tative yields by treating sodium-triphenyl stannide in liquid ammonia with methyl iodide.

3. Dimethyldiphenyl-stannane has been prepared by treating disodium-diphenyl stannide in liquid ammonia with methyl iodide. Treating disodium-dimethyl stannide with phenyl bromide does not give the stannane.

4. Trimethylphenyl-stannane has been prepared by the Grignard reaction. Treatment of sodium-trimethyl stannide with phenyl bromide gives a product consisting of 86% of trimethylstannyl nitride, $[(CH_3)_3Sn]_3N$, and 14% of trimethylphenyl-stannane, $(CH_3)_3SnC_6H_5$.

5. On brominating trimethylphenyl-stannane, the phenyl group is removed.

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RESEARCHES ON THIAZOLES. XIII. THE SYNTHESIS OF 2-ARYL 6-DIMETHYLAMINO-BENZOTHIAZOLES FROM 2-AMINO-5-DIMETHYLANILINE THIOSULFURIC ACID AND AROMATIC ALDEHYDES[1]

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Introduction

Confusion has crept into the literature through the failure of authors to discriminate between thiosulfuric acids, $RSSO_2OH$, and thiosulfonic acids, RSO_2SH, when naming their products, the former frequently being incorrectly designated as thiosulfonic acids.

In the course of his classical work upon the structure of Methylene Red and Methylene Blue, Bernthsen[2] had occasion to prepare and study the monothiosulfuric acids from *p*-phenylenediamine, *p*-aminodimethyl- and -diethylaniline and tetramethyl-*p*-phenylenediamine, and in a subsequent paper[3] described 2-N-dimethyl and diethyl derivatives of 2,5-diaminotoluene.

He was led to undertake this investigation because of the patents taken out by Roth[4] covering the manufacture of blue dyes from the hydrochlorides of *p*-amino dialkyl anilines and of dialkyl anilines, sodium thiosulfate and potassium dichromate. On the assumption that the intermediate product in this reaction was a thiosulfuric acid of one of the amines, which in turn condensed with a second mole of amine to a thiazine,

[1] Presented in abstract before the Organic Division of the American Chemical Society at its Richmond Meeting, April, 1927.

[2] Bernthsen, *Ann.*, **251**, 1–97 (1889).

[3] Bernthsen, *Ber.*, **25**, 3128 (1892).

[4] Roth, Ger. pat. 38,573 (1885); *Winther*, **2**, 452 (1908).

Roth prepared the thiosulfuric acids mentioned by the action of sodium thiosulfate upon the diamine in mineral acid solution, in the presence of aluminum sulfate and potassium dichromate, and from these the desired indamines and thiazines.[5]

Weinberg[6] claimed a theoretical yield of thiosulfuric acid from 2-ethylamino-5-aminotoluene by the Bernthsen method, but stated that no such acid could be secured from the correspondng diethylamino derivative. The correctness of this latter statement was questioned by Bernthsen,[3] who reported that both dimethyl- and diethylamino derivatives gave thiosulfuric acids immediately when treated with a thiosulfate and an oxidizing agent.

Following this pioneer work, a large number of patents were taken out by various corporations for the manufacture of thiazine dyes by processes which involved the intermediate formation of diamine thiosulfuric acids, but which used them in the solution as formed and did not separate or purify them.

Bayer and Company[7] patented the method of producing these thiosulfuric acids from the *p*-nitroso mono- or dialkyl anilines and sodium thiosulfate.

Green and Perkin,[8] who undertook an investigation in this field for the Clayton Aniline Company, made the interesting observation that by the use of sufficient thiosulfate and oxidizing agent, *p*-phenylenediamine gave polythiosulfuric acids, of which they separated and described the di and tetra derivatives. They also improved the Bernthsen method by the use of acetic instead of mineral acids, and in other details.

Wahl,[9] apparently ignorant of the Bayer and Company patent,[7] also prepared a dialkyl *p*-phenylenediamine thiosulfuric acid by the direct action of a thiosulfate upon the hydrochloride of a *p*-nitroso dialkyl aniline.

