

[CONTRIBUTION FROM THE DERMATOLOGICAL RESEARCH LABORATORIES, DIVISION OF ABBOTT LABORATORIES]

**Chemistry and Chemotherapy of 4,4'-Diaminodiphenylsulfone, 4-Amino-4'-hydroxydiphenylsulfone and Related Compounds<sup>1</sup>**

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4,4'-Diaminodiphenylsulfone was prepared by Fromm and Wittmann<sup>2</sup> by reduction of the corresponding dinitro compound which they obtained by the oxidation of 4,4'-dinitrodiphenylsulfide. They prepared the latter compound by action of sodium sulfide on *p*-chloronitrobenzene according to Nietzki and Bothof.<sup>3</sup> Our attempts to follow this method had produced an impure product from which the dinitrosulfide could be obtained only in very poor yields, after numerous recrystallizations. This was in accordance with the findings of Kehrman and Bauer,<sup>4</sup> who showed that the reaction between sodium sulfide and *p*-chloronitrobenzene could produce a mixture of seven compounds.

We prepared the diaminosulfone by oxidation of the 4,4'-diaminodiphenylsulfide (thioaniline), protecting the amino groups by acetylation, and subsequently hydrolyzing. Hoffman<sup>5</sup> had prepared thioaniline by heating aniline, sulfur, and lead oxide (PbO). The yields were not good and the method rather unwieldy. We chose as our starting material 4-nitro-4'-aminodiphenylsulfide which Hodgson and Rosenberg<sup>6</sup> had prepared by reaction of sodium *p*-aminothiophenol and *p*-chloronitrobenzene. Lantz<sup>7</sup> described a two-stage reaction in which an excess of sodium sulfide reacted with *p*-chloronitrobenzene to form sodium *p*-aminothiophenol and without isolating the material another equivalent of *p*-chloronitrobenzene was added to the reaction mixture, the final product was 4-nitro-4'-aminodiphenylsulfide in good yields and fairly pure.

4'-Amino-4'-hydroxydiphenylsulfone was prepared by diazotization of 4-amino-4'-acetylamino-diphenylsulfone and simultaneous deacetylation and replacement of the diazo group by hydroxyl. The 4-amino-4'-acetylamino compound was prepared by reduction of 4-nitro-4'-acetylamino-diphenylsulfone which was obtained by oxidation of the corresponding sulfide.

Buttle<sup>8</sup> and others<sup>9,10</sup> discovered that 4,4'-diaminodiphenylsulfone had a better curative effect in  $\beta$ -hemolytic streptococcus infection of mice than sulfanilamide. In a recent publication we have shown<sup>11</sup> that diaminodiphenylsulfone and the corresponding sulfide were more toxic for rabbits than sulfanilamide. The diacetyl derivatives of the sulfone and sulfide were, however, considerably less toxic than sulfanilamide. We found that the therapeutic effect of diaminodiphenylsulfone was considerably better than that of sulfanilamide. Therapeutic effects of the sulfide and the diacetyl derivatives of the sulfone and sulfide compared favorably with that of sulfanilamide. 4-Amino-4'-acetylamino-diphenylsulfone, 4-amino-4'-hydroxydiphenylsulfone, 4-acetylamino-4'-hydroxydiphenylsulfone and 4-acetylamino-4'-acetoxydiphenylsulfone were of about the same therapeutic effectiveness in experimental streptococcal infection as sulfanilamide, but they were inferior to diaminodiphenylsulfone.

**Experimental Part****Preparation of 4,4'-Diaminodiphenylsulfone**

**4-Nitro-4'-aminodiphenylsulfide.**—The method was essentially that of Lantz: a mixture of 480 g. of sodium sulfide, dissolved in 2000 cc. of water, and 128 g. of *p*-chloronitrobenzene was refluxed for eight hours; 128 g. of *p*-chloronitrobenzene was added and refluxing was continued for fifteen hours. The mixture was steam distilled to remove unchanged *p*-chloronitrobenzene, breaking up lumps which had tendency to form. After cooling the non-volatile portion, the crude orange-yellow crystals were filtered off; yield, 160 g. (80%). The material was recrystallized from alcohol.

**4,4'-Diaminodiphenylsulfide (Thioaniline).**—To a boiling suspension of 200 g. of nitroaminosulfide in a mixture of 530 cc. of concd. hydrochloric acid and 500 cc. of water, 180 g. of tin turnings was added slowly and after solution was complete, 40 cc. of concd. hydrochloric acid and 22 g. of tin were added. After ten minutes of boiling, 2 g. of "darco" was added, the solution then boiled fifteen minutes longer and filtered hot. After thorough cooling, 40% sodium hydroxide solution was added until strongly alkali-

(1) Presented before Division of Medicinal Chemistry, A. C. S., Baltimore, April 6, 1939.

