

CCCXIV.—*Certain Aryl Arsenoxides and the Corresponding Dichloro- and Di-iodo-arsines.*

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IN the course of chemo-therapeutic studies proceeding in these laboratories, a number of dichloro- and di-iodo-arsines and the corresponding arsenoxides were prepared, and some of their chemical properties are now recorded. Some phenyl-arsine derivatives, prepared for comparison, are also described.

In general, the dihalogeno-arsines are hydrolysed by water to give the corresponding arsenoxides, and can be regenerated by the action of the halogen acid. The hydrolysis is obvious in cases such as those of 3 : 5-diacetamido-2- and -4-hydroxyphenyldichloroarsines, where the product of hydrolysis is insoluble in the concentration of mineral acid simultaneously formed (compare the dicyano-arsines, Grischkiewitsch-Trochimovski, Mateyak, and Zablotski, *Bull. Soc. chim.*, 1927, **41**, 1323). The amino-di-iodoarsine hydriodides are much less soluble in water than the corresponding chloro-derivatives, from which they can readily be made by addition of hydriodic acid or potassium iodide in aqueous solution. In general, the attachment of the iodine atom to the arsenic atom appears to be firmer than that of the chlorine atom in the corresponding chloro-compound; this stability extends to concentrated nitric acid, and in one case, *viz.*, 3 : 5-diamino-4-hydroxyphenyldi-iodoarsine dihydriodide, even to 5*N*-sodium hydroxide solution. The di-iodo-arsines are deep yellow, crystalline compounds, whereas the pure chloro-compounds are white.

It is noteworthy that 3 : 5-diacetamido-4-hydroxyphenylarsenoxide, made either by hydrolysis of the dichloro-arsine or by acetylation of 3-amino-5-acetamido-4-hydroxyphenylarsenoxide, appears to exist only as the arsinous acid, which does not lose water at 100°. In this way it differs from the "arsenoxide hydrates" of Lewis and Cheetham (*J. Amer. Chem. Soc.*, 1921, **43**, 2119) and from 3 : 5-diacetamido-2-hydroxyphenylarsenoxide, although it resembles the latter in its ready solubility in ammonium hydroxide and sodium carbonate solutions (compare also benzarsenious acid, La Coste, *Annalen*, 1881, **208**, 14).

Attention must also be directed to a curious property of 3-amino-5-acetamido-2- and -4-hydroxyphenylarsenoxide hydrochlorides and hydriodides. These four compounds will only dissolve in water after standing for a few seconds, and it is possible that they may actually be the free bases corresponding to chloro-hydroxy-arsines of the type $C_6H_2(NH_2)(OH)(NHAc) \cdot As(OH)Cl$, hydrolysed by water

to give $C_6H_2(NH_2, HCl)(OH)(NHAc) \cdot AsO$. Addition of hydrochloric acid to the alkaline solutions until they are acid to Congo-red precipitates the original compounds with their characteristic delayed solubility in water.

In attempts to prepare compounds of the type $As(OH)ClR$ by the action of methyl-alcoholic hydrogen chloride on the corresponding arsenoxide, *methoxy-3-acetamido-4-hydroxy-* and *-5-acetamido-2-hydroxy-phenylchloroarsines* were obtained. These compounds gave the corresponding *arsenoxides* on treatment with water.

EXPERIMENTAL.

3-Nitro-5-acetamido-2-hydroxyphenylarsinic Acid.—This compound was obtained by dissolving 100 g. of 5-acetamido-2-hydroxyphenylarsinic acid (Newbery and Phillips, this vol., p. 116) in sulphuric acid (300 c.c.) at 20° , nitrating it at $10-20^\circ$ with a mixture of nitric acid (d 1.420; 35 c.c.) and sulphuric acid (35 c.c.), and pouring into ice water; the pure nitro-compound separated in 80% yield as yellow prisms, giving red solutions in caustic alkalis and alkali carbonates (Found: As, 23.5. $C_8H_9O_7N_2As$ requires As, 23.4%).

