

CLXXXIX.—*Aromatic Arsonic Acids.*

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IN a previous communication from these laboratories (Trans., 1908, 93, 1180), some account was given of the preparation and properties of certain aromatic arsonic and arsinic acids, and reference was made to the use of substances of this class in trypanosomiasis. At that time, the physiological results obtained with the bis-aminoarylarsonic acids were not sufficiently conclusive for publication, but Dr. Breinl has now found that sodium bis-2-aminotolyl-5-arsinate and sodium bis-2-acetylaminotolyl-5-arsinate are of little use in trypanosomiasis, probably owing to their low arsenic content.

The present communication records the chemical and physical properties of a number of new arsonic acids, which are derivatives of *p*-aminophenylarsonic acid and 2-aminotolyl-5-arsonic acid. These two acids have, of course, a certain toxicity, although this is only a small fraction of that of arsenic acid, and it was thought at one time that they were slowly decomposed in the body with formation of arsenic acid and aniline or *o*-toluidine respectively, and that their toxicity was due partly to the arsenic acid and partly to the aniline. We therefore prepared *p*-hydroxyphenylarsonic acid and 2-hydroxytolyl-5-arsonic acid by diazotising the corresponding amino-acids and removing the nitrogen, in order that when the arsonic acid was decomposed in the body, phenol and *o*-cresol should result instead of

aniline and *o*-toluidine. Physiological investigation of the sodium salts of these acids, however, has proved that they are of no use in trypanosomiasis, behaving in the body like arsenic acid rather than like *p*-aminophenylarsonic acid. The reason for the difference in action between the amino- and hydroxy-arylarsonic acids has now been supplied by Nierenstein (*Annals of Tropical Medicine and Parasitology*, 1908, **2**, 249), who has shown that sodium *p*-aminophenylarsonate and its monoacyl derivatives combine with proteins, whilst its diacyl derivatives, sodium *p*-hydroxyphenylarsonate, and sodium arsenate do not.

During the period of the physiological investigation of these substances, a part of our chemical results has been anticipated, for Berthelm (*Ber.*, 1908, **41**, 1854) described the preparation and properties of sodium *p*-hydroxyphenylarsonate, although he did not isolate the free acid, and Benda and Kahn (*Ber.*, 1908, **41**, 1678) described the preparation and properties of 2-hydroxytolyl-5-arsonic acid; consequently, we have only-recorded here the preparation and properties of salts and derivatives which these chemists have not described.

The trypanocidal action of certain benzidine and triphenylmethane dyes led us to inquire whether dyestuffs which contain a phenylarsonic acid residue would be more effective than the substituted phenylarsonic acids themselves. In order to test this point, we have prepared certain azobenzenearsonic acids and phenazinearsonic acids.

The production of a red dyestuff on diazotising *p*-aminophenylarsonic acid and coupling with β -naphthylamine has already been described by Ehrlich and Berthelm (*Ber.*, 1907, **40**, 3297), but no results of any physiological examination of this substance have as yet been available. By diazotising *p*-aminophenylarsonic acid and 2-aminotolyl-5-arsonic acid, and coupling with phenol, β -naphthol, and dimethylaniline respectively, we have prepared 4-hydroxyazobenzene-4'-arsonic acid, β -naphtholazobenzene-4'-arsonic acid, 4-dimethylaminoazobenzene-4'-arsonic acid, 4-hydroxy-2'-methylazobenzene-4'-arsonic acid, and 4-dimethylamino-2'-methylazobenzene-4'-arsonic acid. Of these, the two last were physiologically examined, and proved to be of very small value against a virulent strain of trypanosomes.

The preparation of a phenazine from *p*-aminophenylarsonic acid by the method of Perkin and Nierenstein (*Trans.*, 1905, **87**, 1412) was suggested to us by Dr. Nierenstein, and this has been carried out by the formation of phenazine-2 : 7-bis-arsonic acid; this, however, proved to have little effect on trypanosomes. The corresponding phenazine from 2-aminotolyl-5-arsonic acid, 4 : 9-dimethylphenazine-2 : 7-bis-arsonic acid, was also prepared, but, in view of the inactivity of the lower homologue, it was not submitted to physiological examination.