This reaction was applied to *p*-nitrosodimethyl- and -diethylanilines, and to 3-nitroso-6-ethylaminotoluene by Heller, Quast and Blanc,[10] who regarded it as preferable to the Bernthsen process and obtained yields of thiosulfuric acids amounting to 30–40%.

In connection with their preparation of the dithiosulfuric acid of *p*-phenylenediamine, Green and Perkin[8] proved its structure by condensation with benzaldehyde and with acetic anhydride, to the corresponding benzobisthiazoles. In the course of the benzaldehyde condensation, they observed the formation of an orange intermediate product, which they did not analyze but believed to be the benzaldehyde derivative.

[5] Badische Anilin Soda-Fabrik, Ger. pat. 45,839 (1887); *Winther*, **2**, 454 (1908). See also Ger. pat. applic. B8343, B8871 and F3798.

[6] Weinberg, *Ber.*, **25**, 1610 (1892).

[7] Bayer and Co., Ger. pat. 84,849 (1895); *Friedländer*, **3**, 1016 (1896).

[8] Green and Perkin, *J. Chem. Soc.*, **83**, 1201 (1903).

[9] Wahl, *Compt. rend.*, **133**, 1215 (1901).

[10] Heller, Quast and Blanc, *J. prakt. Chem.*, [2] **108**, 257 (1924).

In our own experiments it was noted that when the aldehydes were added to the thiosulfuric acids, solutions were obtained which were always much deeper in color than the thiazole finally separated therefrom. In the case of the condensation of *p*-dimethylaminobenzaldehyde with the thiosulfuric acid of *p*-aminodimethylaniline, we succeeded in isolating the intermediate product and in proving that it was the *p*-dimethylaminobenzal derivative, which readily changed into the thiazole on longer boiling of the glacial acetic acid solution.

Heller, Quast and Blanc[10] condensed *p*-aminodimethylaniline thiosulfuric acid with formic acid, with carbon disulfide and with potassium cyanide, and obtained the expected 6-dimethylaminobenzothiazole and its 2-mercapto- and 2-amino derivatives.

From the monothiosulfuric acid of *p*-aminodimethylaniline, we prepared the 2-phenyl and 2-(*o*-, *m*- and *p*-nitrophenyl) derivatives and, by reduction of the latter, the corresponding 2-aminophenyl derivatives.

The 2-(*m*- and *p*-aminophenyl) derivatives were converted into arsonic acids by the Bart reaction, and the 2-(*p*-aminophenyl) into the corresponding Chloramine Yellow type by the usual reactions. The work on this dye has not been completed, but is being followed up, to determine the tinctorial effect of the introduction of amino auxochromes into the Chloramine Yellow molecule.

By the use of the appropriate aldehydes, 2-(*o*- and *p*-hydroxyphenyl) derivatives were produced, and the *meta* isomer from the corresponding *m*-aminothiazole. Pharmacological tests will be conducted with these phenolic types, to ascertain whether or not they possess any antiseptic or germicidal properties.

Experimental Part

2-Amino-5-dimethylaniline Thiosulfuric Acid, $H_2N(2)C_6H_3(5)[N(CH_3)_2]SSO_3H$.—This acid has been prepared by previous investigators.[2,8,9,10] We have modified their procedure as follows.

To a well-cooled mixture of 19 g. of *p*-nitrosodimethylaniline hydrochloride, 120 cc. of water and 40 cc. of glacial acetic acid, there was added during 20 minutes a cold solution of 82 g. of $Na_2S_2O_3.5H_2O$ (10% excess) in 120 cc. of water. The reaction was carried out at about 0° while the mixture was stirred mechanically. After stirring for 30 minutes longer, the mixture was left at 0° for six hours and then allowed slowly to warm up to laboratory temperature. The color of the solution changed from dark brown to light green. The acid began to separate soon after the beginning of the reaction, but was allowed to accumulate for 48 hours before filtration. By carrying out the reaction at low temperature, the separation of sulfur was negligible, whereas at laboratory temperature it was considerably greater. The yield of crude product was 9 g., or 36.4%, in practical agreement with Heller, Quast and Blanc, who obtained 30–40%. The yield was not increased appreciably by the addition of more thiosulfate and acetic acid to the mother liquid, nor by allowing the mixture to stand as long as three months.

