[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

# A STUDY OF THE GERMICIDAL ACTIVITY OF DIARYL-SULFIDE PHENOLS

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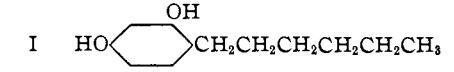
RECEIVED DECEMBER 11, 1928 PUBLISHED MAY 6, 1929

## Introduction

The clinical success of hexylresorcinol, I, as a specific, internal antiseptic[2] was an incentive to extend our researches on germicides still further



I

into the field of aromatic phenols. While various organic radicals have been incorporated into resorcinol with the object of increasing the phenol coefficient, no product has thus far been prepared in this series which has exhibited a higher germicidal value[3] than the hexyl compound. It is not to be assumed, however, that this hexyl combination represents the maximum in antiseptic efficiency that may be expected among organic constructions containing phenolic groups, and it was with the object of increasing this therapeutic or clinical value that we decided to extend our field of investigation along entirely new lines.

We have, therefore, inaugurated in this Laboratory a series of researches dealing with the question of the influence of sulfur linkages in organic combinations on germicidal activity. The study of the antiseptic properties of phenolic sulfur combinations has hitherto received little attention. The growing interest in the biochemistry of organic sulfur groupings[4] has stimulated a desire to acquire a better understanding of the influence of this element on antiseptic properties. The recent important work on

[1] Constructed from a dissertation presented by Guido Edward Hilbert in June, 1928, to the Faculty of the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy. An abstract of this paper was presented at the Annual Meeting of the American Chemical Society held at Swampscott, Massachusetts, from September 10 to 15, 1928.

[2] Johnson and Hodge, THIS JOURNAL, **35**, 1014 (1913); Johnson and Lane, *ibid.*, **43**, 348 (1921); Leonard, *J. Am. Med. Assocn.*, **83**, 2005 (1924); Dohme, Cox and Miller, THIS JOURNAL, **48**, 1688 (1926); Leonard, *J. Urol.*, **12**, 585 (1924); Leonard and Wood, *J. Am. Med. Assocn.*, **85**, 1855 (1925); Henline, *J. Urol.*, **14**, 119 (1925); Scott and Leonard, *Am. J. Dis. Children*, **31**, 241 (1926); Wynne, *Minn. Med.*, April, 156 (1926); Brown, *J. Am. Med. Assocn.*, **86**, 668 (1926); Leonard and Frobishers, *J. Urol.*, **15**, 1 (1926); *Trans. Am. Assocn. Gen. Urol. Surg.*, **18**, 333 (1925); Leonard and Feirer, *Dental Cosmos*, **3**, 559 (1927); Damon, *Am. J. Public Health*, **17**, 279 (1927); Feirer and Leonard, *J. Am. Dent. Assocn.*, 1–17 (1927); *Dental Cosmos*, September, 1–12 (1927); "New and Non-Official Remedies," American Medical Association Council on Chemistry and Pharmacy, **1928**, p. 336.

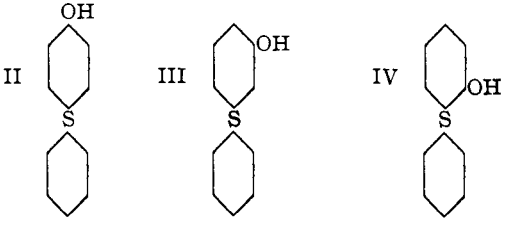
[3] Bartlett and Garland, THIS JOURNAL, **49**, 2098 (1927); Talbot and Adams, *ibid.*, **49**, 2040 (1927); Twiss, *ibid.*, **48**, 2206 (1926); Klarmann, *ibid.*, **48**, 2359 (1926).

[4] Glutathione, ergothioneine, insulin, cystine, taurine, etc.

thyroxine[5] has clearly revealed the significance of the biological effect of incorporating an aromatic ether linkage into di-iodotyrosine[6] and the accepted conclusion regarding the constitution of thyroxine suggests that one might expect sulfur in aromatic sulfide combination to have an important and perhaps a favorable effect on the therapeutic action of phenols. A review of the literature reveals the fact that practically no attention has hitherto been paid to this clinical feature. Furthermore, our knowledge of the chemistry of aryl-sulfide phenols and their derivatives is very limited. New methods of synthesis must be worked up before the development of this field biologically can be advanced.[7]

## Aryl-Sulfide Phenols

The feature of our research to which we desire to direct special attention in this paper is the high phenol coefficient of the sulfide-phenol represented by Formula II, and the influence on germicidal activity by changing the structural position of the phenolic hydroxyl group in diphenyl sulfide. The degree of germicidal activity of the three isomers II, III and IV,




is expressed in the order para > meta > ortho. An account of the preliminary bacteriological and toxicity tests, thus far conducted, is given in the Experimental Part of this paper.

