbonation to IId and IVd, respectively. As the 2-carboxylic acids have both been prepared and identified unequivocally as to the position of the carboxyl group, melting point and mixed melting point were deemed sufficient for proving identity in each case.

Formylation of III gave the 2-formyl derivative (IVb). This was shown to be the case by two comparisons. First IVb was oxidized with silver oxide to the corresponding acid which was shown to be identical with the known 2-carboxylic acid by mixed melting point. The acid obtained, when desulfurized with Raney nickel, gave a compound identical by mixed melting point with one obtained from a pure sample of IVd. The formyl derivative of I was shown to be the 2-isomer (IIb) by conversion to the acid and comparison of melting point and mixed melting point.

Acetylation of I and III gave the 2-isomer in each case, as shown by oxidation *via* the haloform reaction to the respective 2-carboxylic acids.

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA AND MOLAR EXTINCTION COEFFICIENTS OF SUBSTITUTED BENZOTHIOPHENE-2-CARBOXYLIC ACIDS

| | Y=H | | Y=COOH | |
|---|---|---|---|---|
| | $\lambda_{max}^{m\mu}$ | $\epsilon_{max}$ | $\lambda_{max}^{m\mu}$ | $\epsilon_{max}$ |
| Compound Number | I | | IId | |
|  | $236^{a,b}$<br>$263^{a}$<br>$297^{a}$<br>$307^{a}$ | 27,000<br>8,700<br>2,450<br>3,000 | $244^{a}$<br>$265^{a}$<br>$296^{a}$ | 19,000<br>11,900<br>17,800 |
| Compound Number | III | | IVd | |
|  | 237<br>264<br>273<br>303<br>307<br>315 | 24,000<br>8,900<br>9,100<br>3,400<br>3,750<br>3,900 | 245<br><br>271<br>300 | 23,300<br><br>13,300<br>18,700 |
| Compound Number | XI | | X | |
|  | 233<br>258<br>308 | 22,400<br>6,400<br>3,700 | 240<br>285<br>345 | 22,400<br>19,000<br>4,075 |

[a] See ref. 4. [b] The absorption spectra measurements were determined on 0.001% solutions in 95% ethanol using a Beckman DK-1 quartz spectrophotometer with hydrogen discharge tube and 1-cm. quartz cells.

These monosubstitution reactions show that substitution occurs predominantly in the 2-position of benzothiophene when alkoxy groups are present in both the 5- and 6-positions of the benzene moiety. This is remarkable, as it is contrary to predictions based on analogies with both 5-hydroxybenzothiophene and 2,3-dimethoxynaphthalene. Furthermore, the 2-position of benzothiophene is rarely the predominate point of attack except in metalation reactions.

In benzothiophene, the thiophene ring is more reactive toward substitution than the benzene ring. This is true even when the benzene ring carries a weakly electron-releasing group such as acetoxy.[8] The most reactive position is the 3-position, and the second most active the 2-position, since when the 3-position is blocked substitution occurs in the 2-position rather than on the benzene ring, occasionally even if the blocking group is meta-directing.[13] The fact that strongly electron-releasing groups such as hydroxy or amino in the 5-position (VII) cause preferential substitution at the 4-position is surprising, as, although the benzene ring is activated at the 4-position (resonance form VIIa), one can speculate that the thiophene ring might participate in the resonance through forms like VIIb and VIIc, the 3-position being the most active site and the sulfur atom passing on the resonance by expansion of the electron shell.[14] Accord-

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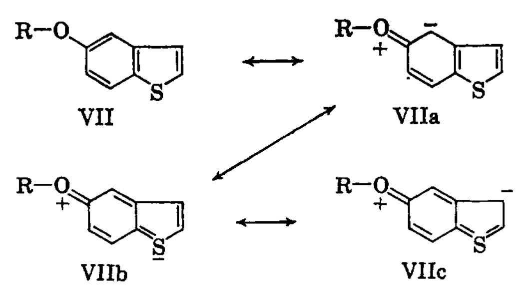
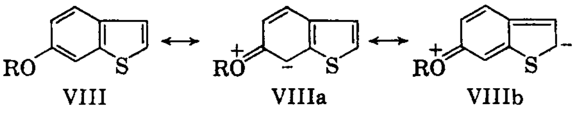
[12] Ng. Ph. Buu Hoï, *Bull. soc. chim. France*, 1594 (1955).

