CXXX.—*The Chemotherapy of some Bromine Derivatives of Phenylarsinic Acids and Arsenobenzenes.*

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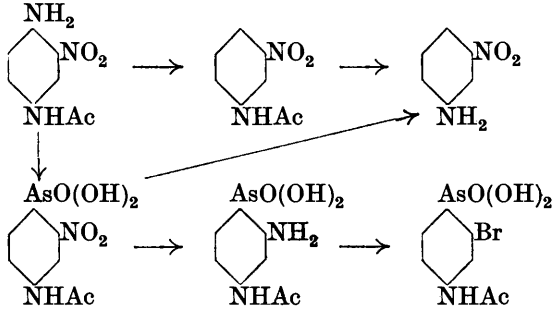
EHRLICH, in his research on salvarsan, prepared 5 : 5′-di-iodo-3 : 3′-diamino-4 : 4′-dihydroxyarsenobenzene (Ehrlich and Hata, " Chemotherapy," p. 34), but owing to its chemotherapeutic index being less than that of salvarsan, he did not pursue further the study of halogen derivatives of organic arsenicals.

The present investigation was undertaken to determine the influence on the chemotherapeutic index of the introduction of bromine into the nucleus of some of the simpler phenylarsinic acids and arsenobenzenes. The bromine was introduced in the *o*-, *m*-, and *p*-positions with respect to the arsenic by the use of Sandmeyer's reaction on the corresponding aminophenylarsinic acids. The synthesis and the orientation of the *o*-bromo-acids were carried out as follows :



In no case did the compound produced show an improved chemotherapeutic index when compared with the corresponding compound containing no bromine.

For the determination of the minimum curative dose (*C*), experiments were performed on mice infected with *Trypanosoma equiperdum* and normal mice were used for the toxicity tests (*T*). The compounds soluble in sodium hydroxide solution were administered intravenously and those insoluble *per os*.

The following table shows the results obtained.

Compound.	Administration.	*T* (mg. per g.).	*C* (mg. per g.).	*T*/*C*.
Phenylarsinic acid	Intravenous	0·05	>0·05	<1
4-Bromophenylarsinic acid	,,	0·01	>0·01	<1
Arsenobenzene	Per os	0·4	>0·4	<1
4 : 4′-*Dibromoarsenobenzene*	,,	0·05	>0·05	<1
4-Aminophenylarsinic acid	Intravenous	0·2	0·2	1
3-Bromo-4-aminophenylarsinic acid	,,	0·06	>0·06	<1
2-*Bromo*-4-*aminophenylarsinic acid*	,,	0·3	0·3	1
4 : 4′-Diaminoarsenobenzene	Per os	0·1	0·02	5
3 : 3′-*Dibromo*-4 : 4′-*diaminoarsenobenzene*	,,	0·1	0·03	3·3
2 : 2′-*Dibromo*-4 : 4′-*diaminoarsenobenzene*	,,	1·0	0·2	5
4-Acetamidophenylarsinic acid	Intravenous	1·0	0·2	5
2-*Bromo*-4-*acetamidophenylarsinic acid*	,,	2·0	2·0	1
4 : 4′-*Diacetamidoarsenobenzene*	Per os	1·5	0·1	15
2 : 2′-*Dibromo*-4 : 4′-*diacetamidoarsenobenzene*	,,	4·0	0·6	6·7
4-Hydroxyphenylarsinic acid	Intravenous	0·2	0·08	2·5
3-*Bromo*-4-*hydroxyphenylarsinic acid*	,,	0·25	0·25	1
4 : 4′-Dihydroxyarsenobenzene	,,	0·05	0·004	12·5
3 : 3′-*Dibromo*-4 : 4′-*dihydroxyarsenobenzene*	,,	0·02	0·015	1·3
3-Amino-4-hydroxyphenylarsinic acid	,,	2·0	0·3	6·6
5-Bromo-3-amino-4-hydroxyphenylarsinic acid	,,	0·75	0·25	3
3 : 3′-Diamino-4 : 4′-dihydroxyarsenobenzene	,,	0·125	0·01	12·5
5 : 5′-*Dibromo*-3 : 3′-*diamino*-4 : 4′-*dihydroxyarsenobenzene*	,,	0·05	0·025	2
3-Acetamidophenylarsinic acid	,,	1·3	1·0	1·3
5-Bromo-3-acetamido-4-hydroxyphenylarsinic acid	,,	0·3	>0·3	<1
3 : 3′-Diacetamido-4 : 4′-dihydroxyarsenobenzene	,,	0·175	0·03	5·8
5 : 5′-*Dibromo*-3 : 3′-*diacetamido*-4 : 4′-*dihydroxyarsenobenzene*	,,	0·1	0·06	1·7

