CX.—*A New Synthesis of 4-Amino-3-hydroxyphenylarsinic Acid.*

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THE ten isomeric aminohydroxyphenylarsinic acids have been prepared, for the most part by Fourneau and his collaborators (*Ann. Inst. Pasteur*, 1923, **37**, 551: 1926, **40**, 933), who have also examined their trypanocidal action on infected mice.

The methods of preparing 4-amino-3-hydroxyphenylarsinic acid ($C/T = \frac{1}{2}$; for definitions, see King and Murch, J., 1924, **125**, 2596) from 3-nitro-4-aminophenylarsinic acid (Benda, *Ber.*, 1911, **44**, 3579) and from 5-aminobenzoxazolone (Cassella and Co., U.S.P. 1,539,798–9) give poor yields, and attempts to use 2-methylbenzoxazole and 2-nitro-5-aminophenol for the purpose have been unsuccessful.

4-Amino-3-hydroxyphenylarsinic acid can, however, be readily prepared by the following series of reactions. The mixture of 4-nitro- and 6-nitro-chloroacetanilides obtained by the nitration of *m*-chloroacetanilide, on hydrolysis with 25% sulphuric acid, gives the corresponding chloronitroanilines, which are readily separable by means of their difference in basicity. 3-Chloro-4-nitroaniline undergoes the Bart–Schmidt reaction to give 3-*chloro*-4-*nitrophenylarsinic acid* in 45% yield, and this acid, on boiling with 25% aqueous sodium hydroxide, furnishes 4-*nitro*-3-*hydroxyphenylarsinic acid*, which on reduction with glucose yields 4-amino-3-hydroxyphenylarsinic acid.

3-*Chloro*-6-*nitrophenylarsinic acid*, prepared from 3-chloro-6-nitroaniline, undergoes dearsenication on treatment with alkali, *p*-nitrophenol being formed. 3-Chloro-6-aminophenylarsinic acid, obtained from it by reduction, has been briefly described by Benda (*Ber.*, 1909, **42**, 3622): when heated with chloroacetamide on the water-bath, it gives 6-*glycineamide*-3-*chlorophenylarsinic acid*.

Attempts to prepare the corresponding arsinic acids from 2 : 3-dinitro-4-aminophenol, 2 : 4-dinitro-3-aminophenol and 4-aminopyrocatechol by the Bart–Schmidt reaction were unsuccessful.

The following results (mg./g. of mouse) were obtained in experi-

ments on mice infected with *Trypanosoma equiperdum*; the administration was intravenous (*i*), subcutaneous (*s*), or oral (*o*).

Phenylarsinic acids.	*T.*	*C.*	*C*/*T.*
4-Amino-3-hydroxy-(*i*)	2·0	0·6	1/3
,, ,, (*s*)	2·0	0·6	1/3
,, ,, (*o*)	6·0	0·4	1/15
4-Acetamido-3-hydroxy-(*i*)	1·0	0·5	1/2
,, ,, (*s*)	0·5	0·5	1
,, ,, (*o*)	1·0	0·4	1/2·5
3-Chloro-6-acetamido-(*o*)	<0·05	>0·05	—
6-Glycineamide-3-chloro-(*o*)	0·05	0·05	1
Arsenobenzenes.			
4 : 4′-Diamino-3 : 3′-dihydroxy-(*o*)	1·0	0·05	20
4-Amino-4′-acetamido-3 : 3′-dihydroxy-(*o*)	4·0	0·05	80
4 : 4′-Diacetamido-3 : 3′-dihydroxy-(*o*)	8·0	0·1	80
3 : 4′-Diamino-4 : 3′-dihydroxy-(*o*)	2·0	0·1	20
3 : 4′-Diacetamido-4 : 3′-dihydroxy-(*o*)	10·0	0·2	50

EXPERIMENTAL.

3-*Chloro*-4-*nitrophenylarsinic Acid.*—3-Chloro-4-nitroaniline (51·75 g.) was ground with concentrated hydrochloric acid (103·5 c.c.) and water (103·5 c.c.), diazotised at 0° (sodium nitrite, 21 g.; water, 63 c.c.), and added to copper arsenite solution (Lewis and Cheetham, *J. Amer. Chem. Soc.*, 1921, **43**, 2119). The mixture was stirred for ½ hour and then heated for ½ hour at 60°, and the filtered liquor was acidified (Congo-paper) with concentrated hydrochloric acid. The crystalline acid obtained (37·5 g.; yield, 45·0%) separated from 2*N*-acetic acid in long, irregular, pale yellow, anhydrous prisms, decomp. 200°, sparingly soluble in cold water, soluble in alcohol (Found: As, 27·1; N, 4·9; Cl, 12·9. $C_6H_3O_5NClAs$ requires As, 26·7; N, 5·0; Cl, 12·6%). The *barium* salt forms prismatic rods; the *calcium* and *magnesium* salts are amorphous.

