evaporated, and the oily residue dissolved in ligroin. The isomeric diol (3β,12α-ursanediol) separated on chilling, m.p. 165.8–167°, 3.59 g. The analytical sample was obtained from ether–ligroin, large white blades, m.p. 169.9–170.4° (evac.), $\alpha_D$ +10.2° (*c* 1.87); $\lambda_{max}^{KBr}$ 2.92–2.97 μ (s), no C=O band, 9.75 μ (s), 9.99–10.03 μ (s), 10.14 μ (m), 10.25 μ (m).

*Anal.* Calcd. for $C_{30}H_{52}O_2$ (444.72): C, 81.02; H, 11.79. Found: C, 81.19; H, 12.07.

The diol forms a diacetate under conditions where the above 12-isomeric diol forms a monoacetate; translucent crystals from methanol, m.p. 205.2–206.4° (evac.), $\alpha_D$ −1.2° (*c* 2.11), $\lambda_{max}^{KBr}$ 5.77 μ (s).

*Anal.* Calcd. for $C_{34}H_{56}O_4$ (528.79): C, 77.22; H, 10.67. Found: C, 77.26; H, 10.58.

A mixture of the 3-mono- and 3,12-diacetates was obtained if acetylation was conducted at 100° for 8 min. These are separable by chromatography. The monoacetate was purified by crystallization from methanol–benzene, m.p. 274.4–276.2° (evac.), $\alpha_D$ +17.8° (*c* 1.49); $\lambda_{max}^{KBr}$ 2.82 μ (s), 5.78 μ (s), 9.79 μ (s), 9.95 μ (s), 10.10 μ (w).

*Anal.* Calcd. for $C_{32}H_{54}O_3$ (486.75): C, 78.96; H, 11.18. Found: C, 78.53; H, 10.90.

Under conditions which convert α-amyrin into the mesylate, this monoacetate affords α-amyrin acetate.

**Reduction of 3β-Acetoxy-12-keto-13-isoursane.**—The unstable keto acetate (1.0 g.) was reduced with lithium aluminum hydride by the method described for the stable keto acid to give a **3,12-diol**, m.p. 189.8–190.6°, 0.545 g. Crystallized ether–ligroin, m.p. 191.6–192.8° (evac.), $\alpha_D$ +52.0° (*c* 2.03); $\lambda_{max}^{KBr}$ 2.98 μ (s), no C=O band, 9.73 μ (s), 10.08 μ (s).

*Anal.* Calcd. for $C_{30}H_{52}O_2$ (444.72): C, 81.02; H, 11.79. Found: C, 80.90; H, 11.82.

The same diol was obtained on reduction of 3β-benzoyloxy-12-keto-13-isoursane ("α-amyrin benzoate oxide"[4]).

On acetylation, acetic anhydride–pyridine, at room temperature for 25 hr., a mixture of 3-mono- and 3,12-diacetates resulted, separable by chromatography. The **3,12-diacetate**, eluted with 3:1 and 2:1 petroleum ether–benzene, was purified by crystallization from methanol; m.p. 163–165.5°, $\alpha_D$ +49.7° (*c* 1.96), $\lambda_{max}^{KBr}$ 5.76 μ (s).

*Anal.* Calcd. for $C_{34}H_{56}O_4$ (528.79): C, 77.22; H, 10.67. Found: C, 76.76; H, 10.37.

**The 3-monoacetate**, eluted with 2:1 petroleum ether–benzene, formed white needles from methanol, m.p. 234–236° (evac.), $\alpha_D$ +62.7° (*c* 2.13[24]); $\lambda_{max}^{KBr}$ 2.83 μ (s), 5.77 μ (s), 9.81 μ (s), 10.01 μ (s), 10.20 μ (w).

*Anal.* Calcd. for $C_{32}H_{54}O_3$ (486.75): C, 78.96; H, 11.18. Found: C, 78.91; H, 11.02.

(24) Literature m.p. 234–235°, $\alpha_D$ +66° (*c* 1.7).[5]

CAMBRIDGE, MASSACHUSETTS

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

# Benzothiophene Chemistry. VII. Substitution Reactions of 5-Hydroxy- and 5-Aminobenzothiophene Derivatives

BY F. G. BORDWELL AND HUGO STANGE[1]

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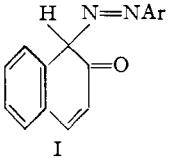
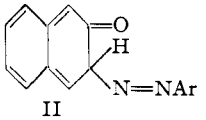
Electrophilic substitution in 5-hydroxy-, 5-acetamido-, and 5-aminobenzothiophene was found to occur at the 4-position. This is analogous to the behavior of similarly substituted naphthalene derivatives. Unlike 2-naphthol, 5-hydroxybenzothiophene undergoes reactions at both positions *ortho* to the hydroxyl group under nearly the same conditions. When the sulfur atom in benzothiophene is oxidized to the sulfone stage, orientation in the benzene ring is changed from predominant 4-substitution to predominant 6-substitution. The results are rationalized in terms of current theory.

The strong preference for α-substitution by electrophilic reagents observed in naphthalene, β-naphthol and many other naphthalene derivatives is well known.[2] This orientation appears to be best correlated at present with the relative stability of possible intermediate addition complexes formed in such reactions.[3] For example, the much greater rate of coupling of β-naphthol at the 1-position as compared to the 3-position corresponds to a greater stability for the intermediate I as compared to II.



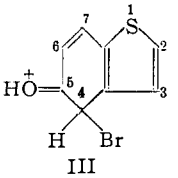
I



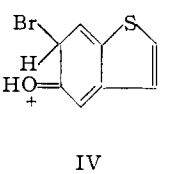
II

This difference in stability can be used to account not only for the position of coupling, but also for the formation of 1,1-dichloro-2-keto-1,2-dihydronaphthalene rather than 1,3-dichloro-2-naphthol in the chlorination of 1-chloro-2-naphthol, and for the expulsion of $Br^+$ from an intermediate similar to I rather than $H^+$ from an intermediate similar to II in coupling reactions of 1-bromo-2-naphthol.[4] The difference in stability of I and II is presumably dependent on the aromatic system in type I as compared to the conjugated polyene system of type II.[3]

It seemed worthwhile to us to compare the reactions of 5-hydroxybenzothiophene and related compounds with those of the corresponding naphthalene derivatives to see whether or not strong preferential orientation effects would also be found in this system. Preferential 4-substitution in 5-hydroxybenzothiophene might be anticipated since, for example, in bromination the stability of intermediate III, which contains a thiophene ring, should exceed that of IV, which contains a conjugated triene system.



