

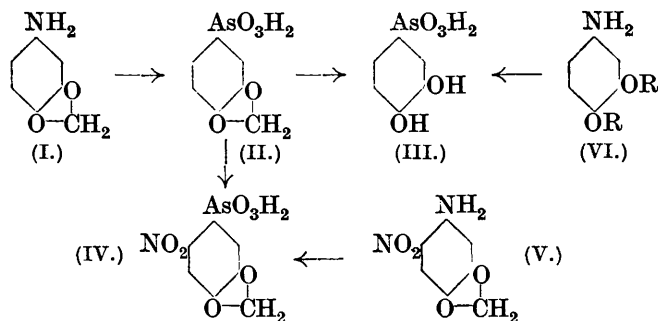
CXLIV.—3 : 4-*Methylenedioxyphenylarsinic Acid*.

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THE only available method for the preparation of 3 : 4-dihydroxyphenylarsinic acid is described in D.R.-P. 271892, the yield being extremely poor; Fargher (J., 1920, **117**, 865) also found the method unsatisfactory, and attempted to obtain the acid by demethylation of 3 : 4-dimethoxyphenylarsinic acid. The desirability of preparing the acid and some of its derivatives and examining them for trypanocidal action led the author to investigate various modes of synthesis.

concentrated to about 20 c.c. in a large Kjeldahl flask. After cooling, 6 c.c. of concentrated sulphuric acid were added and the liquid was heated until free from nitric acid. The liquid was then diluted to about 150 c.c. and saturated with sulphur dioxide, and the excess of the latter boiled off. Slightly more than sufficient dilute hydrochloric acid was added to precipitate the excess of silver and then the solution was made just alkaline (phenolphthalein) with sodium hydroxide and thereafter just acid with sulphuric acid, and about 3 g. of sodium bicarbonate were added. The solution was then titrated against standard iodine (0.1N) with starch as indicator.

It has been reported (Balaban, J., 1928, 809) that 4-aminopyrocatechol failed to undergo the Bart-Schmidt reaction. The following schemes suggested a possible synthesis :



4-Aminopyrocatechol methylene ether (I) is most conveniently prepared by Hesse's method (*Annalen*, 1879, **199**, 341), since reduction of 4-nitropyrocatechol does not proceed smoothly, and the Hofmann reaction with piperonylamide (Rupe and Majewski, *Ber.*, 1900, **33**, 3403) gives but a poor yield. The ether affords a means of obtaining 3 : 4-methylenedioxyphenylarsinic acid (II). Three methods for opening the methylenedioxy-ring were unsuccessfully applied to this acid and to its nitro-derivative described below, *viz.*, the use of (a) thionyl chloride (Barger, J., 1908, **93**, 563), (b) sulphuric acid in the presence of a phenol (Späth and Quietensky, *Ber.*, 1927, **60**, 1882), and (c) anhydrous aluminium chloride in chlorobenzene solution (Mauthner, *J. pr. Chem.*, 1928, **119**, 74); though evidence of the formation of a pyrocatechol derivative was obtained, no arsenic acid could be isolated.

The nitro-acid obtained on nitration of (II) is 6-nitro-3 : 4-methylenedioxyphenylarsinic acid (IV), for it is identical with the nitro-acid prepared from 5-nitro-4-aminopyrocatechol methylene ether (V) : its production is another instance showing that disubstituted pyrocatechol methylene ethers are 4 : 5-derivatives (compare Jones and Robinson, J., 1917, **111**, 904). Reduction of the nitro-acid gave the corresponding *amino-acid*. This and other derivatives were tested in experimental trypanosomiasis : the results are shown in the table below. Unsuccessful attempts were made to prepare 6-hydroxy-3 : 4-methylenedioxyphenylarsinic acid from the corresponding amino-acid, and also 4-hydroxypyrocatechol methylene ether (briefly mentioned by Malagnini and Armani, *Chem.-Ztg.*, 1907, 884) and 5-nitro-4-hydroxypyrocatechol methylene ether by the usual methods; in the last case a poor yield of 4-nitropyrocatechol methylene ether was obtained.

4-Nitro-1 : 2-diacetoxybenzene, prepared by acetylation of 4-nitropyrocatechol, gave on reduction 4-amino-1 : 2-diacetoxybenzene (VI; R = CO-CH₃). This diazotised normally, and the diazo-solution reacted with sodium arsenite in acid solution with the evolution of much gas, but no arsenic acid could be isolated. The acid solution gave with ferric chloride the green coloration characteristic of pyrocatechol derivatives.