4-*Nitro*-3-*hydroxyphenylarsinic Acid.*—A solution of 28·2 g. of the preceding acid in 4*N*-potassium hydroxide (300 c.c.) was boiled under reflux for 3 hours, filtered hot, and acidified with concentrated hydrochloric acid (Congo-paper). The crystalline acid obtained (19·2 g.: yield, 73%) separated from glacial acetic acid in pale yellow, anhydrous needles, sparingly soluble in water but readily soluble in alcohol (Found in substance dried at 100°: As, 28·3; N, 5·4. $C_6H_6O_6NAs$ requires As, 28·5; N, 5·3%). The *magnesium* salt is microcrystalline and the *barium* salt forms minute rods.

This acid (49 g.), dissolved in a hot solution of sodium hydroxide (52·5 g. in 175 c.c. of water), was reduced by glucose (42 g. in 140 c.c. of hot water) to 4-amino-3-hydroxyphenylarsinic acid (Benda, *loc. cit.*), which was isolated (30 g.; yield, 68%) after acidification, treatment with charcoal, filtration, and addition of solid sodium

acetate. This acid crystallises from 2*N*-acetic acid in small, hexagonal, anhydrous prisms (Found: As, 31·7; N, 5·9. Calc.: As, 32·2; N, 6·0%).

The following arsenobenzenes, which are all yellow, amorphous powders and are all soluble in sodium hydroxide solution, were prepared at 55—60° by the well-known hydrosulphite method from the respective phenylarsinic acids or from mixtures of two of them. Bertheim (*Chem. Ztg.*, 1914, **38**, 756) has shown that when two different arsinic acids (1 mol. of each) are so reduced, a mixed arsenobenzene is obtained. The first three arsenobenzenes form soluble hydrochlorides: 4 : 4′-Diamino-3 : 3′-dihydroxyarsenobenzene (Benda, *loc. cit.*) (yield, 45%) (Found in material dried over sulphuric acid: As, 39·6. Calc.: As, 41·0%).

4-*Amino*-4′-*acetamido*-3 : 3′-*dihydroxyarsenobenzene* (yield, 49%) (Found: As, 35·2. $C_{14}H_{14}O_3N_2As_2$ requires As, 36·8%).

3 : 4′-*Diamino*-4 : 3′-*dihydroxyarsenobenzene* (yield, 43·7%) (Found: As, 39·9. $C_{12}H_{12}O_2N_2As_2$ requires As, 41·0%).

4 : 4′-*Diacetamido*-3 : 3′-*dihydroxyarsenobenzene* (yield, 37·5%) (Found: As, 32·0. $C_{16}H_{16}O_4N_2As_2$ requires As, 33·3%).

3 : 4′-*Diacetamido*-4 : 3′-*dihydroxyarsenobenzene* (yield, 40·6%) (Found: As, 32·4. $C_{16}H_{16}O_4N_2As_2$ requires As, 33·3%).

4-Acetamido-3-hydroxyphenylarsinic acid, which has also been prepared by Benda (*Ber.*, 1914, **47**, 995), was obtained (yield, 94·5%) in almost colourless, diamond-shaped plates on acidification of an alkaline solution of the acid. It is almost insoluble in hot water and alcohol and very sparingly soluble in 50% acetic acid, but is readily soluble in cold 80% formic acid (Found: As, 27·4; N, 5·1. Calc.: As, 27·4; N, 5·1%). The *magnesium* salt is amorphous and the *sodium* salt crystallises in fine colourless needles from alcohol.

2-Nitro-4-acetamido-3-hydroxyphenylarsinic acid, prepared according to Benda, crystallises from much boiling water in long, red, glistening, hexagonal, anhydrous prisms, and from glacial acetic acid, in which it is sparingly soluble, in rods. It is moderately easily soluble in alcohol (Found: As, 23·1; N, 8·4. Calc.: As, 23·4; N, 8·7%). The *calcium* salt crystallises in bunches of needles; the *magnesium* and *barium* salts are amorphous.

