2. The influence of progressive substitution of the hydrogen atoms of ammonia by certain organic radicals on the absorption spectrum has been noted.

3. Between 2.7 and 3.4μ, the absorption reveals a pronounced qualitative differentiation between aniline and mono-alkyl anilines and dialkyl anilines.

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[CONTRIBUTION FROM THE DIVISION OF PHARMACOLOGY, HYGIENIC LABORATORY, UNITED STATES PUBLIC HEALTH SERVICE]

SYNTHESIS OF N,N'-DIMETHYLENESULFONATES OF ORTHO-, META- AND PARA-DIAMINO-ARSENOBENZENE

BY KOZO KASHIMA[1]

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Disodium 3,3'-diamino-4,4'-dihydroxyarsenobenzene, N,N'-dimethylenesulfonate, known under the official name sulfarsphenamine, has proved to be of practical value in the treatment of syphilis. A satisfactory method of preparation of this drug has been described by Voegtlin and Johnson.[2] These workers obtained the product by subjecting an aqueous solution of arsphenamine (dihydrochloride of 3,3'-diamino-4,4'-dihydroxyarsenobenzene) to the action of formaldehyde and sodium bisulfite. The work to be reported deals with the preparation of similar dimethylenesulfonates, derived from *o*-, *m*- and *p*-diamino-arsenobenzene. The synthesis of these products involved the preparation of a number of intermediates. One of the latter, 3,3'-diamino-arsenobenzene, had not been described previously. These methylenesulfonates are now being tested in this Laboratory as to their chemotherapeutic potency in experimental syphilis.

Experimental Part

2-Nitrophenylarsonic Acid, $(2)O_2NC_6H_4AsO_3H_2$.—This acid was prepared from *o*-nitro-aniline according to the method of Schmidt.[3] It was found advantageous to use sulfuric acid for the final precipitation of the nitrophenylarsonic acid. When recrystallized, the product was obtained in the form of almost colorless needles; m. p., 231°; yield, 85%.

Anal. Calcd. for $C_6H_6O_5NAs$: As, 30.35. Found: 30.14, 30.25.

2-Aminophenylarsonic Acid, $2\text{-}H_2N.C_6H_4AsO_3H_2$.—Benda[4] obtained the acid from 2-amino-5-nitrophenylarsonic acid by a complicated procedure. A simpler method is the following.

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[1] Lecturer in Chemistry, Tokyo Imperial University.

[2] Voegtlin and Johnson, THIS JOURNAL, **44**, 2573 (1922).

[3] Schmidt, *Ann.*, **421**, 172 (1920). Bart, Ger. pat. 250,264.

[4] Benda, *Ber.*, **44**, 3304 (1911).

A mixture of 560 g. of 4% sodium amalgam and 20 g. of 2-nitrophenylarsonic acid dissolved in 500 cc. of methyl alcohol is placed in a flask provided with a reflux condenser, heated at 55–60° for about 12 hours and shaken frequently. After the alcohol has been distilled, the residue is dissolved in 100 cc. of water, separated from mercury and acidified with concd. hydrochloric acid, until the solution becomes strongly acid to Congo red paper. After standing overnight the sodium chloride and a colored by-product (an azoxy compound?) are filtered off. The addition of a saturated sodium acetate solution to the filtrate yields, after a few days' standing, a slight amount of 2-aminophenylarsonic acid, but owing to the great solubility of this substance in water, the yield is poor.

In subsequent work the final separation was much better accomplished as follows. The aqueous solution of the sodium salt is decomposed by the addition of a slight excess of concd. sulfuric acid. After the mixture has stood for 12 hours the sodium sulfate is filtered off and the filtrate concentrated in a vacuum on the water-bath. On standing, some of the arsonic acid separates as a crystalline product and is filtered off. The mother liquor is treated with concd. barium hydroxide solution, the barium sulfate filtered off and the filtrate concentrated to a small volume on the water-bath. The barium salt of the arsonic acid is then precipitated by the addition of absolute alcohol. After drying, the salt is decomposed by addition of a small amount of 5 *N* sulfuric acid, until the mixture is slightly acid. After filtration from barium sulfate the filtrate on concentration gives almost pure 2-aminophenylarsonic acid in about a 75% yield; m. p., 153–154° (Benda, 153°).

Anal. Calcd. for $C_6H_8O_3NAs$: As, 34.54. Found: 34.31, 34.50.

