

positive at first, no longer diminished in intensity; it was then added in several portions to a boiling solution of 250 cc. of concd. sulfuric acid and 500 cc. of water, and boiling continued for ninety minutes, under reflux. After cooling, solid sodium carbonate was added until just neutral to litmus and the precipitate filtered, washed with water and suspended in 500 cc. of water containing 4.5 g. of sodium hydroxide. After agitating vigorously, any undissolved material was filtered off, and hydrochloric acid (1:1) added to filtrate until just acid to litmus. The precipitate was purified by crystallization from 1000 cc. of boiling water using 2.5 g. of "darco"; yield, 18-20 g. (42-46%).

**4 - Acetylamino - 4' - hydroxydiphenylsulfone.**—Twenty-five grams of aminohydroxysulfone was suspended in 125 cc. of ice water and 25 cc. of acetic anhydride gradually added with mechanical mixing. A gummy mass separated, but on further stirring it hardened to a white crystalline precipitate. After stirring one hour, the material was filtered and washed with water, crystallized from 300 cc. of 50% alcohol, using 1 g. of "darco"; yield, 22 g. (76%).

**4 - Acetylamino - 4' - acetoxydiphenylsulfone.**—Twenty-five grams of aminohydroxysulfone was suspended in 50

cc. of acetic anhydride and 10 drops of concd. sulfuric acid added; the mixture became hot; after boiling under reflux for twenty minutes, the clear solution was cooled and stirred to prevent crystallization to a hard mass, and the crystalline mush added to 500 cc. of water. After adding 40% sodium hydroxide solution until alkaline to litmus, it was filtered and washed well with water, then crystallized from 700 cc. of 50% alcohol using 1 g. of "darco"; yield, 26 g. (78%).

### Summary

Chemical properties and methods of preparation of 4,4'-diaminodiphenylsulfone, 4,4'-diaminodiphenylsulfide, 4-amino-4'-hydroxydiphenylsulfone and their acetyl derivatives are described. The diaminodiphenylsulfone is superior, while the aminohydroxydiphenylsulfone and the acetyl derivatives are about equal to sulfanilamide in their therapeutic effect.

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## Thio Compounds Derived from Aroyl-*o*-benzoic Acids<sup>1</sup>

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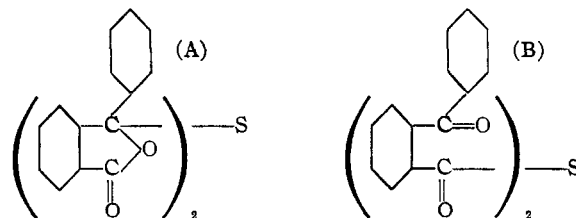
### Introduction

Aroyl-*o*-benzoic acids are of theoretical importance because of their peculiar reactivity to form isomeric derivatives.<sup>2</sup> Blicke and Swisher<sup>3</sup> gave a summary of the evidence for the pseudo and normal forms of these derivatives. A search of the literature revealed no thio compounds of any of the aroyl-*o*-benzoic acids. Hence, a study was undertaken with the object of synthesizing sulfur derivatives of some of these acids, and of investigating their properties. Phosphorus pentasulfide and also hydrogen sulfide were selected as a means for the introduction of sulfur.

A schematic summary of the studies undertaken is given in Chart A. The chart contains the formulas of compounds prepared from *o*-benzoylbenzoic acid. Wherever CH<sub>3</sub> and Cl appear with Roman numerals and arrows on the chart, the analogous types of compounds have also been prepared; these substituents are in the para position.

