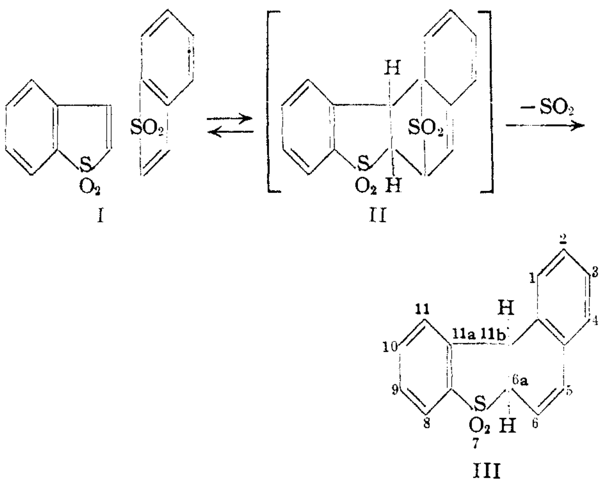
[Contribution from the Chemical Laboratory of Northwestern University]

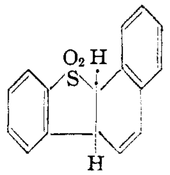
Benzothiophene Chemistry. V. The Pyrolysis of Benzothiophene 1-Dioxide

By F. G. Bordwell, W. H. McKellin[1] and Douglas Babcock[2]

On pyrolysis in the presence or absence of an inert solvent benzothiophene 1-dioxide (I) was found to undergo a Diels-Alder dimerization with subsequent loss of sulfur dioxide to give 6a,11b-dihydronaphtho[2,1-b]benzo[d]thiophene 7-dioxide (III). The structure of III was supported by desulfurization to 1-phenylnaphthalene, and by other reactions. Of particular interest was a base-catalyzed elimination reaction yielding a salt of *o*-(1-naphthyl)-benzenesulfinic acid, which was also degraded to 1-phenylnaphthalene.

In the course of our studies on addition reactions of benzothiophene 1-dioxide (I),[3] it was observed that sulfur dioxide was evolved when I was heated to temperatures of about 200° in an inert solvent, and that a higher melting substance (III), $C_{16}H_{12}O_2S$, was formed. The most likely reaction course appeared to be dimerization by a Diels–Alder reaction to give II, which lost sulfur dioxide at the reaction temperature to yield III. The diene reaction could also yield IV by an alternative arrangement of the dimerizing molecules.



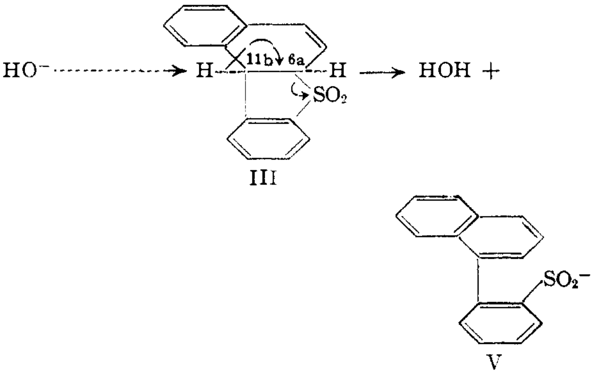


IV

Diels–Alder reactions involving the double bond of a single benzenoid ring are not common, but such reactions have been reported with styrenes where an alkoxyl group is para to the vinyl group,[4a] and with a few other systems.[4b] The present reaction undoubtedly owes a good measure of its success to the loss of sulfur dioxide, which shifts what is probably an unfavorable equilibrium. The loss of sulfur dioxide from II is analogous to the thermal decomposition of 3,4-dihydrothiophene 1-dioxides to butadiene derivatives and sulfur dioxide.

To decide between the alternative structures III and IV, the pyrolysis product was desulfurized with Raney nickel,[5] and the crude material obtained was dehydrogenated to 1-phenylnaphthalene. The degradation product would have been 2-phenylnaphthalene if the pyrolysis product had been IV.

Treatment of III with 2% alcoholic potassium hydroxide brought about a rapid elimination reaction yielding potassium *o*-(1-naphthyl)-benzenesulfinate (V). The most reasonable reaction path would appear to be that shown.[6] By reaction with bromine V was converted to *o*-(1-naphthyl)-benzenesulfonyl bromide, from which the ethyl ester and sulfonanilide were obtained. Oxidation of V with hydrogen peroxide gave *o*-(1-naphthyl)-benzenesulfonic acid, isolated as the S-benzylthiuronium salt. The sulfinic acid (Va) was degraded in poor yield to 1-phenylnaphthalene by treatment with mercuric chloride, followed by hydrolysis of the crude organo mercury compound.



