been included for the index of refraction curve. The values of the material of lesser purity would give a curve of similar slope and would come between the two curves of allene and methylacetylene tetrabromides. Curiously, however, it is nearer the latter than the former. This shows clearly that index of refraction data, and density data as well, are apt to be quite misleading in these two cases as a means of identification unless *pure* substances are at hand. In other words, a mixture of allene and methylacetylene could not be analyzed even with fair accuracy by conversion to the tetrabromide mixture, if boiling point, density or n_D values are the basis of evaluation. Fortunately, however, their analysis[15] may be effected readily in another manner.

Summary

Methylacetylene has been prepared in a high state of purity from methyl iodide and sodium acetylide in liquid ammonia. Preparing it by dehalogenation of propylidene chloride is not to be recommended because of poor yields, whereas similar preparation from propylene bromide invariably gives rise to allene as well. Such a mixture cannot be readily separated by fractional distillation, although the percentage of allene was lowered from 5.5 to 1.2 by this means. Methylacetylene tetrabromide was prepared from all three sources, and the physical constants studied.

Allene tetrabromide was made by the addition of bromine either to allene or to dibromo-2,3-propene-1. For purposes of high purity, it must be purified by several crystallizations as well as by fractional vacuum distillation. Such material melts at 10.7°. Boiling point, specific gravity and index of refraction data were obtained.

Evanston, Illinois

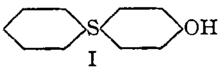
[Contribution from the Department of Chemistry, Yale University]

THE SYNTHESIS OF SOME IODATED DIPHENYL-SULFIDE PHENOLS[1]

By Shailer L. Bass and Treat B. Johnson

Received October 16, 1929 Published March 6, 1930

In quest of phenolic compounds possessing properties requisite for their practical use in internal antisepsis, Hilbert and Johnson[2] have recently extended the research program of this Laboratory on germicides into the field of the diaryl-sulfide phenols. *p*-Hydroxydiphenyl-sulfide, I, with its high germicidal value and low toxicity (phenol coefficient 115) has proved the most promising of these derivatives thus far examined.



I

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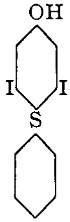
[1] Constructed from a dissertation presented by Shailer L. Bass in June, 1929, to the Faculty of the Graduate School of Yale University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Hilbert and Johnson, This Journal, **51**, 1526 (1929).

It is well known that the substitution of halogen in the benzene nucleus of phenolic compounds leads to derivatives of considerably higher germicidal power than is possessed by the unsubstituted compounds.[3] In order to increase our knowledge of this particular influence on antiseptic power, we have directed our attention in this research to the study of some iodine derivatives of diphenyl-sulfide phenols. This element is known to function in a manner important to animal metabolism when present in compounds structurally related to tyrosine,[4] as in thyroxine.[5] The latter can be regarded as an α-amino acid derivative of a tetra-iodated *p*-hydroxydiphenyl oxide. The results obtained by Harington[5] lend new interest to the postulation that iodated derivatives of the structurally related *p*-hydroxydiphenyl-sulfide, I, may also possess thyroxine-like activity, or exercise some other specific physiological action of therapeutic value.

Two isomeric di-iododiphenyl-sulfide phenols II and IV and their respective methyl homologs III and V have been synthesized. In order to obtain an indication of the possible effect of substituting halogen in the second benzene ring[6] the compound VI has also been prepared. It is to be noted here that no attention has been paid thus far to thyroxine-like constructions in which the iodine atoms occupy *meta* positions with respect to the hydroxyl group, or unsymmetrical positions in the benzene rings. Also, we have practically no knowledge of the spacial influence of iodine with respect to the hydroxyl group in sulfide phenols upon the antiseptic power of such combinations.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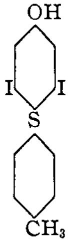
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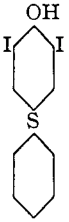
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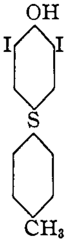
V


VI

A survey of the chemical literature revealed the fact that only a small number of unsymmetrical halogen derivatives of diphenyl-sulfide had been prepared, and no iodated diaryl-sulfide phenols were known when we began this work. In order to obtain the intermediates desired for the final synthesis of the phenols II and III, 3,4,5-tri-iodonitrobenzene, VII, was

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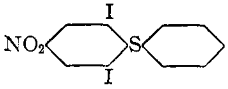
[3] S. Frankel, "Arzneimittel-Synthese," J. Springer, Berlin, 1927, 6th ed., p. 610; Bechold and Ehrlich, *Z. physiol. Chem.*, **47**, 173 (1906).