III



IV

The necessary 5-substituted benzothiophenes

(1) Heyden Chemical Corp. Fellow, 1946–1948; Northwestern University Fellow, 1948–1949.

(2) See the data given by L. F. Fieser and M. Fieser in "Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1944, pp. 760–770.

(3) See the discussion by M. J. S. Dewar in "Electronic Theory of Organic Chemistry," Oxford University Press, New York, N. Y., 1949, pp. 173–176.

(4) T. Hewitt and H. V. Mitchell, *J. Chem. Soc.*, **89**, 1167 (1906).

were prepared from 5-nitrobenzothiophene, which was obtained by a modification of the route used in previous investigations.[5-7]

Mononitration of 5-acetamidobenzothiophene, and monobromination of 5-acetamido-, 5-amino- and 5-hydroxybenzothiophene occurred predominantly in the 4-position, which is analogous to the reactions of similar naphthalene derivatives.

The structure of the nitration product was established as 5-acetamido-4-nitrobenzothiophene by hydrolysis of the amide, and reductive deamination of the amine to 4-nitrobenzothiophene.[8] Reduction of 4-nitrobenzothiophene to 4-aminobenzothiophene and conversion to 4-hydroxybenzothiophene, which has been synthesized in an unequivocal manner,[6] completed the structure proof.

The structure of the bromination product of 5-aminobenzothiophene was established by reductive deamination to 4-bromobenzothiophene, which was characterized by oxidation to the solid 1-dioxide. An authentic sample of 4-bromobenzothiophene was prepared from 4-aminobenzothiophene by the Sandmeyer reaction. A monobromination derivative of 5-aminobenzothiophene was prepared previously,[5b] but evidence for the structure of the compound was lacking.

The structure of the monobromination derivative of 5-hydroxybenzothiophene, which also has been reported previously,[5b] was established by preparation of the same compound from 5-amino-4-bromobenzothiophene.

Bromination of 5-acetoxybenzothiophene gave 5-acetoxy-3-bromobenzothiophene, as was shown by its conversion to 3-bromo-5-hydroxybenzothiophene, which was prepared also from 5-amino-3-bromobenzothiophene. The structure of the amino compound already has been established.[7b] The heterocyclic ring in benzothiophene is considerably more reactive toward substitution than the benzene ring, as is indicated by rapid bromination or chlorination to 2,3-dihalobenzothiophenes.[9] The bromination of 5-acetoxybenzothiophene in the 3-position shows that it is necessary to have a more strongly activating substituent than acetoxyl (*e.g.*, amino, acetamido or hydroxyl) in the benzene ring in order to favor substitution in that ring.

The dibromo derivative prepared from 5-hydroxybenzothiophene,[5b] cannot be 3,4-dibromo-5-hydroxybenzothiophene, as originally supposed[5b] since our results show that the 3,4-dibromo compound has a melting point 40° above that previously reported.[5b] The most reasonable structure for this dibromo compound is then 4,6-dibromo-5-hydroxybenzothiophene. The quinone prepared from this dibromide must then be 6-bromo-4,5-benzothioquinone.[10]

5-Hydroxybenzothiophene was found to resemble phenol[11] rather than 2-naphthol[12] in its ability to undergo two successive rearrangements when converted to the allyl ether. 5-Allyloxybenzothiophene underwent rearrangement upon heating in dimethylaniline to give a product assumed to be 4-allyl-5-hydroxybenzothiophene. When 4-allyl-5-allyloxybenzothiophene was heated in dimethylaniline a second rearrangement occurred. Even with longer heating periods than used for the first rearrangement a greater portion of unrearranged material was recovered in the second reaction.

4-Allyl-5-hydroxybenzothiophene gave a positive color test with diazotized sulfanilic acid. Since a negative test was obtained with 4,6-diallyl-5-hydroxybenzothiophene, this indicates that a coupling reaction may occur at the 6-position in 4-allyl-5-hydroxybenzothiophene. A positive test was obtained also with 4-bromo-5-hydroxybenzothiophene, but this may result from coupling in the 4-position with replacement of $Br^+$, as occurs with 1-bromo-2-naphthol.[4]

These mono- and disubstitution reactions show that substitution occurs in the 4-position of benzothiophene derivatives in preference to the 6-position. This is in keeping with the well-known predominance of $\alpha$-substitution observed with naphthalene derivatives.[2] In terms of current theory[3] it corresponds to postulation of a type III intermediate having greater stability and tendency to form than a type IV intermediate. Successful substitution in the 6-position, when the 4-position is blocked, occurs under conditions not much more strenuous than those used to introduce groups into the 4-position. This is in contrast to the behavior of the corresponding 2-naphthalene derivatives, which show a much greater reluctance to undergo substitution in the 3-position than in the 1-position.[2] This may be interpreted as indicating a smaller difference in stability between intermediates of type III and IV than between I and II. This conclusion is in line with that arrived at from a study of the oxidation–reduction potentials of quinones in the benzene, benzothiophene, and naphthalene series, where it was decided that benzothiophene has an aromatic character intermediate between that of benzene and naphthalene,[6] and with the greater resonance energy of benzene as compared to thiophene.

Oxidation of the sulfur atom of the benzothiophene derivatives to the sulfone stage has a striking effect on the orientation in these molecules. Nitration of 5-acetamidobenzothiophene 1-dioxide gave predominantly 6-nitro-5-acetamidobenzothiophene 1-dioxide, as was shown by hydrolysis and reductive deamination of the product to 6-nitrobenzothiophene 1-dioxide. Similarly, bromination of 5-

(5) (a) K. Hemmecke, Dissertation, Braunschweig, 1929; (b) K. Fries, H. Heering, K. Hemmecke and G. Siebert, *Ann.*, **527**, 83 (1936).

(6) L. F. Fieser and R. G. Kennelly, THIS JOURNAL, **57**, 1611 (1935).