The physiological examination of these substances was carried out at the Runcorn Research Laboratories of the Liverpool School of Tropical Medicine, and we take this opportunity of expressing our thanks to Dr. Breinl, the Director of these Laboratories.

EXPERIMENTAL.

p-Hydroxyphenylarsonic Acid, $\text{HO}\cdot\text{C}_6\text{H}_4\cdot\text{AsO}(\text{OH})_2$.

Two hundred and fifty grams of sodium *p*-aminophenylarsonate (containing $5\text{H}_2\text{O}$) were diazotised with the calculated quantities of sodium nitrite and hydrochloric acid, and the solution evaporated to dryness. The residue was then ground to a fine powder, and again heated on the water-bath until completely dry, when the *p*-hydroxyphenylarsonic acid was separated from the sodium chloride by dissolution in boiling acetone, from which it crystallised on cooling in salmon-pink, prismatic needles. The yield amounted to 125 grams, that is 75 per cent. of the theoretical.

p-Hydroxyphenylarsonic acid is obtained almost colourless by several crystallisations from acetone, but persistently retains a faint pink tinge. It melts at 170 — 174° , and is very easily soluble in water or alcohol, but sparingly so in cold acetone :

0.1724 gave 0.2110 CO_2 and 0.0508 H_2O . $\text{C} = 33.4$; $\text{H} = 3.3$.

$\text{C}_6\text{H}_7\text{O}_4\text{As}$ requires $\text{C} = 33.0$; $\text{H} = 3.2$ per cent.

p-Acetoxyphenylarsonic Acid, $\text{CH}_3\cdot\text{CO}\cdot\text{O}\cdot\text{C}_6\text{H}_4\cdot\text{AsO}(\text{OH})_2$.

Twelve grams of *p*-hydroxyphenylarsonic acid were gently boiled for one hour with 36 grams of acetic anhydride and 0.5 gram of concentrated sulphuric acid. The whole of the arsonic acid first dissolved, and then separated as a jelly, which was ground with petroleum several times to remove the acetic anhydride, and re-crystallised from acetone, giving an almost quantitative yield of the acetyl derivative.

p-Acetoxyphenylarsonic acid crystallises from acetone in matted clusters of fine needles, which do not melt at 250° . It is very easily soluble in cold water, but somewhat sparingly so in cold alcohol or acetone :

0.2092 gave 0.2822 CO_2 and 0.0650 H_2O . $\text{C} = 36.8$; $\text{H} = 3.5$.

$\text{C}_8\text{H}_9\text{O}_5\text{As}$ requires $\text{C} = 36.9$; $\text{H} = 3.5$ per cent.

The sodium salt crystallises from water in matted clusters of fine silky needles, and contains 3 molecules of water of crystallisation. It is very readily soluble in water, giving a neutral solution, but sparingly so in alcohol :

0.3830, air-dried salt, lost 0.0600 at 100°. $\text{H}_2\text{O} = 15.7$.

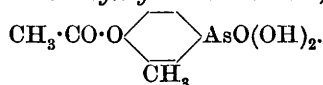
$\text{C}_8\text{H}_8\text{O}_5\text{AsNa}, 3\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 16.1$ per cent.

Sodium 2-hydroxytolyl-5-arsonate crystallises from water in plates, which contain two molecules of water of crystallisation. It is soluble in four times its weight of cold water, giving a neutral solution, and is sparingly soluble in alcohol:

0.4230, air-dried salt, lost 0.0528 at 100°. $\text{H}_2\text{O} = 12.5$.

$\text{C}_7\text{H}_8\text{O}_4\text{AsNa}, 2\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 12.4$ per cent.

2-Acetoxytolyl-5-arsonic Acid,



This acid is prepared from 2-hydroxytolyl-5-arsonic acid in a manner analogous to the preparation of *p*-acetoxyphenylarsonic acid. It separates from acetone in clusters of fine needles, and melts at 164—166°; it is sparingly soluble in cold water or acetone, but readily so in alcohol:

0.1684 gave 0.2438 CO_2 and 0.0600 H_2O . $\text{C} = 39.5$; $\text{H} = 4.0$.

