## CXV.—Aromatic Arsonic and Arsinic Acids.

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For some time past we have been engaged in the preparation of aryl derivatives of arsenic, and, as two recent publications (O. and R. Adler, *Ber.*, 1908, **41**, 931; Benda and Kahn, *Ber.*, 1908, **41**, 1672) show that there are other chemists covering somewhat the same ground, we have deemed it advisable to publish our results so far as they have proceeded.

We had prepared 2-aminotolyl-5-arsonic acid and its acetyl derivative some months ago, and these substances together with sodium p-aminophenylarsonate have been tested physiologically and clinically. Ehrlich had shown that the toxicity of sodium p-acetylaminophenylarsonate is considerably less than that of sodium *p*-aminophenylarsonate, and the same relationship has now been found between the corresponding toluidine derivatives; sodium 2-aminotolyl-5-arsonate has about the same toxicity as sodium p-aminophenylarsonate, whilst that of sodium 2-acetylaminotolyl-5-arsonate is very considerably less. These substances have been specially intended for use in trypanosomiasis (sleeping sickness), and experiments on their effect on different strains of trypanosomes have shown that, whilst certain strains were destroyed by the treatment, others were more resistant. In the treatment of syphilis, however, these substances have proved especially efficacious, and the results obtained in this connexion are exceedingly promising. Since O. and R. Adler and Benda and Kahn (loc. cit.) have already published the method of preparation and physical properties of these substances, we need only state that we confirm their results, and supplement them by recording the state of hydration of the sodium salts, this latter being important from the point of view of their use in medicine.

In the preparation of *p*-aminophenylarsonic acid and 2-aminotolyl 5-arsonic acid, we have obtained as by-products the corresponding bisaminoarylarsinic acids, which have been briefly alluded to by Benda and Kahn (*loc. cit.*), but, as these have been in our hands for some time past, we give in this communication a full description of their preparation and properties. The constitution of these substances has been proved by replacing the arsenic acid residue by iodine according to the method used by Ehrlich and Bertheim (*Ber.*, 1907, **40**, 3292) for *p*-aminophenylarsonic acid.

The arsinic acids are now being investigated clinically with a view to their possible use in trypanosomiasis and syphilis, but the results are as yet not sufficiently conclusive,

## EXPERIMENTAL.

2-Aminotolyl-5-arsonic acid is stated by Benda and Kahn (*loc. cit.*) to melt at  $195^{\circ}$ ; we have found the melting point  $198-200^{\circ}$ . The constitution of this acid was readily shown by boiling it with dilute sulphuric acid and potassium iodide, when a good yield of 5-iodo-o-toluidine melting at  $80-85^{\circ}$  was obtained. After recrystallisation, this iodo-compound melted at  $85^{\circ}$  and its acetyl derivative at  $168^{\circ}$ , and both substances melted at the same temperatures when mixed with the pure substances prepared from aceto-o-toluidide.

Sodium 2-aminotolyl-5-arsonate is obtained in glistening, tabular crystals containing three and a-half molecular proportions of water of crystallisation by mixing a highly concentrated aqueous solution with three times its volume of alcohol. When crystallised from water, however, it separates with five molecules of water of crystallisation:

0.4540 air-dried salt (from alcohol) lost 0.0890  $\rm H_2O$  at 130°.  $\rm H_2O=19.6.$ 

 $\overline{C}_7H_9O_3NAsNa$ ,  $3\frac{1}{2}H_2O$  requires  $H_2O = 19.9$  per cent.

0.4217 air-dried salt (from water) lost 0.1129  $H_2O$  at 130°.  $H_2O = 26.8$ 

 $\overline{C_7}H_9O_3NAsNa,5H_2O$  requires  $H_2O = 26.2$  per cent.

Sodium 2-acetylaminotolyl-5-arsonate separates from 50 per cent. aqueous alcohol in glistening, tabular crystals, which contain five molecules of water of crystallisation. It crystallises from water, however, with seven molecules of water of crystallisation:

0·4774 air-dried salt (from alcohol) lost 0·1102  $\rm H_2O$  at 100°.  $\rm H_2O=23{\cdot}1.$ 

 $\tilde{C_9}H_{11}O_4NAsNa,5H_2O$  requires  $H_2O = 23.4$  per cent.

0.5210 air-dried salt (from water) lost 0.1560  $H_2O$  at 100°  $H_2O = 29.9$ .

 $C_9H_{11}O_4NAsNa,7H_2O$  requires  $H_2O = 29.9$  per cent.