Of the three isomeric phenols represented by Formulas II, III and IV, the para- and ortho-compounds have been previously reported in the literature. The para-compound was first obtained by Hinsberg[8] by allowing phenol to interact with benzenesulfinic acid. He was unsuccessful, however, in his attempts to purify the phenol and described it

$$2C_6H_5SO_2H \longrightarrow C_6H_5SO_2OH + C_6H_5SOH$$
$$C_6H_5SOH + C_6H_5OH = C_6H_5SC_6H_4OH + H_2O$$

as an undistillable oil; he presented no experimental evidence in support of its constitution. Its formation has since been reported by different

[5] C. R. Harington, *Biochem. J.*, **20**, 293, 300 (1926). Harington and Barger, *ibid.*, **21**, 169 (1927).

[6] Wheeler and Jamieson, *Am. Chem. J.*, **33**, 365 (1905).

[7] Two new researches in this field are already in progress in the Sterling Laboratory and are being carried on in coöperation with Messrs. Shailer Bass and George H. Law (T. B. J.).

[8] Hinsberg, *Ber.*, **36**, 107 (1903); German Patent 147,634; *Chem. Zentr.*, **75**, 130 (1904).

investigators,[9] but in no single case have the properties of this phenol been correctly recorded, or has the constitution of Hinsberg's phenol been established. We have repeated Hinsberg's work and have succeeded in obtaining by dealkylation of the methyl ether of this phenol the pure sulfide-phenol, II, and established conclusively its constitution. This was accomplished by heating the methyl ether of the phenol, or the phenol II, with hydrobromic acid in acetic acid under pressure. The sulfide is thereby destroyed with formation of *p*-bromophenol and diphenyldisulfide as is expressed below. This behavior on prolonged heating with strong hydrobromic acid clears up the observation made by Hinsberg that

$$CH_3OC_6H_4SC_6H_5 + HBr = HOC_6H_4SC_6H_5 + CH_3Br$$
$$HOC_6H_4SC_6H_5 + HBr = HOC_6H_4Br + C_6H_5SH$$
$$2C_6H_5SH + O = C_6H_5S_2C_6H_5 + H_2O$$

*p*-methoxydiphenylsulfide yields methyl iodide and diphenyldisulfide when heated with hydriodic acid.

We have also established the constitution of Hinsberg's phenol by a new synthesis of the compound according to the method described by Lecher,[9c] who investigated the action of phenyl sulfochloride on Grignard reagents. This chloride was found to interact smoothly with *p*-bromoanisolemagnesium, yielding *p*-methoxydiphenylsulfide. On demethylating by heating with hydrobromic acid we obtained the same phenol as was formed in the Hinsberg process. Lecher showed also that the sulfide phenol, II, is formed in small yield by direct interaction of phenol with phenyl sulfochloride, but he did not succeed in purifying the compound thus obtained and the method of synthesis is of no practical value.

For the preparation of our three phenols we have made use of the Ziegler reaction. This investigator[10] showed that thiophenols do not interact with diazonium salts in a manner similar to phenols, but combine to give diazothio-ethers which break down at 70° giving an aromatic sulfide and nitrogen. If the reaction is run below 70° the sudden decomposition of an accumulation of the diazothio-ether may result in a violent explosion. The Ziegler reaction is one

$$C_6H_5SNa + C_6H_5N_2Cl = C_6H_5SC_6H_5 + NaCl + N_2$$

that is possible of wide application, but has not been utilized for the preparation of sulfide-phenol combinations. The reaction has been used by Gräebe and Schultess,[11] Weedon and Doughty[12] and Mayer,[13] who applied it successfully with anthranilic acid, thereby leading to the later

[9] (a) Knoevenagel and Polack, *Ber.*, **41**, 3331 (1908); (b) Bourgeois, *Rec. trav. chim.*, **31**, 32 (1912); (c) Lecher, *Ber.*, **58**, 413 (1925).

[10] Ziegler, *Ber.*, **23**, 2469 (1890).

[11] Gräebe and Schultess, *Ann.*, **263**, 1 (1891).

[12] Weedon and Doughty, *Am. Chem. J.*, **33**, 386 (1903).