The crude acid was purified by dissolving it in dil. acetic acid, filtering, partly neu-

tralizing the filtrate with a small amount of sodium carbonate and recrystallizing the precipitate from water. As thus prepared, it formed minute, steel-gray crystals which, after two hours' drying at 110°, melted with decomposition at 204° (corr.), when the temperature was raised at the rate of approximately 3° per minute. Bernthsen reported that it melted at 193–195° when heated slowly, and at 201–204° when heated rapidly. Wahl gave no melting point for his product. Heller, Quast and Blanc found that it melted and decomposed at 196°. Left for 48 hours over concd. sulfuric acid in a desiccator, it lost no weight, whereas the sodium salt when treated similarly lost one molecule of water.

Anal. Calcd. for $C_8H_{12}O_3N_2S_2$: S, 25.86. Found: 25.85.

2-Phenyl-6-dimethylamino-benzothiazole.—When a solution of equimolar quantities of 2-amino-5-dimethylaniline thiosulfuric acid (10 g.) and benzaldehyde (4.2 g.) in glacial acetic acid (50 cc.) was boiled for one hour, the solution became a very dark red, and when poured into a large volume of cold water a voluminous yellow precipitate separated, which was collected and washed with dilute alcohol to remove the excess of benzaldehyde. Since the product when moist decomposed quite easily even below 80°, it was dried at laboratory temperature for a day and then for several hours at 80°. The crude product alone, and in acid or alcoholic solution, possessed a very disagreeable odor, whereas the pure compound was odorless. By repeated crystallization from 50% alcohol and from 40% acetone, pale yellow, glassy needles were obtained, m. p. 134.8° (corr.), in practical agreement with the figure (135°) found by Bogert and Abrahamson,[11] who prepared the compound by the direct methylation of 6-amino-2-phenyl-benzothiazole; yield, less than 10%.

Anal. Calcd. for $C_{15}H_{14}N_2S$: S, 12.62. Found: 12.56.

2-Nitrophenyl-6-dimethylamino-benzothiazoles.—These were prepared by boiling for an hour, under a reflux condenser, molecular proportions of 2-amino-5-dimethylaniline thiosulfuric acid (10 g.) and the appropriate nitrobenzaldehyde (6 g.) in sufficient glacial acetic acid (50–100 cc.) to dissolve the thiazole formed. The hot acetic acid solution was always dark red, being darkest in the case of the *p*-nitro derivative. Some of this color may have been due to unconverted intermediate nitrobenzaldehyde derivative, as noted in the condensation with *p*-dimethylaminobenzaldehyde described later.

The yields of thiazole were not improved by varying the proportions of the reactants

TABLE I

2-NITROPHENYL-6-DIMETHYLAMINO-BENZOTHIAZOLES

Isomer	Yield, %	M. p., °C. (corr.)	Appearance	Crystallized from
Ortho	37.5	146.8	Golden-brown scales	Boiling alcohol
Meta	87.9	176	Red needles	Hot alcohol + water
Para	88.5	246	Dark red needles	Nitrobenzene

The yields recorded are for the partially purified products.

ANALYTICAL RESULTS

Calcd. for $C_{15}H_{13}O_2N_3S$, %		Found, % *Ortho*	*Meta*	*Para*
C	60.18	60.72	60.73	59.42
H	4.38	4.75	4.69	3.99
S	10.70	10.49	10.71	10.21

[11] Bogert and Abrahamson, THIS JOURNAL, 44, 834 (1922). An unfortunate misprint occurs in that article, where the melting point is given as 185° instead of 135°.

or the duration of the heating, and if the amount of acetic acid used was insufficient to maintain complete solution, purification of the final product was more troublesome.