(7) (a) C. J. Albisetti, Jr., Ph.D. Dissertation, Northwestern University, 1947; (b) F. G. Bordwell and C. J. Abisetti, Jr., THIS JOURNAL, **70**, 1955 (1948).

(8) This compound was found to be identical with the product prepared by the action of ammonium sulfide on the dinitrobenzothiophene, m.p. 197–198°, prepared by nitrating 3-nitrobenzothiophene and separating the isomers according to the directions of Fries and coworkers.[5b] This establishes the structure of the dinitro compound as 3,4-dinitrobenzothiophene, which is the structure previously assigned to it.[5b]

(9) G. Komppa, *J. prakt. Chem.*, **122**, 323 (1929). The halogens in the dibromo- and dichlorobenzothiophenes prepared by Komppa have been shown to be in the 2- and 3-positions by B. B. Lampert, Doctoral Dissertation, Northwestern University, 1951.

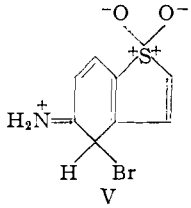
(10) These structures for the dibromo compound and related quinone recently have been established unequivocally by M. Martin-Smith, Doctoral Dissertation, University of Rochester, 1954.

(11) L. Claisen, *Ber.*, **45**, 3157 (1912).

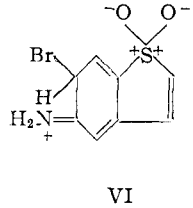
(12) L. Claisen, *Ann.*, 91 (1919).

aminobenzothiophene 1-dioxide gave 6-bromo-5-aminobenzothiophene 1-dioxide. The structure was established by reductive deamination of the product followed by hydrogenation to give 6-bromo-2,3-dihydrobenzothiophene 1-dioxide. An authentic sample of the latter was prepared from 6-nitrobenzothiophene 1-dioxide by reduction to 6-amino-2,3-dihydrobenzothiophene 1-dioxide followed by a Sandmeyer reaction.

This decisive change in orientation coincides with the loss of aromaticity of the thiophene ring on oxidation.[13] Intermediate V is not stabilized relative to VI by the aromaticity of a heterocyclic ring, as was true of III as compared to IV. Instead, the relative stabilities of V and VI must be governed



V



VI

by the factors which lead to predominant substitution in a position *para* to negatively substituted vinyl groups.[14]

## Experimental[15]

**2-Chloro-5-nitrobenzaldehyde.**—Some of this material was kindly furnished by the Heyden Chemical Corporation. Additional quantities were prepared by the method of Erdmann.[16] It was found advantageous to dry this material by azeotropic distillation of the water with benzene. An explosion occurred during an attempted distillation under reduced pressure.

**2-Chloro-5-nitrobenzaldehyde Ethyl Acetal.**—A mixture of 66 g. (0.35 mole) of 2-chloro-5-nitrobenzaldehyde, 57 g. (0.39 mole) of ethyl orthoformate, 0.75 g. of ammonium chloride and 63 ml. of dry ethanol was refluxed for 30 min. The acetal was collected at 142–145° (2–3 mm.). The yield was 82 g. (89%). A redistilled middle fraction, b.p. 142–143° (2 mm.), $n^{20}D$ 1.5312, $d^{31}_4$ 1.2344, was analyzed.

*Anal.* Calcd. for $C_{11}H_{14}ClNO_4$: C, 50.87; H, 5.43. Found: C, 50.88; H, 5.43.

**5-Nitrobenzothiophene.**—The method previously[5–7] developed was shortened by preparing the solution of the sodium salt of 2-mercapto-5-nitrobenzaldehyde directly (without preparation of the disulfide) by adding the alcoholic solution of 2-chloro-5-nitrobenzaldehyde to a well-stirred equivalent solution of sodium sulfide (Hooker Electrochemical Co.) using an efficient reflux condenser which is not easily flooded. Either sodium chloroacetate or ethyl chloroacetate can be used in the second step. Slightly better yields were obtained using ethyl chloroacetate. The yield of 5-nitro-2-benzothiophenecarboxylic acid was 22–38%. After decarboxylation, 5-nitrobenzothiophene was recovered by extraction of the solids with ether rather than acetone.[7] The ether dissolved less colored impurities.

Attempts to improve the synthesis by the use of 2-chloro-5-nitrobenzaldehyde ethyl acetal were unsuccessful.

**5-Aminobenzothiophene.**—Hydrogenation was found more convenient than chemical reduction.[5–7] Hydrogenation at 2 atm. of 5.0 g. (0.028 mole) of 5-nitrobenzothiophene in 100 ml. of dry ethanol in the presence of 0.5 g. of 5% palladium-on-charcoal was complete in one hour. Subsequent to this work hydrogenation using Raney nickel has been reported.[17]

**5-Acetoxybenzothiophene.**—To a solution of 4.1 g. (0.027 mole) of 5-hydroxybenzothiophene[5,6] in 35 ml. of benzene was added 2.8 g. (0.027 mole) of acetic anhydride. After one hour reflux and solvent removal, 5.1 g. (97%) of 5-acetoxybenzothiophene, m.p. 69°, was recovered. After one recrystallization from ethanol it melted at 70°.

*Anal.* Calcd. for $C_{10}H_8O_2S$: C, 62.48; H, 4.20. Found: C, 62.24; H, 4.20.

**5-Acetamido-4-nitrobenzothiophene.**—To 7.3 g. (0.038 mole) of 5-acetamidobenzothiophene[5] in 30 ml. of acetic acid cooled in an ice-bath was added 2.5 ml. (0.039 mole) of concd. nitric acid. After allowing the mixture to stand for 4 hr. at room temperature, 7.8 g. (87%) of crude product, m.p. 115–127°, was precipitated by pouring the solution into excess ice and water. Recrystallization from 50 ml. of ethanol gave 6.3 g. (70%) of pure product, m.p. 131–132°. The product also may be recrystallized from Skellysolve C, and is soluble in benzene and acetic acid.

*Anal.* Calcd. for $C_{10}H_8N_2O_3S$: C, 50.84; H, 3.41. Found: C, 50.65; H, 3.39.

