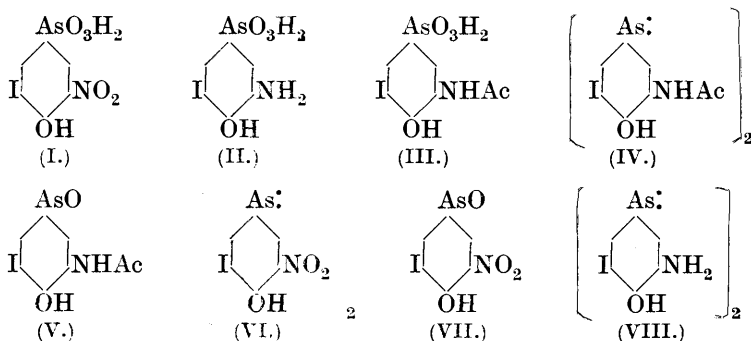


CCXIV.—*Synthesis of Iodine Compounds of the Salvarsan Group.*

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THE difficulty of synthesising 5 : 5'-di-iodo-3 : 3'-diamino-4 : 4'-hydroxyarsenobenzene (VIII), the therapeutic value of which has not been sufficiently recognised (Ehrlich and Hata, "Die experimentelle Chemotherapie der Spirillosen," Berlin, 1910, 34), led the author to prepare a number of compounds intimately related to it. The most effective of these is 5 : 5'-di-iodo-3 : 3'-diacetylamino-4 : 4'-dihydroxyarsenobenzene (IV), which is also remarkably stable in solution and produces no undesirable nervous effects. The maximum dose tolerated by mice is 0.2—0.25 g., and the curative dose for mice infected with *Trypanosoma equiperdum* is 0.015—0.02 g., per kg. of mouse. The substance, in this respect, closely resembles salvarsan.



EXPERIMENTAL.

5-Iodo-3-nitro-4-hydroxyphenylarsinic acid (I) was obtained in yields of about 65% from 3-nitro-4-hydroxyphenylarsinic acid by a slight modification of the mercuration method (Raiziss, Kolmer, and Gavron, *J. Biol. Chem.*, 1919, **40**, 541; Stieglitz, Kharasch, and Hanke, *J. Amer. Chem. Soc.*, 1921, **43**, 1192). The acid darkens at 260—280° and is soluble in methyl alcohol, ethylene glycol, warm glycerol, formic acid, and dilute acetic acid.

5-Iodo-3-amino-4-hydroxyphenylarsinic Acid (II).—Reduction of the foregoing nitro-acid in cold alkaline solution by an excess of freshly-precipitated titanous or ferrous oxide produces the comparatively unstable 5-iodo-3-amino-4-hydroxyphenylarsinic acid. Addition of zinc or lead acetate to the solution, neutralised with acetic acid, precipitates, in 63—66% yield, the zinc or lead salt. These salts, when dry, are colourless powders of fairly constant

composition (Found : As, 16.7, 17.2; I, 28.8; Zn, 10.3, 11.2; H_2O , 7.3. $\text{C}_{18}\text{H}_{17}\text{O}_{12}\text{N}_3\text{I}_3\text{As}_3\text{Zn}_2, 5\text{H}_2\text{O}$ requires As, 17.3; I, 29.4; Zn, 10.0; H_2O , 6.9%). Found : As, 12.3, 12.3; Pb, 38.8, 38.7. $\text{C}_6\text{H}_5\text{O}_4\text{NIAsPb}$ requires As, 13.6; Pb, 37.7%).

A solution of the zinc salt in cold dilute sulphuric acid (1 : 20), when partly neutralised, furnishes the amino-acid in yellow needles which darken at about 95° . The substance is apparently stable at 20° , but decomposes with gradual loss in weight when heated in a vacuum at 65° (Found : As, 20.3; I, 34.2. $\text{C}_6\text{H}_7\text{O}_4\text{NIAs}$ requires As, 20.9; I, 35.2%).

5-Iodo-3-acetylamino-4-hydroxyphenylarsinic Acid (III).—A solution of 3.9 g. of the nitro-acid (I) in 40–80 c.c. of water and 2 c.c. of 10*N*-alkali is treated at 0° with sufficient hyposulphite * powder (6–8 g.) to bleach it. Acetic anhydride is now added at intervals in several portions of 1 c.c. After 2–3 hours, most of the acetyl derivative will have separated, and the sulphite is then destroyed by the gradual addition of 50–60 c.c. of hydrogen peroxide (or until a drop of the solution no longer decolorises potassium triiodide), the solution being kept nearly neutral by suitable additions of sodium bicarbonate. Finally, the whole of the *acetyl* compound is precipitated (yield, 2.99 g.; 74%) by making the solution just acid to Congo paper. The washed and dried product forms a cake of colourless needles, m. p. $158\text{--}159^\circ$, readily soluble in the alcohols or acetone (Found : As, 18.0; I, 31.1. $\text{C}_8\text{H}_9\text{O}_5\text{NIAs}$ requires As, 18.7; I, 31.6%).