3-Amino-5-acetamido-4- and *-2-hydroxyphenylarsinic acids* were obtained by reduction of the corresponding nitro-acids (compare Jacobs, Heidelberger, and Rolf, *J. Amer. Chem. Soc.*, 1918, **40**, 1580; 60% yield in each case), and purified by the method described by Christiansen (*ibid.*, 1920, **42**, 2403) for 3-amino-4-hydroxyphenylarsinic acid. The former consists of stout white prisms, readily soluble in dilute mineral acids, and in alkali hydroxides and carbonates (Found: As, 25.6; N, 9.3. $C_8H_{11}O_5N_2As$ requires As, 25.8; N, 9.7%), whilst the isomeric acid (Found: As, 25.8; N, 9.6%) is only soluble in excess of dilute mineral acids.

3:5-Diacetamido-2-hydroxyphenylarsinic acid and *3:5-diacetamido-4-hydroxyphenylarsinic acid*, the latter of which has been described by Raiziss and Gavron (*ibid.*, 1921, **43**, 584), were best made by the following method: 3-Nitro-5-acetamido-2- or -4-hydroxyphenylarsinic acid (30 g.) was dissolved in 2*N*-sodium hydroxide, and sodium hyposulphite (54 g.) was slowly added at 10° with stirring. After 30 minutes, 10*N*-sodium hydroxide was added, the solution filtered, and acetic anhydride (30 c.c.) run in. After 1 hour the reaction mixture was acidified (Congo-red), and the precipitated arsinic acid purified through its alkaline solution. The yield varied from 10 to 15 g. in each case. The 2-hydroxy-acid forms white needles, readily soluble in alkalis (Found: As, 22.6; N, 8.3. $C_{10}H_{13}O_6N_2As$ requires As, 22.6; N, 8.4%), and its orientation is shown by its conversion into 2:4-diaminophenol (isolated as diacetyl derivative) by boiling with 5 parts of 15% hydrochloric acid.

The aminophenyldichloroarsines were prepared by sulphurous acid reduction of the arsenic acid in hydrochloric acid at room temperature, a trace of potassium iodide being present; some acetamido-derivatives were made by addition of a warm solution of the corresponding arsenic acid in hydrochloric acid to a solution of sulphurous acid containing potassium iodide, and passage of sulphur dioxide at 10° until reduction was complete. The dichloro-arsine was precipitated where necessary by addition of a sufficient amount of concentrated hydrochloric acid. The aminodi-iodoarsine hydriodides were similarly prepared by use of either an acidified solution of potassium iodide or hydriodic acid.

3-Amino-5-acetamido-4-hydroxyphenylarsine Derivatives.—The *dichloro-arsine hydrochloride*, obtained in 60% yield by the general method, formed white prisms, soluble in dilute alkali hydroxide (Found: As, 21.5; N, 8.0; Cl, 30.5. $C_8H_9O_2N_2Cl_2As, HCl$ requires As, 21.6; N, 8.05; Cl, 30.6%). This hydrochloride (5 g.) was suspended in water (30 c.c.) and stirred for 30 minutes; the resulting amorphous solid was collected, washed with water, and crystallised by addition of concentrated hydrochloric acid to the solution in sodium hydroxide until faintly acid to Congo-red (yield, 2.3 g.). *3-Amino-5-acetamido-4-hydroxyphenylarsenoxide hydrochloride* thus obtained formed white prisms, soluble in water after a few seconds' shaking, and readily soluble in dilute caustic alkalis (Found: As, 25.6; N, 9.7; Cl, 12.2. $C_8H_9O_3N_2As, HCl$ requires As, 25.6; N, 9.6; Cl, 12.1%).