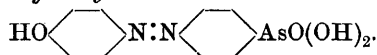
$\text{C}_9\text{H}_{11}\text{O}_5\text{As}$ requires $\text{C} = 39.4$; $\text{H} = 4.1$ per cent.

The *sodium* salt crystallises from water in radial clusters of silky needles, and contains 4 molecules of water of crystallisation. It is readily soluble in water, giving a neutral solution, but sparingly so in alcohol:

0.2594, air-dried salt, lost 0.0498 at 100°. $\text{H}_2\text{O} = 19.2$.

$\text{C}_9\text{H}_{10}\text{O}_5\text{AsNa}, 4\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 19.6$ per cent.

4-Hydroxyazobenzene-4'-arsonic Acid,



Forty-five grams of sodium *p*-aminophenylarsonate (containing $5\text{H}_2\text{O}$) were dissolved in 100 c.c. of water and 40 grams of hydrochloric acid, and diazotised at 0° with an aqueous solution of sodium nitrite until the mixture contained free nitrous acid. A cold solution of 13 grams of phenol in 125 grams of 10 per cent. aqueous sodium hydroxide was then added, followed by a sufficient further quantity of aqueous sodium hydroxide to form a clear solution. After standing for one hour, the deep red solution was acidified with hydrochloric acid, and the dye collected. In order to purify it, it was treated with sufficient 10 per cent. aqueous sodium hydroxide to form the disodium salt, warmed, and saturated with carbon dioxide; on cooling,

the monosodium salt separated in glistening, yellow plates; these were collected, re-dissolved in hot water, and acidified with acetic acid:

0.1193 gave 0.1971 CO_2 and 0.0373 H_2O . $\text{C} = 45.0$; $\text{H} = 3.5$.

$\text{C}_{12}\text{H}_{11}\text{O}_4\text{N}_2\text{As}$ requires $\text{C} = 44.7$; $\text{H} = 3.4$.

4-Hydroxyazobenzene-4'-arsonic acid is a light red powder, and is insoluble in water and all the usual organic solvents. It is readily soluble in alkalis, giving deep red solutions.

The monosodium salt, prepared as above, is almost insoluble in cold water, and sparingly so in hot water. It contains $2\frac{1}{2}$ molecular proportions of water of crystallisation:

0.2816, air-dried salt, lost 0.0322 at 115° . $\text{H}_2\text{O} = 11.4$.

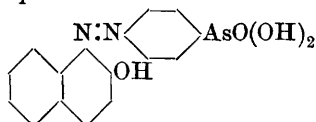
$\text{C}_{12}\text{H}_{10}\text{O}_4\text{N}_2\text{AsNa}, 2\frac{1}{2}\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 11.6$ per cent.

The disodium salt is prepared by dissolving the monosodium salt in one molecular equivalent of aqueous sodium hydroxide, concentrating, and mixing with alcohol, when it is obtained as a light red powder, which is readily soluble in cold water. It contains 8 molecules of water of crystallisation:

0.4576 lost 0.1268 at 115° . $\text{H}_2\text{O} = 27.7$ per cent.

$\text{C}_{12}\text{H}_9\text{O}_4\text{N}_2\text{AsNa}_2, 8\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 28.2$ per cent.

β -Naphtholazobenzene-4-arsonic Acid,



A diazotised solution of *p*-aminophenylarsonic acid was rendered alkaline, and coupled with an alkaline solution of one molecular equivalent of β -naphthol. The resulting acid was precipitated on the addition of hydrochloric acid. It was re-dissolved in sufficient aqueous sodium hydroxide to form a disodium salt, and a stream of carbon dioxide was passed through the solution, when the monosodium salt was obtained as a deep orange, crystalline precipitate. The acid was regenerated from this and analysed:

0.1702 gave 0.3212 CO_2 and 0.0582 H_2O . $\text{C} = 51.5$; $\text{H} = 3.8$.