4-Nitropyrocatechol dibenzyl ether was reduced to 4-aminopyrocatechol dibenzyl ether (VI; R = CH₂Ph), but no arsenic acid could be obtained from this in numerous experiments.

Phenylarsinic acids.	T.	C.	C/T.
3 : 4-Methylenedioxy- (o)	0.1	0.1	1.0
(i)	0.05	0.05	1.0
6-Amino-3 : 4-methylenedioxy- (i)	0.25	0.25	1.0
6-Acetamido-3 : 4-methylenedioxy- (i)	0.5	0.5	1.0
Arsenobenzenes.			
3 : 4 : 3' : 4'-Dimethylenedioxy- (o)	2.0	2.0	1.0
6 : 6'-Diamino-3 : 4 : 3' : 4'-dimethylenedioxy- (o)	2.0	1.0	1/2

(Administration : o = per os, i = intravenous.)

E X P E R I M E N T A L.

3 : 4-Methylenedioxyphenylarsinic Acid (II).—25 G. of 4-amino-pyrocatechol methylene ether hydrochloride in 16% hydrochloric acid (100 c.c.) at 0° were diazotised with 22.0 c.c. of 10% sodium nitrite solution, added to sodium arsenite solution (arsenious oxide, 18.0 g.; sodium hydroxide, 20.0 g.; water, 200 c.c.), and heated on the water-bath. The filtered liquid, after being acidified (Congo-red) with concentrated hydrochloric acid, slowly deposited 14.7 g. (yield, 41.7%) of 3 : 4-methylenedioxyphenylarsinic acid. This acid crystallises from boiling water, in which it is moderately easily soluble, in colourless silky rhomboids containing $\frac{3}{4}$ H₂O, which decompose at 270° after previous darkening (Found : loss at 100°, 5.1; As, 28.8. C₇H₇O₅As, $\frac{3}{4}$ H₂O requires H₂O, 5.2; As, 28.9%). It is soluble in cold 80% formic acid and moderately easily soluble in glacial acetic acid and hot alcohol. The calcium salt forms bunches of fine needles, the barium salt is microcrystalline, and the magnesium salt is amorphous. The acid is extremely stable towards boiling concentrated hydrochloric acid and 25% sodium hydroxide solution. On reduction with sodium hydrosulphite at 60°, arsenopyrocatechol methylene ether (yield, 65%) was obtained as a pale yellow, amorphous, insoluble powder (Found : As, 37.5. C₁₄H₁₀O₄As₂ requires As, 38.2%).

Nitration of 3 : 4-Methylenedioxyphenylarsinic Acid.—The acid (30.75 g.) was nitrated at 0°, and the solution poured on ice and

made just acid to Congo-red with anhydrous sodium carbonate; 21.6 g. (yield, 59.5%) of 6-nitro-3 : 4-methylenedioxyphenylarsinic acid (IV) were then obtained. The nitro-acid crystallises from 2*N*-acetic acid, in which it is moderately easily soluble, in pale brown, anhydrous spikes, and from water, in which it is very sparingly soluble, in short stout prisms, m. p. 231° (decomp.) (Found in air-dried material : As, 25.4; N, 5.0. $C_7H_6O_7NA_s$ requires As, 25.7; N, 4.8%). It is insoluble in alcohol. The magnesium salt is amorphous, the calcium salt forms irregular transparent plates, and the barium salt is microcrystalline.

When 5-nitro-4-aminopyrocatechol methylene ether (Jones and Robinson, *loc. cit.*) is submitted to the Bart-Schmidt reaction, the above nitro-acid is obtained (yield, 36.9% or, allowance being made for recovered initial material, 73.8%). When prepared by this method, it crystallises from water in long, bright yellow, rectangular, anhydrous prisms, m. p. 228° (decomp.) (Found : As, 25.5; N, 4.9%).

The acid from both sources is very stable towards boiling concentrated hydrochloric acid. When heated with 25% sodium hydroxide solution, it gives an intense blood-red solution, from which no products have been isolated. When it is heated with 8% sodium hydroxide solution for 15 minutes, the same colour is produced, but the material obtained now crystallises in diamond-shaped prisms and gives no coloration with ferric chloride (whereas the mother-liquor gives an intense green), has m. p. 225° (decomp.), and gives on analysis the results required for the initial material (compare Jones and Robinson). 4-Bromo-5-nitropyrocatechol methylene ether also produces the blood-red colour under similar conditions, but again no product can be isolated.