The position of the double bond in III has not as yet been established, but the assigned structure appears most reasonable on the basis of the formulation of the Diels–Alder reaction, and since rearrangement in the absence of acid or basic catalysts would not be anticipated. On hydrogenation in the presence of palladium on charcoal catalyst, III readily took up one mole of hydrogen to give 5,6,6a,11b-tetrahydronaphtho[2,1-b]benzo[d]thiophene 7-dioxide (VI). Treatment of VI with alcoholic potassium hydroxide under conditions similar to those used for III brought about an analogous elimination reaction to yield *o*-(3,4-

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[1] Texas Company Research Fellow, 1947–1949.

[2] University Fellow, 1948–1949; Office of Naval Research Fellow, 1950.

[3] F. G. Bordwell and W. H. McKellin, IV, This Journal, **72**, 1985 (1950).

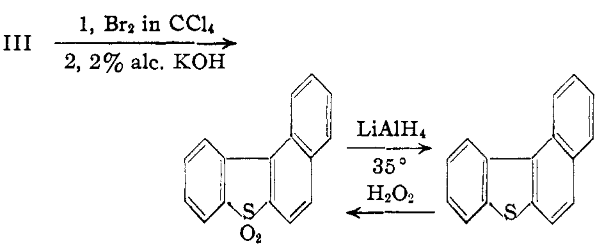
[4] (a) J. F. Hudson and R. Robinson, *J. Chem. Soc.*, 715 (1941); (b) see L. E. Miller and D. J. Mann, This Journal, **73**, 45 (1951), and refs. cited therein.

[5] R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, *ibid.*, **65**, 1013 (1943).

[6] Geometrically III consists of two essentially planar fused ring systems folded over a 6a-11b >CH—CH< hinge. The 11b-hydrogen is *trans* to the sulfonyl group, and the elimination is, therefore, *trans*.

dihydro-1-naphthyl)-benzenesulfinic acid (VII), a dihydro derivative of Va. The ease with which this reaction occurred was unexpected, since it seemed probable that the formation of an aromatic system in the reaction of III with base would provide this reaction with considerably more driving force than would be available in the reaction of VI.[7]

In carbon tetrachloride solution III absorbed bromine slowly to give a dibromide VIII. On treatment with 2% alcoholic potassium hydroxide or triethylamine in benzene, VIII reacted rapidly with the loss of two molecules of hydrogen bromide to give the completely aromatized sulfone, benzo[d]naphtho[2,1-b]thiophene 7-dioxide (X). The sulfone X was readily reduced by lithium aluminum hydride in refluxing ethyl ether solution to benzo[d]naphtho[2,1-b]thiophene (3,4-benzo-9-thiafluorene) (XI). In its ease of reduction X, therefore, corresponds to other five-membered ring sulfones[8]; six-membered ring sulfones and open-chain sulfones require a higher temperature.



X XI

Attempts to extend the Diels–Alder dimerization observed with I to 3-chloro- and 6-nitrobenzothiophene 1-dioxides were unsuccessful, but it is anticipated that less reactive derivatives will undergo the reaction successfully.

The sequence of reactions I→III→VIII→X→XI offers a new synthetic route for compounds such as XI, which may be rather inaccessible by more conventional approaches.[9]

Experimental[10]

Pyrolysis of Benzothiophene 1-Dioxide.—The pyrolysis was carried out successfully in phenyl ether, phenol, ethyl malonate, α-methylnaphthalene, or butyl carbitol at the boiling point, or in the absence of solvent. The isolation of product was more convenient from butyl carbitol. Carbide and Carbon Chemicals Division butyl carbitol, boiling at about 220°, was used without purification. In one experiment use of redistilled butyl carbitol, b.p. 230°, resulted in tar formation and loss of the product. A solution of 10 g. (0.06 mole) of benzothiophene 1-dioxide in 40 ml. of butyl carbitol was refluxed for eight hours; nitrogen gas was bubbled through the solution during this time. The solution was cooled to about 80°, and 40 ml. of 95% alcohol was added. Six grams (74%) of material, m.p. 179–180.5°, crystallized from the solution on cooling. Recrystallization from acetone gave a 90% recovery of **6a,11b-dihydronaphtho[2,1-b]benzo[d]thiophene 7-dioxide** (III) melting at 181–182°.