$\text{C}_{16}\text{H}_{13}\text{O}_4\text{N}_2\text{As}$ requires $\text{C} = 51.6$; $\text{H} = 3.5$ per cent.

β -Naphtholazobenzene-4-arsonic acid is a bright red powder, which is soluble only in alkalis.

The monosodium salt, prepared as above, is sparingly soluble in boiling water; it contains 5 molecules of water of crystallisation:

0.3526, air-dried salt, lost 0.0660 at 115° . $\text{H}_2\text{O} = 18.7$.

$\text{C}_{16}\text{H}_{12}\text{O}_4\text{N}_2\text{AsNa}, 5\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 18.6$ per cent.

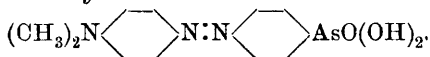
The disodium salt is a dark red powder, which is readily soluble in

water, and contains $6\frac{1}{2}$ molecular proportions of water of crystallisation :

0.3692 lost 0.0823 H_2O . $\text{H}_2\text{O} = 22.3$.

$\text{C}_{16}\text{H}_{11}\text{O}_4\text{N}_2\text{AsNa}_2, 6\frac{1}{2}\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 22.0$ per cent.

4-Dimethylaminoazobenzene-4'-arsonic Acid,



Forty-five grams of sodium *p*-aminophenylarsonate were dissolved in 100 c.c. of water and 40 grams of concentrated hydrochloric acid, and diazotised at 0° with 9.5 grams of sodium nitrite dissolved in 50 c.c. of water. 16.5 Grams of dimethylaniline dissolved in 15 grams of hydrochloric acid and 150 c.c. of water were then added, and, after several hours, the dye was precipitated by the addition of an excess of sodium acetate solution, collected, washed with water, and dried. For analysis, the acid was regenerated from its recrystallised monosodium salt, washed, and dried :

0.1473 gave 0.2584 CO_2 and 0.0580 H_2O . $\text{C} = 47.8$; $\text{H} = 4.4$.

$\text{C}_{14}\text{H}_{16}\text{O}_3\text{N}_2\text{As}$ requires $\text{C} = 48.1$; $\text{H} = 4.6$ per cent.

4-Dimethylaminoazobenzene-4'-arsonic acid is a red powder, which is insoluble in water and the usual solvents, but readily soluble in alkalis and mineral acids. The acid salts are decomposed by water.

The *monosodium* salt crystallises from hot water in glistening, scarlet plates, which are sparingly soluble in cold water, and contain $5\frac{1}{2}$ molecular proportions of water of crystallisation :

0.2398 lost 0.0506 at 115° . $\text{H}_2\text{O} = 21.1$.

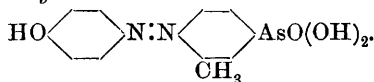
$\text{C}_{14}\text{H}_{15}\text{O}_3\text{N}_2\text{AsNa}, 5\frac{1}{2}\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 21.1$ per cent.

The *disodium* salt was prepared by dissolving the monosodium salt in the calculated quantity of aqueous sodium hydroxide, concentrating to a small bulk, and precipitating with alcohol. It is a scarlet powder, which is soluble in 3 parts of cold water, and contains 6 molecules of water of crystallisation :

0.3644 lost 0.0756 at 115° . $\text{H}_2\text{O} = 20.7$.

$\text{C}_{14}\text{H}_{14}\text{O}_3\text{N}_2\text{AsNa}_2, 6\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 21.4$ per cent.

4-Hydroxy-2'-benzeneazotoluene-5'-arsonic Acid,



Fifty grams of sodium 2-aminotolyl-5-arsonate were diazotised and coupled with an alkaline solution of phenol, as in the preparation of 4-hydroxyazobenzene-4'-arsonic acid. In this case, however, the clear

alkaline solution was treated with carbon dioxide, when a red, crystalline precipitate, consisting of the monosodium salt, was formed, the yield amounting to 84 per cent. of the theoretical. A portion of the salt was recrystallised, dissolved in hot water, and acidified with acetic acid, when a crystalline precipitate of the arsonic acid was obtained :

0.1412 gave 0.2410 CO_2 and 0.0500 H_2O . $\text{C} = 46.5$; $\text{H} = 3.9$,

$\text{C}_{13}\text{H}_{13}\text{O}_4\text{N}_2\text{As}$ requires $\text{C} = 46.4$; $\text{H} = 3.9$ per cent.