The hot acetic acid solution was run slowly into a large volume (2 liters) of cold water, while the latter was agitated vigorously by a mechanical stirrer, and a voluminous reddish-yellow to dark red precipitate separated, which was allowed to settle for several hours and was then removed.

Neutralization of the diluted acetic acid solution proved inexpedient, since it appeared to increase the separation of a tar from which it was difficult to free the thiazoles completely, and which was accomplished only after repeated extractions and crystallizations from various solvents. All three isomers crystallized from toluene in masses of beautiful red needles, whose dilute solutions in various solvents were generally yellow.

o-Nitro Isomer.—When boiled, the acetic acid solution of thiosulfuric acid and nitro aldehyde changed rapidly from a muddy green to a red-brown. The precipitate obtained by pouring this hot solution into cold water was dried for several hours at 80°, since this crude product melted below 100°, and was then ground up with Norite and extracted with two 100cc. portions of hot toluene, followed by 100 cc. of hot alcohol, each of which was evaporated to dryness separately. On concentration of the first 100cc. toluene extract, the impurities separated before much of the thiazole did, so that if these first tarry precipitates were rejected, those subsequent were much purer. After the toluene extraction, very little material was extracted by the alcohol. Final purification by crystallization from 95% alcohol yielded golden-brown, microscopic, lustrous scales. The solubility of the product in various solvents increased in the following sequence: ether, methyl alcohol, ethyl alcohol, benzene, toluene; it was but slightly soluble in ether and quite freely soluble in hot toluene.

m-Nitro Isomer.—The precipitate obtained by diluting the acetic acid solution, after being dried and ground up with Norite, was extracted with three 100cc. portions of boiling toluene. The red needles (10.4 g.) obtained by concentration of these toluene extracts were purified by repeated crystallization from 95% alcohol, and then diluted to turbidity with hot water, appearing as very fine, lustrous, short, red needles, only slightly soluble in ether, benzene, methyl or *n*-butyl alcohol, but more readily in toluene; yield of product, m. p., 173°, 87.9%.

p-Nitro Isomer.—The dark red precipitate from the acetic acid solution, extracted with hot toluene as in the case of the *meta* isomer, gave red needles; m. p., 235–238°; yield, 88.5%. This product was difficultly soluble or insoluble in methyl, ethyl, *n*-butyl or *iso*-amyl alcohol, or in carbon disulfide, somewhat more readily soluble in acetone or benzene, moderately soluble in toluene and quite freely soluble in boiling nitrobenzene. It crystallized from the latter in microscopic, dark red, short needles or scales which were freed from this solvent by washing with alcohol and ether and, after drying for several hours at 120°, melted at 246° (corr.).

2-Aminophenyl-6-dimethylamino-benzothiazoles.—The nitro derivatives (6–10 g.) just described were boiled gently (three to eight hours) with mossy tin (14–20 g., equivalent to an 80–100% excess) and 2–3 *N* hydrochloric acid (200 cc.), with occasional addition of a few cubic centimeters of 12 *N* hydrochloric acid, until the reduction was complete and all the tin had dissolved. The resulting solution was nearly colorless in the case of the *ortho* isomer, but red for the other two. It was filtered hot into sufficient excess of sodium hydroxide solution (approximately 4 *N*) to render the resulting mixture approximately 1 *N* sodium hydroxide. This precipitated the amine and retained the tin in solution. To insure the complete solution of all tin salts in the clotted precipitates, the alkali mixture was heated at 100° for an hour, the supernatant liquid poured off, the residue washed several times by decantation with hot water, transferred to a filter and washed again with hot water. If ignition of this product disclosed the

presence of any tin, it was redissolved in hydrochloric acid and reprecipitated with sodium hydroxide in excess. The crude product was purified by crystallization from suitable solvents until the melting point remained constant.

TABLE II

2-AMINOPHENYL-6-DIMETHYLAMINO-BENZOTHIAZOLES

Isomer	Yield, %	M. p., °C. (corr.)	Appearance	Crystallized from
Ortho	40	130.8	Pale yellow, glassy scales	50% acetone
Meta	72	173.5	Pale yellow, glassy scales	Dil. alcohol
Para	56	221	Greenish-yellow, glassy needles	95% alcohol

Yields recorded are for partly purified products.

