CCXLIX.—*The Arsinic Acids of* p-*Aminophenol.*

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THE methods employed for the preparation of 5-amino-2-hydroxyphenylarsinic acid are based on the reduction of the nitro-compound obtained by (*a*) the application of the Bart reaction to 4-nitro-2-aminophenol (Bart, D.R.-P. 250,264), (*b*) the nitration of 2-hydroxyphenylarsinic acid (Keimatsu and Kakinuma, *J. Pharm. Soc. Japan*, 1925, No. 520, 2), or (*c*) the action of alkali hydroxide on 5-nitro-2-aminophenylarsinic acid (Benda, *Ber.*, 1911, **44**, 3295). The last method has now been modified by the use of the acetyl derivative, obtained by the nitration of 2-acetamidophenylarsinic acid. In addition, the reduction of chloro-2 : 4-dinitrobenzene to 2-chloro-5-nitroaniline provides an easy route to 5-nitro-2-hydroxyphenylarsinic acid (Balaban, this vol., p. 183). 2-Nitro-4-acetamidophenol could not be employed as a source of the amino-acid on account of difficulty of reduction.

The only method given in the literature for the preparation of 2-amino-5-hydroxyphenylarsinic acid is that commencing with 3-oxalylaminophenylarsinic acid (D.R.P. 261,643; compare Fourneau, Navarro-Martin, and Tréfoul, *Ann. Inst. Pasteur*, 1923, **37**, 577). Ready fission of arsenic throughout the process, however, led to the application of the following methods for the preparation of this acid: (*a*) Application of the Bart process to the corresponding nitroaminophenol, (*b*) reduction of 5-nitro-2-acetamidophenylarsinic acid and replacement of the amino- by the hydroxyl group, and (*c*) from 4-nitro-*m*-phenylenediamine. The yield by method (*b*) is good, but purification is difficult.

Method (*c*) depended on Kehrmann and Mermod's proof (*Helv. Chim. Acta*, 1927, **10**, 64) that mono-acetylation of the diamine occurs para to the nitro-group, and this has been confirmed, de-amination of the nitroaminoacetanilide giving *p*-nitroacetanilide. Application of the Bart reaction to 4-nitro-3-aminoacetanilide (m. p. 200°, not 178° as given by Kehrmann and Mermod, *loc. cit.*)

then gave 2-*nitro*-5-*acetamidophenylarsinic acid*, from which, by deacetylation, 2-nitro-5-aminophenylarsinic acid was obtained: the acetyl group appears to cause less de-arsenication than the oxalyl group. The method of D.R.-P. 261,643 for the formation of 2-nitro-5-hydroxyphenylarsinic acid was then followed. Although considerable de-arsenication is caused by the action of alkali on 2-nitro-5-oxalylaminophenylarsinic acid, no nitroresorcinol was isolated in this case, and the yield of the desired acid indicates its greater stability to alkali than that of 5-chloro-2-nitrophenylarsinic acid, which is completely decomposed by boiling alkali (Barber, J., 1929, 2334).

Another *o*-nitro-arsinic acid stable to boiling concentrated alkali is 2-nitro-3-aminophenylarsinic acid, the carbethoxy-derivative of which gives a 68% yield of 2-nitro-3-hydroxyphenylarsinic acid with this reagent after prolonged treatment (compare Newbery, Phillips, and Stickings, J., 1928, 3053).

Reduction of 2-nitro-5-acetamidophenylarsinic acid gives the corresponding *amino*-acid, which, by deacetylation, yields 2 : 5-diaminophenylarsinic acid, also obtainable from 5-*amino*-2-*acetamidophenylarsinic acid* (p. 1915). Finally, by the diazo-reaction applied to 2-amino-5-acetamidophenylarsinic acid, 5-acetamido-2-hydroxyphenylarsinic acid is formed.

