CCLXIV.—*Aromatic Arsenic Compounds containing Sulphur Groups attached to the Nucleus. Part I. Sulphonic Acids and their Derivatives.*

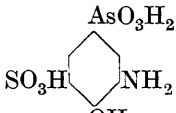
By Harry James Barber.

The possibility that the trypanocidal activity of arsenic compounds is in some way connected with the thiol group present in animal tissue makes the preparation of such compounds containing sulphur groups, and thiol groups in particular, of considerable interest. The object of this work is the systematic investigation of the applicability to arsenic compounds of the methods available for the introduction and transformation of sulphur groups, and, since the sulphonic acids are the most generally useful starting points, they form the subject of Part I of this series.

Leuckardt's xanthate method (*J. pr. Chem.*, 1890, **41**, 179) was used by Hewitt, King, and Murch (J., 1926, 1369) to obtain *p*-sulphophenylarsinic acid, and 3-amino-4-hydroxy-5-sulphophenylarsinic acid (I) was isolated by King (J., 1921, **119**, 1108, 1416) as a by-product in the reduction of 3-nitro-4-hydroxyphenylarsinic acid by sodium hyposulphite, being formed probably by rearrangement of an intermediate sulphamic acid (Christiansen, *J. Amer. Chem. Soc.*, 1922, **44**, 2334). Krishna and Krishna (*J. Indian Chem. Soc.*, 1929, **6**, 666) claim to have obtained 3-sulphophenylarsinic acid by applying Béchamp's direct arsenation method to benzenesulphonic acid. As this method is usually only applicable to amines and phenols which readily undergo direct substitution, and as 3-sulphophenylarsinic acid has now been prepared by the xanthate method and found to present no difficulties in isolation as suggested by Krishna and Krishna, it seems unlikely to have been formed by Béchamp's method. Moreover, in this present work the arsenation of phenol-*p*-sulphonic acid, a substance much more likely to react in this way, was attempted without success.

From experiments with a number of different types of arylarsinic acids, it seems probable that direct sulphonation only occurs with the simple hydroxyphenylarsinic acids. Thus, 4-hydroxy- and 2 : 4-dihydroxy-phenylarsinic acids give *monosulphonic acids* which, in the absence of a satisfactory means of orientation, are represented as (II) and (III) by analogy with the corresponding nitration products.

4-Amino-, 4-acetamido-, 3-hydroxy-4-acetamido-, and 4-chlorophenylarsinic acids all failed to give sulphonation products even under most drastic conditions. The use of chlorosulphonic acid (J., 1922, **121**, 2555) has no advantages over sulphuric acid since,



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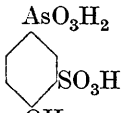

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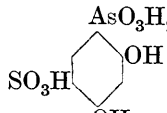

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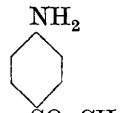


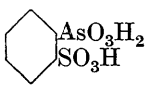
(IV.)

in the case of the hydroxyphenylarsinic acids, the sulphonyl chlorides, if formed, are soluble in water and rapidly hydrolysed, so the products isolated are the sulphonic acids.

The Bart reaction appears not to be applicable to aminophenylsulphonic acids, although in the only case examined, *viz.*, *p*-aminophenylmethylsulphone (IV), the corresponding sulphone reacts normally. The failure may be due to the strongly negative group present : 2 : 4-dinitroaniline will not give the arsinic acid if the Bart reaction is carried out in the usual manner.

The action of sodium sulphite on the various halogenophenylarsinic acids in which the halogen has been found to be reactive (Barber, J., 1929, 2334) has been investigated. Of these, 2-iodo- and 2-*iodo*-5-*aminophenylarsinic acid* gave the corresponding *sulphonic acids*, (V) and (VI). The reaction between sulphite and the halogenonitrophenylarsinic acids does not proceed normally and satisfactory products have not been obtained. 2-Bromo- and 4-iodo-phenylarsinic acids both failed to react under the present conditions.

2-Sulphophenylarsinic acid is remarkably stable towards hydrolysis, being unchanged by boiling with 25% sulphuric acid or sodium hydroxide solution. Treatment of the sodium salt with a



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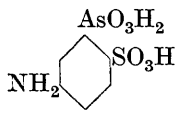

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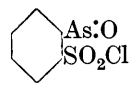

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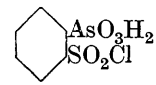
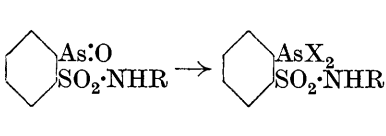


(VIII.)