(2) Fromm and Wittmann, *Ber.*, **41**, 2264 (1908).

(3) Nietzki and Bothof, *ibid.*, **27**, 3261 (1894).

(4) Kehrman and Bauer, *ibid.*, **29**, 2362 (1896).

(5) Hoffman, *ibid.*, **27**, 2807 (1894).

(6) Hodgson and Rosenberg, *J. Chem. Soc.*, 180 (1930).

(7) French Patent 715,359; English Patent 376,961; U. S. Patent 1,965,776.

(8) Buttle, *Lancet*, 1331 (1937).

(9) E. Fourneau, J. and MMe. J. Trefouel, F. Nitti, and D. Bovet, *Bull. Acad. Med.*, **118**, 210 (1937).

(10) H. Bauer and S. M. Rosenthal, *Pub. Health Rept.*, **53**, 40 (1938).

(11) G. W. Raiziss, M. Severac, J. C. Moetsch, and L. W. Clemence, *Proc. Soc. Exptl. Biol. Med.*, **39**, 339 (1938).

line, the thick pasty precipitate changing to a gray-colored curd which was filtered and washed with water until washings were neutral to litmus, and drained well. The material was suspended in 1200 cc. of boiling alcohol, 5 g. of "darco" added and refluxed for thirty minutes. The hot, almost colorless filtrate was added to 10 liters of cold water with stirring, precipitating a white, fluffy precipitate which was filtered and dried in vacuum; yield, 140 g. (80%). The product was fairly pure, it was recrystallized further from 50% alcohol.

**4,4'-Diacetylaminodiphenylsulfide.**—To 140 g. of diaminodiphenylsulfide suspended in 200 cc. of glacial acetic acid, 140 cc. of acetic anhydride was added gradually with stirring, the mixture then refluxed for one hour and poured into 8 liters of ice and water, stirring well to break up lumps. The precipitate was filtered and washed with water until free of acetic acid and dried in vacuum; yield, 190 g. (97%). It was purified by recrystallization from alcohol.

**4,4'-Diacetylaminodiphenylsulfone.**—One hundred and fifty grams of potassium dichromate was dissolved in 2000 cc. of water and 1400 cc. of concd. sulfuric acid added. After cooling to 15° the mixture was added slowly with stirring to a solution of 100 g. of diacetylaminodiphenylsulfide in 1000 cc. of glacial acetic acid (dissolved by warming, then cooled to 20°). The reaction mixture was kept below 20° by external cooling and, after addition was complete, allowed to stand at room temperature for ninety minutes. It was then poured into 24 liters of ice and water, with stirring; the precipitate was filtered and washed with water until free of acid; yield, 70 g. (63%). It was purified by dissolving 50 g. in a boiling mixture of 1500 cc. of alcohol and 200 cc. of water; after adding 2.5 g. of "darco" and refluxing for thirty minutes, it was filtered hot and added to 6000 cc. of ice water; yield 35 g.

**4,4'-Diaminodiphenylsulfone.**—A suspension of 100 g. of crude diacetylaminodiphenylsulfone in 360 cc. of concd. hydrochloric acid and 300 cc. of water was heated under reflux for two hours. To the solution which was obtained 4 g. of "darco" was added and heating continued twenty minutes, then filtered and cooled well. Solid sodium carbonate was added with stirring until slightly alkaline to litmus. The precipitate was filtered and washed with water. The crude product, after vacuum drying, weighed

65 g. (87%). It was purified by refluxing in 1000 cc. of 40% alcohol, to which 5 g. of "darco" was added, for thirty minutes, and after filtering through a steam funnel and adding to 1000 cc. of hot water, it was mixed well with 3000 g. of ice; yield, 55–60 g.

#### Preparation of 4-Amino-4'-hydroxydiphenylsulfone

**4-Nitro-4'-acetylaminodiphenylsulfide.**—Two hundred and fifty grams of 4-nitro-4'-aminodiphenylsulfide was suspended in 500 cc. of glacial acetic acid and 150 cc. of acetic anhydride added gradually with stirring. The mixture was refluxed for two hours and poured into 7500 cc. of ice water with efficient stirring to break up lumps, then filtered and the crystalline precipitate washed with water until free of acid; yield, 290 g. (98%). It was purified by recrystallization from alcohol.

**4-Nitro-4'-acetylaminodiphenylsulfone.**—One hundred grams of nitro-acetylaminosulfide was oxidized using the quantities and method described in the case of diacetylaminosulfide; yield, 90 g. (81%). The material was only slightly soluble in hot alcohol and required a large volume for recrystallization.