**5-Acetamido-4-nitrobenzothiophene 1-Dioxide. Preparation of 1-Dioxide Derivatives.**—The 1-dioxide derivatives of benzothiophene compounds were prepared by treatment of a solution of 0.25 g. of the benzothiophene compound in 3 ml. of acetic acid with 1–3 ml. of 30% hydrogen peroxide. The mixture was heated for one hour on a steam-bath. The derivative precipitated upon the addition of excess water.

The yield of 5-acetamido-4-nitrobenzothiophene 1-dioxide was 67%. After two recrystallizations from ethanol it decomposed at 227°.

*Anal.* Calcd. for $C_{10}H_8N_2O_5S$: C, 44.77; H, 3.01. Found: C, 45.07; H, 3.13.

**5-Amino-4-nitrobenzothiophene.**—5-Acetamido-4-nitrobenzothiophene (3.5 g., 0.015 mole) was hydrolyzed by heating for 15 min. with an equivalent of sodium hydroxide in 55 ml. of 90% ethanol. After adding 75 ml. of water 2.8 g. (97%) of product, m.p. 186–187°, was collected. Recrystallization from methanol gave yellow needles, m.p. 190°.

*Anal.* Calcd. for $C_8H_6N_2O_2S$: N, 14.43. Found: N, 14.46.

**4-Nitrobenzothiophene.**—A suspension of 4.1 g. (0.021 mole) of 5-amino-4-nitrobenzothiophene was dissolved in 100 ml. of sulfuric acid (50% by volume) by heating and was diazotized with 1.5 g. (0.022 mole) of sodium nitrite at 0°. Eight ml. of 50% hypophosphorous acid was added, and the solution kept overnight at 0° and for an additional 8 hr. at room temperature. The product was isolated by chloroform extraction (300 ml.). The extract was washed with 10% sodium hydroxide solution to remove colored impurities. The residue weighed 2.55 g. (67%), m.p. 72–78°. Recrystallization from Skellysolve C gave 1.95 g. (47%) of product, m.p. 80–82°.

4-Nitrobenzothiophene also was prepared by the method of Fries, *et al.*[5b] A yield of 1.9 g. (77%) of product, m.p. 78–81°, was obtained from 3.1 g. (0.014 mole) of 3,4-dinitrobenzothiophene. After recrystallization from Skellysolve C the product melted at 84–85° (reported[5b] 88°). A mixed melting point of 4-nitrobenzothiophene prepared by the two methods was 82–83°.

**4-Nitrobenzothiophene 1-Dioxide.**—The 1-dioxide derivative was prepared from 4-nitrobenzothiophene made from 5-amino-4-nitrobenzothiophene. The yield of the derivative, m.p. 167–172°, was 85%. After four recrystallizations from ethanol it melted at 177–178°.

*Anal.* Calcd. for $C_8H_5NO_4S$: N, 6.63. Found: N, 6.62.

The dioxide also was prepared from 4-nitrobenzothiophene made from 3,4-dinitrobenzothiophene. The yield of product, m.p. 167–172°, was 72%. After one recrystallization it melted at 174–175°. A mixed melting point of the two products was 174–176°.

**4-Aminobenzothiophene.**—In addition to the method of Fries, *et al.*,[5b] this compound also was prepared by catalytic hydrogenation. The hydrogenation of 2.0 g. (0.01 mole) of 4-nitrobenzothiophene in 30 ml. of ethanol with 0.2 g. of 5% palladium-on-charcoal was complete in 2 hr. using a Parr low pressure hydrogenation apparatus. Only 4-nitrobenzothiophene prepared from 5-amino-4-nitrobenzothiophene could be hydrogenated. Traces of ammonium sulfide in the 4-nitrobenzothiophene prepared from 3,4-dinitrobenzothiophene are believed to have poisoned the catalyst.

(13) F. G. Bordwell and W. H. McKellin, THIS JOURNAL, **72**, 1985 (1950).

(14) F. G. Bordwell and K. Rohde, *ibid.*, **70**, 1191 (1948).

(15) All melting points were taken on a Fisher–Johns melting point apparatus. Microanalyses were performed by Misses V. Hobbs, M. Ledyard, M. Nielsen and J. Sorensen.

(16) H. Erdmann, *Ann.*, **272**, 148 (1893).

(17) K. Rabindran, A. V. Sunthankar and B. D. Tilak, *Proc. Indian Acad. Sci.*, **36A**, 405 (1952); *C. A.*, **47**, 11189 (1953).

**4-Hydroxybenzothiophene.**—The diazonium salt was prepared at 0° from 0.3 g. (2 mmoles) in 36 ml. of water and 2 ml. of sulfuric acid with an equimolar amount of sodium nitrite. It was hydrolyzed by heating to 90° for 30 min. After cooling the filtered, hot solution, 0.15 g. of crude product precipitated. Recrystallization from Skellysolve C gave 0.05 g., m.p. 77–78°. Extraction of the insoluble tars with hot water and of the aqueous filtrates with ether gave an additional 0.06 g., m.p. 75–78°. The total yield was 37%. An additional recrystallization raised the m.p. to 78–79° (reported[6] 80–81°). A mixed melting point with an authentic sample, m.p. 74–76°, kindly furnished by L. F. Fieser was 76–78°.

From 15 mg. of 4-hydroxybenzothiophene, prepared from 4-aminobenzothiophene, 7 mg. of the aryloxyacetic acid derivative, m.p. 147–149°, was obtained. After three recrystallizations from water it melted at 149–150° (reported[6] 152–153°).

**5-Amino-4-bromobenzothiophene.**—To a solution of 2.4 g. (0.017 mole) of 5-aminobenzothiophene in 10 ml. of acetic acid was added a 10% acetic acid solution containing 2.7 g. (0.017 mole) of bromine. After warming the mixture a few minutes on a steam-bath 75 ml. of water was added. The crude product was decolorized in 100 ml. of boiling dilute hydrochloric acid with charcoal, Norite A, and precipitated with sodium carbonate or ammonium hydroxide. The yield was 2.4 g. (63%), m.p. 69–71°. After one recrystallization the product melted at 71–72° (reported[5] 75°). Bromination in carbon tetrachloride gave a lower yield of a less pure product.