The mechanism of the reaction of phosphorus pentasulfide upon *o*-benzoylbenzoic acid (I), *p*-

toluyl-*o*-benzoic acid (IX) and 4'-chloro-*o*-benzoylbenzoic acid (XIV), to form 3,3'-diphenyldiphthalidyl sulfide (II), 3,3'-di-(*p*-toluyl)-diphthalidyl sulfide (X) and 3,3'-di-(*p*-chlorophenyl)-diphthalidyl sulfide (XV), respectively, shows the pseudo structures of the aroyl benzoic acids. The fact that hydrogen peroxide oxidation gave (I) and phenyl phthalide (VII), along with the molecular weight indication of a dimolecular type, suggested that the sulfur atom may be attached to a (I) and a (VII) fragment. The analysis checked for the following structures for compound (II)



Both structures (A) and (B) could yield *o*-benzoylbenzoic acid by hydrolysis but it was difficult to account for the formation of phenyl phthalide (VII) by hydrogen peroxide oxidation of a compound with the structure of (B). The graphic representation (B) was further eliminated

(1) Abstracted from a Thesis presented by John O'Brochta to the Graduate School in partial fulfillment of the requirements for the Ph.D. degree.

(2) Meyer, *Monatsh.*, **25**, 475 (1904).

(3) Blicke and Swisher, *THIS JOURNAL*, **56**, 902 (1934).



The m. p. 247° and a mixed m. p. of 247° checked with the previously prepared (II).

(c) **From the Acid Chloride of (I) and Hydrogen Sulfide.**—Compound (I), 100 g., was converted to the acid chloride by the thionyl chloride method.<sup>7</sup> The resultant thick sirup was dissolved in 400 cc. of dry benzene and dry hydrogen sulfide was passed into the boiling solution. There was an immediate and strong evolution of hydrogen chloride. Hydrogen sulfide was passed through the dry solution until the evolution of hydrogen chloride ceased. A heavy white precipitate formed. After cooling, precipitation was completed by adding 200 cc. of petroleum ether. The resultant solid was filtered and extracted with cold 3% sodium hydroxide solution, filtered, and washed free of alkali. A very small amount of (I) was recovered on acidification. After drying the alkali-insoluble residue, followed by three recrystallizations from xylene, washing with petroleum ether, and drying, 60 g. of a white crystalline product resulted; m. p. 246–247°. A mixed m. p. of the product with compound (II), as prepared by the above phosphorus pentasulfide methods, showed no depression.

**Reactions of 3,3'-Diphenyldiphthalidyl Sulfide (II).**—Sodium hydroxide fusion<sup>8</sup> gave a positive test for a divalent sulfur atom. Hydrolysis by refluxing with a 5% alcoholic potassium hydroxide solution and subsequent purification yielded compound (I). The sulfur of (II) was eliminated as hydrogen sulfide. Dehydration with sulfuric acid, according to the conditions prescribed for *o*-benzoylbenzoic acid dehydration,<sup>9</sup> gave anthraquinone. Oxidation with chromic or nitric acid in glacial acetic acid resulted in the formation of (I). Oxidation with 30% hydrogen peroxide at 100° in glacial acetic acid yielded (I) and phenyl phthalide (VII), m. p. 115°. <sup>10</sup> Boiling with aqueous-alcoholic lead acetate solution resulted in the elimination of sulfur from (II) with the formation of lead sulfide and (I). Reactions with phenylhydrazine, aniline and phenol yielded compounds which checked for those obtained by the corresponding reactions of these reagents with the acid (I).<sup>11–13</sup>

**3,3'-Diphenyldiphthalidyl (VI).**—Three grams of 3,3'-diphenyldiphthalidyl sulfide (II) and 6 g. of copper dust were refluxed for three hours in 40 cc. of freshly distilled cymene. A grayish-black precipitate formed. The mixture was filtered hot and the solution deposited a grayish-white solid upon cooling. This was filtered, washed with petroleum ether, and dried. After two recrystallizations from xylene, 2 g. of a white compound (VI) resulted; m. p. 265–266°. The m. p. had to be determined by very slow heating. The mixed m. p. and hydrolytic products, *o*-benzoylbenzoic acid (I) and phenyl phthalide (VII), checked with a purified sample of 3,3'-diphenyldiphthalidyl, prepared according to the method of Eckert and Pollak.<sup>14</sup> This reaction was repeated with thin silver foil and an analogous result was obtained.

