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.

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

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

E. CAMPAIGNE AND W. E. KREIGHBAUM[2]

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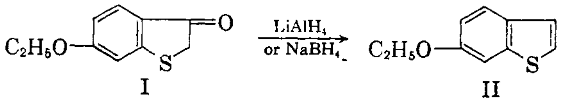
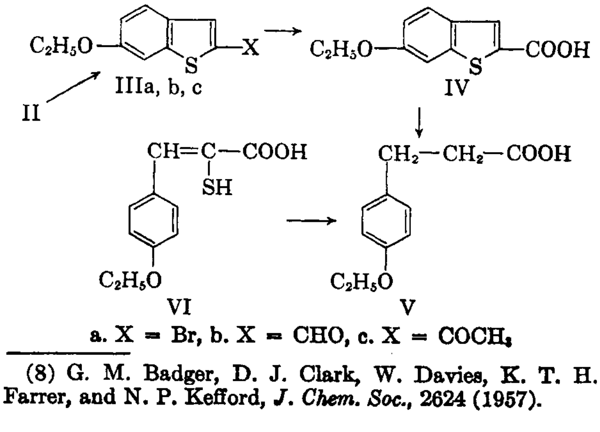
6-Ethoxybenzothiophene has been prepared in good yield by the hydride reduction of 6-ethoxy-3-hydroxybenzothiophene and has been subjected to the electrophilic substitution reactions, bromination, acetylation, and formylation. Substitution occurs principally at the 2-position in all cases, as had been 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.

[2] Lubrizol Fellow, 1959–60.

[3] E. Campaigne and W. E. Kreighbaum, *J. Org. Chem.*, **25**, 359 (1960).

[4] (a) F. G. Bordwell and Hugo Stange, *J. Am. Chem. Soc.*, **77**, 5939 (1955). (b) M. Martin-Smith and S. T. Reid, *J. Chem. Soc.*, 939 (1960).

[5] K. Fries, *Ann.*, **334**, 342 (1904).

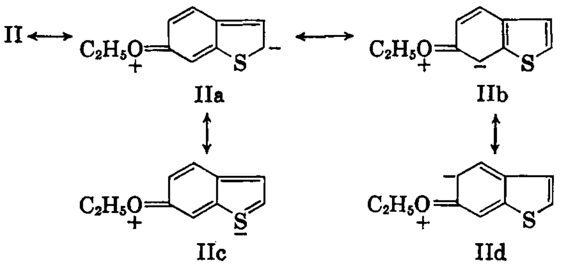
[6] Ng. Ph. Buu Hoï and D. Lavit, *J. Org. Chem.*, **21**, 21 (1956).

[7] D. S. Tarbell, D. K. Fukushima, and H. Dam, *J. Am. Chem. Soc.*, **67**, 1643 (1945).

[8] G. M. Badger, D. J. Clark, W. Davies, K. T. H. Farrer, and N. P. Kefford, *J. Chem. Soc.*, 2624 (1957).

benzothiophene-2-carboxylic acid (IV) could not be obtained from other sources for comparison, the acid derived from the substitution products was shown to be the 2-carboxylic acid by Raney nickel desulfurization to obtain a compound which did not depress the melting point of an authentic sample of *p*-ethoxyphenylpropionic acid (V). The latter was prepared unequivocally by hydrolysis of 5-(*p*-ethoxybenzylidene)rhodanine and Raney nickel desulfurization of the resulting β-(*p*-ethoxyphenyl)-α-mercaptoacrylic acid (VI). The infrared spectra of the two desulfurized products were also identical.

The substitution of 6-ethoxybenzothiophene in the 2-position, as predicted,[3] is in agreement with the rationalization that the 6-alkoxyl group is responsible for the observed substitution in 5,6-dialkoxybenzothiophenes, since a 5-alkoxyl group orients to the 4-position[4] while 6-alkoxyl or 5,6-dialkoxyl groups orient to the 2-position.[3] Apparently the stabilization of IIa due to resonance of the carbanion adjacent to sulfur (IIc) is sufficient to cause the 2-position to be more nucleophilic than either than 5- or the 7-positions, IId and IIb, respectively.