The *methyl* ether of 5-acetamido-2-hydroxyphenylarsinic acid could not be obtained by methylation in alkali of the hydroxy-acid. This may be a general property of *o*-hydroxyphenylarsinic acids since the parent acid could not be methylated in alkali. By application of the Bart reaction to *o*-anisidine, followed by nitration, 5-*nitro*-2-*methoxyphenylarsinic acid* was obtained; reduction and subsequent acetylation then gave 5-*acetamido*-2-*methoxyphenylarsinic acid*.

EXPERIMENTAL.

Nitration of o-*Acetamidophenylarsinic Acid*.—To this acid (50 g.), dissolved at 20° in sulphuric acid (400 c.c.), was added a mixture of nitric acid (13 c.c.; *d* 1·42) and sulphuric acid (20 c.c.) at 5°. After precipitation in ice-water (1·5 l.), and purification by reprecipitation of its alkaline solution by hydrochloric acid, 5-nitro-2-acetamidophenylarsinic acid (42 g.; Found: As, 24·5. Calc.: As, 24·7%) was obtained. It forms pale yellow prisms insoluble in water, and hydrolyses to 5-nitro-2-aminophenylarsinic acid.

5-*Amino*-2-*acetamidophenylarsinic Acid*.—To the above nitro-acid (8 g.) in 2*N*-caustic soda (100 c.c.) at 10°, sodium hyposulphite (20 g.) was added. After some minutes, acetic acid (15 c.c.) was added, and the precipitated *amino-acid* purified by solution in dilute

hydrochloric acid and reprecipitation with sodium acetate (4 g.). It forms colourless prisms soluble in alkalis, alkali carbonates, and dilute mineral acids, but insoluble in water (Found: As, 27·5; N, 10·0. $C_8H_{11}O_4N_2As$ requires As, 27·4; N, 10·2%).

5-*Nitro*-2-*hydroxyphenylarsinic Acid*.—5-Nitro-2-acetamidophenylarsinic acid (40 g.) was refluxed with 50% sodium hydroxide solution (100 c.c.) for 3 hours. On cooling and acidification with hydrochloric acid (Congo-red) the above nitro-acid was precipitated in an almost pure condition (30 g.) (Found: As, 28·7. Calc.: As, 28·5%).

5-Amino-2-hydroxyphenylarsinic acid was obtained by reduction of this nitro-acid by using sodium hyposulphite (compare Newbery and Phillips, *loc. cit.*, p. 122), ferrous sulphate and sodium hydroxide (compare Jacobs, Heidelberger, and Rolf, *J. Amer. Chem. Soc.*, 1918, **40**, 1580), or glucose and alkali (compare Newbery, Phillips, and Stickings, *loc. cit.*). On acetylation in alkaline solution, 5-acetamido-2-hydroxyphenylarsinic acid (Found: As, 27·4. Calc.: As, 27·3%), colourless plates, m. p. 230—235° (decomp.), is obtained; the calcium and magnesium salts are amorphous, the barium salt forms colourless boat-shaped needles. This acid was also obtained in an impure condition by heating the diazo-compound of 2-amino-5-acetamidophenylarsinic acid with acid copper sulphate solution.

m-*Arsanilic Acid*.—To a solution of ferrous sulphate (hydrated, 400 g.) in water (350 c.c.) was added a solution of sodium hydroxide (125 g.) in water (250 c.c.) at 90° with shaking, and, to the resulting paste of ferrous hydroxide, *m*-nitrophenylarsinic acid (50 g.) in 30% sodium carbonate solution (350 c.c.) was added in portions. After filtration, the solution was made faintly acid to Congo-red, and the pure amino-acid separated; yield 57%.

3-*Oxalylaminophenylarsinic Acid*.—*m*-Arsanilic acid (120 g.) was heated at 150° for 5 hours with 190 g. of oxalic acid crystals. The product was dissolved in 2*N*-sodium carbonate, the solution filtered, and acidified (Congo-red); a 75% yield of the above acid (Found: As, 26·0. Calc.: As, 25·9%) was obtained.