[13] Mayer, *Ber.*, **42**, 3046 (1909).

development of the chemistry of phenylthiosalicylic acid and the thioxanthones. Mauthner,[14] however, reports no success in his attempts to apply the Ziegler reaction. We likewise have had no success in applying the Ziegler reaction with diazotized aminophenols. However, by treating thiophenol with the diazotized anisidines it is possible to obtain the methoxydiphenyl sulfides in good yields. For the practical application of the Ziegler reaction, two experimental conditions are essential: (1) that the interaction between diazonium salt and thiophenol take place at a temperature at which the former is stable, and thus prevent the formation of a phenol; (2) that the diazonium salt be soluble in water. If the diazonium salt is unstable at 70°, the reaction is best carried out at a lower temperature in the presence of copper powder, which was found to catalyze the decomposition of the diazothio-ether, thus avoiding a possible explosion.

In our study of this reaction we observed that a diazothio-ether can break down with formation of a sulfide and nitrogen and also with production of a diphenyldisulfide and nitrogen. The mechanism of this second change is not correctly understood. For a successful application of the Ziegler reaction it is necessary, therefore, to operate under experimental conditions which favor the decomposition expressed by the first equation.

$$C_6H_5N_2SC_6H_5 \longrightarrow N_2 + C_6H_5SC_6H_5 \quad (1)$$
$$C_6H_5N_2SC_6H_5 \longrightarrow N_2 + C_6H_5S_2C_6H_5 \quad (2)$$

## Experimental Part

**Benzenesulfinic Acid.**—This acid was prepared according to a slight modification of the method of Knoevenagel,[15] by passing sulfur dioxide into a mixture of benzene and aluminum chloride. The sodium benzenesulfinate was isolated and recrystallized twice from water. Because of the instability of the free acid it was kept in the form of the sodium salt until shortly before the acid was required, which was then obtained in the usual manner.

***p*-Methoxydiphenylsulfide.**—This was prepared after a modification of the Hinsberg method,[3,16] by treating freshly distilled phenol with 2 moles of dry benzenesulfinic acid melting at 83°. Dimethyl sulfate was used as the methylating agent instead of methyl iodide. The crude *p*-methoxydiphenylsulfide was found to contain methylphenylsulfone and an oil which was probably *o*-methoxydiphenylsulfide. The methylphenylsulfone separated out of the crude distilled oil, from which it was filtered. It was crystallized from a mixture of ethyl alcohol and water and separated in thin plates melting at 88°.

*Anal.* Calcd. for $C_7H_8O_2S$: S, 20.50. Found: S, 20.48.

This sulfone results from the methylation of benzenesulfinic acid. Its formation was prevented by shaking, before methylation, an ether solution of the crude *p*-hydroxydiphenylsulfide with a solution of sodium carbonate.

The crude *p*-methoxydiphenylsulfide was purified by repeated fractional distillation

[14] Mauthner, *Ber.*, **39**, 1347 (1906).

[15] Knoevenagel, *ibid.*, **41**, 3318 (1908).

[16] See Mauthner, *ibid.*, **39**, 3593 (1906).

and boiled at 194–195° at 13 mm. A 10% yield of a colorless oil having a slight ethereal odor was obtained.

*Anal.*[17] Calcd. for $C_{13}H_{12}OS$: S, 14.80. Found: S, 14.97.

Attempts to improve the yield by a variation of the proportions of reactants and of the reaction temperature were without success. The use of a catalyst such as calcium chloride increased the amount of resinification.

**Demethylation of *p*-Methoxydiphenylsulfide.**—Hinsberg[8] used hydrochloric acid at 180° as the demethylating agent. His work was repeated and the method found to be unsatisfactory, because of the poor yield obtained (17.3%). Attempts to improve it by raising the temperature or increasing the amount of hydrochloric acid led to still further decomposition. The use of aluminum chloride to demethylate was investigated and also found to be unsatisfactory.

The use of a solution of hydrobromic acid in glacial acetic acid under pressure proved to be satisfactory, but a simpler and better procedure is to use a mixture of acetic anhydride and 48% aqueous hydrobromic acid in which the use of pressure bottles and the solution of hydrobromic acid in glacial acetic acid is obviated.

