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

DIARSONO-DIPHENYL AND DERIVATIVES

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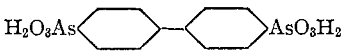
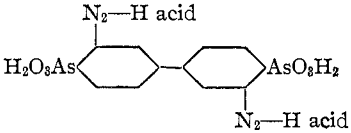
In spite of the vast amount of work on organic arsenicals, the derivatives of diphenyl have not been studied. Since diphenyl offers a nucleus from which a large variety of arsenic compounds of possible therapeutic value may easily and cheaply be formed, methods for preparing these compounds have been developed.

By tetrazotization of benzidine and treatment with sodium arsenite according to the method of Bart, two arsonic acid groups may be introduced. The product thus formed, however, is always impure and not until repeated partial precipitations with acid were used, was a pure and white diarsono-diphenyl I, obtained. The by-product which is generally brown was never prepared in a state of purity, but its arsenic content and general properties indicated that it was probably 4-hydroxy-4′-arsono-diphenyl.



I



II

Since the majority of therapeutically effective arsenic compounds toward trypanosomes contain nitrogen, an attempt was made to nitrate diarsono-diphenyl but without success. Apparently considerable oxidation of the molecule always occurred and only a complex mixture of products resulted.

The preparation of a dinitro-diarsono-diphenyl was successful, however, through the replacement of the amino groups in *o*-dinitro-benzidine by arsonic acid groups in exactly the same way as with benzidine itself. The amino groups in *m*-dinitro benzidine just as the amino group in *m*-nitroaniline could not be readily replaced in the usual way with arsonic acid groups.

The *o*-dinitro-diarsono-diphenyl, upon reduction with ferrous chloride and sodium hydroxide, yielded the diamino derivative which showed all the properties of amino-arsonic acids of the benzene series. By tetrazotization and coupling with various dye intermediates, a variety of dyes may be produced. Using H-acid the compound II corresponding closely to Trypan Blue was formed.

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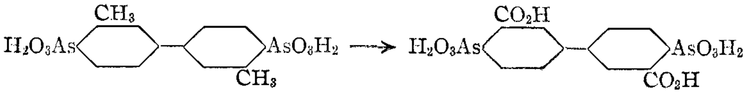
[1] This communication is an abstract of a thesis submitted by W. W. Bauer in partial fulfilment of the requirements for the Degree of Doctor of Philosophy in Chemistry at the University of Illinois. The expenses of the research described in this communication were partially defrayed by a grant from the United States Interdepartmental Social Hygiene Board.

Tolidine was also tetrazotized and arsonic acid radicals introduced. The dimethyl-diarsono-diphenyl III produced was readily oxidized to the dicarboxy-diarsono-diphenyl, IV.

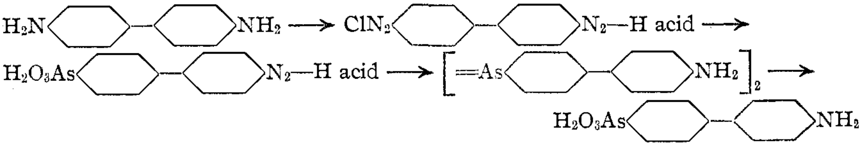


III IV

A study has also been made of the preparation of arsenic compounds which contain an arsonic acid radical attached to one ring and a group such as the hydroxyl or amino attached to the other. Such compounds are of interest because of their analogy with the corresponding phenylarsonic acids.

An attempt to diazotize benzidine and replace one amino group by an arsonic acid group was unsuccessful, since the by-products were so numerous and in such quantity that no pure substance was obtained. The problem of preparing the compound desired was solved, however, by using either of the two following processes: (1) benzidine was tetrazotized, one diazonium group was replaced by an arsonic acid radical and the second diazonium group was coupled with a component which could be reduced to give an amino group; (2) benzidine was tetrazotized, one diazonium group was coupled with a component which could be reduced to give an amino group, and the second diazonium group replaced with an arsonic acid radical. The second procedure proved to be the more satisfactory.

H-acid was used as a very suitable coupling component. Upon reduction of the azo compound with sodium hydrosulfite, a diamino-diphenyl-arseno compound was formed which could be separated from the amino H-acid because of its insolubility in alkali. The arseno compound was then oxidized with alkaline hydrogen peroxide to give the amino-arsonic acid. The product resembles, in its reactions, arsanilic acid, although it is considerably less soluble than the latter substance.