2-Nitro-4-amino-3-hydroxyphenylarsinic acid, obtained according to Benda (*loc. cit.*), crystallises from water, in which it is appreciably soluble, in long, red, glistening, boat-shaped plates; these, on drying at 100°, change to a brown *monohydrate*, the water in which is not lost at 110° (Found in material dried at 110°: As, 25·1; N, 9·8. $C_6H_7O_6N_2As,H_2O$ requires As, 25·3; N, 9·5%). It is soluble in alcohol and moderately easily soluble in glacial

acetic acid, from which it crystallises in small prisms. The *magnesium* salt is amorphous when precipitated from an ammoniacal solution of the acid.

2-*Amino*-4-*acetamido*-3-*hydroxyphenylarsinic Acid*.—The nitroacetamidohydroxy-acid described above (22 g.) was reduced at 30° by ferrous sulphate according to Jacobs, Heidelberger, and Rolf (*J. Amer. Chem. Soc.*, 1918, **40**, 1581), 14·6 g. (yield, 73·8%) of crystalline material being obtained. The *acid* crystallises from boiling water (solubility, 1 in 22) in long, colourless, rectangular, anhydrous prisms (Found: As, 26·1; N, 9·7. $C_8H_{11}O_5N_2As$ requires As, 25·9; N, 9·6%). It is soluble in excess of 2*N*-hydrochloric acid, readily soluble in cold 80% formic acid, moderately easily soluble in glacial acetic acid, but almost insoluble in alcohol. On treatment with nitrous acid it gives an insoluble *diazo-oxide*, which crystallises in yellow, quadrilateral plates and does not couple with sodium β-naphthoxide. The *calcium* salt is microcrystalline and the *magnesium* salt amorphous.

2 : 4-*Diacetamido*-3-*hydroxyphenylarsinic acid*, prepared from the above by acetylation in alkaline solution with acetic anhydride, crystallises from 2*N*-acetic acid, in which it is moderately easily soluble, in clusters of colourless, silky, anhydrous needles (Found: As, 23·1; N, 8·8. $C_{10}H_{13}O_6N_2As$ requires As, 22·6; N, 8·4%).

3-*Chloro*-6-*nitrophenylarsinic acid* was obtained from 3-chloro-6-nitroaniline by the Bart–Schmidt reaction (yield, 64·1%). It crystallises from water in anhydrous rods which shrink at 240° and melt at 250° (Found: As, 27·1; N, 4·8. $C_6H_5O_5NClAs$ requires As, 26·7; N, 4·8%). It is very sparingly soluble in glacial acetic acid, crystallising therefrom in long, colourless, rectangular prisms, and soluble in hot alcohol. The *magnesium* salt is amorphous.

On reduction with ferrous sulphate the acid gives an almost quantitative yield of 3-chloro-6-aminophenylarsinic acid (compare Benda, *Ber.*, 1909, **42**, 3622). This acid crystallises from water, in which it is moderately easily soluble, in long, colourless, rectangular, anhydrous prisms (Found: As, 30·0; N, 5·4. Calc.: As, 29·8; N, 5·6%). It is soluble in cold concentrated hydrochloric acid; the solution develops a bright red colour on diazotisation and treatment with sodium β-naphthoxide. The acid is readily soluble in 80% formic acid and sparingly soluble in alcohol and glacial acetic acid; it crystallises in clusters of needles from the last-mentioned solvent. The *calcium* salt forms rosettes of needles and the *barium* salt is amorphous.

3-*Chloro*-6-*acetamidophenylarsinic acid*, obtained on acetylation of the preceding acid, crystallises from water (solubility, 1 in 15)

in long, colourless, rectangular prisms (yield, 57·5%) (Found: As, 25·6; N, 5·1. $C_8H_9O_4NClAs$ requires As, 25·5; N, 4·8%). It is fairly readily soluble in glacial acetic acid and almost insoluble in alcohol. The *magnesium* salt is microcrystalline.

6-*Glycineamide*-3-*chlorophenylarsinic Acid.*—3-Chloro-6-aminophenylarsinic acid (5 g.) in 2*N*-sodium hydroxide (15 c.c.) was heated on the water-bath for 2 hours with chloroacetamide (1·9 g.); on acidification, 5·3 g. (yield, 81·0%) of product were obtained. This *acid* dissolves to the extent of 1 part in 30 parts of boiling water and crystallises in fine, anhydrous needles, m. p. 195° (decomp.) (Found: As, 24·3; N, 9·0. $C_8H_{10}O_4N_2ClAs$ requires As, 24·3; N, 9·1%). It is moderately easily soluble in glacial acetic acid and readily soluble in alcohol. The *magnesium* salt is microcrystalline and the *calcium* salt crystallises in glistening plates.

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