Ninety grams of 48% hydrobromic acid was slowly added to 224 g. of acetic anhydride with cooling in an ice–salt bath. Fifty grams of *p*-methoxydiphenylsulfide was dissolved in this solution, which was contained in a round-bottomed flask provided with a reflux condenser fitted with a calcium chloride tube, and heated at 80–90° for six hours. After completion of the reaction the excess of hydrobromic and acetic acids was removed by distillation under diminished pressure. The remaining oil was treated with a 10% sodium hydroxide solution and heated on a steam-bath for one hour, in order to hydrolyze any acetylated product. After removing the unchanged methoxy compound with ether, the alkaline solution was acidified with hydrochloric acid, when *p*-hydroxydiphenylsulfide separated as an oil. This was extracted with ether and dried over sodium sulfate. After removal of ether, the sulfide was purified by repeated distillation. It boiled at 164–165° at 3 mm. and the yield was 32 g. (68.5%) of a colorless oil, which crystallized in long prisms. They belong to the monoclinic system[18] and have good cleavage into rhomboid fragments. It was recrystallized from petroleum ether, in which it is slightly soluble, and melted at 50–51°. *p*-Hydroxydiphenylsulfide is exceedingly soluble in alcohol, acetic acid, ether and benzene, and soluble to the extent of 34 parts in 100,000 of water. It gives no color test with ferric chloride and Millon's reagent and yields a yellowish-green color with concentrated sulfuric acid, which turns dark blue on heating. The Folin and Denis phosphotungstic acid reagent[19] gives a positive test.

*Anal.* Calcd. for $C_{12}H_{10}OS$: S, 15.86. Found: S, 15.64, 15.50.

***p*-Diphenylsulfide-*p*-nitrobenzoate.**—This was prepared by application of the Schotten–Baumann reaction to *p*-hydroxydiphenylsulfide and *p*-nitrobenzoyl chloride. It crystallized from 95% alcohol in large, yellow prisms melting at 74–75°.

*Anal.* Calcd. for $C_{19}H_{13}O_4NS$: S, 9.19. Found: S, 9.28.

**Destruction of the Sulfide Linkage.**—Sixteen grams of *p*-methoxydiphenylsulfide was dissolved in 62 g. of a 21% solution of hydrobromic acid in glacial acetic acid and then heated for twenty hours at 60° in a pressure bottle. After removal of excess hydrobromic acid and acetic acid, the remaining oil was shaken with 10% sodium hydroxide solution. A white flocculent precipitate separated which was removed with ether. The ether was distilled off and the solid, after recrystallization from 80%

[17] Rogers and Dougherty, THIS JOURNAL, **50**, 1231 (1928).

[18] The crystallographic examination was kindly made by Dr. E. J. Roberts.

[19] Folin and Denis, *J. Biol. Chem.*, **12**, 240 (1912).

alcohol, was identified as diphenyldisulfide. The above 10% sodium hydroxide solution was acidified with hydrochloric acid, extracted with ether, the ether removed and the remaining oil distilled, which proved to be *p*-bromophenol.

Refluxing *p*-methoxydiphenyl sulfide with a 48% hydrobromic acid solution also yielded *p*-bromophenol, diphenyldisulfide and a considerable amount of a resinous product.

**Modification of Hinsberg's Reaction to Obtain *p*-Hydrodiphenylsulfide Directly.**—By this process the steps of methylation and demethylation and their attendant losses are eliminated. Thirty-two grams (2 moles) of benzenesulfinic acid was mixed with 11.5 g. (1 mole) of phenol and heated on a water-bath for two hours. The dark red reaction mixture was shaken with a sodium carbonate solution and distilled with steam to remove the excess of phenol. The contents of the flask were then acidified with hydrochloric acid, which precipitated a resin and caused an oil to separate. This oil was extracted with ether, the ether extract repeatedly washed with sodium carbonate solution, finally with water and then dried over sodium sulfate. After removal of ether the remaining oil was distilled under diminished pressure; 8 g. of crude *p*-hydroxydiphenylsulfide boiling at 165–167° at 4 mm. was obtained. The yield was 30% of the theoretical. By repeated distillation and crystallization this yield was considerably reduced. Three grams of a pale yellow oil boiling at 160–165° at 4 mm. and which did not crystallize on cooling was also obtained. It is probable that we were dealing here with the ortho isomer of our reaction product, but its structure was not established.

***p*-Methoxydiphenylsulfone.**—A modification of Hinsberg's method[20] for the oxidation of sulfides to sulfones by hydrogen peroxide was used. Ten grams of *p*-methoxydiphenylsulfide dissolved in 100 g. of glacial acetic acid, purified by the method of Orton and Bradfield,[21] was treated with 13 g. of 30% hydrogen peroxide solution. The reaction mixture was allowed to stand at room temperature for one hour and finally heated on a hot-plate for another hour. After the acetic acid had been removed the resulting dark brown oil, which solidified on cooling, was dissolved in hot 60% alcohol, treated with boneblack and the solution cooled, when *p*-methoxydiphenylsulfoxide and its sulfone crystallized. The sulfone was obtained free from the sulfoxide by recrystallization from alcohol until the product gave no color with concentrated sulfuric acid. *p*-Methoxydiphenylsulfone[22] crystallizes from alcohol in clusters of colorless needles melting at 90–91° and is soluble in ether, benzene, alcohol and insoluble in petroleum ether and water. A yield of 6 g. of the pure sulfone was obtained (52%).