2-*Nitro*-5-*oxalylaminophenylarsinic Acid*.—The above acid (57 g.) mixed with potassium nitrate (20 g.) was added to sulphuric acid (200 c.c.) at 0°, and poured into ice-water (1 litre); the nitro-acid was precipitated (yield 30%), and a large amount of inorganic arsenic remained in the filtrate. Purified by solution in sodium carbonate and reprecipitation by mineral acids, the nitro-acid forms pale yellow prisms, insoluble in water (Found: As, 22·4. Calc.: As, 22·45%).

4-*Nitro*-3-*aminoacetanilide*.—4-Nitro-*m*-phenylenediamine (60 g.) was refluxed for 2 hours with acetic acid (300 c.c.); acetic anhydride

(35 c.c., 1 mol.) was then cautiously added. When the reaction was over, the mixture was boiled for 1 hour and poured into water (1 l.). A mixture of 4-nitro-3-aminoacetanilide and of the 1 : 3-diacetamido-compound in the proportion of 2 : 1 was precipitated, from which the former was isolated, after many crystallisations from 30% acetic acid, as red prisms m. p. 200° (Found : N, 21·5. Calc. : N, 21·5%).

Deamination of 4-Nitro-3-aminoacetanilide.—The amino-compound (3·5 g.) in hydrochloric acid suspension (50 c.c.; 3%) at 0° was diazotised by sodium nitrite (1·3 g.), the solution added to 250 c.c. of boiling alcohol, and the mixture evaporated to dryness, giving *p*-nitroacetanilide, m. p. 207° (yield, 63%).

3-Chloro-4-nitroaniline.—4-Nitro-3-aminoacetanilide (3·5 g.) was diazotised as above; cuprous chloride (1·8 g.) was added, and after decomposition at 50°, the solid was collected and hydrolysed with boiling 25% sulphuric acid (10 c.c.; 30 mins.). The filtered solution was made alkaline with ammonia, and the solid crystallised from alcohol, m. p. 152°, alone and mixed with 3-chloro-4-nitroaniline from the nitration of *m*-chloroacetanilide.

2-Nitro-5-aminophenol.—(*a*) 4-Nitro-3-aminoacetanilide (3·5 g.) was diazotised as above in sulphuric acid, the diazo-solution added to a mixture of 30 c.c. each of 2*N*-copper sulphate solution and 2*N*-sulphuric acid, the solution concentrated to half volume, and the solid collected, washed, and hydrolysed with 25% sulphuric acid (10 c.c.). By neutralisation with ammonia, 1·1 g. of 2-nitro-5-aminophenol (m. p. 163°, from water) were obtained (Found : N, 18·1%).

(*b*) (compare Barbaglia, *Ber.*, 1874, **7**, 1259). 4-Nitro-1 : 3-diacetamidobenzene (20 g.) and 40% potassium hydroxide solution (100 c.c.) were refluxed for 6 hours. Addition of sodium acetate to the filtered solution gave the nitroaminophenol, orange needles, m. p. 163° after crystallisation from water (Barbaglia gives m. p. 135°). It did not depress the m. p. of the product from (*a*) (Found : N, 18·0. Calc. : N, 18·2%). The *acetyl* derivative, m. p. 200°, from water or aqueous alcohol consists of pale yellow prisms (Found : N, 14·4. $C_8H_8O_4N_2$ requires N, 14·3%), and the *diacetyl* derivative formed white needles, m. p. 118° (Found : N, 12·0. $C_{10}H_{10}O_5N_2$ requires N, 11·8%), from water.

5-Chloro-2-nitrophenol.—2-Nitro-5-aminophenol (1 g.) in 4*N*-hydrochloric acid (2 mols.) was diazotised at 0° with sodium nitrite (1 mol.) and 1 g. of cuprous chloride was added. Steam-distillation gave the chloro-compound, m. p. 40°, not depressed when mixed with the product from nitration of *m*-chlorophenol or from dearsenication of 5-chloro-2-nitrophenylarsinic acid (Barber, *loc. cit.*).