2,2′-Diamino-arsenobenzene, $H_2N.C_6H_4As{:}AsC_6H_4.NH_2$.—The hydrochloride of this compound has been previously prepared in small amount by Fichter and Elkind[5] from 2-nitrophenylarsonic acid by electrolytic reduction, but this method is not suitable for the preparation of large amounts. It was prepared, therefore, from 2-nitrophenylarsonic acid by reduction with sodium hydrosulfite or from 2-aminophenylarsonic acid by reduction with hypophosphorous acid.

Five g. of 2-nitrophenylarsonic acid is dissolved in 70 cc. of water with an equivalent amount of 5 *N* sodium hydroxide solution. Seventeen g. of crystallized magnesium chloride is dissolved in 400 cc. of water, to which 100 g. of sodium hydrosulfite (purity, 80%) is gradually added during agitation. After filtration this solution is added to the solution containing the nitro acid which is placed in a wide-mouthed bottle, provided with a stirrer and immersed in water at 55–60°. A yellow precipitate gradually separates. After three hours, the precipitate is separated from the liquid by centrifuging, washed with a small amount of water, dil. sodium hydroxide solution and water. It is then filtered by suction and dried over solid sodium hydroxide in a vacuum desiccator; yield, 1.8 g. It is a yellow, crystalline powder, decomposing at 115–125°. When thoroughly dried the base is almost insoluble in mineral acids.

Anal. Calcd. for $C_{12}H_{12}N_2As_2$: N, 8.38; As, 44.89. Found: N, 8.11, 8.05; As, 44.69, 45.01.

To 1.25 g. of 2-aminophenylarsonic acid dissolved in 70 cc. of water are added 15 cc. of 50% hypophosphorous acid and a small crystal of potassium iodide. The solution is heated at 50° during vigorous stirring for two hours; a yellow precipitate gradually separates. The mixture is cooled, made alkaline with 5 *N* sodium hydroxide solution, and centrifuged. The solid is thoroughly washed with cold water and dried over sodium hydroxide in a vacuum desiccator; yield, 0.8 g.

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[5] Fichter and Elkind, *Ber.*, **49**, 246 (1916).

Anal. Calcd. for $C_{12}H_{12}N_2As_2$: N, 8.38; As, 44.89. Found: N, 8.22, 8.13; As, 44.26, 44.48.

N,N′-Methylene-sulfonic Acid of 2,2′-Diamino-arsenobenzene, $HO_3S.CH_2.NH.C_6H_4As{:}AsC_6H_4.NH.CH_2.SO_3H$.—This compound is obtained from freshly prepared 2,2′-diamino-arsenobenzene by condensation with formaldehyde and sodium bisulfite.

Freshly prepared, moist 2,2′-diamino-arsenobenzene (obtained from 15 g. of 2-nitrophenylarsonic acid) is suspended in 40 cc. of *N* hydrochloric acid. During vigorous stirring, 4 cc. of formaldehyde (36%) is added, this being followed immediately by a saturated solution containing 4.5 g. of sodium bisulfite. The resulting dark red solution is poured into 350 cc. of 97% alcohol and the light red precipitate thus formed is separated, washed with alcohol and dried in a vacuum desiccator over sodium hydroxide; yield, 3.7 g.

Anal. Subs., 0.1500, 0.1500: 11.31, 11.18 cc. of 0.1 *N* $Na_2S_2O_3$ (Lehmann). Subs., 0.2000, 0.2000: 6.91, 7.01 cc. of 0.1 *N* acid (Kjeldahl). Subs., 0.1500: $BaSO_4$, 0.1157. Calcd. for $C_{12}H_{16}O_6N_2S_2As_2$: N, 5.36; S, 12.28; As, 28.71; calcd. for $C_{12}H_{14}O_6N_2S_2As_2Na_2$: N, 4.95; S, 11.33; As, 26.49. Found: N, 4.83, 4.91; S, 10.59; As, 28.25, 27.93.

Ratio: As:N = 1:0.93; As:S = 1:0.89.

These results indicate that the product is a mixture of free acid and its sodium salts.