Anal. Calcd. for $C_{16}H_{12}O_2S$: C, 71.62; H, 4.51; S, 11.95. Found: C, 72.00; H, 4.38; S, 11.41.

Comparable experiments run for two, five and sixteen hours gave 47, 55 and 84% yields of crude products.

In attempts to effect a similar reaction with 6-nitrobenzothiophene 1-dioxide and 3-chlorobenzothiophene 1-dioxide, sulfur dioxide was evolved, but the products were dark colored and intractable. Attempts to bring about a Diels–Alder reaction between benzothiophene 1-dioxide and excess maleic anhydride in the presence or absence of solvents have not been successful, small quantities of III being the only product isolated.

Conversion of III to 4-Nitro-1-phenylnaphthalene by Desulfurization, Dehydrogenation and Nitration.—A solution of 2.0 g. (0.008 mole) of III in 200 ml. of alcohol was refluxed with 27 g. of Raney nickel[5] for seven hours and then diluted with 300 ml. of water. After filtering off the nickel, the alcohol was distilled and the product steam distilled. Extraction with ether and evaporation left 0.8 g. of liquid product. This material was heated with 0.4 g. of 5% palladium-on-charcoal for 1.5 hours at about 250°. The 0.7 g. of product recovered by ether extraction was partly crystalline. Nitration was effected by the method described for 1-phenylnaphthalene.[11] After crystallization from alcohol the 4-nitro-1-phenylnaphthalene melted at 129–131° and did not depress the melting point of a similar sample prepared from 1-phenylnaphthalene.[12]

***o*-(1-Naphthyl)-benzenesulfinic Acid (Va).**—A solution of 15 g. (0.056 mole) of III in 180 ml. of 2% alcoholic potassium hydroxide was refluxed for 20 minutes. After filtration the solution was made slightly acidic to litmus with 6 *N* hydrochloric acid, and the product precipitated by slow addition of 300 ml. of ice water. There was thus obtained 14.3 g. (95%) of material decomposing at 116–118°. The sulfinic acid (Va) is unstable to heat so purification was effected by dissolving in alcohol and precipitation with water. After repeating this procedure twice, titration of a sample in 95% alcohol with standard sodium hydroxide to a phenolphthalein end-point gave a neutral equivalent of 272 as compared to the calculated value of 268.

Anal. Calcd. for $C_{16}H_{12}O_2S$: C, 71.62; H, 4.51. Found: C, 71.84; H, 4.66.

The formation of the sulfinate also took place when III was refluxed in alcohol solution with excess piperidine. The reaction was much slower (70% of III was recovered after one hour), and the reaction is less satisfactory for the preparation of Va.

A 0.46-g. (0.0017 mole) sample of Va was dissolved in a slight excess of 1 *N* sodium hydroxide and 3 ml. (0.026 mole) of 30% hydrogen peroxide added dropwise. After warming on the steam-bath for one-half hour, the solution was neutralized with 1 *N* hydrochloric acid and 0.34 g. (0.0017 mole) of S-benzylthiuronium chloride dissolved in 8 ml. of 0.25 *N* hydrochloric acid was added. After crystallization of the resulting solid from 200 ml. of 0.25 *N* hydrochloric acid, 0.48 g. (63%) of **S-benzylthiuronium *o*-(1-naphthyl)-benzenesulfonate**, m.p. 222–225°, was obtained. After three crystallizations from 95% alcohol, the m.p. was 224–225°.

Anal.[13] Calcd. for $C_{24}H_{22}N_2O_3S_2$: C, 63.98; H, 4.92. Found: C, 64.01; H, 4.97.

***o*-(1-Naphthyl)-benzenesulfonyl Bromide.**—A 2.0-g. (0.0075 mole) sample of Va suspended in 75 ml. of water was neutralized with 5% sodium hydroxide and a 0.1 *M* solution of bromine water added until the yellow color persisted. After standing for one hour at 0°, the resulting solid was collected and washed, yielding 2.24 g. (88%) of product melting at 142–144°. Two crystallizations from carbon tetrachloride gave material melting at 143–145°.

Anal. Calcd. for $C_{16}H_{11}BrO_2S$: C, 54.34; H, 3.19. Found: C, 54.28; H, 3.26.