This compound also was prepared by the hydrolysis of 0.15 g. (0.56 mmole) of 5-acetamido-4-bromobenzothiophene. After refluxing the amide for 30 min. in 20 ml. of concd. hydrochloric acid the yield was 0.10 g. (94%) of material, m.p. 70–71°. A mixed melting point with material prepared by the bromination of the amine was undepressed.

**5-Acetamido-4-bromobenzothiophene.**—To a solution of 0.50 g. (2.6 mmoles) of 5-acetamidobenzothiophene and 0.5 g. of sodium acetate in 5 ml. of acetic acid was added a solution of 0.42 g. (2.6 mmoles) of bromine in 4 ml. of acetic acid. After heating the solution 15 min. on a steam-bath, 0.58 g. (80%) of product, m.p. 126–134°, was precipitated by adding water. Trituration with concd. hydrochloric acid followed by washing with acetone and ammonium hydroxide gave 0.35 g. (50%) of material, m.p. 139–140° (reported[5] 143°).

When no sodium acetate was present, 0.89 g. (96%) of 5-acetamido-4-bromobenzothiophene hydrobromide, m.p. 153–156°, precipitated from the solution. It dissolved upon the addition of a few drops of water.

*Anal.* Calcd. for $C_{10}H_9Br_2NOS$: neut. equiv., 351; $Br^-$, 22.8. Found: neut. equiv., 347, 351; $Br^-$, 25.5, 22.0.

**4-Bromobenzothiophene 1-Dioxide.**—One-half gram (2.3 mmoles) of 5-amino-4-bromobenzothiophene was dissolved in 20 ml. of sulfuric acid (50% by volume) by heating and diazotized at 0° with an equimolar amount of sodium nitrite. The diazonium salt was reduced with 10 ml. of 50% hypophosphorous acid for 24 hr. at 0°, and an additional 24 hr. at room temperature. Ether extraction followed by steam distillation gave 0.10 g. (0.47 mmole, 21%) of 4-bromobenzothiophene. This oil was converted to 0.06 g. (0.25 mmole) of solid dioxide. After recrystallization from ethanol and water as well as from benzene it melted at 141–143°.

4-Bromobenzothiophene also was prepared from 0.50 g. (3.4 mmoles) of 4-aminobenzothiophene in 4 ml. of dil. hydrobromic acid through the diazonium salt. The salt was treated with a suspension of cuprous bromide prepared from 0.52 g. of sodium bromide.[18] Following steam distillation 0.09 g. (0.4 mmole, 12%) of pale yellow oil was recovered. This oil was oxidized to 0.11 g. (0.4 mmole) of the dioxide. After recrystallization, this product melted at 143–144°. A mixed melting point of the product prepared by the two methods was undepressed.

*Anal.* Calcd. for $C_8H_5BrO_2S$: C, 39.20; H, 2.06. Found: C, 38.78; H, 2.01.

**4-Bromo-5-hydroxybenzothiophene.**—The product was prepared by the treatment of 0.50 g. (3.3 mmoles) of 5-hydroxybenzothiophene in 8 ml. of acetic acid with 5 ml. of acetic acid containing 0.54 g. (3.3 mmoles) of bromine according to Fries, *et al.*[5b] The yield was 0.75 g. (97%) of product, m.p. 95–104°. Two recrystallizations from Skellysolve B raised the melting point to 109–110° (reported[5b] 112°).

This compound also was prepared from the diazonium salt made using 0.5 g. (2.2 mmoles) of 5-amino-4-bromobenzothiophene in 10 ml. of sulfuric acid (50% by volume). After heating the salt solution to boiling, the product was extracted by ether and extracted from the ether by a 10% sodium hydroxide solution. The yield was 0.11 g. (22%), m.p. 105–106°. After one recrystallization from Skellysolve B it melted at 108–109°. A mixed melting point with the product prepared by the bromination of 5-hydroxybenzothiophene was undepressed.

**4,6-Dibromo-5-hydroxybenzothiophene.**—To a solution of 0.45 g. (3.0 mmoles) of 5-hydroxybenzothiophene and 0.90 g of sodium acetate in 5 ml. of acetic acid was added at 10° 0.96 g. (6.0 mmoles) of bromine. A black oil which eventually solidified separated upon the addition of excess water. The product was purified by extraction from an ethereal solution with a 10% sodium hydroxide solution and by treatment of the extract with charcoal, Norite A. The yield was 0.48 g. (52%), m.p. 87–92°. Several recrystallizations from ethanol and water failed to raise the melting point above 93–94° (reported[5] as 3,4-dibromo-5-hydroxybenzothiophene, m.p. 103°). Martin-Smith[10] also obtained a product melting at about 94°. His work shows that at least 75% of this material is 4,6-dibromo-5-hydroxybenzothiophene.

**5-Acetoxy-3-bromo- and 3-Bromo-5-hydroxybenzothiophene.**—A solution of 0.50 g. (2.6 mmoles) of 5-acetoxybenzothiophene in 3 ml. of acetic acid was treated with 0.46 g. (2.9 mmoles) of bromine in 5 ml. of acetic acid and warmed on a steam-bath for 30 min. Addition of excess water precipitated a crude product which was freed of a phenolic compound by extraction of an ethereal solution with a 10% sodium hydroxide solution. Recrystallization of the neutral residue gave white needles, m.p. 100.5–101.0°, 5-acetoxy-3-bromobenzothiophene.

*Anal.* Calcd. for $C_{10}H_7BrO_2S$: C, 44.29; H, 2.60. Found: C, 43.90; H, 2.67.

After recrystallization of the phenolic compound, 3-bromo-5-hydroxybenzothiophene, from Skellysolve B and from ethanol and water it melted at 137.5–138.0°.

*Anal.* Calcd. for $C_8H_5BrOS$: C, 41.94; H, 2.20. Found: C, 41.39; H, 2.11.

3-Bromo-5-hydroxybenzothiophene was prepared in 89% yield by hydrolysis of the acetoxy compound with dil. sodium hydroxide. When 3-bromo-5-hydroxybenzothiophene, m.p. 136–137°, freshly recrystallized from Skellysolve B was heated very slowly above 130°, the fine white powder melted at 132°, solidified into needles at 134° and remelted at 136–137°.