Since this work was completed a description of 5-bromo-3-amino-4-hydroxyphenylarsinic acid and its acetyl derivative has been given by Fisher and Raiziss (*J. Amer. Chem. Soc.*, 1929, **51**, 527), but the method of preparation is different.

EXPERIMENTAL.

3-Nitro-4-aminoacetanilide was prepared from *p*-aminoacetanilide according to the methods described in the literature (*Ber.*, 1884, **17**, 148), but as these give no definite proof of the position of the nitro-group, its orientation was carried out as follows.

3-Nitro-4-aminoacetanilide (5 g.), suspended in a mixture of 8 c.c. of sulphuric acid (*d* 1·84) and 100 c.c. of water, was diazotised below 10° (sodium nitrite, 1·8 g.; water, 20 c.c.), 100 c.c. of absolute alcohol

were added, and after some time the solid was collected, suspended in 50 c.c. of absolute alcohol, and heated with 2 g. of copper powder until the evolution of nitrogen ceased. The filtered solution, when poured into an excess of water, gave *m*-nitroacetanilide (m. p. 150·5° after recrystallisation from water; yield, 1·9 g.), from which *m*-nitroaniline was obtained on hydrolysis.

2-*Nitro*-4-*acetamidophenylarsinic Acid* (compare D.R.-P. 267307; Fourneau, Navarro-Martin, and Trefouel, *Ann. Inst. Pasteur*, 1923, 590).—3-Nitro-4-aminoacetanilide (18 g.) was diazotised as described above (concentrated hydrochloric acid, 18 c.c.; water, 30 c.c.; sodium nitrite, 7·2 g.; water, 30 c.c.), the diazo-solution added to copper arsenite solution (Lewis and Cheetham, *J. Amer. Chem. Soc.*, 1921, **43**, 2119) and boiled with charcoal, and the filtered liquid acidified. The arsinic acid obtained (12·8 g.) (Found: As, 24·6. Calc.: As, 24·7%) gave *m*-nitroaniline when boiled with 50% sulphuric acid, and 2-amino-4-acetamidophenylarsinic acid (compare Fourneau, etc., *loc. cit.*) when reduced at 30° by ferrous sulphate (Jacobs, Heidelberger, and Rolf, *J. Amer. Chem. Soc.*, 1918, **40**, 1581) (Found: As, 27·2. Calc.: As, 27·4%).

2-*Bromo*-4-*acetamidophenylarsinic Acid.*—The preceding amino-acid (30 g.) was diazotised at 0—5° (concentrated sulphuric acid, 36 c.c.; water, 200 c.c.; sodium nitrite, 8 g.; water, 24 c.c.), the solution poured into hot cuprous bromide solution (copper sulphate, 18 g.; copper foil, 14 g.; potassium bromide, 72 g.; water, 90 c.c.) and kept over-night, and the crude acid purified by means of the sodium salt. 2-*Bromo*-4-*acetamidophenylarsinic acid* (10 g.) separated on acidification (Congo-red) in white irregular plates (Found: As, 21·9; Br, 23·4. $C_8H_9O_4NBrAs$ requires As, 22·2; Br, 23·7%). It crystallised in hexagonal plates from hot water and was soluble in hot alcohol. The barium and calcium salts crystallised in rosettes of needles, the magnesium salt was amorphous.