Preparation of Bis-2-aminotolyl-5-arsinic Acid,



Two hundred grams of air-dried o-toluidine arsenate and 400 grams of o-toluidine were heated over a free flame with constant shaking until the mixture became fluid, and then gently boiled under a reflux condenser for one hour, the heat being regulated so that a thermo-

meter immersed in the liquid registered 180-185°. The mixture was allowed to cool, and extracted with a 10 per cent. solution of sodium carbonate as long as effervescence occurred. The aqueous solution was then evaporated until crystallisation commenced, and allowed to cool. The first crop of sodium 2-aminotolyl-5-arsonate was then separated, well washed with alcohol, and set aside; the mother liquor and alcoholic washings were combined and evaporated to a thick syrup, and this was mixed with several times its volume of alcohol. A second crop of sodium 2-aminotolyl-5-arsonate was thus precipitated, and this was also separated, washed with alcohol, and set aside. The final mother liquors, together with the alcoholic washings, on evaporation to remove the alcohol and subsequent precipitation by hydrochloric acid gave 15 grams of a purple tar; this was dissolved in aqueous sodium hydroxide, evaporated to a small bulk, and allowed to cool, when a quantity of large, prismatic needles separated from the deep-red liquor. These were purified by several crystallisations from water, and proved to be sodium bis-2aminotolyl-5-arsinate. The quantity of salt actually isolated in a pure state amounted to 6 grams, which represents 3 per cent. of the theoretical, but a considerable quantity, possibly as much again, remained in the deep-red, syrupy mother liquors.

Bis-2-aminotolyl-5-arsinic acid is obtained by adding the calculated quantity of a mineral acid to the solution of its sodium salt. On crystallisation from boiling water, it forms highly refracting, pointed, microscopic needles, which melt and decompose at  $247-249^{\circ}$ . It is practically insoluble in cold water and the usual organic solvents, but fairly easily soluble in glacial acetic acid. It is readily soluble in dilute alkalis or mineral acids:

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0.1724 gave 0.3332 CO<sub>2</sub> and 0.0840 H<sub>2</sub>O. C=52.7; H=5.5.
0.0726 , 5.5 c.c. N<sub>2</sub> at 21° and 763 mm. N=8.7.
C_{14}H_{17}O_2N_2As requires C=52.5; H=5.4; N=8.7 per cent.
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The acid gave a good yield of 5-iodo-o-toluidine (m. p. 80-85°) when boiled with dilute sulphuric acid and potassium iodide. After recrystallisation, this iodo-compound melted at 85° and its acetyl derivative at 168°, and both substances melted at the same temperatures when mixed with the pure substances prepared from aceto-o-toluidide.

The sodium salt, which separates from its aqueous solution in large, hard, prismatic needles, melts in its water of crystallisation at  $74-75^{\circ}$ , and on further heating loses water, re-solidifies, and does not then melt at  $250^{\circ}$ . It dissolves in one and a-half times its weight of water at  $16^{\circ}$ , giving an alkaline solution, and is very easily soluble in alcohol. It contains seven and a-half molecular proportions

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of water of crystallisation, of which five are lost at  $100^{\circ}$  and the remainder at  $130^{\circ}$ :

Bis-2-acetylaminotolyl-5-arsinic Acid,

 $\begin{array}{c} \mathrm{CH}_3 \cdot \mathrm{CO} \cdot \mathrm{NH} \underbrace{ & - \overset{\parallel}{\operatorname{As}} - \overset{\parallel}{\operatorname{As}} - \overset{- \operatorname{NH} \cdot \mathrm{CO} \cdot \mathrm{CH}_3, \overset{2}{_3} \mathrm{H}_2 \mathrm{O}. \\ \mathrm{CH}_3 & \overset{- \operatorname{OH} \cdot \mathrm{CH}_3 - \overset{- \operatorname{OH} \cdot \mathrm{CH}_3}{\mathrm{OH}} \\ \end{array}$ 

Twenty grams of bis-2-aminotolyl-5-arsinic acid were mixed with 60 grams of acetic anhydride and allowed to stand. After a few minutes, a violent reaction took place, resulting in a clear solution. The liquid was poured into 250 c.c. of water, and, on scratching, 12 grams of white crystals separated. A second crop of 6 grams was obtained by evaporation of the mother liquor; the total yield, 18 grams, represents 71 per cent. of the theoretical.

Bis-2-acetylaminotolyl-5-arsinic acid crystallises from boiling water in highly refracting, microscopic prisms and melts at  $242-244^{\circ}$ . It is practically insoluble in cold water and the usual organic solvents, but fairly easily soluble in glacial acetic acid. It is readily soluble in dilute alkalis, but is insoluble in dilute acids. The acid separates from aqueous solutions with two-thirds of a molecular proportion of water of crystallisation:

- 0.1656 air-dried salt gave 0.3148  $\rm CO_2$  and 0.0772  $\rm H_2O.~C=51.8$  ;  $\rm H=5.2.$
- 0.4180 air-dried salt lost 0.0124  $H_2O$  at 150°.  $H_2O = 3.0$ .
- 0.1898 dried at 150° gave 0.3698  $\rm CO_2$  and 0.0908  $\rm H_2O.~C=53.1$  ;  $\rm H=5.4.$

 $C_{18}H_{21}O_4N_2As, {}^2_3H_2O$  requires C = 51.9; H = 5.4;  $H_2O = 2.9$  per cent.  $C_{18}H_{21}O_4N_2As$  requires C = 53.4; H = 5.2 per cent.