**4-Amino-4'-acetylaminodiphenylsulfone.**—A solution of 203 g. of stannous chloride in 600 cc. of alcohol was added to a boiling suspension of 100 g. of the crude nitro compound in 600 cc. of alcohol; the mixture was refluxed for fifteen minutes and a clear solution was obtained. After thorough cooling an excess of 40% sodium hydroxide solution (about 750 cc.) was added, followed by the addition of 10 liters of water, stirring to break up lumps. The precipitate was filtered and washed with water until the washings were neutral, and sucked fairly dry on the funnel; it was then refluxed in 1300 cc. of alcohol for one hour with 5 g. of "darco" added, filtered hot, and the solution diluted with five volumes of ice water. On stirring a crystalline precipitate separated; yield, 60 g. (66%). It was purified by recrystallization from 50% alcohol.

**4-Amino-4'-hydroxydiphenylsulfone.**—A suspension of 50 g. of aminoacetylamine in 380 cc. of water and 33 cc. of concd. sulfuric acid, was cooled to 0–5°, and diazotized by a solution of 12.5 g. of sodium nitrite in 40 cc. of water. The nitrite solution was added dropwise, with mechanical mixing, in thirty minutes. The mixture was further stirred until a test with starch-iodide paper, which was strongly

TABLE I  
COMPOUNDS, PROPERTIES AND ANALYSES

Diphenylsulfide	Appearance	M. p. °C.	Formula	Analyses			
				% N Calcd.	% N Found	% S Calcd.	% S Found
4-Nitro-4'-amino-	Orange-yellow plates	145 <sup>a</sup>	NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> SC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	11.38	11.17	13.00	12.70
4,4'-Diamino-	Colorless needles	108	NH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> SC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	12.96	12.93	14.81	14.62
4,4'-Diacetylamino-	Colorless plates	223–224 <sup>b</sup>	CH <sub>3</sub> CONHC <sub>6</sub> H <sub>4</sub> SC <sub>6</sub> H <sub>4</sub> NHOCCH <sub>3</sub>	9.33	9.22	10.66	10.62
4-Nitro-4'-acetylamino-	Pale yellow needles	198 <sup>c</sup>	NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> SC <sub>6</sub> H <sub>4</sub> NHOCCH <sub>3</sub>	9.72	9.48	11.11	10.80
Diphenylsulfone							
4,4'-Diamino-	Almost colorless plates	175 <sup>d</sup>	NH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	11.29	10.98	12.88	12.99
4,4'-Diacetylamino-	Pale yellow leaflets	285 <sup>d</sup>	CH <sub>3</sub> CONHC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> NHOCCH <sub>3</sub>	8.43	8.18	9.63	9.70
4-Nitro-4'-acetylamino-	Cream colored needles	229–230	NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> NHOCCH <sub>3</sub>	8.75	8.44	10.00	9.74
4-Amino-4'-acetylamino-	Pale yellow leaflets	242–243	NH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> NHOCCH <sub>3</sub>	9.65	9.31	11.03	10.74
4-Amino-4'-hydroxy-	Colorless prisms	193–194	NH <sub>2</sub> C <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> OH	5.62	5.50	12.80	12.69
4-Acetylamino-4'-hydroxy-	Colorless leaflets	274–275	CH <sub>3</sub> CONHC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> OH	4.81	4.85	10.99	11.04
4-Acetylamino-4'-acetoxy-	Colorless prisms	171–172	CH <sub>3</sub> CONHC <sub>6</sub> H <sub>4</sub> SO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> OOCCCH <sub>3</sub>	4.20	4.22	9.60	9.90

<sup>a</sup> Kehrman and Bauer and Lantz reported 143°. <sup>b</sup> Merz and Weith [*Ber.*, **4**, 390(1871)] reported 213–215°, Nietzki and Bothof reported 211°. <sup>c</sup> Kehrman and Bauer reported 193°. <sup>d</sup> Fromm and Wittmann reported 174° for diamino, 280° for diacetyl.

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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RECEIVED JULY 19, 1939

[CONTRIBUTION NO. 383 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

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

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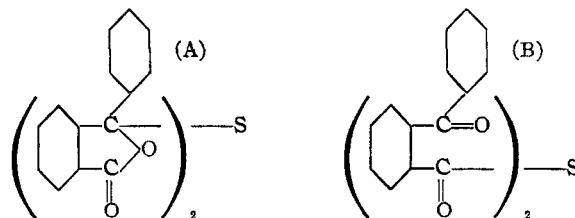
### Introduction

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).