[13] Hartough and Meisel, *The Chemistry of Heterocyclic Compounds, Compounds with Condensed Thiophene Rings*, Interscience Publishers, Inc., New York, 1954, p. 9.

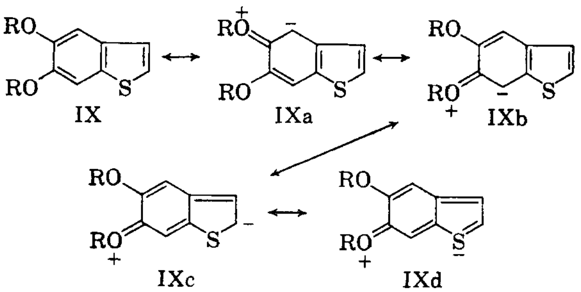
[14] L. Pauling, *The Nature of the Chemical Bond*, Cornell University Press, Ithica, N. Y., 1944, p. 60.



ing to the results of Bordwell and Stange[3] the 3-position was not activated; therefore, resonance form VIIc must be insignificant. An electron-releasing group in the 6-position of benzothiophene (*e.g.* VIII) could activate the thiophene ring in the 2-position through resonance forms such as VIIIb not involving participation by the sulfur atom (except as a stabilizing influence), as well as the 7-position, VIIIa.



The preferential substitution of a 5,6-dialkoxybenzothiophene (IX) in the 2-position may then be explained on the basis of the relative activity of the three activated positions, (IXa, IXb, IXc). The product is formed from structure IXc rather than IXb or IXa, probably because of the stabilization of IXc through resonance structure IXd, involving expansion of the sulfur shell.[15]



If the above explanation is true, benzothiophenes carrying electron-releasing groups in the 6-position, such as VIII should be preferentially substituted in the 2-position, but no data are at present available for such compounds. Studies on the synthesis and reactions of 6-substituted benzothiophenes are under way.

## EXPERIMENTAL[16]

*5,6-Methylenedioxybenzothiophene-2-carboxylic acid* (IVd). Fifty-five grams (0.245 mole) of $\beta$-(3,4-methylenedioxyphenyl)-$\alpha$-mercaptoacrylic acid[8] was dissolved in 600 ml. of dioxane and added in small portions over 20 hr. to a stirred solution of 100 g. (0.39 mole) of iodine in 300 ml. of dioxane at 60°. The resulting mixture was stirred an additional 12 hr. at 60° and then poured into 4 l. of cold water. The precipitate was purified by recrystallization as the sodium salt from 10% sodium hydroxide solution. Precipitation of the acid gave 34 g. (62%) of material which melted at 290–291° after one recrystallization from dilute acetic acid.

*Anal.* Calcd. for $C_{10}H_6O_4S$: S, 14.40. Found: S, 14.30.

*5,6-Methylenedioxybenzothiophene* (III). Sixty-three grams (0.28 mole) of IVd was heated slowly with 20 g. of copper powder in 500 ml. of quinoline until the temperature rose to 210° (about 2.5 hr.). The reaction mixture was cooled to room temperature and stirred with 300 ml. of isopropyl ether. The solution was filtered to remove the copper and shaken vigorously with dilute hydrochloric acid until acid to Congo red. The aqueous layer was discarded and the ether layer was evaporated and steam-distilled rapidly to give 41.5 g. (83%) of colorless leaflets melting 96–97°.

*Anal.* Calcd. for $C_9H_6O_2S$: S, 18.00. Found: S, 17.92.