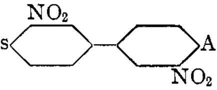
V

Preliminary pharmacological tests have kindly been made by Dr. G. W. Raiziss. The compound 4-aceto-amino-4′-arsono-diphenyl has approximately the same toxicity as arsanilic acid, while the compound 3,5′-diamino-4,4′-diarsono-diphenyl has considerably less toxicity.

Experimental Part

4,4′-Diarsono-diphenyl, I.—In a mixture of 250 cc. of 2 *N* hydrochloric acid and 150 cc. of water, 18.4 g. of benzidine was dissolved by heating to 70°. After the solution was filtered and cooled to 0°, 100 cc. of 2 *N* sodium nitrite was gradually added and an excess of nitrite was maintained for 30 minutes. The clear solution of the tetrazotized benzidine was made neutral to Congo red by the addition of 50 cc. of 2 *N* sodium carbonate which had been diluted to 100 cc. A solution of sodium arsenite was prepared by dissolving 30 g. of arsenious oxide in 300 cc. of 2 *N* sodium carbonate and to it was added a solution of 2 g. of copper sulfate to serve as catalyst. After this had been cooled to 0°, the tetrazotized benzidine solution was siphoned into the arsenite solution during 15–20 minutes. After the combination, the mixture gave a slightly alkaline reaction (pink color) with Brilliant Yellow test paper and the temperature was 5° or below. The brown solution was stirred for two to three hours longer, while the temperature was allowed to rise gradually to about 20°. After the presence of diazo was no longer shown by testing with a solution of R-salt, the solution was warmed to 50° and the stirring continued at this temperature until nitrogen was no longer evolved. The alkaline solution was then filtered and the filtrate, was made slightly acid to litmus by the addition of dil. hydrochloric acid. The brown precipitate thus formed was filtered on a large glass funnel from a clear yellow filtrate again dissolved in alkali, and the precipitation repeated. This process of partial precipitation was continued until the filtrate from the brown solid gave no precipitate when acidified with hydrochloric acid. The filtrates were finally combined and acidified with hydrochloric acid giving a yellowish-white precipitate of the diarsonic acid. After this had been filtered, washed with water and dried, a neutral solution of the diarsonodiphenyl was prepared by dissolving 25 g. in 250 cc. of water and 12.4 cc. of 10 *N* sodium hydroxide, and treating with boneblack at 90° for one hour. The slightly yellow solution thus obtained was acidified with hydrochloric acid, giving then a white gelatinous precipitate. This was filtered, washed and dried, yielding a white powder which is practically insoluble in all ordinary solvents. The substance does not melt below 300°. From a typical experiment, 23 g. of pure diarsonic acid or a yield of 55% of that calculated, was obtained.

Anal. Subs., 0.2170: 23.22 cc. of 0.0928 *N* I_2. Calc. for $C_{12}H_{42}O_6As_2$: As, 37.31. Found: 37.23.



3,5′-Dinitro-4,4′-diarsono-diphenyl, $H_2O_3As\text{-}C_6H_3(NO_2)\text{-}C_6H_3(NO_2)\text{-}AsO_3H_2$.—Symmetrical *o*-dinitrobenzidine[2] dissolves only in concd. sulfuric acid and care must be exercised in diluting the acid solution to avoid precipitation of the insoluble sulfate which does not tetrazotize readily. If the tetrazo solution has been properly prepared, the arsenation proceeds more smoothly and with better yields than in the case of benzidine itself.

To the solution of 31 g. of *o*-dinitro benzidine in 60 cc. of concd. sulfuric acid, 80 cc. of water was slowly added and the mixture stirred, giving a brown paste of the sulfate. This suspension was cooled to 0°, and stirred mechanically while solid sodium nitrite was added in small amounts until a test portion dissolved completely upon dilution with water. About 16 g. of nitrite was usually required. The reddish-brown solution was then added to 1 liter of ice and water and the mixture filtered from any insoluble material.