ANALYTICAL RESULTS

Calcd. for $C_{15}H_{15}N_3S$, %		Found, % *Ortho*	*Meta*	*Para*
C	66.84			68.00
H	5.62			5.82
S	11.88	11.83	11.62	11.88

o-Amino Isomer.—The crude product was crystallized by dissolving in boiling alcohol, diluting to turbidity with hot water and allowing the solution to cool. Small, pale, greenish-yellow needles separated; m. p., 116–117° (corr.); yield, 40%. These were recrystallized several times from ethyl and methyl alcohols and finally from 50% acetone until the melting point remained constant at 130.8° (corr.). Alcoholic solutions of the pure compound were yellow, with a light blue fluorescence.

m-Amino Isomer.—Reduction of the nitro derivative yielded a red solution which, when allowed to cool overnight, separated long, pale yellow needles (presumably of the amine tin double chloride) and some red tar. The crystals and liquid were removed and the residual tar was boiled for several hours with more tin and an additional 200 cc. of 2–3 *N* hydrochloric acid, and the solution was cooled. The second crop of crystals so obtained was washed from the small amount of tar still remaining and united with the first lot of double salt. The solution containing the suspended double salt was heated until all dissolved, when it was filtered hot into alkali as usual. When the acid filtrate struck the alkali, a reddish precipitate formed which changed almost immediately into a yellow, flocculent one. This alkali mixture was heated and the precipitate washed as described above. Purification was effected by crystallization from ethyl and methyl alcohols, in some cases diluting the boiling solutions carefully with water. The yield, after one crystallization, was 72%. Solutions of the pure compound in alcohol or acetone were yellow, the former showing a greenish-blue and the latter a brilliant blue fluorescence.

Although the melting point of this product (173.5°) is quite near that of its antecedent nitro derivative (176°), an intimate mixture of the two melted at 141°.

p-Amino Isomer.—Due to the difficulty in getting the *p*-nitro derivative pure, the product used for these reductions had been crystallized but once from toluene and melted at 238° (corr.).

The reduction followed practically the same course as for the *meta* isomer and the product was worked up similarly, except that crystallization from rapidly cooled, boiling ethyl alcohol readily gave a pure product, whose melting point was not altered by further crystallization from the same solvent or from methyl alcohol or acetone. Solutions of the amine in alcohol or acetone were yellow, the former exhibiting a bluish and the latter a purplish fluorescence. This isomer was the hardest of the three to reduce, but the easiest to purify.

When an alcoholic solution of the amine and benzaldehyde was boiled for some time, no condensation occurred and the amine was recovered quantitatively, although under similar conditions dehydrothio-*p*-toluidine and benzaldehyde condense readily and rapidly.[12]

A Chloramine Yellow Dye from 2-(*p*-Aminophenyl)-6-dimethylamino-benzothiazole.—As compared with the sulfonation of dehydrothio-*p*-toluidine,[13] this base required the use of fuming acid and a higher temperature.

To a solution of 2 g. of the amine in 25 cc. of concd. sulfuric acid, there was added 7 cc. of fuming sulfuric acid (containing 40% of free sulfur trioxide) and the mixture was heated at 160–180° for two hours, when a test portion no longer formed a precipitate in an excess of ammonium hydroxide solution and the sulfonation, therefore, was adjudged completed. The cooled acid mixture was poured upon cracked ice, the solution made slightly alkaline with sodium hydroxide, diluted to 500 cc., heated at 100° for an hour and filtered. The alkaline filtrate was dark red, with a greenish fluorescence. It was nearly neutralized with sulfuric acid, and a slight excess of sodium hypochlorite solution, prepared by the action of sodium hydroxide solution upon calcium hypochlorite, was added. A yellow precipitate, presumably the calcium salt of the dye acid, separated almost immediately. When this mixture was acidified strongly with hydrochloric acid, the color of the suspended solid changed to a brownish-red, which appeared as an amorphous product when dry. This product was insoluble in water, but dissolved in aqueous alkali. It has not been prepared as yet in sufficient amount or purity to carry out comparative dyeing tests.