[4] Wheeler and Jamieson, *Am. Chem. J.*, **33**, 365 (1905); Harington and Randall, *Chem. Ind.*, **48**, 296 (1929).

[5] Harington and Barger, *Biochem. J.*, **21**, 169 (1927).

[6] *Cf.* "Halogen Derivatives of Benzyl-resorcinol," Klarmann and Von Wowern This Journal, **51**, 605 (1929).

condensed with sodium thiophenate and sodium *p*-thiocresolate, respectively. This reaction is applied with the greatest success by working in 90% alcohol solution.



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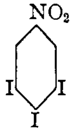
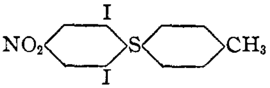


VII



IX

The nitro compounds VIII and IX were reduced with stannous chloride and hydrochloric acid to the corresponding amines. Using these reagents the iodine atoms substituted in the benzene nucleus were not replaced. These amines were so weakly basic that their hydrochlorides were unstable in water and were prepared for our work by passing anhydrous hydrogen chloride into absolute ether solutions of the amines. Diazotization was applied with success by treating the hydrochloride suspended in glacial acetic acid with butyl nitrite. The resulting solutions of the diazonium salts were then diluted with water, and poured slowly into boiling 60% sulfuric acid, when the phenols II and III were formed. Attempts to utilize the Ziegler reaction[7] for the synthesis of iodated sulfide derivatives applicable for the synthesis of the phenols IV and V were without success. The interaction of 2,6-di-iodo-4-amino-anisole-diazonium chloride,[8] for example, with thiophenol in alkaline solution yielded a very stable diazothio-ether. When this latter compound was decomposed, a complex mixture of products was obtained from which diphenyl disulfide, but none of the methyl ether of the phenol IV, could be isolated.

The fact that this type of decomposition can be effected in an anhydrous solvent such as toluene suggests that the reaction does not proceed in accordance with the mechanism proposed by Hantzsch and Freese;[9] that the formation of diphenyl disulfide results from hydrolysis of the diazothioether, and the subsequent oxidation of the thiophenol by the air. When *p*-anisidine diazonium chloride solution is allowed to interact with an alkaline solution of thiophenol, the diazothio-ether is so unstable that it cannot be isolated. Decomposition leads to the formation of *p*-methoxydiphenyl-sulfide,[2] which can easily be demethylated to form the phenol I.

The great difference in the stability and the character of the decomposition of these two very similar diazothio-ethers may be explainable by the structural relation between the nitrogen and the sulfur atoms as expressed by Hantzsch and Freese's[9] "anti" and "syn" forms. Theoretically the "syn" form should readily yield sulfides. However, the reaction between diazonium salts and mercaptans in alkaline solution is practically instan-

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

[8] Kalb, Schweizer, Zellner and Berthold, *ibid.*, **59**, 1869 (1926).

[9] Hantzsch and Freese, *ibid.*, **28**, 3237 (1895).

taneous, so that diazothio-ethers may also exhibit the type of structural isomerism postulated by Hantzsch[10] for the diazonium salts. More work must be done upon the structure of the diazonium salts and their diazothio-ethers before this point can be decided finally.

The two *ortho*-di-iodated phenols, IV and V, were obtained by iodation of *p*-hydroxy-diphenyl sulfide I and the corresponding *p*-hydroxy-*p'*-methyl-diphenyl sulfide, respectively. The method of Datta and Prosad,[11] as modified by Harington,[12] was used. Iodine in potassium iodide solution was added to a warm solution of the diphenyl sulfide phenol in a large quantity of concentrated ammonia which contained ammonium sulfate. Under these conditions the hydroxyl group directed the entering halogen atoms instead of the sulfur atom as in all previous experiments on the halogenation of aromatic sulfides.[13] Iodation in the cold, however, or in ammonium hydroxide solutions containing methyl alcohol as a solvent resulted in the formation of a large amount of tar insoluble in dilute sodium hydroxide.

On account of the extreme insolubility of our iodated sulfide phenols in water, they did not exhibit any pronounced bactericidal properties. Saturated solutions of all five iodated compounds in water, 5 or 20% alcohol solutions, were without effect on *Bact. typhosum*, as compared with phenol in the same solvents. The pharmacological properties of these compounds, in particular the thyroxine-like action, will be investigated. Other halogenated compounds of this series will also be examined and their pharmacological properties determined.