(7) Meyer, *Monatsh.*, **22**, 787 (1901).

(8) Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1904, Vol. IV, p. 11.

(9) Dougherty and Gleason, *THIS JOURNAL*, **52**, 1024 (1930).

(10) Beilstein, "Handbuch der organischen Chemie," fourth edition, Band X, System No. 1297, pp. 727, 759.

(11) Meyer, *Monatsh.*, **30**, 481 (1909).

(12) Meyer, *ibid.*, **28**, 1211 (1907).

(13) Von Pechmann, *Ber.*, **13**, 1613 (1880).

(14) Eckert and Pollak, *Monatsh.*, **38**, 16 (1917).

**Thiodiphenyl phthalide (III).**—Twenty-five grams of 3,3'-diphenyldiphthalidyl sulfide (II) was mixed with 25 g. of anhydrous aluminum chloride in 300 cc. of benzene. The mixture was heated at 75–78° for eighteen hours in analogous manner to the preparation of *o*-benzoylbenzoic acid (I) from phthalic anhydride and benzene. Hydrogen chloride was evolved copiously but only traces of hydrogen sulfide. The reddish-brown mass was cooled, decomposed with cold dilute hydrochloric acid, and was extracted with 200 cc. of benzene. The extract was washed with water and vacuum distilled to dryness; a faintly yellow solid remained. Four recrystallizations from ethanol and a final recrystallization from a 2:1 benzene-petroleum ether solution yielded 6 g. of white crystals (III); m. p. 162°. A mixed m. p. checked with thiodiphenyl phthalide as prepared by Kleibacker.<sup>15</sup> Diphenyl phthalide (VIII)<sup>4</sup> was recovered from the filtrates.

*Anal.* Calcd. for C<sub>20</sub>H<sub>14</sub>OS: S, 10.60. Found: S, 10.77; 10.84.

Kleibacker's structure for thiodiphenyl phthalide (III) was concurred by hydrogen peroxide oxidation in acetic acid of (III) to (VIII) and by the conversion with phosphorus pentasulfide of (III) to dithiodiphenyl phthalide (IV).

*Anal.* Calcd. for C<sub>20</sub>H<sub>14</sub>S<sub>2</sub>: S, 20.14. Found: S, 20.05, 20.08.

Hydrogen peroxide oxidation in acetic acid of (IV) yielded diphenyl phthalide (VIII).

**2-Phenyl-3,4-benzothiophene (V).**—Fifty grams of (I) was mixed in 600 cc. of xylene in a reflux apparatus equipped with a calcium chloride drying tube. The mixture was heated to boiling on an oil-bath; 50 g. of phosphorus pentasulfide was added, and the mixture refluxed for four hours. Hydrogen sulfide was evolved and a purplish-brown color appeared within an hour. This coloration deepened as the reaction proceeded. The hot solution was filtered; a charry residue and some unchanged phosphorus pentasulfide remained. The xylene solution was steam distilled, leaving a reddish-brown gum which solidified on cooling. It was boiled for two hours with 10 g. of sodium hydroxide in 300 cc. of 80% ethanol. The mixture was cooled and filtered. The filtrate was reddish-brown in color but on acidification it gave only traces of hydrogen sulfide and a slight turbidity; no *o*-benzoylbenzoic acid (I) was recovered. The alcoholic-alkali insoluble residue was washed with water and dried in a vacuum desiccator. The solid was then boiled in 200 cc. of xylene and filtered hot. Upon cooling, the filtrate yielded a reddish-brown solid it was filtered; the residue weighed 7 g. after drying. It was treated again with alcoholic sodium hydroxide and then recrystallized 3 times from xylene. Four grams of reddish-brown needles (V), m. p. 236–237°, was obtained. The combined xylene filtrates were steam distilled and 35 g. of a brownish-red gum remained in the distilling flask. The gum was dried, after which it solidified to a brittle mass. Attempts to crystallize something from it proved unsuccessful. By dissolving the gum in 500 cc. of xylene and refluxing for three hours with 25 g. of phosphorus pentasulfide, as in its original preparation, three more

(15) W. Kleibacker, Ph.D. Thesis, University of Pittsburgh, June, 1938.