The amorphous arsenoxide, obtained as described above from 2 g. of dichloro-arsine hydrochloride, was collected, washed with water, and stirred into a mixture of hydriodic acid (d 1.7; 40 c.c.) and water (20 c.c.); the gum formed soon crystallised as prisms and was found to be pure *3-amino-5-acetamido-4-hydroxyphenyldi-iodoarsine hydriodide* (Found: As, 11.9; N, 4.4; I, 61.9. $C_8H_9O_2N_2I_2As, HI$ requires As, 12.0; N, 4.5; I, 61.2%). This compound was also obtained by the general method; its acetyl group is remarkably stable to hot mineral acids, and it readily dissolves in water to give a yellow solution which deposits crystals of the arsenoxide. *3-Amino-5-acetamido-4-hydroxyphenylarsenoxide hydriodide* forms white prisms, soluble in water only after a few seconds' shaking (Found: As, 19.7; I, 32.6. $C_8H_9O_3N_2As, HI$ requires As, 19.5; I, 33.0%).

3 : 5-Diamino-4-hydroxyphenyldichloroarsine dihydrochloride. The above dichloro-arsine hydrochloride (30 g.) was boiled for 15 minutes with 120 c.c. of 5*N*-hydrochloric acid, and sufficient hot water to dissolve the solid was then added. Addition of an equal volume of concentrated hydrochloric acid to the hot filtered solution gave, on

cooling, a 50% yield of the required *dihydrochloride* as white plates, readily soluble in water (Found : As, 21.7; N, 8.1; Cl, 41.0. $C_6H_7ON_2Cl_2As, 2HCl$ requires As, 21.9; N, 8.1; Cl, 41.5%).

To this chloro-compound (5 g.) in water (50 c.c.), hydriodic acid (*d* 1.7; 30 c.c.) was added; the solid was collected, washed with alcohol and ether, and dried in a vacuum over caustic soda and calcium chloride, 3 : 5-*diamino-4-hydroxyphenyldi-iodoarsine dihydriodide* being thus obtained as yellow prisms, readily soluble in water (yield, 7 g.) (Found : As, 10.7; I, 72.0. $C_6H_7O_2N_2I_2As, 2HI$ requires As, 10.1; I, 72.0%).

3-Amino-5-acetamido-2-hydroxyphenylarsine Derivatives.—The *di-iodoarsine hydriodide* was obtained by the general method as yellow, boat-shaped crystals (Found : As, 11.9; N, 4.6; I, 62.1%), soluble in water to give a yellow solution, which slowly deposits crystals of the oxide hydriodide.

The *arsenoxide hydriodide* forms white prisms, soluble in water only after shaking for a few seconds (Found : As, 19.6; I, 33.0%).

3 : 5-Diacetamido-2- and -4-hydroxyphenyldichloroarsines.—These were obtained by the general method, or by the action of alcoholic hydrogen chloride on the corresponding arsenoxide, as clusters of needles readily soluble in water, by which they were slowly hydrolysed. They could not be obtained sufficiently pure for analysis.

3 : 5-Diacetamido-4-hydroxyphenylarsinous acid was obtained (1) by hydrolysis of the dichloro-arsine; (2) by acetylation of 3-amino-5-acetamido-4-hydroxyphenyldichloroarsine hydrochloride as described under 5-acetamido-2-hydroxyphenylarsenoxide (see below); or (3) by acetylation of 3 : 5-diamino-4-hydroxyphenyldichloroarsine dihydrochloride. It was purified by solution in caustic alkali and acidification by hydrochloric acid (Congo-red), and consisted of white plates or needles, insoluble in water, dilute mineral acids, or sodium bicarbonate solution, but soluble in aqueous solutions of sodium hydroxide, sodium carbonate, or dilute ammonia (Found : As, 23.8; N, 8.9. $C_{10}H_{13}O_5N_2As$ requires As, 23.7; N, 8.9%).

3 : 5-Diacetamido-2-hydroxyphenylarsenoxide, obtained by aqueous hydrolysis of the corresponding dichloro-arsine, is an amorphous, white solid with solubilities identical with the above arsenious acid. It was purified similarly, and dried at 100° (Found : As, 24.8; N, 9.4. $C_{10}H_{11}O_4N_2As$ requires As, 25.1; N, 9.4%).