2-(*p*-Dimethylaminobenzalamino)-5-dimethylaniline Thiosulfuric Acid, $(CH_3)_2NC_6H_3(SSO_3H)N{:}CHC_6H_4N(CH_3)_2$ (*p*).—When a solution of 9 g. of 2-amino-5-dimethylaniline thiosulfuric acid and 6 g. of *p*-dimethylaminobenzaldehyde in 50 cc. of glacial acetic acid was heated to boiling, it speedily assumed a dark red color and a dark red crystalline solid precipitated. After the mixture had been boiled for one hour, the precipitate was removed, washed with water and dried, when it formed a purplish-red solid; yield, 7.5 g., or 53%. This crude anil was extracted in a Soxhlet apparatus with benzene, to remove any thiazole, and was then crystallized from hot 95% alcohol by careful dilution with water. It formed deep dull red, microscopic, felted crystals which decomposed at 210–215° (corr.), and were practically insoluble in benzene or toluene, and only slightly soluble in alcohol. The compound dissolved in dilute acids or bases, and was appreciably soluble in aqueous solutions of sodium carbonate or acetate, the color of all these solutions being yellow.

Anal. Calcd. for $C_{17}H_{21}O_3N_3S_2$: S, 17.03. Found: 17.59.

When a solution of this red anil in a large volume of glacial acetic acid was boiled for a short time and the solution poured into water, a yellow solid separated which was crystallized from benzene, acetone and alcohol, and proved to be the thiazole. The conversion was practically quantitative.

2-(*p*-Dimethylaminophenyl)-6-dimethylamino-benzothiazole.—The acetic acid filtrate from the crude anil was stirred into a large excess of cold water and the turbid solution allowed to settle. The thiazole which separated was collected, washed with water and dried at 110°; yield, 2 g., or 16.8%. Dissolved in hot benzene or toluene, it gave a reddish-brown solution with bluish fluorescence, from which it separated in masses of yellow needles as the solution cooled. After several crystallizations from 95% alcohol, it formed microscopic, dull olive-green crystals, m. p. 230° (corr.), insoluble in alkalies but moderately soluble in acids.

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[12] Bogert and Meyer, THIS JOURNAL, **44**, 1568 (1922).

[13] Bogert and Bergeim, *Color Trade J.*, **15**, 63 (1924).

Anal. Calcd. for $C_{17}H_{19}N_3S$: S, 10.79. Found: 10.41.

2-Hydroxyphenyl-6-dimethylamino-benzothiazoles.—Of the three isomers, the *ortho* and *para* were obtained by condensing the 2-amino-5-dimethylaniline thiosulfuric acid with the *o*- or *p*-hydroxybenzaldehyde, and the *meta* from the corresponding *m*-aminophenyl benzothiazole through the diazo reaction.

The *ortho* and *para* isomers were prepared by refluxing for an hour a solution of 6.1 g. of the aldehyde and 12 g. of the thiosulfuric acid (molecular equivalent amounts) in 50 cc. of glacial acetic acid. The solution, pale red at first, gradually became dark green. While still hot, it was stirred into 2 liters of cold water, and a voluminous yellow precipitate separated. After standing for several hours, the mixture was filtered and the precipitate dried at 100°. This product seemed to change quite rapidly in the air, the exposed surfaces assuming a greenish color. Purification was accomplished by crystallization from suitable solvents.

All three isomers were soluble in dil. sodium hydroxide solution or in dil. hydrochloric acid, but not in sodium carbonate solution. The sodium salts were insoluble in strong sodium hydroxide solution, separating therefrom in iridescent, greenish-yellow flakes.