Nitration of m-*Acetamidophenol.*—*m*-Acetamidophenol (30 g.) was added at 0° during 2 hours to nitric acid (*d* 1·45; 220 c.c.), and poured into ice-water (800 c.c.); the precipitate (21 g.) was soluble in 12 parts of boiling alcohol. Fractionation from alcohol then gave (*a*) 8 g., m. p. 260°, soluble in 25 parts, and (*b*) 4 g., m. p. 221°, soluble in 9 parts of boiling alcohol. Fraction (*a*) on hydrolysis with 25% sulphuric acid and crystallisation from water gave 5 g. of 4-nitro-3-aminophenol, m. p. 185° (Found: N, 18·0%), which on deamination gave *p*-nitrophenol (68%) (compare Meldola and Stephens, J., 1900, **77**, 924; Morgan and Porter, J., 1915, **107**, 657). Fraction (*b*) on hydrolysis gave 2·1 g. of a nitroaminophenol (Found: N, 18·3. Calc.: N, 18·2%), which melted at 163° after repeated crystallisation from aqueous alcohol but depressed the m. p. of 2-nitro-5-aminophenol; its acetyl derivative, m. p. 221° (Found: N, 14·6. Calc.: N, 14·3%), also depressed the m. p. of 2-nitro-3-acetamidophenol. The constitution of this compound, stated by Meldola and Stephens (*loc. cit.*) to be 6-nitro-3-aminophenol, is being investigated.

2-*Nitro*-5-*acetamidophenylarsinic Acid.*—10 G. of the mixture of compounds obtained from the acetylation of 4-nitro-*m*-phenylenediamine, together with water (150 c.c.) and hydrochloric acid (*d* 1·16, 10 c.c.), were diazotised at 10° by 4 g. of sodium nitrite. After 1 hour's stirring, the mixture was filtered from unchanged 4-nitro-1 : 3-diacetamidobenzene (3·5 g., m. p. 246° from alcohol) and the filtrate added to a copper arsenite suspension (arsenious oxide, 7·5 g.; sodium hydroxide, 8·4 g.; water, 50 c.c.; 2*N*-copper sulphate solution, 14 c.c.). The solution was boiled, filtered, and acidified to Congo-red (hydrochloric acid), and the arsinic *acid* (Found: As, 24·9. $C_8H_9O_6N_2As$ requires As, 24·7%) was precipitated on cooling in 67% yield (calculated on the nitroaminoacetanilide present in the original mixture). It forms yellow plates from 30% acetic acid, insoluble in mineral acids and water, soluble in alkalis and alkali carbonates. The calcium and magnesium salts are amorphous.

2-*Amino*-5-*acetamidophenylarsinic acid*, prepared from the nitro-acid by reduction with sodium hyposulphite as before (p. 1911), forms white prisms (Found: As, 27·8. $C_8H_{11}O_4N_2As$ requires As, 27·4%).

2-*Nitro*-5-*aminophenylarsinic Acid.*—(*a*) 2-Nitro-5-oxalylaminophenylarsinic acid (95 g.) was refluxed for 30 minutes with 2*N*-hydrochloric acid (120 c.c.); on cooling, the nitroamino-acid separated (38 g.; 50%). The filtrate contained large amounts of inorganic arsenic, and on addition of sodium acetate gave 18 g. of *p*-nitroaniline. The acid forms pale yellow needles from alkaline solution by precipitation with dilute minerals acids, in which it is insoluble (Found: As, 28·4; N, 10·9. Calc.: As, 28·6; N, 10·7%).

(*b*) 2-Nitro-5-acetamidophenylarsinic acid (80 g.) was similarly treated with 2*N*-hydrochloric acid (250 c.c.), and 55 g. (80%) of the nitroamino-acid were obtained (Found: As, 28·6; N, 10·5%). There was a trace of inorganic arsenic in the filtrate.