Derivatives of 3-Amino-4-hydroxyphenylarsine.—The dichloro-arsine was obtained by the general method as a monohydrate. On treatment of its aqueous solution with excess of hydriodic acid, it gave the corresponding *di-iodoarsine hydriodide*, which was also obtained by the general method; this formed yellow prisms, giving a yellow solution in water. The iodine attached to the arsenic atom

showed some resistance to the action of hot 8*N*-nitric acid, only one-third of the total iodine being removed (Found: As, 13.5; I, removed by concentrated nitric acid, 68.0. $C_6H_6ONI_2As, HI$ requires As, 13.3; I, 67.5%).

The hydrolysis of the dichloro-arsine hydrochloride was accomplished by dissolution in water (3 g. in 10 c.c.); the solution deposited the crude oxide hydrochloride, whilst the filtrate contained approximately two-thirds of the total chlorine introduced.

3-Acetamido-4-hydroxyphenylarsenoxide. This compound was obtained by the methods since given in E.P. 254,186 and F.P. 606,238, but is best obtained as follows: To 3-amino-4-hydroxyphenyldichloroarsine (25 g.), dissolved in water (80 c.c.), acetic anhydride (37.5 c.c.) is added, followed at once by sodium acetate until the mixture no longer reacts acid to Congo-red. After acidification (Congo-red) by 25% sulphuric acid, the crude acetyl derivative is collected and washed. The *oxide*, purified by acidification of its solution in sodium hydroxide by 25% sulphuric acid, forms a tetrahydrate consisting of white prisms, which lose water at 100°. It is insoluble in water, sodium bicarbonate, or sodium carbonate solution, but soluble in excess of caustic alkalis and in large excess of ammonia (Found: H_2O lost at 100°, 23.1. Calc.: H_2O , 23.0. Found, in dried material: As, 30.9; N, 5.7. Calc.: As, 31.1; N, 5.8%).

Derivatives of 5-Amino-2-hydroxyphenylarsine.—Sulphur dioxide was passed for 90 minutes through a solution of 20 g. of 5-amino-2-hydroxyphenylarsinic acid in water (60 c.c.) and hydrochloric acid (200 c.c.). The precipitated *5-amino-2-hydroxyphenyldichloroarsine hydrochloride*, purified by solution in water (80 c.c.) and reprecipitation by 160 c.c. of hydrochloric acid (yield, 15.5 g.), consisted of anhydrous, white prisms, soluble in four parts of water (Found: As, 25.5; N, 4.8; Cl, 37.0. $C_6H_6ONCl_2As, HCl$ requires As, 25.7; N, 4.8; Cl, 36.8%); the basified solution is much more stable to aerial oxidation than that of its isomeride.

5-Amino-2-hydroxyphenylarsenoxide hydrochloride, white prisms soluble in water, was obtained by dissolving the above dichloroarsine hydrochloride (2 g.) in water (8 c.c.) and collecting the crystals which separated after some hours (Found: As, 31.5; Cl, 15.1. $C_6H_6O_2NAs, HCl$ requires As, 31.9; Cl, 15.1%).

5-Amino-2-hydroxyphenyldi-iodoarsine hydriodide, made by the general methods, consisted of yellow prisms, soluble in water to give a yellow solution (Found: As, 13.5; N, 2.7. I, removed by hot 8*N*-nitric acid, 22.8; I, removed by concentrated nitric acid, 67.7. $C_6H_6ONI_2As, HI$ requires As, 13.3; N, 2.5; I, 67.5%).

5-Amino-2-hydroxyphenylarsenoxide hydriodide was obtained as

stout, white prisms, by shaking the above di-iodoarsine hydriodide (1 g.) with water (10 c.c.); it resembles its isomeride in properties and solubilities (Found: As, 22.7; I, 40.0. $C_6H_6O_2NAs, HI$ requires As, 22.9; I, 38.9%).