TABLE I

No.	Compound	Reagents used	Solvent, cc.	Time, hrs. at b. p. of solvent	Yield, %	M. p., °C.
1	3,3'-Di-( <i>p</i> -tolyl)-diphthalidyl sulfide (X) <sup>a</sup>	20 g. (IX), 20 g. P <sub>2</sub> S <sub>5</sub>	700 benzene	24	30	212
2	3,3'-Di-( <i>p</i> -chlorophenyl)-diphthalidyl sulfide (XV) <sup>b</sup>	20 g. (XIV), 20 g. P <sub>2</sub> S <sub>5</sub>	500 benzene	24	40	232
3	2-( <i>p</i> -Tolyl)-3,4-benzothiophene (XI)	50 g. (IX), 50 g. P <sub>2</sub> S <sub>5</sub>	600 xylene	2.5	8	217
4	2-( <i>p</i> -Chlorophenyl)-3,4-benzothiophene (XVI)	8 g. (XIV), 8 g. P <sub>2</sub> S <sub>5</sub>	200 xylene	5	12	241-42
5	3,3'-Di-( <i>p</i> -tolyl)-diphthalidyl (XII) <sup>c</sup>	5 g. (X), 28 g. Ag foil	50 cymene	14	70	247-48
6	3,3'-Di-( <i>p</i> -chlorophenyl)-diphthalidyl (XVII) <sup>d</sup>	1 g. (XV), 8 g. Ag foil	75 cymene	6	90	247
7	<i>p</i> -Tolylphthalide (XIII) <sup>e</sup>	2.5 g. (X), 2 g. 30% H <sub>2</sub> O <sub>2</sub>	50 HOAc	3 <sup>o</sup>		128
8	<i>p</i> -Chlorophenyl phthalide (XVIII) <sup>f</sup>	10 g. (XV), 20 g. 30% H <sub>2</sub> O <sub>2</sub>	100 HOAc	2 <sup>o</sup>	50	124

No.	Formula	Calcd.	Carbon, % Found	Calcd.	Hydrogen, % Found	Calcd.	Sulfur, % Found	Calcd.	Chlorine, % Found
1	C <sub>30</sub> H <sub>22</sub> O <sub>4</sub> S	75.29	75.15, 75.37	4.63	4.53, 4.59	6.69	6.52, 6.62		
2	C <sub>28</sub> H <sub>18</sub> O <sub>4</sub> SCl <sub>2</sub>					6.17	6.27, 6.18	13.65	13.77, 13.70
3	C <sub>18</sub> H <sub>12</sub> S	80.31	80.06, 80.28	5.39	5.21, 5.29	14.30	14.31, 14.21		
4	C <sub>14</sub> H <sub>8</sub> SCl	68.70	68.31, 68.38	3.71	4.09, 4.06	13.10	12.89, 13.05	14.49	14.60, 14.75
5	C <sub>30</sub> H <sub>22</sub> O <sub>4</sub>								
6	C <sub>28</sub> H <sub>18</sub> O <sub>4</sub> Cl <sub>2</sub>								
7	C <sub>18</sub> H <sub>12</sub> O <sub>2</sub>								
8	C <sub>14</sub> H <sub>8</sub> O <sub>2</sub> Cl	68.70	68.60, 68.42	3.71	3.45, 3.59			14.50	14.42, 14.66