*Anal.* Calcd. for $C_{13}H_{12}O_3S$: S, 12.92. Found: S, 13.03.

***p*-Hydroxydiphenylsulfone.**—Six grams of *p*-methoxydiphenylsulfone was dissolved in a mixture of 48% aqueous hydrobromic acid and 20.4 g. of acetic anhydride and heated for six hours at 90°. After removal of the excess of hydrobromic acid and acetic acid, the remaining oil, which solidified on cooling, was treated with a 10% sodium hydroxide solution and extracted with ether. The alkaline solution on acidifying with hydrochloric acid yielded an oil which was dissolved in ether, washed with sodium carbonate solution, water and dried over sodium sulfate. The ether was removed and 3 g. of a brown solid recovered. This was purified by crystallization from alcohol when the sulfone separated in clusters of colorless needles melting at 136–137°. It is difficultly soluble in water and petroleum ether and soluble in hot alcohol and benzene. A water solution gave no color with ferric chloride.

[20] Hinsberg, *Ber.*, **41**, 2836, 4294 (1908).

[21] Orton and Bradfield, *J. Chem. Soc.*, **125**, 960 (1924).

[22] Böeseken, *Rec. trav. chim.*, **19**, 19 (1900).

*Anal.* Calcd. for $C_{12}H_{10}O_3S$: S, 13.68. Found: S, 14.08.

**p-Hydroxydiphenylsulfide by Application of the Grignard Reaction.**—Phenylsulfochloride was prepared from diphenyldisulfide according to the method of Lecher.[9c] This was modified slightly by using carbon bisulfide instead of carbon tetrachloride as the solvent during chlorination. Better results were also obtained by distilling the phenylsulfochloride in an atmosphere of carbon dioxide. It boiled at 60–61° at 3 mm. and the yield was 73.5% of the theoretical.

Twelve and one-half grams (1 mole) of *p*-bromo-anisole was slowly added to 1.75 g. of magnesium turnings in 150 cc. of cold dry ether and the reaction started by means of Gilman's activated magnesium–copper alloy.[23] After refluxing the final reaction mixture for six hours, it was cooled and 9.5 g. of phenylsulfochloride dissolved in 20 cc. of ether slowly added. After the vigorous reaction had subsided, it was digested for an hour on a water-bath and then poured into a mixture of ice and sulfuric acid. The ether layer was separated, washed with 5% sulfuric acid, 5% sodium hydroxide and finally dried over sodium sulfate. After removal of ether the *p*-methoxydiphenylsulfide was distilled and boiled at 161–163° at 6 mm. pressure. The yield was 4.5 g., corresponding to 31.6% of the theoretical.

The *p*-methoxydiphenylsulfide was demethylated according to the directions already given and the resulting *p*-hydroxydiphenylsulfide proved to be identical with that obtained by Hinsberg's method.

**Preparation of *p*-Methoxydiphenylsulfide by a Modification of Ziegler's Method.**[10]—71.5 g. of thiophenol was dissolved in a solution of 50 g. of sodium hydroxide and 300 cc. of water. 100 g. of *p*-anisidine was dissolved in 17 g. of hydrochloric acid and 600 cc. of water and then diazotized in the usual manner with a solution of 56 g. of sodium nitrite in 250 cc. of water. After completion of diazotization a solution of sodium acetate was added to reduce the free hydrochloric acid.

The solution of diazotized anisidine was slowly dropped with constant stirring into the alkaline thiophenate solution which was held at 70°. A yellow precipitate was formed which rapidly decomposed with the evolution of nitrogen and the formation of a brown oil. After the major portion of the diazonium salt solution had been added, the reaction mixture became quite viscous because of the emulsification of the oil. It was finally heated upon a steam-bath for one hour to allow any remaining diazothioether to decompose completely. The final reaction product had a slightly aromatic ethereal odor.

The mixture was then acidified with hydrochloric acid and after adding zinc was refluxed for one hour in order to reduce any diphenyldisulfide to thiophenol, which was removed by distilling with steam. The contents of the flask were cooled and extracted with ether. A brown, solid tar, which was insoluble in acid, alkali or ether remained behind. The brown ether extract was repeatedly washed with 5% sodium hydroxide solution until the alkaline solution no longer turned brown, then with dilute hydrochloric acid, water and finally dried over sodium sulfate. After removal of ether, the remaining oil was distilled when a yield of 67 g. of *p*-methoxydiphenylsulfide was obtained boiling at 150–152° at 3 mm. pressure. This corresponds to 66.0% of the theoretical.