*Desulfurization of* IVd. Five grams of Raney nickel alloy was added in small portions with vigorous swirling to a warm (60–70°) solution of 0.9 g. of the acid in 70 ml. of 10% sodium hydroxide. The mixture was held just under boiling for 45 min. and was filtered hot. The filtrate was acidified with dilute hydrochloric acid to Congo red and chilled in the refrigerator overnight. The yield of colorless prisms melting 85–86° was 0.35 g. (45%). Lorenz[10] reported 3,4-methylenedioxyhydrocinnamic acid to melt at 84–85°.

*Anal.* Calcd. for $C_{10}H_{10}O_4$: neut. equiv., 194. Found: neut. equiv., 197.

*5,6-Methylenedioxybenzothiophene-2-carboxaldehyde* (IVb). The procedure of Campaigne and Archer[17] for preparation of 9-anthraldehyde was modified as follows: A mixture of 5 g. (0.028 mole) of III, 5 g. (0.068 mole) of dimethylformamide, 7 g. of phosphorus oxychloride, and 20 ml. of benzene was swirled just under boiling for 45 min. in a 100-ml. round bottomed flask fitted with reflux condenser and drying tube. After cooling to room temperature, the mixture was cautiously neutralized with aqueous sodium acetate and then poured into 750 ml. of water. The benzene was evaporated under an air stream and the product was collected on a Buchner funnel and recrystallized from absolute ethanol to give 2 g. (34%) of colorless needles which melted at 162–163°.

*Anal.* Calcd. for $C_{10}H_6O_3S$: S, 15.53. Found: S, 15.69.

*5,6-Methylenedioxybenzothiophene-2-carboxaldehyde oxime.* This derivative was found to melt at 198–200°, after one recrystallization from ethanol.

*Anal.* Calcd. for $C_{10}H_7O_3NS$: S, 14.50. Found: S, 14.54.

*5,6-Dimethoxybenzothiophene-2-carboxaldehyde* (IIb). A mixture of 2 g. (0.01 mole) of I,[4] 2 g. (0.027 mole) of dimethylformamide and 10 ml. of dioxane in a 25-ml. Erlenmeyer flask was treated with 3 ml. of phosphorus oxychloride, and worked up as described above. The product was recrystallized from 95% ethanol to give 0.6 g. (26%) of colorless needles melting at 153–154°.

*Anal.* Calcd. for $C_{11}H_{10}O_3S$: S, 14.40. Found: S, 14.33.

*5,6-Dimethoxybenzothiophene-2-carboxaldehyde oxime.* This derivative melted at 205–206°, after two recrystallizations from ethanol.

*Anal.* Calcd. for $C_{11}H_{11}NO_3S$: S, 13.50. Found: S, 13.35.

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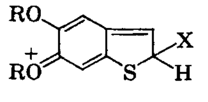
(15) (a) G. Cilento, *Chem. Rev.*, (2) **60**, 147 (1960). (b) A referee has kindly reminded us that the alternate approach of considering the resonance stabilization of the transition states, used by Bordwell and Stange (Ref. 3), leads to the same conclusions. Substitution at the 2-position is stabilized by the contribution of structures such as



The 5-substituent cannot be involved in similar structures having an oxygen doubly bonded to the ring. This additional stabilization would account for the preferential attack on the thiophene ring.

(16) All melting points are uncorrected.

(17) E. Campaigne and W. L. Archer, *J. Am. Chem. Soc.*, **75**, 989 (1953).

*Oxidation of* IVb. The procedure of Campaigne and LeSuer[18] was modified as follows: five grams of silver nitrate was dissolved in 150 ml. of distilled water, 3 g. of sodium hydroxide was added and the mixture was stirred to obtain a uniform suspension of silver oxide. One gram of formyl derivative was added and the mixture was stirred 45 min. on the steam bath at about 75°. The solid material was filtered and washed with dilute sodium hydroxide. The combined filtrates were acidified with dilute hydrochloric acid to Congo red and the product was collected and dried to give 1 g. (99%) of acid melting at 290–291° after one recrystallization from dioxane. Mixed melting point with 5,6-methylenedioxybenzothiophene-2-carboxylic acid was 289–291° (not depressed). The latter compound melts 290–291°.