4-Hydroxy-2'-benzeneazotoluene-5'-arsonic acid is a light red, crystalline powder, which is practically insoluble in boiling water and the usual organic solvents, but readily soluble in alkalis.

The monosodium salt crystallises from water in red leaflets. It is moderately soluble in hot water, sparingly so in cold, and contains $2\frac{1}{2}$ molecular proportions of water of crystallisation :

0.5797 lost 0.0655 at 115° . $\text{H}_2\text{O} = 11.3$.

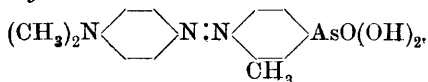
$\text{C}_{13}\text{H}_{12}\text{O}_4\text{N}_2\text{As}, 2\frac{1}{2}\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 11.1$ per cent.

The disodium salt was prepared by dissolving the monosodium salt in the calculated quantity of aqueous sodium hydroxide, concentrating to a small bulk, and adding alcohol. It is a red powder soluble in 3 parts of cold water, and contains $4\frac{1}{2}$ molecular proportions of water of crystallisation :

0.6185 lost 0.1081 at 115° . $\text{H}_2\text{O} = 17.5$.

$\text{C}_{13}\text{H}_{11}\text{O}_4\text{N}_2\text{AsNa}_2, 4\frac{1}{2}\text{H}_2\text{O}$ requires $\text{H}_2\text{O} = 17.6$ per cent,

4-Dimethylamino-2'-benzeneazotoluene-5'-arsonic Acid,



Forty-five grams of sodium 2-aminotolyl-5-arsonate were dissolved in dilute hydrochloric acid, diazotised, and coupled with an acid solution of dimethylaniline. The solution was allowed to stand for an hour and neutralised with sodium carbonate, and the resulting solid was collected, dissolved in sodium hydroxide, and precipitated as the crystalline monosodium salt by carbon dioxide, the yield amounting to 82 per cent. of the theoretical. The acid was obtained from the monosodium salt, by acidifying the hot aqueous solution with acetic acid, as a red, crystalline powder, which formed salts with mineral acids and with bases :

0.1456 gave 0.2642 CO_2 and 0.0630 H_2O . $\text{C} = 49.5$; $\text{H} = 4.8$.

$\text{C}_{15}\text{H}_{18}\text{O}_3\text{N}_3\text{As}$ requires $\text{C} = 49.6$; $\text{H} = 4.9$ per cent.

The monosodium salt is a red, crystalline, powder which is moderately

easily soluble in hot water, but sparingly so in cold. It contains 5 molecules of water of crystallisation:

0.4418 lost 0.0840 at 115°. $H_2O = 19.0$.

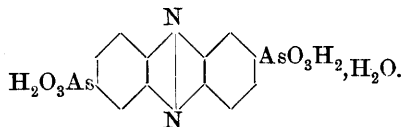
$C_{15}H_{17}O_3N_3AsNa, 5H_2O$ requires $H_2O = 18.9$ per cent.

The *disodium* salt, prepared in the usual manner, is a red powder, which is soluble in 3 parts of cold water, and contains 4 molecules of water of crystallisation:

0.4250 lost 0.0628 at 115°. $H_2O = 14.8$.

$C_{15}H_{16}O_3N_3AsNa_2, 4H_2O$ requires $H_2O = 15.0$ per cent.

Phenazine-2:7-bis-arsonic Acid,



Twenty grams of *p*-aminophenylarsonic acid were suspended in 100 c.c. of water, and dissolved by the addition of 15 c.c. of concentrated sulphuric acid. To the warm solution, 23 grams of finely-powdered ammonium persulphate were added in small quantities during an hour with thorough stirring. The light brown liquor was then gently heated on the water-bath, when it darkened in colour, and, after about ten minutes, a brisk evolution of gas commenced and small, leafy crystals were deposited. The solution was removed from the water-bath until the action had moderated, then replaced for a further five minutes, and finally allowed to cool for one and a-half hours. The light brown, leafy crystals were collected, well washed, and air-dried; the yield was 7.2 grams, that is, 35 per cent. of the theoretical. The acid was purified by converting it into the sodium salt, crystallising this, and regenerating.