EXPERIMENTAL[9,10]

Purification of 6-ethoxy-3-hydroxybenzothiophene (I). The crude sample from I.C.I. Ltd. was recrystallized from water to give flat, colorless needles melting at 123–125°. Friedlander[11] reported the compound to melt at 124–125°.

Anal. Calcd. for $C_{10}H_{10}O_2S$: S, 16.48. Found: S, 16.45.

Preparation of 6-ethoxybenzothiophene (II) *using lithium aluminum hydride.* 6-Ethoxy-3-hydroxybenzothiophene (I.C.I.) (10.9 g. or 0.05 mole) was dissolved in 350 ml. of ether in a 1-l. round-bottomed flask fitted with stirrer, condenser, and dropping funnel. A solution of 1.9 g. (0.05 mole—a substantial excess) of lithium aluminum hydride in 250 ml. of ether was added dropwise at a rate such that the mixture refluxed gently. The mixture was stirred during and for 1 hr. after the addition was complete and was finally allowed to stand at room temperature overnight. Excess aqueous ethanol was added very cautiously with stirring to decompose the excess hydride and the mixture was acidified strongly with 10% sulfuric acid by adding the latter slowly through the dropping funnel with vigorous stirring. The mixture (two layers) was filtered to remove a red insoluble material. The ether layer was separated, dried over anhydrous sodium sulfate and distilled from a side-arm flask. The product, boiling at 138–140° (6 mm.) weighed 7 g. (69%) and crystallized upon standing. One recrystallization from petroleum ether (b.p. 30–60°) gave beautiful colorless slabs melting at 40–41°.

Anal. Calcd. for $C_{10}H_{10}OS$: S, 17.95. Found: S, 17.82.

6-Ethoxybenzothiophene picrate. This derivative was recrystallized as orange needles from ethanol and melted at 114.5–115.0°.

Anal. Calcd. for $C_{16}H_{13}N_3O_8S$: N, 10.31. Found: N, 10.50.

Preparation of 6-ethoxybenzothiophene using sodium borohydride. To a solution of 14.2 g. (0.066 mole) of 6-ethoxy-3-hydroxybenzothiophene (I.C.I.) in 300 ml. of methanol containing 50 ml. of 10% sodium hydroxide solution was added a solution of 2.54 g. (0.065 mole) of sodium borohydride in 50 ml. of methanol and 15 ml. of 10% sodium hydroxide solution. The mixture was refluxed in a 1-l. round-bottomed flask for 1 hr. on the steam bath and allowed to stand just under boiling for 12 hr. The solution was concentrated to 200 ml. and acidified cautiously with 10% sulfuric acid (Congo Red). The mixture was cooled and diluted to 700 ml. with water. Extraction with benzene and evaporation of the extracts gave the crude benzothiophene which was dissolved in hexane and filtered to remove some tarry material. The hexane solution was distilled from a side-arm flask to give 10.5 g. (81%) of product which boiled at 138–140° (6 mm.). The distillate solidified and was recrystallized from petroleum ether (b.p. 30–60°) to give colorless prisms melting at 41–42°.

2-Bromo-6-ethoxybenzothiophene (IIIa). One gram (0.0056 mole) of 6-ethoxybenzothiophene was dissolved in 10 ml. of dry chloroform and 1 g. (0.0056 mole) of *N*-bromosuccinimide was added. The mixture was refluxed 1 hr. and allowed to stand overnight. The succinimide was removed by extraction with several portions of boiling water; the chloroform was evaporated under an air stream and the product was recrystallized once from methanol to give 1.2 g. (69%) of long colorless needles which melted at 75.5–76.5°. The analytical sample was recrystallized once more from petroleum ether and melted sharply at 77°.

Anal. Calcd. for $C_{10}H_9OSBr$: S, 12.45; Br, 31.13. Found: S, 12.48; Br, 31.10.

Grignard carbonation of 2-bromo-6-ethoxybenzothiophene to form 6-ethoxybenzothiophene-2-carboxylic acid (IV). Nine-tenths gram (0.0035 mole) of 2-bromo-6-ethoxybenzothiophene (IIIa), 0.6 g. of magnesium turnings, and 1 g. of methyl iodide in 50 ml. of dry ether were allowed to react without external heating for 3 hr. (A crystal of iodine was added to start the reaction.) The mixture was concentrated to 25 ml. and poured onto excess powdered Dry Ice. The slurry was stirred well for 2 min. and acidified strongly with 10% sulfuric acid. The ether was allowed to evaporate and the precipitate was collected and washed well with water. The solid material was dissolved in dilute base, and the solution treated with Norit and filtered. The filtrate was acidified to give 0.6 g. (77%) of acid which was recrystallized twice from aqueous ethanol to give colorless needles melting at 221°.