Experimental Part

4-Nitro-2,6-di-iodo-diphenylsulfide, VIII.—Twenty grams of 3,4,5-tri-iodo-nitrobenzene[5,8] was suspended in 800 cc. of boiling 90% alcohol and a solution containing one equivalent of sodium thiophenate added. The latter was prepared by adding 0.92 g. of sodium to 4.4 g. of thiophenol in 50 cc. of alcohol. The tri-iodonitrobenzene rapidly dissolved and the solution acquired a light orange color. After heating under a reflux condenser for five hours, one-half of the alcohol was distilled off and the hot solution then diluted with water. On cooling, an 86% yield of the pure nitro compound was obtained. Two crystalline modifications were observed; canary-yellow needles separated from warm 90% acetic acid solution, but slowly redissolved and separated on further cooling as orange rhomboids. Both forms melt at 105.5° and their mixture also melts at this temperature.

Anal. Calcd. for $C_{12}H_7O_2NSI_2$: I, 52.56; S, 6.64. Found: I, 53.1, 53.1; S, 6.74, 6.67.

4-Nitro-2,6-di-iodo-phenyl-*p*-tolylsulfide, IX.—This sulfide was prepared in a

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[10] Hantzsch and Reddelien, "Die Diazoverbindungen," J. Springer, Berlin, **1921.**

[11] Datta and Prosad, THIS JOURNAL, **39**, 441 (1917).

[12] Harington, *Biochem. J.*, **22**, 1429 (1928).

[13] Böeseken, *Rec. trav. chim.*, **29**, 322 (1910); Fries and Vogt, *Ann.*, **381**, 337 (1911). See also Krafft, *Ber.*, **7**, 1165 (1874); Loth and Michaelis, *ibid.*, **27**, 2547 (1894); Blanksma, *Rec. trav. chim.*, **20**, 402 (1900); Bourgeois, *Ber.*, **28**, 2321 (1895).

manner similar to its lower homolog; the yield was 83% of the theoretical. Here again two crystalline modifications were observed. Fan-shaped aggregates of light yellow needles crystallized from alcohol, but redissolved and crystallized, on cooling, as yellow rhomboids. Both forms melted at 121–122° with preliminary softening at 120°.

Anal. Calcd. for $C_{13}H_9O_2NSI_2$: I, 51.08; S, 6.45. Found: I, 51.1, 50.1; S, 6.4, 6.2.

4-Amino-2,6-di-iodo-diphenylsulfide.—Ten grams of the nitro compound, VIII was reduced by digesting for two hours with 26 g. of stannous chloride and 30 cc. of hydrochloric acid (sp. gr. 1.16) in 250 cc. of alcohol. After evaporating the resulting solution under diminished pressure, the sirupy residue was dissolved in water and treated with an excess of a 10% solution of sodium hydroxide. The precipitate was filtered by suction and the amine extracted with boiling alcohol; the solution was decolorized with norite and then diluted with water. On cooling, colorless prisms deposited which melted at 146°. The yield was 70%.

Anal. Calcd. for $C_{12}H_9NSI_2$: I, 56.04; S, 7.08. Found: I, 56.9, 57.0; S, 6.4, 7.0.

The hydrochloride was obtained by passing dry hydrogen chloride into an ether solution of the amine. It melted at 192° with decomposition.

4-Amino-2,6-di-iodo-phenyl-*p*-tolylsulfide.—This was obtained by reduction of the nitro compound IX with stannous chloride. The amine was obtained as colorless lance-shaped crystals which melted at 197–198°. The yield was 70% of the theoretical.

Anal. Calcd. for $C_{13}H_{11}NSI_2$: I, 54.36; S, 6.87. Found: I, 53.4, 53.6; S, 6.9, 6.8.

The hydrochloride of this base melts at 182° with decomposition.

4-Hydroxy-2,6-di-iodo-diphenyl-sulfide, II.—Nine grams of the hydrochloride of 4-amino-2,6-di-iodo-diphenyl-sulfide was suspended in 50 cc. of glacial acetic acid and diazotized at 5–10° by interaction with 3 g. of *n*-butyl nitrite in 25 cc. of glacial acetic acid. The deep red solution of the diazonium salt was diluted with an equal volume of water and added slowly to 200 cc. of a mixture of equal volumes of concentrated sulfuric acid and water. The reaction solution was maintained at 135–140° during this operation. The phenol was separated from the tarry product resulting from this reaction by extraction with a mixture of 20% sodium hydroxide and alcohol. The alcoholic layer was filtered and the filtrate saturated with carbon dioxide; the solution was filtered and then acidified with hydrochloric acid. The colorless oil that separated was dissolved in dilute alcohol, from which the phenol crystallized in long prisms. A yield of 3.4 g. was obtained. The crystals contained one molecule of alcohol of crystallization (9.4%) and rapidly disintegrated to a white powder when exposed to the air. The crystals did not melt but dissolved in their alcohol of crystallization at 92–95°. The powder melted at 139°.