3,3′-Diamino-arsenobenzene, $(3)NH_2.C_6H_4As{:}AsC_6H_4.NH_2(3')$.—This compound was prepared by reduction with hypophosphorous acid from 3-aminophenylarsonic acid (obtained by reduction of 3-nitrophenylarsonic acid with sodium amalgam, according to Bertheim.[6]

A solution of 4.3 g. of 3-aminophenylarsonic acid in 100 cc. of water containing an equivalent amount of 5 *N* sodium hydroxide solution is mixed with 35 cc. of 50% hypophosphorous acid and to the mixture is added a small crystal of potassium iodide. The solution is mechanically agitated at 50–55°; no yellow precipitate is produced. After two hours the solution is cooled to room temperature, filtered and made alkaline with 5 *N* sodium hydroxide solution. The resulting light yellow precipitate is separated from the liquor, well washed with cold water, filtered off and dried over solid sodium hydroxide in a vacuum desiccator; yield, 3.5 g. The substance is a yellow powder, insoluble in water and organic solvents.

Anal. Calcd. for $C_{12}H_{12}N_2As_2$: N, 8.38; As, 44.89. Found: N, 8.22, 8.17; As, 44.28, 44.49.

The DIHYDROCHLORIDE is prepared by the following method. After reduction is complete, the solution is cooled with a mixture of ice and salt and gradually poured into a mixture of 23 parts of hydrochloric acid (d., 1.8) and 15 parts of water, cooled by the same freezing mixture. A gray precipitate is produced. After this is separated from the liquor, it is washed with concd. hydrochloric acid, then with a mixture of alcohol and ether (1:1), filtered off and dried.

Anal. Calcd. for $C_{12}H_{12}N_2As_2.2HCl$: N, 6.88; As, 36.84. Found: N, 6.67; As, 37.03.

Disodium 3,3′-Diamino-arsenobenzene-N,N′-dimethylenesulfonate, $NaO_3S.CH_2.NH.C_6H_4As{:}AsC_6H_4.NH.CH_2.SO_3Na$.

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[6] Bertheim, *Ber.*, **41**, 1657 (1908); **44**, 3299 (1911).

Freshly prepared and still moist 3,3′-diamino-arsenobenzene obtained from 4.3 g. of 3-aminophenylarsonic acid by reduction with hypophosphorous acid is dissolved in a mixture of 25 cc. of *N* hydrochloric acid and 50 cc. of water. The solution is vigorously shaken with 2 cc. of 36% formaldehyde and then with an aqueous solution of 2.1 g. of sodium bisulfite. The solution becomes viscous and then reddish-brown. It is poured into 500 cc. of 97% alcohol in a thin stream during agitation of the mixture and yields a brownish-yellow precipitate. The latter is separated from the liquor, washed with alcohol, filtered off and dried over solid sodium hydroxide in a vacuum desiccator; yield, 4.3 g. It is easily soluble in water and reduces iodine solution.

Anal. Subs., 0.1500, 0.1500: 10.12, 9.86 cc. of 0.1 *N* $Na_2S_2O_3$ (Lehmann). Subs., 0.2000, 0.2000: 6.51, 6.37 cc. of 0.1 *N* acid (Kjeldahl). Subs., 0.2000, 0.2000: 0.1617, 0.1638 $BaSO_4$. Calcd. for $C_{12}H_{14}O_6N_2S_2As_2Na_2$: N, 4.95; S, 11.33; As, 26.49. Found: N, 4.56, 4.46; S, 11.10, 11.25; As, 25.25, 24.63.

Ratio: As:N = 1:0.97; As:S = 1:1.05.

4,4′-Diamino-arsenobenzene, (4)$NH_2.C_6H_4As:AsC_6H_4.NH_2$(4′).—This compound has been prepared by many different methods. We have found that it can be easily prepared from 4-aminophenylarsonic acid by reduction with hypophosphorous acid, using potassium iodide as a catalyst.

With 16 g. of the sodium salt of 4-aminophenylarsonic acid dissolved in 100 cc. of water is mixed 105 cc. of 50% hypophosphorous acid and an aqueous solution of 0.25 g. of potassium iodide. The mixture is warmed at 50–55° during mechanical agitation for two hours; a yellow precipitate is gradually produced. After the mixture has been cooled, an excess of 5 *N* sodium hydroxide solution is added and the precipitate is separated from the liquor by centrifuging; it is washed with water, filtered off and dried in a vacuum desiccator; yield, 8.5 g. The substance is insoluble in water and the usual organic solvents.