When 0.5 g. of sodium acetate was present in the acetic acid the yield of 5-acetamido-3-bromobenzothiophene was 82%. This product was contaminated with a bright red impurity, which was not removed by recrystallization but was destroyed during saponification to the phenolic compound.

3-Bromo-5-hydroxybenzothiophene also was prepared from 0.08 g. (0.35 mmole) of 5-amino-3-bromobenzothiophene,[7] which was dissolved in 15 ml. of sulfuric acid (50% by volume) by heating and diazotized at 0°. The diazonium salt was hydrolyzed by boiling the solution to give 0.02 g. (25%), m.p. 134–136°. A mixed melting point of this product with that prepared from 5-acetoxybenzothiophene was undepressed.

**3,4-Dibromo-5-hydroxybenzothiophene.**—A solution of 0.093 g. (0.59 mmole) of bromine in 1 ml. of acetic acid was added to 0.134 g. (0.59 mmole) of 3-bromo-5-hydroxybenzothiophene in 3 ml. of acetic acid. After the bromine color had faded, 0.15 g. (81%) of crude product, m.p. 87–145°, was obtained. One recrystallization from Skellysolve B gave 0.05 g. (28%), m.p. 143–146°. An additional recrystallization raised the melting point to 146–148°.

*Anal.* Calcd. for $C_8H_4Br_2OS$: C, 31.19; H, 1.31. Found: C, 31.34; H, 1.54.

**Claisen Rearrangement of 5-Allyloxybenzothiophene.**—5-Allyloxybenzothiophene was prepared from 0.36 g. (0.015 mole) of sodium in 50 ml. of ethanol, 2.3 g. (0.015 mole) of

(18) L. A. Bigelow in "Organic Syntheses," Coll. Vol. I, Edited by H. Gilman and A. H. Blatt, Second Edition, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 136.

5-hydroxybenzothiophene and excess allyl bromide (4 ml.) by refluxing the mixture for 15 min. An ethereal solution was extracted with a 10% sodium hydroxide solution to remove any unreacted material. The yield of the liquid allyl ether was 2.7 g. (93%). The allyl ether was rearranged by refluxing for one hour in 15 ml. of dimethylaniline. The mixture was dissolved in 50 ml. of benzene, the dimethylaniline removed by dil. hydrochloric acid extraction and the rearranged product extracted with three 25-ml. portions of Claisen alkali.[19] After purification by steam distillation the yield was 1.80 g. (67%), b.p. 145–150° (2 mm.) and 183–185° (15 mm.). The recovery of the unrearranged product was 0.45 g. (17%). When the heating time was increased to two hours the yield of rearranged product was 75%. Following recrystallization from carbon tetrachloride and from Skellysolve C the α-naphthylurethan derivative of 4-allyl-5-hydroxybenzothiophene melted at 166–168°.

*Anal.* Calcd. for $C_{22}H_{17}NO_2S$: N, 3.90. Found: N, 3.83.

**Claisen Rearrangement of 4-Allyl-5-allyloxybenzothiophene.**—4-Allyl-5-allyloxybenzothiophene was prepared from 4-allyl-5-hydroxybenzothiophene in a manner similar to the preparation of 5-allyloxybenzothiophene. Claisen alkali[19] was used to remove any unreacted starting material. The yield was 89%. After refluxing 1.85 g. (8.0 mmoles) of the allyloxy compound in 20 ml. of dimethylaniline for 9.5 hours, 0.95 g. (51%) of unrearranged material and 0.60 g. (32%) of rearranged product, b.p. 155–160° (2 mm.), were recovered. When the heating time was only 4 hr., 63% of the starting material and 23% of rearranged product were isolated. The α-naphthylurethan derivative of the rearranged product, 4,6-diallyl-5-hydroxybenzothiophene, melted after two recrystallizations from Skellysolve C at 152–154°.

*Anal.* Calcd. for $C_{25}H_{21}NO_2S$: N, 3.51. Found: N, 3.65.

**Reaction of *p*-Diazobenzenesulfonate with 5-Hydroxybenzothiophene Derivatives.**—The method of Fieser and Lothrop[20] was used to test the coupling of *p*-diazobenzenesulfonate with 5-hydroxybenzothiophene derivatives. The following colors were noted: 5-hydroxybenzothiophene, red; 4-bromo-5-hydroxybenzothiophene, red-brown; 4-allyl-5-hydroxybenzothiophene, red; 4,6-diallyl-5-hydroxybenzothiophene, very pale yellow (no reaction).

**5-Amino- and 5-Acetamidobenzothiophene 1-Dioxide.**—5-Nitrobenzothiophene was oxidized to the 1-dioxide and reduced to the amine by the method described previously.[7] A drop of sulfuric acid was added to a slurry of 5.0 g. (0.027 mole) of the amine in 10 ml. of acetic anhydride. Following filtration and washing with water 5.8 g. (94%) of the acetamide, m.p. 221–223°, was obtained. Recrystallization from ethanol gave 5.2 g. (85%), m.p. 225–226°.

*Anal.* Calcd. for $C_{10}H_9NO_3S$: C, 53.80; H, 4.06. Found: C, 53.87; H, 4.34.

This compound also was prepared by the oxidation of 7.9 g. (0.041 mole) of 5-acetamidobenzothiophene in 80 ml. of acetic acid with 40 ml. of 30% hydrogen peroxide. After 24 hr. at room temperature the dioxide was precipitated by the addition of one liter of water. A small amount of additional product was obtained by evaporation. The yield was 6.7 g. (73%), m.p. 208–213°.

**5-Amino-2,3-dihydrobenzothiophene 1-Dioxide.**—A solution of 0.18 g. (1.0 mmole) of 5-aminobenzothiophene 1-dioxide in 5 ml. of ethanol was hydrogenated at one atmosphere pressure using 0.02 g. of 5% palladium-on-charcoal in two hours. Evaporation of the solvent gave 0.18 g. (99%), m.p. 139–140°. After two recrystallizations from ethanol it melted at 147.0–147.5°.

*Anal.* Calcd. for $C_8H_9NO_2S$: C, 52.44; H, 4.95. Found: C, 52.58; H, 4.85.