Anal. Calcd. for $C_{11}H_{10}O_3S$: S, 14.40. Found: S, 14.35.

Desulfurization of 6-ethoxybenzothiophene-2-carboxylic acid. Four-tenths gram of the carboxylic acid obtained in the preceding experiment was dissolved in a mixture of 20 ml. of 10% sodium hydroxide solution and 15 ml. of water. Two grams of Raney nickel alloy was added in small portions with vigorous swirling over a period of 30 min. The mixture was finally heated on the steam bath for 2 hr. and filtered. The filtrate was strongly acidified (Congo Red) and chilled overnight to give 0.2 g. (57%) of acidic material melting at 95–97° after one recrystallization from aqueous ethanol and 102–103° after two more recrystallizations from carbon tetrachloride. Bougault[12] reported 4-ethoxyphenylpropionic acid (V) to melt at 104°.

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(9) All melting points were determined in open capillaries on an uncalibrated thermometer and are not corrected for stem exposure.

(10) The infrared spectra were determined in potassium bromide with a Perkin-Elmer Infracord.

(11) P. Friedlander, *Ber.*, **49**, 955 (1916).

(12) J. Bougault, *Comp. rend.*, **131**, 44 (1900).

6-Ethoxybenzothiophene-2-carboxaldehyde (IIIb). Two grams (0.011 mole) of 6-ethoxybenzothiophene, 2.0 g. (0.026 mole) of dimethylformamide and 3.0 g. of phosphorus oxychloride were dissolved in 10 ml. of dioxane and allowed to stand at room temperature for 2 hr. The mixture was heated at 70° for 3 hr. and poured into an aqueous solution of excess sodium acetate. After the mixture had been allowed to stand overnight, the precipitate was collected and recrystallized from dilute ethanol to give 0.8 g. (34%) of light straw-colored needles melting at 99°.

Anal. Calcd. for $C_{11}H_{10}O_2S$: S, 15.52. Found: S, 15.44.

6-Ethoxybenzothiophene-2-carboxaldehyde oxime. This derivative was found to melt at 171°.

Anal. Calcd. for $C_{11}H_{11}NO_2S$: S, 14.47. Found: S, 14.39.

Oxidation of the formyl derivative of 6-ethoxybenzothiophene. A 0.1-g. portion (0.0003 mole) of the aldehyde (IIIb) was added to a suspension formed by mixing 0.8 g. of silver nitrate and 0.5 g. of sodium hydroxide in 15 ml. of water. The mixture was heated on the steam bath for 1 hr. and filtered. The filtrate was acidified and the precipitate was recrystallized from ethanol to give 70 mg. (70%) of colorless needles melting at 221°. A mixed melting point with the acid obtained from the bromo derivative was not depressed, and their infrared spectra were identical.

6-Ethoxy-2-benzothienyl methyl ketone (IIIc). One gram (0.0056 mole) of 6-ethoxybenzothiophene (II) and 0.60 g. (0.0059 mole) of acetic anhydride were dissolved in 25 ml. of chloroform and 5 ml. of anhydrous stannic chloride was added. The green solution was warmed at 60° for 0.5 hr. after which 40 ml. of 10% hydrochloric acid was added and the mixture was boiled to decompose the complex. The organic layer was separated and evaporated to dryness to afford tan crystals which were recrystallized from 95% ethanol to give 1.0 g. (80%) of flat colorless needles melting at 107–108°.

Anal. Calcd. for $C_{12}H_{12}O_2S$: S, 14.53. Found: S, 14.47.

6-Ethoxy-2-benzothienyl methyl ketone oxime. This derivative melted at 178–179°.

Anal. Calcd. for $C_{12}H_{13}NO_2S$: S, 13.61. Found: S, 13.70.