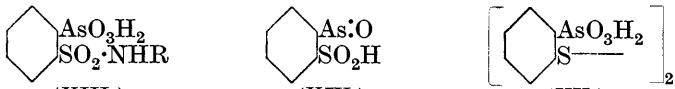
mixture of phosphorus trichloride and pentachloride and subsequent partial hydrolysis gives 2-*chlorosulphonylphenylarsenious oxide*

(VII), which is converted into the *arsinic acid* (VIII) by oxidation with cold hydrogen peroxide. With ammonia and amines, the sulphonyl chloride (VII) forms sulphonamides (IX; R = H, Ph) which are remarkable in being soluble in organic non-hydroxylic solvents; it seemed probable that they had the cyclic structure (X) analogous to the saccharin ring system and to the imide derived from benzene-*o*-disulphonic acid (Hurtley and Smiles, J., 1926, 1822). With hydrogen iodide or thiolacetamide, this cyclic system should, unless ring fission occurs, give rise to the monosubstituted derivatives (XI; X = I or S·CH_2·CO·NH_2), but actually the normal *di-iodoarsine* or the *phenylthioarsinite* (XII) is formed. Moreover,



(IX.) (XII.) (X.) (XI.)

these sulphonamides are readily oxidised by iodine or hydrogen peroxide to the arsinic acids (XIII).



(XIII.) (XIV.) (XV.)

Reduction of the sulphonyl chloride (VII) with sodium sulphite produces 2-*sulphinophenylarsenious oxide* (XIV). This behaves abnormally in giving no colour reaction with anisole and concentrated sulphuric acid, in giving no iron salt with acid ferric chloride (J., 1909, **95**, 342), and in not reacting with nitrous acid to give a disulphohydroxylamine (Koenigs, *Ber.*, 1878, **11**, 615). Further, it is unusually stable in acid solution, being transformed very slowly into a mixture of disulphide and disulphoxide which on mild oxidation gives the arsinic acid (XV). It forms a normal *silver* salt which, with methyl iodide, gives the sulphone, and this is oxidised by iodine to 2-*methylsulphonylphenylarsinic acid.* The sulphinic acid appears to react with quinones and this reaction and others are being investigated with a view to obtain the arsenic analogues of the thioxanthone and thionaphthen derivatives obtainable from 2-sulphinobenzoic acid (Price and Smiles, J., 1928, 2860, 3155).

EXPERIMENTAL.

3-*Sulphophenylarsinic Acid.*—3-Aminophenylarsinic acid was diazotised and treated with a solution of potassium ethyl xanthate exactly as described for the 4-isomeride (King, *loc. cit.*). The yield

was poor and no disulphide was encountered as an intermediate stage in the oxidation. The product was isolated as a somewhat soluble barium salt, from which the free *acid* was obtained in the usual way as large colourless prisms extremely soluble in water but sparingly soluble in glacial acetic and concentrated mineral acids (Found: As, 26·4; S, 11·7. $C_6H_7O_6SAs$ requires As, 26·6; S, 11·35%).

Attempted arsenation of phenol-*p*-sulphonic acid was carried out in the usual way at 140—150° with crystalline arsenic acid, and the reaction mixture worked up to give barium salts, but only that of the phenolsulphonic acid could be obtained, no arsenation having occurred.

3-*Sulpho*-4-*hydroxyphenylarsinic Acid* (II).—4-Hydroxyphenylarsinic acid (30 g.) was heated for 1½—2 hours at 100° with concentrated sulphuric acid (120 c.c.), and the whole then poured into water (2 litres). After being neutralised with barium carbonate, filtered and evaporated, the liquor deposited the barium salt of the required acid. After removal of the barium as sulphate and concentration of the liquors to small bulk, the *acid* was obtained; it was freed from adhering mother-liquor with glacial acetic acid, in which it is nearly insoluble; yield 15 g. (Found: As, 25·2; S, 11·25. $C_6H_7O_7SAs$ requires As, 25·2; S, 10·75%). It is extremely soluble in water, giving a strongly acid solution, with which ferric chloride gives a wine-red colour.