5-Acetamido-2-hydroxyphenylarsenoxide was best prepared by dissolving the corresponding aminodichloroarsine hydrochloride (15 g.) in water (50 c.c.), cooling during addition of acetic anhydride (25 c.c.), and adding sodium acetate. The acetyl compound which separated was purified as in the case of its isomeride, and formed white anhydrous prisms having similar solubilities (Found: As, 31.3; N, 5.7. $C_8H_8O_3NAs$ requires As, 31.1; N, 5.8%).

3-Acetamido-4-hydroxy- and 5-Acetamido-2-hydroxy-phenyldichloroarsines.—These derivatives were obtained by trituration of the corresponding arsenoxide with excess of alcoholic hydrogen chloride. On spontaneous evaporation, crystals of the dichloro-arsine were obtained, which were purified by solution in alcohol and precipitation by ether. They formed white or pale yellow needles, soluble in cold alcohol and in cold water; the latter hydrolysed them slowly to give the corresponding arsenoxide (Found, for *3-acetamido-4-hydroxyphenyldichloroarsine*: As, 25.1; N, 4.7; Cl, 24.1; for *5-acetamido-2-hydroxyphenyldichloroarsine*: As, 25.1; N, 4.8; Cl, 24.0. $C_8H_8O_2NCl_2As$ requires As, 25.1; N, 4.75; Cl, 24.0%).

3-Nitro-4-hydroxy-5-aminophenyldi-iodoarsine hydriodide, made from the corresponding arsenic acid (compare Fourneau, *loc. cit.*) by the general method, consisted of yellow prisms, dissolving in water to give a yellow and in alkali carbonate or hydroxide to give red solutions (Found: As, 12.1; N, 5.0; I, 58.5. $C_6H_5O_3N_2I_2As$ requires As, 12.3; N, 4.6; I, 62.4%). On acetylation in alkaline solution, it gave *3-nitro-4-hydroxy-5-acetamidophenylarsenoxide*, an amorphous, white solid, insoluble in water and giving deep red solutions with caustic alkalis (Found: As, 25.8. $C_8H_7O_5N_2As$ requires As, 26.2%).

3-Acetamido-4-hydroxy- and 5-Acetamido-2-hydroxy-phenylmethoxychloroarsines.—To the corresponding arsenoxide (4.8 g.), dissolved at room temperature in methyl alcohol (90 c.c.), 15% methyl-alcoholic hydrogen chloride (2.4 c.c.) was added, the solution kept for 30 mins., and concentrated under reduced pressure to 10 c.c.; the methoxychloro-compound then crystallised out (yield, 70% in each case). *3-Acetamido-4-hydroxyphenylmethoxychloroarsine* (Found: As, 25.8; N, 4.8; Cl, 12.2%) and *5-acetamido-2-hydroxyphenylmethoxychloroarsine* (Found: As, 25.7; N, 5.0; Cl, 12.2; MeO, 10.3. $C_9H_{11}O_3NClAs$ requires As, 25.7; N, 4.8; Cl, 12.2; MeO, 10.6%) each consisted of white prisms, readily converted by warm water into the corresponding arsenoxide.

3-Acetamido-4-hydroxyphenylarsine.—A mixture of 3 : 3'-diamino-4 : 4'-dihydroxyarsenobenzene (5 g.) and zinc dust (16 g.) was added to concentrated hydrochloric acid (70 c.c.) and water (50 c.c.) at 90—100°; after cooling, the clear supernatant liquid was filtered into a solution of sodium acetate (20 g.) in water (20 c.c.) containing acetic anhydride (15 c.c.) in suspension. On shaking, *3-acetamido-4-hydroxyphenylarsine* separated in 90% yield (Found : As, 33.0; N, 6.3. $C_8H_{10}O_2NAs$ requires As, 33.0; N, 6.2%); it formed white plates, insoluble in water but soluble in excess of caustic alkalis.

5-Acetamido-2-hydroxyphenylarsine, similarly prepared from the corresponding arsenobenzene, also forms white plates (Found : As, 32.8; N, 6.3%). Both arsines are readily oxidised by air to the corresponding arseno-compound.

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