*Anal.* Calcd. for $C_{10}H_6O_4S$: S, 14.40. Found: S, 14.30.

*Desulfurization of the oxidation product of* IVb. One gram of acid was treated with 4 g. of Raney nickel alloy in 70 ml. of 10% sodium hydroxide in the manner previously described. Cooling the acidified filtrate gave 0.45 g. (51%) of colorless prisms which melted at 84.5–86°. A mixed melting point with the compound obtained previously was 84.5–86° (not depressed).

*Oxidation of* IIb. The procedure is similar to that outlined for oxidation of the formyl derivative above. A 0.6-g. portion of aldehyde, added to a suspension formed by mixing 8 g. of silver nitrate and 50 ml. of 10% sodium hydroxide, gave 0.6 g. (99%) of an acid melting at 259–260°. The mixture melting point with an authentic sample of IId was 259–260°[4] (undepressed).

*5,6-Dimethoxy-2-benzothienyl methyl ketone* (IIc). To a solution of 1.65 g. (0.008 mole) of I and 0.9 g. (0.009 mole) of acetic anhydride in 25 ml. of dry chloroform was added 5 ml. of anhydrous stannic chloride with rapid stirring. The mixture was warmed 1 hr. at 60–70°. The green suspension was acidified strongly with 15% hydrochloric acid and boiled to decompose the complex. The aqueous layer was discarded and the chloroform layer was evaporated to dryness under an air stream. The residue was recrystallized from benzene (Norit) to give 1.6 g. (80%) of colorless plates melting at 131–132°.

*Anal.* Calcd. for $C_{12}H_{12}O_3S$: S, 13.55. Found: S, 13.60.

*5,6-Dimethoxy-2-benzothienyl methyl ketone oxime.* This oxime melted at 228–229°, after two recrystallizations from ethanol.

*Anal.* Calcd. for $C_{12}H_{13}NO_3S$: S, 12.75. Found: S, 12.71.

*5,6-Methylenedioxy-2-benzothienyl methyl ketone* (IVc). To a solution of 6 g. (0.034 mole) of III and 2.6 g. (0.034 mole) of acetyl chloride in 75 ml. of dry chloroform was added 9 g. (0.035 mole) of anhydrous stannic chloride with rapid stirring. A red solid formed as the temperature rose to 30° and was then allowed to fall slowly to room temperature over one hour. The suspension was acidified strongly with 15% hydrochloric acid and heated to decompose the complex. The aqueous layer was discarded; the organic layer was dried over anhydrous sodium sulfate, filtered, concentrated, and allowed to cool. Four and one-half grams of white flakes were deposited which melted 157–162°. Recrystallization from 95% ethanol gave 4 g. of pure white leaflets melting 169–170°. The mother liquors afforded an additional gram of material melting at 170°. The total yield was 5 g. (67%).

*Anal.* Calcd. for $C_{11}H_8O_3S$: S, 14.54. Found: S, 14.59.

*5,6-Methylenedioxy-2-benzothienyl methyl ketone oxime.* This derivative was found to melt at 212–212.5°, after two recrystallizations from ethanol.

*Anal.* Calcd. for $C_{11}H_9O_3NS$: S, 13.62. Found: S, 13.52.

*Haloform oxidation of the acetyl derivatives of 5,6-substituted benzothiophenes.* One-half gram of ketone was refluxed 1 hr. with 7 g. of iodine, 50 ml. of 10% sodium hydroxide solution and 30 ml. of dioxane. The solution was filtered hot, cooled to room temperature and the acid precipitated with 15% hydrochloric acid. Excess iodine was destroyed with aqueous sodium bisulfite. The precipitates were collected and recrystallized from methanol, giving sharp-melting products in about 80% yield. The mixed melting points with the corresponding benzothiophene-2-carboxylic acids were not depressed.