TABLE III

2-HYDROXYPHENYL-6-DIMETHYLAMINO-BENZOTHIAZOLES

Isomer	Yield, %	M. p., °C. (corr.)	Appearance	Crystallized from
Ortho	80.0	183	Bright greenish-yellow, lustrous scales	80% acetone
Meta	67.5	227–228	Dull orange-red crystals	Insoluble
Para	79.5	290	Pale yellow, glassy needles	80% acetone

Yields given are for partly purified products.

Anal. Calcd. for $C_{15}H_{14}ON_2S$: S, 11.87. Found: (*ortho*) 11.53, (*meta*) 11.49, (*para*) 11.66.

***o*-Hydroxy Isomer.**—The crude product was crystallized from benzene, carbon tetrachloride and from 80% acetone. The solution in acetone or in alkali was yellow with a pale blue fluorescence.

***p*-Hydroxy Isomer.**—On standing in the air the crude product turned green more quickly than the *ortho* isomer. It was but slightly soluble in ether, chloroform, carbon tetrachloride, benzene, toluene, methyl or ethyl alcohols, but could be crystallized in yellow spherulitic masses from mixtures of ethyl alcohol with benzene or toluene, or from glacial acetic acid. For final purification, the product was twice dissolved in caustic alkali and reprecipitated with hydrochloric acid, after which it was crystallized from alcohol and from 80% acetone. Its solutions in alkali, alcohol, benzene or toluene, possessed a greenish-blue fluorescence.

***m*-Hydroxy Isomer.**—A solution of 4 g. of the corresponding amine in 20 cc. of concd. sulfuric acid was poured onto cracked ice, and the resultant dark solution was diluted to 250 cc. with ice water and diazotized at 0° with a solution of 1.2 g. of sodium nitrite in 50 cc. of water. After being stirred for 30 minutes at 0°, the diazotized solution was allowed to warm up gradually to laboratory temperature. A flocculent red precipitate separated, which melted and increased in quantity when the mixture was boiled for an hour to complete the decomposition of the diazo body. When the mixture had cooled, the separated solid was broken up, sodium hydroxide was added until the mixture was alkaline and it was heated to boiling again to bring the hydroxy derivative into solution. The filtrate was bright red without fluorescence. When it was acidified with glacial acetic acid, a brownish-red precipitate separated which formed an amorphous product when dry. This purification was repeated. Because of its insolubility in neu-

tral organic solvents, the product was digested thrice with hot 20 and 30% acetone, after which purification it appeared in dull, orange-red, microscopic scales or short needles, which turned red above 150° and melted at 227–228° (corr.).

2-Phenyl-6-dimethylamino-benzothiazole-3′- and -4′-arsonic acids, $(CH_3)_2NC_6H_3\langle{}^{S}_{N}\rangle C.C_6H_4AsO(OH)_2$, were obtained from the corresponding 2-aminophenyl derivatives by the application of the diazo reaction as worked out by Bart,[14] and already utilized in the thiazole group by Bogert and Corbitt.[15]

The appropriate amine (2.7 g.) was dissolved in 2 *N* hydrochloric acid (40 cc.), water (60 cc.) was added and the solution cooled to 0°, which caused some of the hydrochloride to separate. This suspension was diazotized at 0° by adding an aqueous solution of sodium nitrite (0.8 g. in 10 cc. of water), and a dark red, voluminous precipitate separated. This mixture was added promptly to an ice-cold, alkaline solution prepared from potassium arsenite (10 g.), a saturated aqueous solution (60 cc.) of sodium carbonate, and water (50 cc.), which contained slightly more than sufficient alkali to combine with the hydrochloric acid and the arsonic acid formed. It was stirred vigorously at low temperature for an hour or two when, without interrupting the stirring, the temperature was permitted to rise gradually to that of the laboratory, after which it was heated at 100° for one hour. Cuprous oxide, as catalyst, was omitted in these reactions, since it appeared to increase the amount of hydroxyphenyl derivative at the expense of the arsonic acid. The precipitate formed was removed and treated with solutions of sodium carbonate and of sodium hydroxide, neither of which extracted anything from it.