By recrystallisation from dilute acetic acid (1 : 1), the acetyl compound was obtained in prisms, m. p. $190\text{--}191^\circ$ (Found : As, 18.5%).

Under the above conditions, a diacetyl derivative was not produced (compare King and Murch, J., 1925, 127, 2632).

5-Iodo-3-carbethoxyamino-4-hydroxyphenylarsinic acid, prepared as above, ethyl chloroformate being substituted for acetic anhydride, is a powder, m. p. $182\text{--}183^\circ$ (decomp.). It is soluble in methyl alcohol, acetone, or pyridine (Found : As, 17.2. $\text{C}_9\text{H}_{11}\text{O}_6\text{NIAs}$ requires As, 17.4%).

5 : 5' - Di-iodo-3 : 3' - diacetylamino - 4 : 4' - dihydroxyarsenobenzene (IV).—A solution of 2.7 g. of the preceding acetyl compound in 100 c.c. of water containing 3 g. of sodium bicarbonate is warmed at $55\text{--}60^\circ$ with 15 g. of hyposulphite in an atmosphere of nitrogen for 4–5 hours. The well-washed *arseno*-compound, after drying in a vacuum, is a lemon-yellow powder (yield 1.66 g.; 70%), m. p. 194° after sintering at about 180° (Found : As, 21.1; I, 36.2).

* This is a more suitable reducing agent than titanous or ferrous oxide for the preparation of the acetyl compound.

$C_{16}H_{14}O_4N_2I_2As_2$ requires As, 21.3; I, 36.1%. It is soluble in acetone, phenol, benzaldehyde, or pyridine, and its dilute solutions in alkali carbonates or hydroxides undergo little apparent change on exposure to the air.

Oxidation of the arseno-compound, suspended in aqueous bicarbonate, with *N*/10-iodine (Required: 118 c.c. per g. Calc. for oxidation of the arseno-group: 114.6 c.c.) reproduces the original acetyl-amino-acid, m. p. 160°.

5 : 5'-*Di-iodo-3 : 3'-dinitro-4 : 4'-dihydroxyarsenobenzene* (VI) is a stable orange-yellow powder, darkening at about 200°, obtained in 78—79% yield by treating a methyl-alcoholic solution of 5-iodo-3-nitro-4-hydroxyphenylarsinic acid with hypophosphorous acid at 55—60°. It dissolves readily in phenol, benzaldehyde or pyridine, and, like the acetyl-amino-compound, is rendered water-soluble by addition of either alkali carbonate or hydroxide (Found: As, 21.9; I, 36.7. $C_{12}H_6O_6N_2I_2As_2$ requires As, 22.1; I, 37.4%).

5-*Iodo-3-acetyl-amino-4-hydroxyphenylarsenious oxide* (V) is readily obtained by hydrolysing with aqueous bicarbonate the arsine di-iodide produced by treating with iodine a suspension of 5 : 5'-di-iodo-3 : 3'-diacetyl-amino-4 : 4'-dihydroxyarsenobenzene in ether. The ethereal solution of the *oxide* thus obtained is dried with sodium sulphate, the solvent evaporated at room temperature, and the residue triturated with bicarbonate solution. The *oxide* is a colourless powder, m. p. 182—183°, soluble in alcohol or acetone (Found: As, 19.1; H_2O , 6.7. $C_8H_7O_3NIA_s, 1\frac{1}{2}H_2O$ requires As, 19.4; H_2O , 6.8%).

5-*Iodo-3-nitro-4-hydroxyphenylarsenious oxide* (VII), prepared from 5 : 5'-di-iodo-3 : 3'-dinitro-4 : 4'-dihydroxyarsenobenzene in a similar manner, is an orange-yellow powder sintering and melting indefinitely between 170° and 210°. It is sparingly soluble in water, but more readily soluble in alcohol, acetone, ether, benzaldehyde, or pyridine (Found: As, 21.2. $C_6H_3O_4NIA_s$ requires As, 21.1%).

Numerous attempts to prepare 5 : 5'-di-iodo-3 : 3'-diamino-4 : 4'-dihydroxyarsenobenzene from the corresponding nitro- and amino-hydroxyiodophenylarsinic acids failed to give a uniform product. It is doubtful whether the pure compound has yet been obtained.

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