*2-Bromo-5,6-dimethoxybenzothiophene* (IIa). To a solution of 14 g. (0.072 mole) of I in 130 ml. of chloroform was added 13 g. (0.072 mole) of *N*-bromosuccinimide in small portions. The mixture was swirled to dissolve the solid and allowed to stand at room temperature overnight after which it was refluxed gently for 30 min. The succinimide was removed by extraction with several portions of boiling water and the chloroform was evaporated on the steam bath. The remaining dark red solid was recrystallized from 95% ethanol to give 18 g. (91%) of colorless leaflets of IIa melting 101–102°. A mixed melting point with the starting material was 71–76° (depressed). Bromination of I with bromine in glacial acetic acid gave a mixture of IIa plus higher bromination products which was difficult to separate.

*Anal.* Calcd. for $C_{10}H_9O_2SBr$: Br, 29.22. Found: Br, 29.21.

*2-Bromo-5,6-methylenedioxybenzothiophene* (IVa). To a solution of 3.5 g. (0.02 mole) of III and 25 ml. of dry chloroform in a 50-ml. round bottomed flask was added 3.5 g. (0.02 mole) of *N*-bromosuccinimide. The mixture was swirled for about 3 min. and cooled under the tap to keep the temperature below 30°. The solution was allowed to stand at room temperature for 5 hr. Long flat colorless needles deposited in the bottom of the flask and prisms of succinimide appeared on the meniscus of the liquid. The succinimide and supernatant liquid were poured off and the succinimide was separated by filtration. The product remaining in the flask weighed 3.0 g. and melted at 161–162° after one recrystallization from 95% ethanol. The filtrate from the reaction mixture was concentrated to give one additional gram melting at 160–161°. (A sassafras-like odor was noted when the compound was heated.) The total yield was 4.0 g. (78%).

*Anal.* Calcd. for $C_9H_5O_2SBr$: Br, 31.05. Found: Br, 31.09.

*Grignard carbonation of the bromo derivatives of 5,6-disubstituted benzothiophenes.* To prepare the Grignard reagent, 2.0 g. (*ca.* 0.0078 mole) of the bromo compound and 1.5 g. (0.015 mole) of methyl iodide in 50 ml. of dry ether were treated with 0.60 g. (0.025 mole) of magnesium turnings and allowed to react at room temperature for 2 hr. The ether solution was poured over 15 g. of crushed Dry Ice with vigorous stirring. The acid was liberated with 150 ml. of 5% hydrochloric acid, digested on the steam bath for a few minutes and collected. The filter cake was dissolved in dilute sodium hydroxide, filtered from insoluble material, reprecipitated with dilute hydrochloric acid, and recrystallized from toluene. In this way, IVa gave 1.1 g. (63%) of acid melting at 290–291°. A mixed melting point with authentic IVd was not depressed. Similarly, IIa gave 46% of an acid melting at 258–259° whose melting point was not depressed when mixed with authentic IId.

*4,5-Dimethoxybenzothiophene-2-carboxylic acid* (X). Ten grams (0.04 mole) of β-(2,3-dimethoxyphenyl)-α-mercaptoacrylic acid (prepared from 2,3-dimethoxybenzaldehyde according to Barltrop[19]) in 250 ml. of dioxane was added with stirring over a period of 12 hr. to a warm (75°) solution of 15 g. (0.06 mole) of iodine in 100 ml. of dioxane. Stirring was continued for an additional 12 hr. at the same temperature, after which the mixture was poured into 1.5 l. of water and decolorized with 5% sodium bisulfite solution. The brown precipitate was collected, reprecipitated several times (Norit) and finally recrystallized from aqueous dioxane to give 3 g. (30%) of pale yellow needles melting at 240–241°.

*Anal.* Calcd. for $C_{11}H_{10}O_4S$: S, 13.46. Found: S, 13.46.

*4,5-Dimethoxybenzothiophene* (XI). A 14-g. portion of crude 4,5-dimethoxybenzothiophene-2-carboxylic acid (X)

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(18) E. Campaigne and Wm. LeSuer, *J. Am. Chem. Soc.*, 70, 1555 (1948).