Material of considerably lower purity was obtained from the reaction of Va with bromine in carbon tetrachloride solution.

***o*-1-(Naphthyl)-benzenesulfonanilide** was prepared from the sulfonyl bromide and excess aniline in benzene solution by allowing the solution to stand at room temperature for two weeks. After crystallization from aqueous alcohol, the yield of product, m.p. 162–163°, was 85%. After two further crystallizations the m.p. was 163–163.5°.

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(7) A kinetic study of these reactions is being made by Dr. Glenn D. Cooper of this Laboratory.

(8) F. G. Bordwell and W. H. McKellin, THIS JOURNAL, **73**, 2251 (1951).

(9) C. R. Neumoyer and E. D. Amstutz, *ibid.*, **66**, 1680 (1944).

(10) Melting points are uncorrected. Microanalyses were by Miss Joyce Sorensen, unless other reference is given.

(11) R. Weiss and K. Wodich, *Monatsh.*, **46**, 457 (1925); V. Vesely and F. Stursa, *Collection Czechoslov. Chem. Commun.*, **5**, 343 (1933).

(12) R. Weiss, *Org. Syntheses*, **24**, 84 (1944).

(13) Microanalysis by Charles Beazley, Micro-Tech Laboratories, Skokie, Illinois.

Anal. Calcd. for $C_{22}H_{17}NO_2S$: C, 73.51; H, 4.76. Found: C, 73.84; H, 4.65.

Ethyl *o*-1-(Naphthyl)-benzenesulfonate was obtained in excellent yield by refluxing the sulfonyl bromide in ethyl alcohol for 15 minutes. After crystallization from alcohol the product melted at 108–109°.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 69.21; H, 5.16. Found: C, 69.41; H, 5.29.

Conversion of Va to 1-Phenylnaphthalene.—A solution of 1.4 g. of *o*-(1-naphthyl)-benzenesulfinic acid (Va) and 6 g. of mercuric chloride in 40 ml. of alcohol was refluxed for 1.5 hours. The solid precipitating on cooling was extracted three times with 25-ml. portions of acetone, and the residue from evaporation of the acetone was crystallized from alcohol. The crude *o*-(1-naphthyl)-benzenemercuric chloride, m.p. 169–175°, thus obtained was refluxed for eight hours with hydrochloric acid and the product steam distilled. Nitration of the resulting oil gave a crude nitro compound, which after purification was shown by a mixed melting point determination to be identical with the product prepared by nitrating 1-phenylnaphthalene.

Addition of Bromine to III.—One gram (0.0037 mole) of III was suspended in 40 ml. of carbon tetrachloride and treated with 0.59 g. (0.0037 mole) of bromine in 10 ml. of carbon tetrachloride. After standing two days at room temperature the mixture was warmed to effect solution and the product allowed to crystallize. After an additional crystallization from 25 ml. of carbon tetrachloride, 0.70 g. (44%) of material melting at 170–172° was obtained. Two further crystallizations raised the melting point to 175–176°.

Anal. Calcd. for $C_{16}H_{12}Br_2O_2S$: C, 44.88; H, 2.82. Found: C, 44.43; H, 2.63.

Later attempts to repeat this experiment were unsuccessful. Under apparently identical conditions evolution of hydrogen bromide was observed and a mixture was obtained the melting point of which could not be raised above 165° by crystallization. The aromatized sulfone (X) was identified as one of the products of the bromination. By pulverizing III and shaking with bromine in carbon tetrachloride, the time for complete up-take of the bromine was reduced to two hours; no hydrogen bromide was apparent during the reaction and a 33% yield of dibromide VIII, m.p. 175–176°, was obtained.[14]

Benzo[d]naphtho[2,1-b]thiophene 7-Dioxide (X).—The dibromide (VIII) (1.2 g., 0.0028 mole) dissolved rapidly in 35 ml. of hot 2% alcoholic potassium hydroxide, and an insoluble product soon formed. After refluxing the mixture for two hours, the solid was filtered and washed free of potassium bromide. The yield of X, m.p. 228–229°, was 0.68 g. (90%). The melting point remained unchanged after two further crystallizations from alcohol.

Anal. Calcd. for $C_{16}H_{10}O_2S$: C, 72.16; H, 3.78. Found: C, 72.37; H, 3.70.

Dehydrobromination of VIII to X was also accomplished with triethylamine in benzene solution.