A solution of sodium arsenite was prepared by dissolving 45 g. of arsenious oxide in a mixture of 100 cc. of 4 *N* sodium carbonate and 400 cc. of water, and adding to this a solution of 3 g. of copper sulfate. The tetrazotized solution was added to the arsenite solution at 0° by means of a dropping funnel while sodium carbonate was added from a second dropping funnel at such a rate that the reaction mixture gave only a slight pink color on Brilliant Yellow paper. About 450 cc. of 4 *N* sodium carbonate was required to

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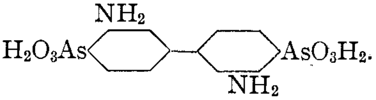
[2] Strakosch, *Ber.*, **5**, 236 (1872). Brunner and Witt, *Ber.*, **20**, 1024 (1887). Cain, *J. Chem. Soc.*, **101**, 2298 (1912); **103**, 2074 (1913); **105**, 1437 (1914).

maintain the desired alkalinity. At 0° the tetrazo disappeared as soon as it came in contact with the arsenite solution. The yellow-to-brown solution was immediately warmed to 60° and filtered by suction from a small amount of brown residue. The filtrate was partially precipitated once with dil. hydrochloric acid and after the solution of the yellow dinitro-diarsono-diphenyl had been filtered this substance was precipitated from the clear yellow filtrate by acidifying strongly with concd. hydrochloric acid and stirring or shaking vigorously. The dinitro acid was filtered, washed and dried to give 35 g. or a yield of 65%.

The crude material is sometimes colored a pink to brown upon drying, but this color is removed by heating its neutral aqueous solution with boneblack. This substance as finally obtained is a light yellow solid. It may be recrystallized from boiling glacial acetic acid, but even in this solvent it dissolves to the extent of only about 3 g. per liter.

Anal. Subs., 0.2047, 0.2192: 17.76 cc., 19.12 cc. of 0.0928 N I_2. Calc. for $C_{12}H_{10}O_{10}N_2As_2$: As, 30.48. Found: 30.19, 30.28.

3,5'-Diamino-4,4'-diarsono-diphenyl,

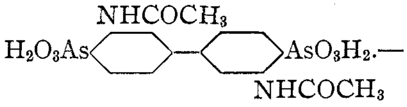


—Reduction of the corresponding dinitro-diarsono-diphenyl by means of alkaline ferrous hydroxide[3] gave the diamino compound.

Instead of using ferrous sulfate, a solution of ferrous chloride, obtained by treating a definite amount of hydrochloric acid with an excess of powdered iron, was used for the preparation of the ferrous hydroxide. The product was obtained in 79% yield as a yellowish-white powder. It is somewhat soluble in *n*-butyl alcohol from which it may be recrystallized by adding water to the hot solution until the latter is slightly turbid and then cooling in a freezing mixture or by distilling most of the alcohol and precipitating the dihydrochloride by means of hydrogen chloride. Although the butyl alcohol solution was heated with boneblack repeatedly, the product was always slightly yellow in color. The base obtained by neutralization of the dihydrochloride was almost pure white.

Anal. Subs., 0.2175: 21.48 cc. of 0.0928 N I_2. Calc. for $C_{12}H_{14}O_6N_2As_2$: As, 34.72. Found: 34.36.

3,5'-Diaceto-amino-4,4'-diarsono-diphenyl,



Three g. of the diamino compound was refluxed with a mixture of 10 cc. of acetic anhydride and 50 cc. of glacial acetic acid for five hours. The diacetyl compound was then boiled with 500 cc. of glacial acetic acid and the mixture filtered from some undissolved material. A white solid was obtained from the acetic acid filtrate which gave no reaction with nitrous acid but dissolved in dil. sodium carbonate solution. It was insoluble in excess of mineral acid.

Anal. Subs., 0.2200: 18.27 cc. of 0.0928 N I_2. Calc. for $C_{16}H_{18}O_8N_2As_2$: As, 29.07. Found: 28.89.

Tetrazotization of 3,5'-diamino-4,4'-diarsono-diphenyl and coupling with H-acid, II.—This dye was prepared by coupling one molecule of

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[3] Benda, *Ber.*, **44**, 3302 (1911). Heidelberger and Jacobs, THIS JOURNAL, **40**, 1580 (1918).

tetrazotized diamino-diarsono-diphenyl with two molecules of H-acid in alkaline solution.