2-*Bromo*-4-*aminophenylarsinic Acid.*—30 G. of the preceding acid were refluxed for 10 minutes with 300 c.c. of water and 90 c.c. of concentrated hydrochloric acid. The *amino-acid*, precipitated with sodium acetate solution and purified by Christiansen's method (*J. Amer. Chem. Soc.*, 1920, **42**, 2403), crystallised in white irregular plates (yield, 15 g.) (Found: As, 25·1; Br, 26·6. $C_6H_7O_3NBrAs$ requires As, 25·3; Br, 27·0%). It crystallised from hot water in colourless plates and was soluble in hot alcohol. The calcium and magnesium salts were amorphous.

3-*Bromo*-4-*hydroxyphenylarsinic acid* was prepared from 3-amino-4-hydroxyphenylarsinic acid (20 g.) in the usual way and purified through the sodium salt (yield, 8·5 g.) (Found: As, 25·4; Br, 26·5. $C_6H_6O_4BrAs$ requires As, 25·3; Br, 26·9%). It was soluble in hot

alcohol and crystallised from hot water in irregular plates. The crystalline calcium salt was insoluble in hot water but very soluble in cold. The magnesium salt was amorphous.

5-Bromo-3-acetamido-4-hydroxyphenylarsinic acid (compare Fisher and Raiziss, *loc. cit.*) (9 g.) was similarly prepared from 5-amino-3-acetamido-4-hydroxyphenylarsinic acid (15 g.) and purified (Found : As, 21·0; Br, 22·4. Calc. : As, 21·2; Br, 22·6%). It gave 5-bromo-3-amino-4-hydroxyphenylarsinic acid in 60% yield when hydrolysed with 25% sodium hydroxide solution (Found : As, 23·9; Br, 25·4. Calc. : As, 24·0; Br, 25·6%).

The following arsenobenzenes, which are all yellow, amorphous powders, were prepared by means of sodium hydrosulphite from the respective phenylarsinic acids : 4 : 4′-*Dibromoarsenobenzene* (Found : As, 32·2; Br, 32·8. $C_{12}H_8Br_2As_2$ requires As, 32·5; Br, 34·6%); 3 : 3′-*dibromo*-4 : 4′-*diaminoarsenobenzene* (Found : As, 29·3; Br, 29·0. $C_{12}H_{10}N_2Br_2As_2$ requires As, 30·5; Br, 32·5%); 2 : 2′-*dibromo*-4 : 4′-*diaminoarsenobenzene* (Found : As, 28·5; Br, 32·2%); 4 : 4′-*diacetamidoarsenobenzene* (Found : As, 35·0. $C_{16}H_{16}O_2N_2As_2$ requires As, 35·9%); 2 : 2′-*dibromo*-4 : 4′-*diacetamidoarsenobenzene* (Found : As, 25·0; Br, 27·7. $C_{16}H_{14}O_2N_2Br_2As_2$ requires As, 26·0; Br, 27·8%). All the above arsenobenzenes are insoluble in sodium hydroxide solution, and the following are all soluble : 3 : 3′-*Dibromo*-4 : 4′-*dihydroxyarsenobenzene* (Found : As, 29·2; Br, 28·4. $C_{12}H_8O_2Br_2As_2$ requires As, 30·4; Br, 32·4%); 5 : 5′-*dibromo*-3 : 3′-*diamino*-4 : 4′-*dihydroxyarsenobenzene* (Found : As, 27·3; Br, 29·1. $C_{12}H_{10}O_2N_2Br_2As_2$ requires As, 28·6; Br, 30·5%); 5 : 5′-*dibromo*-3 : 3′-*diacetamido*-4 : 4′-*dihydroxyarsenobenzene* (Found : As, 25·0; Br, 24·9. $C_{16}H_{14}O_4N_2Br_2As_2$ requires As, 24·7; Br, 26·3%).

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