5-*Sulpho*-2 : 4-*dihydroxyphenylarsinic Acid* (III).—2 : 4-Dihydroxyphenylarsinic acid (*Ber.*, 1915, **48**, 515) was sulphonated exactly as above; the *sulpho-acid* has similar properties to the monohydroxy-compound and also gives a red colour with ferric chloride (Found: As, 23·4; S, 10·35. $C_6H_7O_8SAs$ requires As, 23·8; S, 10·2%).

4-*Methylsulphonylphenylarsinic Acid*.—4-Aminophenylmethylsulphone when submitted to the Bart reaction gave the required *acid* (36% yield) (Found: As, 26·1; S, 11·9. $C_7H_9O_5SAs$ requires As, 26·8; S, 11·4%).

2-*Sulphophenylarsinic Acid* (V).—An aqueous solution of sodium 2-iodophenylarsinate (350 g.), sodium sulphite (140 g.), and copper acetate (trace) was concentrated until it had b. p. 106—110°, and was then boiled under reflux for an hour. The solution was diluted with water (*ca.* 3 litres), heated to boiling, and filtered (charcoal), and a hot solution of barium chloride (260 g.) was added. The *barium* salt at once crystallised as plates, and was filtered off hot and dried; yield 385—395 g. (90—95%) (Found: As, 17·6. $C_6H_5O_6SAsBa$ requires As, 18·0%). The *sulphonic acid* was obtained from this salt in the usual way as large prisms extremely

soluble in water (200%) and alcohol, sparingly soluble in concentrated hydrochloric acid, in 25% sulphuric acid (5%), and in glacial acetic acid (1%); it was recrystallised from the last solvent (Found: As, 26·7; S, 11·6. $C_6H_7O_6SAs$ requires As, 26·6; S, 11·35%). It titrates as a dibasic acid (litmus), and when it is boiled with hydrogen iodide (1 g. in 10 c.c.) for a few minutes arsenious iodide begins to separate.

2-*Iodo*-5-*aminophenylarsinic Acid.*—2-Iodo-5-nitrophenylarsinic acid (J., 1929, 2336; 20 g.) reduced at 50° with ferrous hydroxide gave the required *amino*-compound in 65% yield; this forms prisms from 50% acetic acid (Found: As, 21·8; N, 4·0; I, 34·0. $C_6H_7O_3NIAs$ requires As, 21·8; N, 4·1; I, 34·1%). The *acetyl* derivative forms monohydrated diamond-shaped plates from 50% acetic acid (Found: As, 18·4; H_2O, 4·6. $C_8H_9O_4NIAs,H_2O$ requires As, 18·6; H_2O, 4·5%).

The preparation of 2-iodo-4-hydroxy- and -4-acetamido-phenylarsinic acids was attempted by applying the Sandmeyer reaction to the corresponding amino-compounds (compare J., 1929, 2335), but in each case rapid elimination of arsenic occurred.

2-*Sulpho*-5-*aminophenylarsinic acid* (VI) was obtained from the iodo-arsinic acid as for (V), but was isolated directly by acidification of the diluted reaction mixture. It forms fibrous needles sparingly soluble in water (Found: As, 25·0; S, 11·0. $C_6H_8O_6NSAs$ requires As, 25·2; S, 10·75%). The acetyl derivative was formed both by the action of acetic anhydride and also from 2-iodo-5-acetamidophenylarsinic acid with sodium sulphite, but was contaminated with the amino-compound owing to the extreme ease with which it hydrolyses. It forms colourless prisms readily soluble in cold water.

2-*Chlorosulphonylphenylarsenious Oxide* (VII).—Sodium 2-sulphophenylarsinate (20 g.) was ground with phosphorus trichloride (10 c.c.), and the pentachloride (40 g.) was added in small quantities as the vigorous reaction moderated. After standing for ½ hour, the mass was treated with crushed ice and after a further hour the oily product was separated. This substance was soluble in most organic solvents and was probably 2-*chlorosulphonylphenylchlorohydroxyarsine* (Found: Cl, 21·9. $C_6H_5O_3Cl_2SAs$ requires Cl, 23·4%). It did not solidify on standing in a vacuum desiccator at 0° for several days. It is slowly hydrolysed by cold water to the arsenious oxide, and if its acetone solution is poured into a large volume of cold water, the required 2-*chlorosulphonylphenylarsenious oxide* separates as a white microcrystalline powder, insoluble in water and organic solvents (yield 11—12 g.; 70—75%) (Found: As, 27·8; Cl, 13·7. $C_6H_4O_3ClSAs$ requires As, 28·1; Cl, 13·4%).