Anal. Calcd. for $C_{12}H_8O_5I_2$: I, 55.9; S, 7.06. Found: I, 56.9; S, 7.0.

4-Hydroxy-2,6-di-iodo-phenyl-*p*-tolyl-sulfide, III.—Six grams of the above amine hydrochloride were diazotized with butyl nitrite and the solution of the diazonium salt poured into one liter of cold absolute ether. The red-brown powder which separated was filtered off, suspended in ice water and finally added to the boiling sulfuric acid. The phenol formed was extracted as described above and was obtained in a yield of 25%. It crystallized from dilute alcohol in needles which melted at 154°. It is soluble in dilute sodium hydroxide solution, and dissolves in boiling 5% alcohol to the extent of 1:20,000, but on cooling crystallizes from dilutions as high as 1:80,000.

Anal. Calculated for $C_{13}H_{10}OSI_2$: I, 54.24; S, 6.85. Found: I, 54.7, 55.0; S, 6.7, 6.8.

4-Methoxy-3,5-di-iodobenzene-diazo-thiophenyl Ether.—Ten grams of di-iodo-*p*-anisidine,[8] dissolved in 200 cc. of 40% alcohol and 120 cc. of hydrochloric acid (sp. gr.

1.16) was diazotized at 0° by interaction with sodium nitrite. After adding urea and sodium acetate, the solution was added slowly with stirring to a solution of 3 g. of thiophenol and 40 g. of sodium hydroxide in 500 cc. of water, keeping the temperature below 80°. A yellow precipitate of the above diazo compound was obtained. This was filtered and washed with dilute sodium hydroxide and with water, and finally dried in vacuo over calcium chloride. The yield was nearly the theoretical. The compound crystallizes from alcohol in yellow plates which melt sharply at 91° with evolution of nitrogen.

Anal. Calcd. for $C_{13}H_{10}OSN_2I_2$: I, 51.16; S, 6.46; N, 5.65. Found: I, 51.2; S, 6.2; N, 5.9.

Attempts to convert this diazo compound into 4-methoxy-3,5-di-iodo-phenyldisulfide were unsuccessful. Only viscous oils were obtained by heating from which no sulfide could be obtained in a pure condition.

Formation of 3,5-Di-iodo-4-hydroxydiphenyl-sulfide, IV, by Iodation of *p*-Hydroxyphenyl Sulfide, I.—Ten grams of *p*-hydroxy-diphenyl-sulfide I were dissolved in 450 cc. of aqueous ammonia (sp. gr. 0.9) and combined at 35–40° with 65 cc. of 2.5 *N* iodine solution. The ammonium salt of the di-iodated phenol separated in the form of colorless needles mixed with considerable tarry material. The reaction product was separated by filtration, acidified to liberate the free phenol, the latter extracted from the tar by trituration with dilute sodium hydroxide and the alkaline solution decolorized with norite. On saturating the alkaline solution with carbon dioxide the phenol separated and was crystallized from dilute methyl alcohol. It crystallized in long prisms which melted at 84–85°. The yield was 7.5 g. It is extremely soluble in the common organic solvents and is very insoluble in water.

Anal. Calcd. for $C_{12}H_8OSI_2$: S, 55.92; I, 7.06. Found: S, 55.8; I, 6.8.

3,5-Di-iodo-4-hydroxy-4'-methyl-diphenyl-sulfide, V, by Iodation of *p*-Hydroxy-*p*'-methyl-diphenyl Sulfide.[2]—This compound crystallizes from dilute methyl alcohol in clusters of colorless needles which melt at 112–113°.

Anal. Calcd. for $C_{13}H_{10}OSI_2$: S, 54.2; I, 6.85. Found: S, 54.6; I, 6.90.

By application of the technique described in the preceding preparations, the following compounds were also prepared (Table I).