The original alkali filtrate from this precipitate was made slightly acid with hydrochloric acid and allowed to stand for about an hour. The solid which separated was collected and dried at 110°; average yield, 18.5%. It was extracted with aqueous sodium carbonate solution, which dissolves the arsonic acid but not the hydroxyphenyl derivative, and the alkali solution was then precipitated by addition of hydrochloric acid. Further purification was effected by repeated crystallization from 50% alcohol.

TABLE IV

2-PHENYL-6-DIMETHYLAMINO-BENZOTHIAZOLE-3′- AND -4′-ARSONIC ACIDS

	3′-Arsonic acid	4′-Arsonic acid
Yield, % (crude)	18.5	18.5
M. p., °C. (corr.)	Above 300°	Above 300°
Appearance	Dull, light brick-red, granular solid	Red powder
Crystallized from	50% alcohol	50% alcohol

ANALYSES OF $C_{15}H_{15}O_3N_2SAs$

Calcd., %	Found, % 3′-Arsonic acid	Found, % 4′-Arsonic acid
C 47.62	43.02, 42.86	
H 4.0	3.58, 4.07	
As 19.82	19.44, 19.48	20.26, 20.66

Considerable difficulty was experienced in the determination of carbon in these compounds, so that we believe that the *meta* isomer was really more nearly pure than our analytical figures for carbon would indicate.

[14] Bart, Ger. pat. 250,264 (1910); 254,092 (1910); 268,172 (1912); *Friedländer*, **10**, 1254 (1913); **11**, 1030, 1032 (1915); *Ann.*, **429**, 55 (1922).

[15] Bogert and Corbitt, *Proc. Nat. Acad. Sci.*, **11**, 768 (1925).

3'-Arsonic Acid.—The alkali solution of the crude product was yellow with red fluorescence, which fluorescence was not observed in the case of the purified arsonic acid.

4'-Arsonic Acid.—Addition of the diazo mixture to the alkaline arsenite solution immediately caused the latter to turn almost black, and the precipitate which separated when this mixture was heated was dark red.

2'-Arsonic Acid.—Attempts to prepare this acid by the method used for the 3'- and 4'-isomers proved futile. The yield of alkali-soluble material averaged only about 7%, and no arsonic acid could be isolated from it.

Summary

1. By condensing the monothiosulfuric acid of *p*-amino-dimethylaniline with nitrobenzaldehydes, 2-nitrophenylbenzothiazoles have been obtained, reduction of which gave the corresponding amino derivatives, from which in turn arsonic acids were prepared. In one of these initial aldehyde condensations, the intermediate benzal derivative was isolated and identified.

2. By similar reactions, using hydroxybenzaldehydes, the corresponding 2-*o*- and -*p*-hydroxyphenyl-benzothiazoles have been secured, and the *meta* isomer from the *m*-amino derivative.

3. The new compounds described are the following: the 2-phenyl, 2-(*o*-, *m*- and *p*-nitrophenyl), 2-(*o*-, *m*- and *p*-aminophenyl) and 2-(*o*-, *m*- and *p*-hydroxyphenyl) derivatives of 6-dimethylamino-benzothiazole; 2-phenyl-6-dimethylamino-benzothiazole-3'- and -4'-arsonic acids; 2-(*p*-dimethylaminophenyl)-6-dimethylamino-benzothiazole and the intermediate anil.

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[CONTRIBUTION FROM THE CLEVELAND CLINIC]

THE PREPARATION OF A STABLE COLLOIDAL SOLUTION OF LEAD

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When Sir William Blair Bell[1] announced the results of his treatment of cancer by colloidal lead, the need at once became apparent of finding a method of preparing colloidal solutions of lead which would be stable and which could be used for intravenous injection. It was to find such a method that the studies were undertaken which are reported here. Our problem was to prepare a solution which could be boiled and could be kept for a long time without precipitation, and at the same time would have a rather high concentration and could be prepared without the aid of protective colloids.

A search of the literature has supplied abundant data concerning methods for preparing colloidal lead and lead compounds. Bredig ob-

[1] Bell and others, *Lancet*, **1**, 537 (1926).