After removal of *p*-methoxydiphenylsulfide, the distillation was continued and 11.5 g. of a yellowish-brown oil with a mercaptan odor and boiling over a range of 152–212° at 3 mm. was obtained. Above 212° decomposition set in. From this oil was isolated a solid, which crystallized from 95% alcohol in colorless, matted plates melting at 130–131°. Neither of these substances was further investigated.

An attempt to prepare *p*-hydroxydiphenylsulfide directly by treating sodium thiophenate and diazotized *p*-aminophenol was unsuccessful.

[23] Gilman and Harris, THIS JOURNAL, **49**, 546 (1927).

*o*-**Methoxydiphenylsulfide.**[16]—This was prepared according to a new procedure from sodium thiophenate and diazotized *o*-anisidine in a manner similar to that described for *p*-methoxydiphenylsulfide. *o*-Methoxydiphenylsulfide is a colorless, refractive oil boiling at 150–152° at 3 mm., having a slight aromatic ethereal odor, and was obtained in good yield.

*Anal.* Calcd. for $C_{13}H_{12}OS$: S, 14.8. Found: S, 14.52.

*o*-**Hydroxydiphenylsulfide.**[9b]—The *o*-methoxydiphenylsulfide was demethylated in a manner similar to that described for *p*-methoxydiphenylsulfide. A yield of 68.5% of *o*-hydroxydiphenylsulfide boiling at 140° at 3 mm. was obtained. It was a colorless oil with a phenolic odor and resisted all attempts to effect crystallization. Its solubility in various solvents and its color tests were the same as those described for the para-isomer.

*Anal.* Calcd. for $C_{12}H_{10}OS$: S, 15.85. Found: S, 15.87, 15.35.

*o*-Diphenylsulfide-*p*-nitrobenzoate was prepared and it crystallized from 95% alcohol in large pale yellowish-green prisms melting at 72–73°.

*Anal.* Calcd. for $C_{19}H_{13}O_4NS$: S, 9.19. Found: S, 9.53.

*m*-**Methoxydiphenylsulfide.**—Diazotized *m*-anisidine was treated with an alkaline solution of sodium thiophenate in a manner similar to that described for the preparation of *p*-methoxydiphenylsulfide. In this case the diazothio-ether formed was of a dark red color and the solution rapidly turned dark brown, finally becoming so darkly colored that it was impossible to follow the course of the reaction. As the reaction was taking place there was always a strong odor of aromatic ethers present, evidently due to the formation of *m*-methoxyphenol. A large amount of resin and dyes was also formed. As the diazonium salt of *m*-anisidine is less stable than those of *o*- and *p*-anisidine, the yield was correspondingly lower. *m*-Methoxydiphenylsulfide is a colorless oil boiling at 156° at 4 mm. and the yield was 25.2 g. or 34.7% of the theoretical.

*Anal.* Calcd. for $C_{13}H_{12}OS$: S, 14.8. Found: S, 14.72.

*m*-**Hydroxydiphenylsulfide.**—This was prepared by demethylating the above compound with hydrobromic acid. *m*-Hydroxydiphenylsulfide is a colorless oil which has a slight phenolic odor and boils at 159–161° at 3 mm. The solubility and color tests were the same as those for the para-isomer.

*Anal.* Calcd. for $C_{12}H_{10}OS$: S, 15.85. Found: S, 15.86.

*m*-**Diphenylsulfide-*p*-nitrobenzoate** crystallizes from 95% alcohol in large, yellow plates melting at 103°.

*Anal.* Calcd. for $C_{19}H_{13}O_4NS$: S, 9.19. Found: S, 9.28.

*p*-**Methoxy-*p*-methyldiphenylsulfide.**—This was prepared by treating an alkaline solution of sodium thiocresate with diazotized *p*-anisidine. In this case, however, the oil obtained after removal of the excess of thiocresol solidified on cooling. *p*-Methoxy-*p'*-methyldiphenylsulfide was obtained as an oil boiling at 181–182° at 4 mm. It solidified on cooling and was purified by recrystallizing from 95% alcohol, separating as colorless plates melting at 45–46°. The compound is very soluble in benzene and hot ethyl alcohol.

*Anal.* Calcd. for $C_{14}H_{14}OS$: S, 13.9. Found: S, 13.84.

*p*-**Hydroxy-*p*-methyldiphenylsulfide.**—This was prepared from the above methyl ether by demethylation with hydrobromic acid in glacial acetic acid solution. *p*-Hydroxy-*p'*-methyldiphenylsulfide distilled as a yellow oil boiling at 178–180° at 3 mm., which quickly solidified on standing. It crystallizes from petroleum ether in colorless, oblong plates melting at 67–68°. It is soluble in the common organic solvents and is difficultly soluble in water. It gives no color test with ferric chloride.