<sup>a</sup> (X) was prepared (60% yield) by the action of hydrogen sulfide on the acid chloride of (IX) as described above for (II). <sup>b</sup> (XV) was prepared (68% yield) by the action of hydrogen sulfide on the acid chloride of (XIV) as described above for (II). <sup>c</sup> Previously prepared by phosphorus-hydriodic acid reduction of (IX), reported by Limaye [*Chem. Zentr.*, **104**, I, 1777 (1933)]. <sup>d</sup> Previously prepared by aluminum-sulfuric acid reduction of (XIV), method described by Eckert and Pollak.<sup>14</sup> <sup>e</sup> Previously prepared by reduction of (IX) with zinc dust and ammonia, Limpricht [*Ann.*, **314**, 251 (1901)]. <sup>f</sup> Converted to (XIV) by chromic anhydride oxidation according to the method described for the oxidation of (VII) to (I), (Beilstein, "Handbuch der organischen Chemie," fourth edition, Band XVII, System No. 2467, p. 361). <sup>o</sup> At 100°.

grams of compound (V) was recovered. The combined products (V), 7 g., were recrystallized from xylene; m. p. 236-237°. 2-Phenyl-3,4-benzothiophene (V) is slightly soluble in cold benzene, toluene, xylene, carbon disulfide and hot glacial acetic acid; very soluble in hot xylene and nitrobenzene; insoluble in hot or cold alcohol, ether, petroleum ether and aqueous media.

*Anal.* Calcd. for C<sub>14</sub>H<sub>10</sub>S: C, 79.96; H, 4.79; S, 15.25; mol. wt., 210. Found: C, 80.01, 80.29; H, 4.72, 4.73; S, 15.02, 15.05; mol. wt., 223, 239.

**Reactions of 2-Phenyl-3,4-benzothiophene (V).**—Sodium hydroxide fusion was carried out according to the method described by Mulliken,<sup>8</sup> except that a steel bomb and five minutes of heating at 340-350° were used. A positive test for a divalent sulfur was obtained. Attempted hydrolysis with alcoholic sodium hydroxide resulted in no change. Stability toward metals: 2 g. of (V) and 8 g. of copper powder were heated in diphenyl at 255-265° for four and one-half hours. Compound (V) was recovered unchanged. Boiling the compound in xylene with an equal weight of metallic sodium or mercuric oxide gave the same result. The isatin thiophene test was negative. Oxidations of (V) in glacial acetic acid with potassium permanganate, hydrogen peroxide, 1:1 nitric acid or chromium anhydride yielded a yellow compound melting at 186°.

In addition to the above compounds, the following homologs and analogs have been prepared and their data given in Table I. The respective oxidation, reduction and hydrolytic products are given in Chart A.

## Summary

1. Thio compounds and derivatives of three aryl-*o*-benzoic acids have been prepared and their properties studied.

2. The following new compounds have been prepared by the reaction of phosphorus pentasulfide in benzene: (a) 3,3'-diphenyldiphthalidyl sulfide (II), (b) 3,3'-di-(*p*-tolyl)-diphthalidyl sulfide (X), (c) 3,3'-di-(*p*-chlorophenyl)-diphthalidyl sulfide (XV). These sulfides were also prepared by the corresponding reactions of the acid chlorides with hydrogen sulfide.

3. The reaction of phosphorus pentasulfide in boiling xylene produced colored sulfur-containing compounds to which a thiophene type structure was ascribed tentatively: (a) 2-phenyl-3,4-benzothiophene (V), (b) 2-(*p*-tolyl)-3,4-benzothiophene (XI), (c) 2-(*p*-chlorophenyl)-3,4-benzothiophene (XVI).

4. A new method of preparation of the following compounds is reported: (a) 3,3'-diphenyldiphthalidyl (VI), (b) 3,3'-di-(*p*-tolyl)-diphthalidyl (XII), (c) 3,3'-di-(*p*-chlorophenyl)-diphthalidyl (XVII).

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