A solution of 4.5 g. of the diamino compound in 40 cc. of water was obtained by the addition of 10 cc. of 4 *N* sodium carbonate. The dihydrochloride was then precipitated in a finely-divided state by the addition of 45 cc. of 2 *N* hydrochloric acid, and rapid stirring. After the mixture had been cooled to 0°, 10 cc. of 2 *N* sodium nitrite was gradually added and an excess of nitrite was maintained for one hour at 0°. The clear solution of the tetrazo compound was added by means of a dropping funnel to an alkaline solution of H-acid which was prepared by dissolving 7.2 g. of H-acid (monosodium salt) in a mixture of 40 cc. of water and 6 cc. of 4 *N* sodium carbonate solution. An additional 15 cc. of 4 *N* sodium carbonate was added to the H-acid solution to maintain the desired alkalinity during the coupling. After the mixture had been stirred for 1 hour at 0°, the alkaline solution of the dye was concentrated on the steam-bath to about 100 cc. The dye was precipitated as the free acid by the addition of 10 cc. of concd. hydrochloric acid. This was filtered off and dried, giving 11.2 g. of a bronzy powder. The finely powdered dye was stirred with 30 cc. of water to dissolve the inorganic salts, and the mixture filtered when the solid was dissolved almost completely in 200 cc. of water. This solution was filtered from a slight residue, concentrated on the steam-bath to 50 cc. and 10 cc. of glacial acetic acid was added. The pasty mass was filtered and washed with alcohol, yielding 7 g. of bright, bronze-colored solid. The dye dissolves in water to give a bluish-red solution.

Anal. Subs., 0.2203, 0.2198: 7.95 cc., 8.04 cc. 0.0968 *N* I_2. Calc. for $C_{32}H_{26}O_{20}N_6S_4As_2$: As, 13.73. Found: 13.10, 13.27.

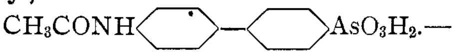
4-Amino-4′-arsono-diphenyl, V.—Of the two methods used for the preparation of this compound, that in which one of the diazonium groups of tetrazotized benzidine was first coupled with some component such as H-acid was found more satisfactory. While the coupling of tetrazotized benzidine with one molecule of H-acid is more nearly quantitative in acid than in alkaline solution, the latter was found to favor the subsequent replacement and was, therefore, used.

A solution of tetrazotized benzidine from 18.4 g. of benzidine was prepared as described for the preparation of 4,4′-diarsono-diphenyl. This solution was made slightly alkaline to Brilliant Yellow by the addition of 30 cc. of 10 *N* sodium hydroxide solution which had been diluted to a volume of 200 cc. It is necessary to keep the temperature of the tetrazo solution at 0° or below at this point. A solution of H-acid was prepared by dissolving 37 g. of the monosodium salt in a mixture of 200 cc. of water and 50 cc. of 2 *N* sodium carbonate solution. An additional 50 cc. of 2 *N* sodium carbonate was then added to the H-acid solution to provide alkalinity during the coupling, and after the solution had been cooled to 0°, it was added by means of a dropping funnel to the tetrazo solution which was well agitated with a mechanical stirrer. When most of the H-acid had been added, the coupling mixture was tested with R-salt to determine when one of the diazonium groups had been coupled. After no further blue color was obtained with R-salt, the benzidine H-acid combination was siphoned into a solution of sodium arsenite prepared by dissolving 15 g. of arsenious oxide in a mixture of 30 cc. of 10 *N* sodium hydroxide solution and 200 cc. of water. A solution of 1 g. of copper sulfate was added to the sodium arsenite. The replacement was carried out in the presence of sodium hydroxide instead of sodium carbonate since the reaction mixture was completely soluble in the former at 5°. The temperature of the solution was allowed to rise to 20° during three to four hours and the stirring was continued until a test for diazo compound was no longer given. The presence of diazo compound in such a solution is best determined as follows. Equal amounts of the reaction mixture, which has been diluted with water, are placed in two test-tubes of the same size. A small amount of H-acid is added to one tube. When both tubes are warmed to about 60° for a few minutes and the contents poured on filter paper, identical shades of color are obtained if no diazo is present. If the tube containing the H-acid shows a bluer shade, the presence of diazo compound is indicated.

When such a test showed the absence of diazo, the reduction of the azo group was carried out as follows. Fifty cc. of 10 *N* sodium hydroxide and 250 g. sodium hydrosulfite were added to the bluish-red solution and the mixture was warmed to 55–60° for two hours. The brown suspension was made distinctly alkaline to Brilliant Yellow by the addition of 125 cc. of 10 *N* sodium hydroxide solution, filtered and the precipitate washed. The brown solid was suspended in 200 cc. of water and oxidized by stirring with 25 cc. of 10 *N* sodium hydroxide solution and 250 cc. of hydrogen peroxide. A brown solution was obtained after one to two hours and this was made acid to congo red before filtering. The insoluble material was repeatedly extracted with dil. hydrochloric acid. The pink filtrates were combined and made slightly alkaline to Brilliant Yellow and filtered from a slight residue. Acidification of the solution (alkaline to litmus) gave a white flocculent precipitate. This product was finally isolated as the hydrochloride by suspending the solid in 20 cc. of water and gradually adding an equal volume of concd. hydrochloric acid. As this mixture cooled, a white precipitate of the hydrochloride formed. After two hours, it was filtered off and washed with dry ether to give 6 g. or a yield of 19%. The hydrochloride is readily soluble in water. Exact neutralization with sodium carbonate precipitates the base.