*Anal.* Calcd. for $C_{13}H_{12}OS$: S, 14.82. Found: 14.50, 14.52.

General Method for Preparation of Sulfides.—The method as outlined for the preparation of the methoxydiphenylsulfides is not applicable for the preparation of many aromatic sulfides, as many diazonium salts are very unstable at 70° and immediately break down to form the corresponding phenols. A modified method which promises to be applicable for the general preparation of sulfides of the aryl type, was found by using copper as a catalyst for the decomposition of the diazothio-ether.

Fifteen grams of aniline was dissolved in 19.75 g. of concentrated sulfuric acid and 300 cc. of water; 100 g. of ice was added and the mixture diazotized at 0° with a solution of 12 g. of sodium nitrite in 100 cc. of water. The free sulfuric acid was neutralized with sodium acetate.

To a solution of 17.75 g. of thiophenol, 19.3 g. of sodium hydroxide and 100 cc. of water was added 11.5 g. of copper powder. This mixture was constantly stirred during the cooling to 5° and the benzene diazonium salt solution then slowly added through a dropping funnel. The yellow diazothio-ether rapidly broke down with the evolution of nitrogen.

The remainder of this procedure was the same as that for preparing *p*-methoxydiphenylsulfide. After distillation from copper powder, diphenylsulfide was obtained as a colorless oil in a yield of 12.5 g. boiling at 162° at 20 mm.

**Preliminary Examination of the Bacteriological Behavior of the Aromatic Sulfide Phenols.**—A preliminary investigation of the germicidal activity of the sulfide-phenols described above was made by using *B. typhosum* as the test organism and determining the phenol coefficient according to the method developed by the Hygienic Laboratory.

The same results were also obtained with *p*-hydroxydiphenylsulfide after its aqueous solution had been allowed to stand for one year.

TABLE I

COMPARISON OF ANTISEPTIC STRENGTH OF *p*-HYDROXYDIPHENYLSULFIDE AND PHENOL

| Compound | Dilution | Time culture was exposed to action of disinfectant, minutes 2.5 | 5.0 | 7.5 | 10.0 | 12.5 | 15.0 |
|---|---|---|---|---|---|---|---|
| Phenol | 1:80 | − | − | − | − | − | − |
| Phenol | 1:90 | + | − | − | − | − | − |
| Phenol | 1:100 | + | + | + | − | − | − |
| Phenol | 1:110 | + | + | + | + | + | − |
| Phenol | 1:120 | + | + | + | + | + | + |
| *p*-Hydroxydiphenylsulfide | 1:9000 | − | − | − | − | − | − |
| *p*-Hydroxydiphenylsulfide | 1:10000 | − | − | − | − | − | − |
| *p*-Hydroxydiphenylsulfide | 1:11000 | + | + | + | − | − | − |
| *p*-Hydroxydiphenylsulfide | 1:11500 | + | + | + | + | − | − |
| *p*-Hydroxydiphenylsulfide | 1:12000 | + | + | + | + | − | − |

TABLE II

COMPARATIVE PHENOL COEFFICIENTS

| | | |
|---|---|---|
| *p*-Hydroxydiphenylsulfone | Less than | 10 |
| *o*-Hydroxydiphenylsulfide | | 33 |
| *p*-Hydroxy-*p'*-methyldiphenylsulfide | | 50 |
| *m*-Hydroxydiphenylsulfide | | 68 |
| *p*-Hydroxydiphenylsulfide | | 115 |

The phenol coefficients of *o*-hydroxydiphenylsulfide and *p*-hydroxy-*p'*-methyldiphenylsulfide were determined by using them in 20% alcohol solution. Experiments using *p*-hydroxydiphenylsulfide showed that its phenol coefficient factor was only slightly decreased in 20% alcohol. The phenol coefficient of *p*-hydroxydiphenylsulfone was shown to be less than 10 and as it consequently could have no use as an antiseptic, work on this was discontinued.

The case of *p*-hydroxy-*p'*-methyldiphenylsulfide represents an anomaly to a quite general rule that an increase in the carbon chain in a phenolic compound increases its bactericidal action. Its phenol coefficient was calculated by the method of Tilley and Schaffer[24] to be about 300.

The antisepticity of the isomeric hydroxydiphenylsulfides increased in the order of ortho, meta and para substitution. This is in agreement with the work of Schaffer and Tilley[25] on the isomeric cresols and cyclohexanols.