The sodium salt crystallises from water in radial clusters of silky needles; it melts in its water of crystallisation at 106-107, and on further heating resolidifies and does not then melt at  $250^{\circ}$ . It dissolves in twice its weight of water at  $16^{\circ}$ , giving an alkaline solution, and is very easily soluble in alcohol. It contains six molecules of water of crystallisation:

0 1943 air-dried salt lost 0 0393  $H_2O$  at 150°.  $H_2O = 20.2$ .

 $C_{18}H_{20}O_4N_2AsNa, 6H_2O$  requires  $H_2O = 20.2$  per cent.



This acid results as a by-product in the preparation of p-aminophenylarsonic acid by Bechamp's method (Compt. rend., 1863, 56, It is most readily isolated in the following manner. 1173).The product obtained by heating aniline arsenate with excess of aniline at 180° is extracted with 10 per cent. sodium carbonate solution, the aqueous solution concentrated, and completely precipitated by hydrochloric acid. The precipitate is then digested with just sufficient aqueous sodium hydroxide to give a faintly alkaline solution and filtered from the undissolved matter, which consists of the crude The latter is then converted into the barium salt, and arsinic acid. this is crystallised several times from water, using animal charcoal, The pure barium salt is dissolved in water and until colourless. mixed with the calculated quantity of hydrochloric acid, when the arsinic acid is obtained as a dense, white precipitate of matted needles. The yield amounts to about 2-3 per cent. of the theoretical.

Bis-p-aminophenylarsinic acid melts and decomposes at  $248-249^{\circ}$ . It is very sparingly soluble in water and the usual organic solvents, moderately so in glacial acetic acid, and readily so in dilute alkalis and acids :

0.1358 gave 0.2440 CO<sub>2</sub> and 0.0534 H<sub>2</sub>O. C = 49.0; H = 4.4. C<sub>12</sub>H<sub>13</sub>O<sub>2</sub>N<sub>2</sub>As requires C = 49.3; H = 4.5 per cent.

The acid gave a good yield of *p*-iodoaniline (m. p.  $62-63^{\circ}$ ) when boiled with sulphuric acid and potassium iodide.

The sodium salt crystallises from water in large, monoclinic plates, and melts in its water of crystallisation at  $83^{\circ}$ , after sintering from  $75^{\circ}$  onwards. On further heating, it loses water, resolidifies, and does not then melt at  $250^{\circ}$ ; it is soluble in an equal weight of water, giving an alkaline solution, and is very soluble in alcohol. It contains a slightly variable amount of water of crystallisation, the figures obtained on analysis lying between those required for five and six molecular proportions :

0.3979 air-dried salt lost 0.0928 H<sub>2</sub>O at 120°.  $H_{0}O = 23.3$ . 0.0591 H<sub>2</sub>O , 120°.  $H_{0}O = 24.1$ 0.2450,, ,, ,, 0.0616 H<sub>2</sub>O ,, 120°.  $H_{2}O = 24.7.$ 0.2492;, ,, ;,  $C_{12}H_{12}O_2N_2AsNa,5H_2O$  requires  $H_2O = 22.3$  per cent. C12H12O2N2AsNa,6H2O  $H_{0}O = 25.6$ ,, ,,

The *barium* salt, which crystallises from water in large, hard prisms, contains seven and a-half molecular proportions of water of crystallisation; it is soluble in twice its weight of cold water, giving an alkaline solution, and is sparingly soluble in alcohol:



This acid is obtained in an almost quantitative yield by the action of acetic anhydride on bis-*p*-aminophenylarsinic acid. It crystallises from water in rosettes of needles, and melts at  $275^{\circ}$ . It is very sparingly soluble in the usual organic solvents or cold water, readily so in boiling water, and moderately so in glacial acetic acid. It separates from aqueous solution with three molecules of water of crystallisation:

0.2532 air-dried salt lost 0.0312 H<sub>2</sub>O at  $120^{\circ}$ . H<sub>2</sub>O = 12.3.

0.1860 dried at 120° gave 0.3484 CO<sub>2</sub> and 0.0740 H<sub>2</sub>O. C = 51.1; H = 4.5.

$$\begin{split} & C_{16}H_{17}O_4N_2As, 3H_2O \text{ requires } H_2O = 12\cdot6 \text{ per cent.} \\ & C_{16}H_{17}O_4N_2As \text{ requires } C = 51\cdot1 \text{ ; } H = 4\cdot6 \quad ,, \end{split}$$

The sodium salt, which separates from water in prismatic needles, melts at about  $50^{\circ}$  in its water of crystallisation, and on further heating loses water, resolidifies, and does not then melt at  $250^{\circ}$ . It is soluble in an equal weight of cold water, giving an alkaline solution, and is readily soluble in alcohol. It contains nine molecules of water of crystallisation:

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