Benzo[d]naphtho[2,1-b]thiophene (XI).—Reduction of 1.1 g. of VIII with excess lithium aluminum hydride in ethyl ether[8] gave material melting, after crystallization from alcohol, at 101–102.5°; yield 65%. Two more crystallizations from alcohol raised the melting point to 102–102.5°.[15]

Anal. Calcd. for $C_{16}H_{10}S$: C, 82.01; H, 4.30. Found: C, 81.91; H, 4.51.

Oxidation of XI in acetic acid solution with a ten-fold quantity of 30% hydrogen peroxide gave a practically quantitative yield of X after a 20-minute reflux period.

5,6,6a,11b-Tetrahydronaphtho[2,1-b]benzo[d]thiophene 7-Dioxide (VI).—Five grams of III in alcohol solution was reduced in a Parr apparatus using 0.1 g. of 5% palladium-on-charcoal catalyst. Addition of water to the hot alcohol solution from which the catalyst had been removed gave 4.5 g. (89%) of crystalline material melting at 179–181°. Two recrystallizations from acetone–alcohol and two from benzene–pentane raised the melting point to 180–181°. Mixed m.p. with III, m.p. 183–184°, was approximately 161–171°.

Anal. Calcd. for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22. Found: C, 71.47; H, 5.02.

***o*-(3,4-Dihydro-1-naphthyl)-benzenesulfinic Acid (VII).**—A solution of 0.93 g. of VI dissolved in 50 ml. of 2% alcoholic potassium hydroxide was refluxed for one hour. The solution was cooled and acidified with 6 *N* hydrochloric acid. Slow addition of 180 ml. of ice water yielded 0.85 g. (92%) of the sulfinic acid, m.p. 121–122°. Three recrystallizations from 50% aqueous alcohol did not raise the melting point.

Anal. Calcd. for $C_{16}H_{14}O_2S$: C, 71.08; H, 5.22. Found: C, 71.28; H, 4.77.

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[14] We wish to thank Dr. Glenn D. Cooper for carrying out these later experiments.

[15] In an attempted synthesis of this compound from phenyl 1-amino-2-naphthyl sulfide by a Pschorr ring closure, Neumoyer and Amstutz[9] obtained a 0.4% yield of a product melting at 174.2-175.7° (sulfone, m.p. 258.4-259.7°); the sulfur analysis of neither this compound nor that of the sulfone agreed with the calculated values for XI and X.

EVANSTON, ILLINOIS RECEIVED MAY 21, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

Kinetic Evidence on the Mechanism of the Acid Denaturation of Horse CO Hemoglobin[1]

BY ETHEL M. ZAISER AND JACINTO STEINHARDT

Equilibrium measurements have shown that exposure of horse carbonylhemoglobin to dilute acid initiates a time-dependent reaction which liberates 36 acid-binding groups. The relation of this process to denaturation has now been explored by kinetic measurements. The rates of denaturation of COHb by acid have been determined as a function of *p*H, ionic strength and temperature, by three different methods: loss of characteristic absorption at 5380 Å., loss of solubility at the isoelectric point, and increase in available acid-combining groups. The reaction is at least partially reversible. The initial formation of ferrihemoglobin plays an essential part in the process as usually observed. The velocity constants measured by all three methods are identical. It is concluded that the liberation of 36 basic groups incident to denaturation occurs essentially as an all-or-nothing phenomenon, *i.e.*, no delayed acid combination occurs in undenatured molecules, or in denatured molecules in amounts smaller than the full complement.

Over a wide range of *p*H values, the acid-binding capacity of horse carbonylhemoglobin when determined by a technique permitting measurement at 3 seconds after mixing with acid[2] is less than the amount predicted from its amino acid composition, and less than one-half of the amount found by the usual methods of titration which require long periods for attainment of equilibrium.[3] The amount of acid bound increases with time at rates which increase with the acid concentration. After brief exposure to acid at *p*H 2.8 or below, a back-titration curve may be obtained which, on comparison with the 3-second curve (Fig. 1) reveals that the acid bound has increased by as much as 0.52 mmole/gram (Fig. 1, inset curve 2). This

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[1] A preliminary account of this work was presented at the meeting of the American Chemical Society at Chicago, Ill., in September, 1950.

[2] J. Steinhardt and E. M. Zaiser, *J. Biol. Chem.*, **190**, 197 (1951).

[3] E. J. Cohn, A. A. Green and M. Blanchard, THIS JOURNAL, **59**, 509 (1937).