TABLE I

RESULTS OF PREPARATIONS

No.	-Diphenyl sulfide	Formula	M. p., °C.	Yield, %	Analyses	S, %
1	*p*-Methoxy-*p*'-nitro-[a]	$CH_3OC_6H_4SC_6H_4NO_2$	71	92	.....	12.00[15]
2	*p*-Methoxy-*p*'-amino-[b]	$CH_3OC_6H_4SC_6H_4NH_2$	96	80	N, 6.38	13.5
3	*p*-Methoxy-*p*'-iodo-[c]	$CH_3OC_6H_4SC_6H_4I$	102	68	I, 37.2	9.0
4	*p*-Hydroxy-*p*'-iodo-(VI)[d]	$HOC_6H_4SC_6H_4I$	111–112	51	I, 38.4	9.30

[a] From $CH_3OC_6H_4SNa$[14] and $NO_2C_6H_4Cl$. Purified by crystallization from alcohol. [b] By reduction of the nitro compound with stannous chloride and hydrochloric acid in alcohol. The hydrochloride melts at 205–207°. [c] B. p., 202–205° at 3–4 mm. crystallized from methyl alcohol. [d] By demethylation of the methyl ether according to Hilbert and Johnson's procedure.[2] B. p., 205–210° at 3–4 mm. Crystallized from methyl alcohol. Solubility in water, 1:14000 at 100°.

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[14] Prepared in 72% yield from *p*-anisidine by the method of Leuckart, *J. prakt. Chem.*, **41**, 179 (1890).

[15] Carius method as modified by Rogers and Dougherty, THIS JOURNAL, **50**, 1231 (1928).

Summary

1.[7] Five new iodine derivatives of *p*-hydroxydiphenyl-sulfide have been described, namely: 4-hydroxy-2,6-di-iododiphenyl-sulfide, 4-hydroxy-2,6-di-iodo-4′-methyl-diphenyl-sulfide, 4-hydroxy-3,5-di-iododiphenyl-sulfide, 4-hydroxy-3,5-di-iodo-4′-methyldiphenyl-sulfide and 4-hydroxy-4′-iododiphenyl-sulfide.

2. All of these phenols are characterized by their extreme insolubility in water; consequently they do not exhibit any bactericidal activity when tested in the usual way.

3. The study of phenolic derivatives of diphenylsulfide will be continued.

New Haven, Connecticut

[Contribution from the Department of Chemistry, Yale University]

RESEARCHES ON PYRIMIDINES. CXIII. AN IMPROVED METHOD FOR THE SYNTHESIS OF CYTOSINE[1]

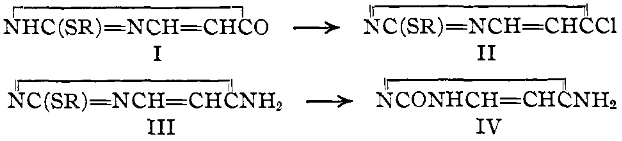
By Guido E. Hilbert[2] and Treat B. Johnson

Received October 16, 1929 Published March 6, 1930

The pyrimidine—*cytosine*—was first isolated from a nucleic acid by Kossel and Neumann[3] in 1894. It was subsequently synthesized by Wheeler and Johnson[4] and the structure of this naturally occurring compound thereby definitely established.

The successful synthesis developed by Wheeler and Johnson involves the condensation of a pseudothiourea with the sodium salt of ethyl formylacetate, resulting in the formation of a 2-mercapto-6-oxypyrimidine, I. By interaction of this cycle with phosphorus pentachloride, the corresponding 2-mercapto-6-chloropyrimidine, II, is formed, which is finally converted into the corresponding aminopyrimidine, III, by the action of ammonia. This latter pyrimidine, when digested with hydrochloric acid, is changed almost quantitatively into the hydrochloride of cytosine, IV. These various changes are expressed by the following formulas

$$\mathrm{RSC(NH_2){=}NH + NaOCH{=}CHCOOC_2H_5} \longrightarrow$$



$$\mathrm{NHC(SR){=}NCH{=}CHCO} \longrightarrow \mathrm{NC(SR){=}NCH{=}CHCCl}$$

I II

$$\mathrm{NC(SR){=}NCH{=}CHCNH_2} \longrightarrow \mathrm{NCONHCH{=}CHCNH_2}$$

III IV

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[1] A preliminary report of this research was given at the Spring Meeting of the American Chemical Society held in Columbus, Ohio, in April, 1929.

[2] Sterling Research Fellow 1928–1929.

[3] Kossel and Neumann, *Ber.*, 27, 2215 (1894).

[4] Wheeler and Johnson, *Am. Chem. J.*, 29, 492, 505 (1903).