**5-Hydroxybenzothiophene 1-Dioxide.**—A solution of the diazonium salt prepared from 0.90 g. (5.0 mmoles) of 5-aminobenzothiophene 1-dioxide in 20 ml. of sulfuric acid (50% by volume) with an equimolar amount of sodium nitrite at 0° was refluxed for 15 min. and filtered hot through Celite. Ether extraction of the filtrate and extraction of the ether with a 10% solution of sodium hydroxide gave on acidification of the caustic solution 0.31 g. (31%) of product, m.p. 131–140°. After recrystallization from water in the presence of charcoal, Norite A, and two additional recrystallizations from water it melted at 152.0–152.5°.

*Anal.* Calcd. for $C_8H_6O_3S$: C, 52.74; H, 3.32. Found: C, 52.76; H, 3.53.

**5-Acetamido-6-nitrobenzothiophene 1-Dioxide.**—To 10 ml. of fuming nitric acid (d. 1.50) was added slowly with stirring at 0° 4.0 g. (0.018 mole) of 5-acetamidobenzothiophene 1-dioxide and the mixture maintained at 10° for 30 min. After pouring the solution into 500 ml. of cold water 4.2 g. (87%) of crude product precipitated. Recrystallization from 600 ml. of ethanol gave 3.3 g. (68%), m.p. 214–215°. Further recrystallizations raised the melting point to 215–216°.

*Anal.* Calcd. for $C_{10}H_8N_2O_5S$: N, 10.45. Found: N, 10.45.

The product was also recrystallizable from acetic acid. A mixed melting point with 5-acetamido-4-nitrobenzothiophene 1-dioxide was depressed to 195–200°. The nitration of 5-acetamidobenzothiophene 1-dioxide failed under the conditions used to nitrate 5-acetamidobenzothiophene.

**5-Amino-6-nitrobenzothiophene 1-Dioxide.**—A suspension of 3.3 g. (0.012 mole) of 5-acetamido-6-nitrobenzothiophene 1-dioxide in a mixture of 60 ml. of acetic acid and 50 ml. of concd. hydrochloric acid was heated under reflux for 30 minutes. Filtration gave 2.8 g. (100%) of a yellow solid which was almost completely insoluble in common solvents. Recrystallization from large amounts of acetone gave fine yellow needles, which gradually decomposed above 270° turning to a blackened mass at 286–290°.

*Anal.* Calcd. for $C_8H_6N_2O_4S$: C, 42.47; H, 2.67; N, 12.39. Found: C, 42.60; H, 2.54; N, 12.24. Difficulty was encountered in the combustion. The nitrogen value is the average of five determinations, average deviation 0.64. The carbon and hydrogen values were determined by the Micro-Tech Laboratories, Skokie, Ill.

**6-Nitrobenzothiophene 1-Dioxide.**—5-Amino-6-nitrobenzothiophene 1-dioxide could not be diazotized by conventional methods. The special procedure developed by Misslin[21] for negatively substituted amines proved effective. To a solution of 0.25 g. (3.6 mmoles) of sodium nitrite in 20 ml. of concd. sulfuric acid cooled to −12° was added 0.50 g. (2.2 mmoles) of 5-amino-6-nitrobenzothiophene 1-dioxide. Ice was added slowly at −10° to bring the volume to 100 ml. The diazonium salt was reduced using 25 ml. of cold hypophosphorous acid and a few small crystals of copper sulfate.[22] After 4 hr. at 10° the solids were collected and washed with a sodium bicarbonate solution. The product was recovered from the solids by extraction with 25 ml. of benzene to give 0.12 g. (30%), m.p. 175–178°. After two recrystallizations from ethanol and one from benzene it melted at 181–182°. A mixed melting point with a sample of 6-nitrobenzothiophene 1-dioxide prepared by the nitration of benzothiophene 1-dioxide[23] was undepressed.

**5-Amino-6-bromobenzothiophene 1-Dioxide.**—A solution of 1.6 g. (0.01 mole) of bromine in 16 ml. of acetic acid was added at 65° to a stirred solution of 1.81 g. (0.01 mole) of 5-aminobenzothiophene 1-dioxide in 35 ml. of acetic acid containing 1.8 g. of sodium acetate. After cooling 2.3 g. (88%) of product, m.p. 221–223° dec., was collected. After recrystallization from ethanol and sublimation at 2 mm. it decomposed at 229–231°.

*Anal.* Calcd. for $C_8H_6BrNO_3S$: N, 5.39. Found: N, 5.35.

**6-Bromobenzothiophene 1-Dioxide.**—The suspension of the amine sulfate prepared from 1.1 g. (4.2 mmoles) of 5-amino-6-bromobenzothiophene 1-dioxide dissolved in 20 ml. of warm sulfuric acid (50% by volume) was diazotized at 0° using 0.5 g. of sodium nitrite. Reduction of the diazonium salt was accomplished with 20 ml. of 50% hypophosphorous acid and a few small crystals of copper sulfate[22] in 3 hr. at 10°. The yellow precipitate was extracted in a continuous extraction apparatus with 50 ml. of ethanol. Concentration of the extract to 15 ml. gave 0.55 g. of pure prod-

(19) D. S. Tarbell, "Organic Reactions," Edited by Roger Adams, Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 28.

(20) L. F. Fieser and W. C. Lothrop, THIS JOURNAL, **57**, 1459 (1935).

(21) E. Misslin, *Helv. Chim. Acta*, **3**, 626 (1920).

(22) N. Kornblum, G. D. Cooper and J. E. Taylor, THIS JOURNAL, **72**, 3013 (1950).

(23) F. Challenger and P. H. Clapham, *J. Chem. Soc.*, 1615 (1948).

uct, m.p. 139°. Further concentration gave additional less pure product. The total yield was 7.3 g. (71%). A mixed melting point with 4-bromobenzothiophene 1-dioxide was depressed to 103–120°.

*Anal.* Calcd. for $C_8H_5BrO_2S$: C, 39.20; H, 2.06. Found: C, 39.24; H, 2.04.