Anal. Calcd. for $C_{12}H_{12}N_2As_2$: N, 8.38; As, 44.89. Found: N, 7.85, 8.08; As, 44.69, 44.90.

Disodium 4,4′-Diamino-arsenobenzene-N,N′-dimethylenesulfonate, $NaO_3S.CH_2.NH.C_6H_4As:AsC_6H_4.NH.CH_2SO_3Na$.—4,4′-Diamino-arsenobenzene condenses with formaldehyde and sodium bisulfite in acid solution. The condensation is best accomplished in 50% acetic or 1 *N* hydrochloric acid. The yield is larger when the condensation is carried out in hydrochloric acid.

4,4′-Diamino-arsenobenzene, obtained by reduction of 5.5 g. of 4-aminophenylarsonic acid, is dissolved without previous drying in 75 cc. of 50% acetic acid, and 0.9 g. of 36% formaldehyde is added during vigorous shaking. The dark red, gelatinous precipitate thus formed is separated by means of the centrifuge, suspended in 250 cc. of water and shaken with 1.8 g. of sodium bisulfite dissolved in a small amount of water. The resulting clear red solution is filtered in order to remove a small amount of undissolved material and the filtrate is poured into 1 liter of 97% alcohol. The reddish-yellow precipitate is separated by centrifuging, washed with alcohol and dried over sodium hydroxide in a vacuum desiccator; yield, 2.1 g. The condensation product is soluble in water, reduces iodine solution, but not indigo carmin.

Anal. Subs., 0.2000, 0.2000: 13.23, 13.36 cc. of 0.1 *N* $Na_2S_2O_3$ (Lehmann). Subs., 0.2000, 0.2000: 6.52, 6.38 cc. of 0.1 *N* acid (Kjeldahl). Subs., 0.2000, 0.2000: $BaSO_4$, 0.1699, 0.1752. Calcd. for $C_{12}H_{14}O_6N_2S_2As_2Na_2$: N, 4.95; S, 11.33; As, 26.49. Found: N, 4.57, 4.47; S, 11.68, 12.03; As, 24.79, 25.02.

Ratio: As:N = 1:0.97; As:S = 1:1.11.

The author desires to express his sincere thanks to Professor C. Voegtlin for the suggestions and advice which rendered the work possible.

Summary

1. New methods for the preparation of 2-aminophenylarsonic acid, 2,2′- and 4,4′-diamino-arsenobenzenes have been developed.

2. 3,3′-Diamino-arsenobenzene and the N,N′-dimethylenesulfonates of 2,2′-, 3,3′- and 4,4′-diamin-oarsenobenzenes have been prepared.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

STUDIES ON THE DIRECTIVE INFLUENCE OF SUBSTITUENTS IN THE BENZENE RING. II. THE RELATIVE RATES OF BROMINATION OF CERTAIN ORTHO, META AND PARA ISOMERS[1,2]

BY A. W. FRANCIS, A. J. HILL AND JOHN JOHNSTON

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In a previous paper[3] there was described an analytical method for the estimation of the *meta* isomer of various monosubstituted amines, phenols and nitro compounds in mixtures with the corresponding *ortho* and *para* compounds. This method depends upon the fact that amines and phenols are brominated quantitatively in aqueous solution, the *meta* in each case yielding the tribromo compound whereas the *ortho* and *para* are only dibrominated. This substitution offers also a convenient method of studying the directive influence of substituents, for it seemed probable that the rates of bromination of various compounds, and in the two or three available positions of a single compound, would vary considerably with change of the groups present, and that from these differences some estimate could be formed of the directive influences of the substituent groups.

The following pages recount the results of experiments upon the rate of bromination, in dilute aqueous solution, of a number of aromatic amino and phenolic compounds. The work was undertaken as a means of ascertaining how the nature of the group already attached to the benzene nucleus affects the rate at which the bromine enters the ring in the several possible positions; and the results, it is believed, are of some significance in connection with the general problem of the factors which determine the

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[1] This paper is constructed from Part II of a dissertation presented by Alfred W. Francis to the Faculty of the Graduate School of Yale University in candidacy for the degree of Doctor of Philosophy, 1924.

[2] Presented in part at the Sixty-seventh Meeting of the American Chemical Society, Washington, D. C., April, 1924.

[3] Francis and Hill, THIS JOURNAL, **46**, 2498 (1924).