(19) J. A. Barltrop, *J. Chem. Soc.*, 958 (1946).

was heated with 5 g. of copper powder in 30 ml. of quinoline as described above for the 5,6-methylenedioxy derivative. The 10 g. of crude material was dissolved in petroleum ether (b.p. 30–60°), filtered, and distilled to give 6 g. (53% based on the crude acid) of product boiling at 138–140° (4 mm.).

*Anal.* Calcd. for $C_{10}H_{10}O_2S$: S, 16.51. Found: S, 16.24.

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BLOOMINGTON, IND.

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[CONTRIBUTION NO. 971 FROM THE LABORATORIES OF INDIANA UNIVERSITY]

# Preparation and Electrophilic Substitution Reactions of 6-Ethoxybenzothiophene[1]

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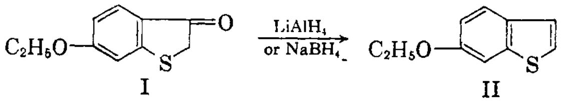
*Received May 31, 1960*

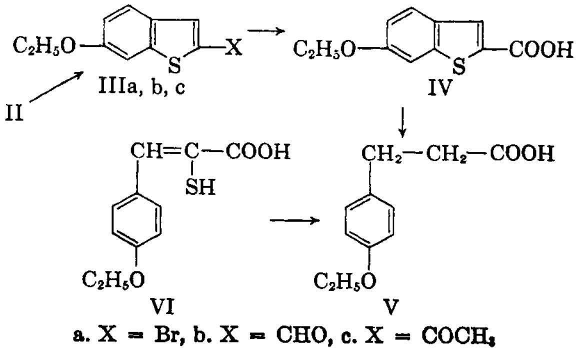
6-Ethoxybenzothiophene has been prepared in good yield by the hydride reduction of 6-ethoxy-3-hydroxybenzothiophene and has been subjected to the electrophilic substitution reactions, bromination, acetylation, and formylation. Substitution occurs principally at the 2-position in all cases, as had been predicted. This orientation can be rationalized on the basis of the relative stability of contributing resonance structures.

An investigation of the electrophilic substitution reactions of 5,6-dimethoxy- and 5,6-methylenedioxybenzothiophene[3] has indicated that these compounds orient predominately to the 2-position in the case of acetylation, bromination and formylation. This rather unexpected[4–6] result was rationalized on the basis of resonance stabilization of the carbanion adjacent to sulfur with expansion of the sulfur shell. This explanation suggested that the 6-alkoxyl (and not the 5- or a combination of the two) was responsible for the intermediate structure which gives rise to the activation at the 2-position; therefore it was predicted that a 6-alkoxybenzothiophene would also orient to the 2-position. Since substitution reactions of benzothiophenes having electron-releasing groups in only the 6-position have not previously been reported, it was necessary to investigate these for support of the hypothesis.

A sample of 6-ethoxythioindoxyl (I) was kindly provided by Imperial Chemical Industries, Ltd. Procedures for the reduction of thioindoxyls to benzothiophenes by zinc and glacial acetic acid[7] or amalgamate of mossy zinc and acetic acid[8] gave only dark oils which would not form a picrate even after distillation. Evidently the product was contaminated with a considerable amount of the 2,3-dihydro derivative. The successful reduction of I (69% yield) was accomplished with lithium aluminum hydride in ether or better yet (81%) with sodium borohydride in alkaline methanol. Considering the extra care which must be exercised with lithium aluminum hydride reactions and the better yield with borohydride, the latter procedure is preferable.



6-Ethoxybenzothiophene (II) was subjected to three electrophilic substitution reactions: acetylation, bromination, and formylation. In each case the 2-isomer was the only substitution product isolated. The orientation was shown by conversion of all products to the corresponding carboxylic acids which were found by mixed melting point and infrared spectral comparisons to be the same acid in each case. Since an authentic sample of 6-ethoxy-



a. X = Br, b. X = CHO, c. X = $COCH_3$

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[1] Taken from a portion of the thesis of W. E. K. submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, Indiana University, June 1960. Presented before the Organic Division at the 137th Meeting of the American Chemical Society, Cleveland, Ohio, April 1960.

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