6-Amino-3 : 4-methylenedioxyphenylarsinic Acid.—The nitro-acid (18.7 g.) was reduced at 70° with ferrous sulphate (yield, 10.18 g.; 60.5%). The *amino-acid* crystallises from boiling water, in which it is moderately easily soluble, in long, colourless, fine, silky, anhydrous needles (Found : As, 29.1; N, 5.1. $C_7H_8O_5NA_s$ requires As, 28.7; N, 5.4%). It is readily soluble in 2*N*-hydrochloric acid and diazotises normally, is soluble in 80% formic acid and moderately easily soluble in acetic acid, but almost insoluble in alcohol. The magnesium salt is amorphous and the calcium salt forms irregular prisms.

6 : 6'-*Diaminoarsenopyrocatechol methylene ether* was prepared by reduction of the above acid and obtained as a bright yellow, amorphous powder, soluble in hydrochloric acid (Found : As, 33.3. $C_{14}H_{12}O_4N_2As_2$ requires As, 35.5%).

6-*Acetamido-3 : 4-methylenedioxyphenylarsinic acid* was obtained

by acetylation in alkaline solution of the corresponding amino-acid, and crystallised from 2*N*-acetic acid in colourless, rectangular, anhydrous prisms (Found in different samples : As, 24.5, 24.5; N, 4.1, 4.2. $C_9H_{10}O_6NA_s$ requires As, 24.7; N, 4.6%). It is moderately easily soluble in water, but sparingly soluble in glacial acetic acid. The magnesium salt is amorphous.

4-Nitro-1 : 2-diacetoxybenzene.—A mixture of 4-nitropyrocatechol (15.5 g.), acetic anhydride (31 c.c.), and sulphuric acid (2 c.c.) was heated for $\frac{1}{2}$ hour on the water-bath and poured on ice. The product (22 g.; yield, 92%) crystallised from 95% alcohol (charcoal) in colourless rectangular prisms, m. p. 98° (Found : N, 6.0. $C_{10}H_9O_6N$ requires N, 5.8%). It is moderately easily soluble in boiling water, readily soluble in alcohol, ether, chloroform, benzene, and acetone, and readily hydrolysed by cold 2*N*-sodium hydroxide, but only slowly by hot dilute hydrochloric acid.

4-Amino-1 : 2-diacetoxybenzene (VI; R = CO·CH₃) can be obtained by reducing the nitro-compound with iron and water (1 drop of acetic acid), but is more conveniently prepared by Bell and Kenyon's method (J., 1926, 954). The nitro-compound (5.0 g.) in moist ether (70 c.c.) is treated with aluminium amalgam (1.5 g.), and the reaction started by warming on the water-bath. After 3 hours, the ether, together with washings, is removed and 2.2 g. (yield, 41.8%) of product obtained, crystallising from 95% alcohol in thick prisms, m. p. 114° (Found : N, 6.6, 6.55. $C_{10}H_{11}O_4N$ requires N, 6.7%). It is sparingly soluble in hot water, readily soluble in alcohol, acetone, and chloroform, and somewhat less soluble in benzene and ether. It dissolves readily in dilute hydrochloric acid and diazotises normally. The *N*-acetyl derivative crystallises from water (moderately easily soluble) in diamond-shaped plates, m. p. 144°.

4-Nitropyrocatechol Dibenzyl Ether.—A mixture of 4-nitropyrocatechol (15.5 g.), sodium hydroxide (8 g.), and benzyl chloride (26 g.) in absolute alcohol (300 c.c.) was heated for 15 hours on the steam-bath, the alcohol removed, and the residue extracted with *N*-sodium hydroxide solution; 16.3 g. (yield, 48.7%) of the *dibenzyl* ether were obtained, which crystallised from 95% alcohol (charcoal) in long, fine, colourless needles, m. p. 97° (Found : N, 4.4. $C_{20}H_{17}O_4N$ requires N, 4.2%). It is very sparingly soluble in alcohol, but readily soluble in acetone, benzene, chloroform, and ether, and is only slowly hydrolysed to the phenol by concentrated hydrochloric acid. It is unaffected by sodium hydroxide.

4-Aminopyrocatechol Dibenzyl Ether (VI; R = CH₂Ph).—The above nitro-compound can be reduced by West's method (J., 1925, 127, 494) or by that of Bell and Kenyon (*loc. cit.*), the yield

being about 50% in both cases; the *amine* crystallises from chloroform in laminæ, m. p. 92° (Found: N, 4.8. $C_{20}H_{19}O_2N$ requires N, 4.6%). It is moderately easily soluble in alcohol and readily soluble in acetone, benzene, chloroform, and ether. The hydrochloride crystallises from dilute hydrochloric acid, in which it is almost insoluble in the cold, in colourless needles, m. p. 197°; the solution diazotises normally. The acetyl derivative forms colourless rods from alcohol (moderately easily soluble), m. p. 150°.

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