**6-Amino-2,3-dihydrobenzothiophene 1-Dioxide.**—A suspension of 2.1 g. (0.01 mole) of 6-nitrobenzothiophene 1-dioxide in 50 ml. of ethanol was hydrogenated using 0.2 g. of 5% palladium-on-charcoal catalyst in a Parr low pressure hydrogenation apparatus. After one hour 0.04 mole of hydrogen was consumed. Concentration to 30 ml. gave 1.4 g. (78%) of yellow needles, m.p. 195–199°. One recrystallization from ethanol raised the melting point to 198–200°.

*Anal.* Calcd. for $C_8H_9NO_2S$: N, 7.65. Found: N, 7.87, 7.59.

**6-Bromo-2,3-dihydrobenzothiophene 1-Dioxide.**—A suspension of 2.45 g. (0.01 mole) of 6-bromobenzothiophene 1-dioxide in 50 ml. of ethanol was hydrogenated in a few minutes using 0.2 g. of 5% palladium-on-charcoal in a Parr low pressure hydrogenation apparatus. Concentration to 15 ml. gave 1.5 g. (61%) of white crystals, m.p. 136–139°. Recrystallization from ethanol gave 1.2 g. (49%), m.p. 142–144°. Further concentration of the original mother liquor gave an oil. The presence of hydrogen bromide in the liquor indicated some hydrogenolysis of the halide also occurred.

*Anal.* Calcd. for $C_8H_7BrO_2S$: C, 38.88; H, 2.86. Found: C, 38.61; H, 2.99.

This compound also was prepared by the diazotization of 0.50 g. (2.7 mmoles) of 6-amino-2,3-dihydrobenzothiophene 1-dioxide in 10 ml. of sulfuric acid (50% by volume) using 0.20 g. of sodium nitrite. The diazonium salt solution was added to 50 ml. of a boiling suspension of cuprous bromide.[18] Boiling was continued for 10 min. Extraction of the solids with acetone gave 0.45 g. (67%) of product, m.p. 133–140°. Three recrystallizations from ethanol raised the melting point to 142–143°. A mixed melting point of the product prepared by both methods was undepressed.

EVANSTON, ILLINOIS

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

# Studies in the Thianthrene System: Bromination and Reductive Bromination

BY HENRY GILMAN AND DHAIRYASHEEL R. SWAYAMPATI

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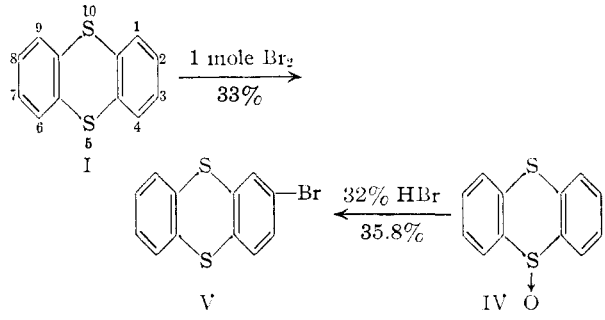
One molar equivalent of bromine and thianthrene gave 2-bromothianthrene in fair yield, while two molar equivalents of bromine and thianthrene gave a mixture of 2,7- and 2,8-dibromothianthrene. The same isomeric mixture was obtained by the action of bromine on thianthrene-5-oxide, and of hydrobromic acid on thianthrene-5,10-dioxide. Bromine did not react with thianthrene-5-dioxide. Hydrobromic acid reacted with thianthrene-5-oxide to give 2-bromothianthrene in fair yield, and with thianthrene-5,5,10-trioxide to give a quantitative yield of thianthrene-5-dioxide. Reductive bromination of sulfoxides appears to proceed through the initial reduction of the sulfoxide to the sulfide with the liberation of bromine, which then attacks the heterocycle. Thianthrene-5-dioxide and thianthrene-5,5,10-trioxide were obtained by improved methods in excellent yields.

The bromination of dibenzothiophene (II),[1] and the dibromination of II[2] and its sulfoxide III[3] have been reported, but a bromination of thianthrene or its derivatives has not been reported where a derivative of known structure was obtained. We were able to show that the reported dibromothianthrene,[4,5] whose structure and physical characteristics were not given, is a mixture of 2,7- and 2,8-dibromothianthrene.

The purpose of this study has been to investigate the possibility of preparing bromo derivatives of thianthrene of known structure. Two methods seemed feasible: (1) the action of bromine on thianthrene, and (2) the action of hydrobromic acid on the sulfoxides of thianthrene. The reaction, termed reductive chlorination of sulfoxide,[6] has been successfully applied in the case of thianthrene-5-oxide (IV) to give 2-chlorothianthrene,[7] but a corresponding reaction with hydrobromic acid has not been reported.

We found that 2-bromothianthrene (V) can be obtained by the action of hydrobromic acid on thianthrene-5-oxide, as well as by the action of one molar equivalent of bromine on thianthrene in boiling acetic acid. At room temperature the action of hydrobromic acid on thianthrene-5-oxide did not proceed beyond reduction to thianthrene.




It was found that an approximately 32% solution of hydrobromic acid gave the best yield of the pure product. The yield was considerably decreased with 48 and 16% solutions of hydrobromic acid.

The action of two molar equivalents of bromine on thianthrene gave a product which was identical with the product obtained by the action of hydrobromic acid on thianthrene-5,10-dioxide (VI). The same product was also obtained by refluxing a solution of thianthrene-5-oxide and one molar equivalent of bromine in glacial acetic acid. Attempts to obtain a sharp-melting substance from it were unsuccessful. From its analysis, the examination of its infrared spectrum, and the comparison with the dibromination of dibenzothiophene, it is

(1) N. M. Cullinane, C. G. Davis and G. I. Davis, *J. Chem. Soc.*, 1435 (1936).

(2) C. R. Neumoyer and E. D. Amstutz, THIS JOURNAL, **69**, 1920 (1947).

(3) H. Gilman and R. K. Ingham, *ibid.*, **73**, 4982 (1951).

(4) Ciba Ltd., Swiss Patent 240,129, Apr. 1, 1946 [*C. A.*, **43**, 8691 (1949)].

(5) Ciba Ltd., Swiss Patent 243,008, Nov. 16, 1946 [*ibid.*, **43**, 7966 (1949)].

(6) H. J. Page and S. Smiles, *J. Chem. Soc.*, **97**, 1112 (1910).

(7) K. Fries and W. Vogt, *Ann.*, **381**, 312 (1911).