Haloform oxidation of 6-ethoxy-2-benzothienyl methyl ketone. One-tenth gram of the ketone (IIIc) was refluxed 1 hr. with 1 g. of iodine, 5 ml. of dioxane, and 10 ml. of 10% sodium hydroxide solution. The reaction mixture was diluted with water, filtered, and acidified. The excess iodine was destroyed with 5% sodium bisulfite. The precipitate was collected and recrystallized from aqueous ethanol to give 40 mg. (40%) of white needles melting at 220–221°. A mixed melting point with the product obtained from the bromo derivative was not depressed, and their infrared spectra were identical.

5-(p-Ethoxybenzylidene)rhodanine. Five grams (0.033 mole) of *p*-ethoxybenzaldehyde (Aldrich Chemical Co.) was condensed with 5 g. of rhodanine in 40 ml. of glacial acetic acid using 10 g. of fused sodium acetate as catalyst, according to the method of Julian and Sturgis.[13] Isolation in the prescribed manner gave 8 g. (91%) of rhodanine derivative which was recrystallized from ethanol as yellow needles melting at 225–226°.

Anal. Calcd. for $C_{12}H_{11}NO_2S_2$: S, 24.15. Found: S, 24.19.

β-(p-Ethoxyphenyl)-α-mercaptoacrylic acid (VI). Eight grams (0.019 mole) of 5-(*p*-ethoxybenzylidene)rhodanine was hydrolyzed in 100 ml. of 10% sodium hydroxide on the steam bath for 0.5 hr. Isolation as described in reference 13 and recrystallization from acetone-ethanol gave 5 g. (62%) of orange prisms melting at 181–183° with gas evolution.

Anal. Calcd. for $C_{11}H_{12}O_3S$: S, 14.30. Found: S, 14.35.

Desulfurization of β-(p-ethoxyphenyl)-α-mercaptoacrylic acid. The procedure was the same as for desulfurization of 6-ethoxybenzothiophene-2-carboxylic acid above. One gram of the mercaptoacrylic acid was dissolved in 30 ml. of 10% sodium hydroxide solution and 10 ml. of water and treated with 4 g. of Raney nickel alloy. Workup as described above and several recrystallizations from aqueous ethanol gave 0.45 g. (55%) of colorless needles melting at 102°. A mixed melting point with the product obtained from IV was 102–103° (not depressed), and their infrared spectra were identical.

BLOOMINGTON, IND.

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(13) P. L. Julian and B. M. Sturgis, *J. Am. Chem. Soc.*, 57, 1126 (1935).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF COLORADO]

The Addition of *p*-Thiocresol to Two Conjugated Dienes

STANLEY J. CRISTOL AND KRISHEN L. NAGPAL

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Free-radical addition of *p*-thiocresol to 3-methylenecyclohexene (II) and to 1,2-dimethylenecyclohexane (I) led solely to the 1,4-addition products 1-cyclohexenylmethyl *p*-tolyl thioether (V) and 2-methyl-1-cyclohexenylmethyl *p*-tolyl thioether (III), respectively, no detectable amounts of the 1,2-addition products being formed. Comparison samples of the thioethers were prepared by alternative syntheses involving displacement reactions, as were the isomeric thioethers, 3-cyclohexenylmethyl *p*-tolyl thioether (VI) and 2-methylenecyclohexylmethyl *p*-tolyl thioether (IV); these isomers would have been formed had 1,2-addition obtained.

Free-radical addition of *p*-thiocresol to butadiene gave a 1:1 addition product which appeared to be largely the 1,4-addition product, *trans*-crotyl *p*-tolyl thioether,[1] little or no 1,2-addition product being formed. In order to test whether 1,4-*vs.* 1,2- addition might be affected by the *cis* or *trans* nature of the final product (and thus possibly of the intermediate radical), we have studied the addition of thiocresol to 1,2-dimethylenecyclohexane (I) and to 3-methylenecyclohexene (II). Of the possible addition products to I, the 1,4-addition product III appeared to be formed exclusively, no 1,2-addition product (IV) being noted. Similarly addition to II led to V with no evidence for VI in the product, although infrared spectra of V and VI were too similar to be certain that no VI was present.

Samples of III–VI were prepared by straightforward syntheses. III was prepared by reaction

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(1) J. A. Reeder, Ph.D. thesis, University of Colorado, 1958.