A comparison of the results obtained with *p*-hydroxydiphenylsulfide and *p*-hydroxydiphenylsulfone indicates that the sulfide linkage is the most favorable construction for stimulating high germicidal activity.[26]

**Toxicity of *p*-Hydroxydiphenylsulfide.**—The minimum lethal dose on small rabbits was determined by administering with a stomach tube definite weights of *p*-hydroxydiphenylsulfide until a large enough dose had been given to cause death. These experiments were carried out on young rabbits weighing one pound. Administration of a dose of 1 g. of this sulfur combination produces no apparent effect on the animal. However, when a dosage of 1.4 g. was administered the animal became paralyzed but recovered within twenty-four hours. The test animals died a few hours after the administration of 1.5 g.

The minimum lethal dose for small rabbits, which are no doubt more susceptible than adult rabbits, is 1.5 g. per pound. The phenol is, therefore, comparatively non-toxic. These preliminary toxicity tests were kindly carried out for us by Dr. Paul Pittenger, Pharmacologist, of Baltimore, Maryland.

## Summary

1. In this paper are described methods for obtaining in a pure state the three isomeric monophenols of diphenylsulfide.

2. A preliminary bactericidal and toxicity study of the phenols has been made.

3. The *p*-hydroxydiphenylsulfide shows the highest phenol coefficient of any phenol thus far studied and is a non-toxic substance.

[24] Tilley and Schaffer, *J. Bact.*, **12**, 303 (1926).

[25] Schaffer and Tilley, *ibid.*, **14**, 259 (1927).

[26] We wish to thank Professor W. L. Kulp and Dr. George Hunt of the Department of Bacteriology for their assistance in the determination of the phenol coefficients.

4. The investigation of the phenol derivatives of aromatic sulfides is being continued in this Laboratory.

NEW HAVEN, CONNECTICUT

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

# THE MECHANISM OF THE CLEAVAGE OF DIETHYL $\alpha,\alpha'$-DIBROMO-ADIPATE BY SECONDARY AMINES. A NEW SYNTHESIS OF CYCLOBUTANE DERIVATIVES[1]

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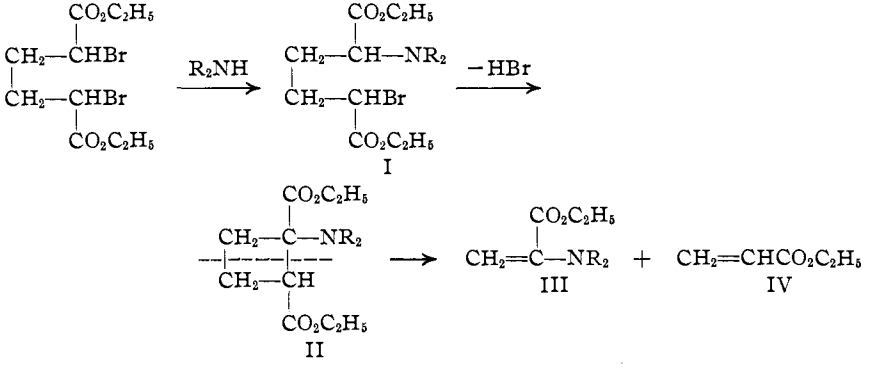
RECEIVED DECEMBER 13, 1928 PUBLISHED MAY 6, 1929

According to evidence presented in previous papers by Fuson[2] and Fuson and Bradley,[3] the cleavage of diethyl $\alpha,\alpha'$-dibromo-adipate by secondary amines discovered by von Braun, Leistner and Münch[4] probably takes place in the following manner



The first step in the reaction is assumed to be the normal replacement of one of the bromine atoms by a dialkylamino group. The cyclobutane intermediate (II) is then produced by the elimination of a molecule of hydrobromic acid. This aminocyclobutane derivative, being unstable under the conditions of the experiment, undergoes dissociation into ethyl acrylate (IV) and ethyl $\alpha$-dialkylamino-acrylate (III).

The cleavage products actually isolated are ethyl pyruvate and ethyl $\beta$-dialkylaminopropionate and are satisfactorily accounted for by the assumption that the $\alpha$-dialkylamino-acrylic ester is hydrolyzed to the pyruvic ester and that ethyl acrylate unites with the dialkylamine to give the $\beta$-dialkylaminopropionic ester.

[1] Presented before the Midwest Regional Meeting of the American Chemical Society at Minneapolis, June 9, 1928.

[2] Fuson, THIS JOURNAL, **50**, 1444 (1928).

[3] Fuson and Bradley, *ibid.*, **51**, 599 (1929).

[4] Von Braun, Leistner and Münch, *Ber.*, **59B**, 1950 (1926). See also von Braun, Jostes and Wagner, *ibid.*, **61B**, 1423 (1928).