Anal. Subs., 0.1647, 0.2114: 10.62 cc., 13.69 cc. of 0.0928 *N* I_2. Calc. for $C_{12}H_{13}O_3NClAs$: As, 22.80. Found: 22.43, 22.52.

4-Aceto-amino-4′-arsono-diphenyl,



Two g. of the 4-amino-4′-arsono-diphenyl was warmed on a water-bath with 10 cc. of acetic anhydride for 15 minutes. To this was then added 200 cc. of glacial acetic acid and the mixture refluxed for one hour. It was heated for 10 minutes longer with boneblack and filtered. A white solid separated upon standing. This substance is slightly soluble in water and may be crystallized in this way. It dissolves in dil. sodium carbonate solution, but is insoluble in mineral acids and does not react with nitrous acid as the amino compound does.

Anal. Subs., 0.1703, 0.1986: 10.78 cc., 12.65 cc. of 0.0928 *N* I_2. Calc. for $C_{14}H_{14}O_4NAs$: As, 22.38. Found: 22.01, 22.18.

The experimental work on derivatives of tolidine described below was carried out by Katherine Ogden.

3,5′-Dimethyl-4,4′-diarsono-diphenyl, III.—A solution of tolidine was made by warming 17 g. to 70° in 250 cc. of water and 200 cc. of 2 *N* hydrochloric acid. This gave a clear solution from which the hydrochloride separated in fine crystals when the solution was cooled rapidly to 0° and constantly stirred. To this was slowly added 80 cc. of 2 *N* sodium nitrite solution. It was desirable to stir the solution for an hour longer and test it occasionally with starch iodide paper to be sure nitrous acid was still in excess. The tetrazotized solution was added to a solution of 24 g. of arsenious oxide and 0.5 g. of copper sulfate in 480 cc. of 2 *N* sodium carbonate at 15°. The color of the alkaline solution changed immediately to brown. Carbon dioxide and nitrogen were rapidly evolved, causing foaming which was lessened materially by a layer of benzene. The alkaline solution was filtered on a large gravity funnel. This process required from 24 to 48 hours but seemed to be much the most satisfactory method for removing the fine, reddish-brown by-product. The filtrate, which was clear yellow, gave on acidification with dil. hydrochloric acid a precipitate which was practically white. This was washed with water until free from chlorides and dried at 70°. The yield was 15 g. (44%). It does not melt up to 310°, is insoluble in water and organic solvents including glacial acetic acid, but the alkali salts are easily soluble in water.

Anal. Subs., 0.2054, 0.1990: 16.7 cc., 12.3 cc. of 0.1134 *N* I_2. Calc. for $C_{14}H_{16}O_6As_2$: As, 34.88. Found: 34.56, 34.64.

3,5′-Dicarboxy-4,4′-diarsono-diphenyl, IV.—To a solution of 10 g. of 3,5′-dimethyl-4,4′-diarsono-diphenyl and 5 g. of potassium hydroxide in 250 cc. of water was added a solution of 14 g. of potassium permanganate in 750 cc. of water. This mixture was refluxed until the color disappeared (five hours) when the manganese dioxide that had formed was filtered off. After the filtrate had been concentrated on the steam-bath to about 500 cc., concd. hydrochloric acid was added in excess. The yellow, tarry material that first separated redissolved in the acid solution; the solution was filtered and the clear, almost colorless filtrate was heated on the steam-bath until fine, white crystals formed which were quite insoluble in water. The yield was 15 g. (67%).

Anal. Subs., 0.2167, 0.2420: 18.10 cc., 20.20 cc. of 0.0980 *N* I_2. Calc. for $C_{14}H_{12}O_{10}As_2$: As, 30.61. Found: 30.74, 30.72.

Summary

1. Benzidine has been tetrazotized and the amino groups have been replaced by arsonic acid radicals.
2. Substituted benzidines such as the dinitro derivatives have been arsenated and the dinitro-diarsonic acids have been reduced to the corresponding diamino compounds.
3. A number of derivatives of these diamino derivatives have been prepared, among which are azo dyes of the Trypan Blue type.
4. A method of preparation has been developed for derivatives of diphenyl in which an arsonic acid radical is attached to one ring and various substituted groups attached to the other ring.

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