Phenazine-2:7-bis-arsonic acid does not melt at 300°. It is insoluble in water, very sparingly soluble in alcohol or acetic acid, and insoluble in the other usual organic solvents. It gives a blood-red coloration with concentrated sulphuric acid. It contains one molecule of water of crystallisation, which is not lost either by standing in a vacuum desiccator or on heating at 120°. At 150°, however, the acid loses 2 molecules of water, and must therefore form an internal anhydride:*

0.2112, after drying in a vacuum desiccator, gave 0.2524 CO_2 and 0.0518 H_2O . $C = 32.6$; $H = 2.7$.

0.2470 gave 13.4 c.c. N_2 at 17° and 769 mm. $N = 6.3$.

* *p*-Aminophenylarsonic acid loses one molecule of water at 150°, giving an anhydride, $NH_2 \cdot C_6H_4 \cdot AsO_2$.

0.2609 lost 0.0205 at 150°. $H_2O = 7.9$.

$C_{12}H_{10}O_6N_2As_2 \cdot H_2O$ requires $C = 32.3$; $H = 2.7$; $N = 6.4$; and loss of $2H_2O = 8.5$ per cent.

0.1830, dried at 150°, gave 0.2358 CO_2 and 0.0362 H_2O . $C = 35.1$; $H = 2.2$.

$C_{12}H_8O_5N_2As_2$ requires $C = 35.1$; $H = 2.0$ per cent.

The *tetrasodium* salt was prepared by suspending the acid in water, and adding sufficient aqueous sodium hydroxide to dissolve it:

0.2526 acid required 0.0943 NaOH, that is, one mol. acid required 4.1 mols. NaOH.

On evaporating the aqueous solution to small bulk and adding alcohol, the salt was obtained as a buff-coloured crystalline powder, which contained 11 molecules of water of crystallisation. It is soluble in one and a-half times its weight of water at 20°, giving an alkaline solution, and is insoluble in alcohol:

0.5229, air-dried salt, lost 0.1462 at 100°. $H_2O = 28.0$.

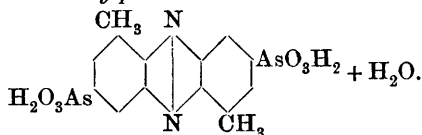
$C_{12}H_6O_6N_2As_2Na_4 \cdot 11H_2O$ requires $H_2O = 27.8$ per cent.

When this salt is allowed to stand in a vacuum desiccator, it loses $1\frac{1}{2}$ molecules of water, and changes colour, becoming bright red. After removing the residual water of crystallisation at 100°, the substance again becomes buff-coloured:

0.5736, desiccator-dried salt, lost 0.1435 at 100°. $H_2O = 25.0$.

$C_{12}H_6O_6N_2As_2Na_4 \cdot 9\frac{1}{2}H_2O$ requires $H_2O = 24.9$ per cent.

4 : 9-Dimethylphenazine-2 : 7-bis-arsonic Acid,



This acid was prepared by the oxidation of 2-aminotolyl-5-arsonic acid in a manner similar to the preparation of phenazine-2:7-bis-arsonic acid. The yield, however, was smaller, and the acid was obtained in the form of a fine, buff-coloured powder, which did not melt at 300°. It is insoluble in water, very sparingly soluble in alcohol and acetic acid, and insoluble in the other usual organic solvents. It gives a blood-red coloration with concentrated sulphuric acid:

0.1287 gave 0.1682 CO_2 and 0.0393 H_2O . $C = 35.6$; $H = 3.4$.

$C_{14}H_{14}O_6N_2As_2 \cdot H_2O$ requires $C = 35.4$; $H = 3.4$ per cent.

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