2-*Chlorosulphonylphenylarsinic Acid* (VIII).—The above oxide (2 g.) was suspended in hydrogen peroxide solution (25 c.c.; 6%) until it was all converted (*ca.* ½ hour) into the crystalline *arsinic acid* (prisms); yield 1 g. (Found: As, 25·1; Cl, 11·7. $C_6H_6O_5ClSAs$ requires As, 25·0; Cl, 11·8%). The transformation is readily followed by microscopic examination.

2-*Sulphonamidophenylarsinic Acid* (XIII; R = H).—The sulphonyl chloride (2 g.) was treated with ammonia (5 c.c.; *d* 0·880) and, when solution was complete, with hydrogen peroxide solution (6 c.c.; 6%). On acidification, the *acid* crystallised in square plates (Found: As, 26·2. $C_6H_8O_5NSAs$ requires As, 26·6%). The *thiolacetamide* derivative had m. p. 171—173° (Found: *M*, 396. $C_{10}H_{14}O_4N_3S_3As$ requires *M*, 411).

2-*Sulphonanilidophenylarsenious Oxide* (IX; R = C_6H_5).—The sulphonyl chloride (1 g.) was treated with aniline (3 c.c.), warmed until solution was complete, and the mixture added to excess of dilute sulphuric acid. The *oxide* was collected and purified by solution in ammonia and precipitation by sulphuric acid (Found: As, 23·0. $C_{12}H_{10}O_3NSAs$ requires As, 23·2%). It is a white amorphous powder soluble in alkalis, alcohol, acetic acid, benzene, and ether. With thiolacetamide it gives *di*(*carbamidomethyl*) 2-*sulphonanilidophenylthioarsinite* (XII; R = C_6H_5, X = $S{\cdot}CH_2{\cdot}CO{\cdot}NH_2$) (Found: *M*, 485. $C_{16}H_{18}O_4N_2S_3As$ requires *M*, 487).

2-*Sulphonanilidophenyldi-iodoarsine* (XII; X = I).—The oxide, suspended in excess of hydriodic acid (*d* 1·7), was treated with just sufficient ether to give a homogeneous solution, and gently warmed to expel the solvent; the *di-iodoarsine* crystallised in yellow prisms (Found: I, 45·0. $C_{12}H_{10}O_2NI_2SAs$ requires I, 45·3%).

2-*Sulphonanilidophenylarsinic acid* (XIII; R = C_6H_5), obtained by oxidation of the oxide (IX) or by the action of aniline on (VIII), forms square plates from 50% acetic acid (Found: As, 20·6. $C_{12}H_{12}O_5NSAs$ requires As, 21·0%).

2-*Sulphinophenylarsenious Oxide* (XIV).—The sulphonyl chloride (VII) (12 g.) was shaken with anhydrous sodium sulphite (20 g.) in water (200 c.c.) until solution ensued, slight alkalinity being maintained by addition of sodium carbonate solution. On strong acidification with 50% sulphuric acid, the product crystallised in white prisms; yield 8·5 g. (80%) (Found: As, 32·3; S, 14·25. $C_6H_5O_3SAs$ requires As, 32·3; S, 13·8%). The *acid* absorbs 2 atoms of iodine on titration in bicarbonate solution. It gives no colour or precipitate with ferric chloride solution and is recovered unchanged on acidification of an alkaline solution containing sodium nitrite. The *silver* salt (Found: Ag, 31·1. $C_6H_4O_3SAsAg$

requires Ag, 31·8%) was obtained as a white amorphous precipitate on addition of the calculated quantity of silver nitrate to a hot neutral solution of the acid in ammonia; it reacted readily when refluxed with methyl iodide in methyl-alcoholic solution for ½ hour. On removal of silver iodide and oxidation of the product in the usual way, *2-methylsulphonylphenylarsinic acid* was obtained in colourless prisms (Found: C, 30·4; H, 3·5. $C_7H_9O_5SAs$ requires C, 30·0; H, 3·2%).

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