2-Nitro-5-hydroxyphenylarsinic Acid.—(*a*) 4-Nitro-3-aminophenol (3 g.) was arsenated by the modified Bart method described on p. 1914; the yield of purified nitro-acid was 2 g. (37%) (Found: As, 27·0%). (*b*) 2-Nitro-5-aminophenylarsinic acid (50 g.) was refluxed for 3 hours with 25% sodium hydroxide solution (250 c.c.), the mixture cooled, acidified with hydrochloric acid (Congo-red), and the acid purified by acidification of its alkaline solution; yield 35 g. (70%) (Found: As, 26·9; N, 5·2. $C_6H_6O_6NAs,H_2O$ requires As, 26·7; N, 5·0%): the filtrate contained inorganic arsenic. The acid forms a *monohydrate* (yellow laminæ) and does not lose water at 100°, but melts at 175°, resolidifying and melting again at 205°. On reduction with ferrous sulphate and sodium hydroxide it gives the amino-acid (yield 60%) (compare Fourneau, Navarro-Martin, and Tréfoul, *loc. cit.*), which on acetylation in caustic alkali solution gives 2-acetamido-5-hydroxyphenylarsinic acid (Found: As, 27·1; N, 4·9. Calc.: As, 27·3; N, 5·1%) in 75% yield. This forms colourless prisms, m. p. 230° (decomp.), insoluble in water and mineral acids, readily soluble in alkalis, etc. The magnesium salt is amorphous, the barium salt microcrystalline, and the calcium salt forms hexagonal plates. This acid is also obtained in small yield from 5-amino-2-acetamidophenylarsinic acid by diazotisation in sulphuric acid and treatment of the diazo-solution at 90° with acidified copper sulphate solution, the dark brown amorphous solid being repeatedly treated in alkaline solution with small amounts of sodium hyposulphite (Found: As, 27·3%).

2:5-Diaminophenylarsinic acid (Found: As, 32·2; N, 12·0. Calc.: As, 32·3; N, 12·1%), obtained by acid hydrolysis of either of its monoacetyl derivatives, consists of colourless prisms, m. p. 220°, readily soluble in mineral acids, alkalis, and alkali carbonates, but insoluble in water. The calcium salt forms polyhedra, and the magnesium salt is amorphous. On acetylation, 2:5-*diacetamidophenylarsinic acid* was obtained as white plates, m. p. 225° (decomp.), containing 1 mol. of water not lost at 100° (Found: As, 22·8; N, 8·8. $C_{10}H_{13}O_5N_2As,H_2O$ requires As, 22·4; N, 8·4%). The calcium salt forms colourless needles, and the barium salt moderately soluble needles, but the magnesium salt is amorphous.

5-Nitro-2-methoxyphenylarsinic Acid.—2-Methoxyphenylarsinic acid (45 g.; from *o*-anisidine by the method of Johnson and Adams, *J. Amer. Chem. Soc.*, 1923, **45**, 1311) was dissolved at 20° in sulphuric acid (130 c.c.), and a mixture of nitric acid (14 c.c.; *d* 1·42) and

sulphuric acid (20 c.c.) was added at 5°. After 1 hour the mixture was poured on ice and the separated solid crystallised by solution in caustic alkali and reprecipitation by mineral acids. The arsinic *acid* (60% yield) consists of white needles, dissolving in alkalis and alkali carbonates to yellow solutions (Found: As, 27·2. $C_7H_8O_6NAs$ requires As, 27·1%). On reduction by ferrous sulphate and sodium hydroxide, 5-*amino*-2-*methoxyphenylarsinic acid* was obtained (yield 55%); it forms white needles decomposing at 240—245°, readily soluble in alkalis and acids (Found: As, 30·4; N, 5·65. $C_7H_{10}O_4NAs$ requires As, 30·4; N, 5·7%). The *acetyl* derivative (Found: As, 26·0; N, 5·0. $C_9H_{12}O_5NAs$ requires As, 26·1; N, 4·85%), decomposing at 260—262°, consists of colourless needles insoluble in water or mineral acids, readily soluble in alkalis and alkali carbonates. The *monosodium* salt forms a monohydrate which loses its water at 90° (Found, on vacuum-dried material: As, 22·6; H_2O, 5·6. $C_9H_{11}O_5NAsNa,H_2O$ requires As, 22·8; H_2O, 5·4%).

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