CCCCXIII.—*Heterocyclic Compounds containing Arsenic. Part IV. Carbamido-derivatives of Arylarsinic Acids.*

By RALPH WILLIAM EWART STICKINGS.

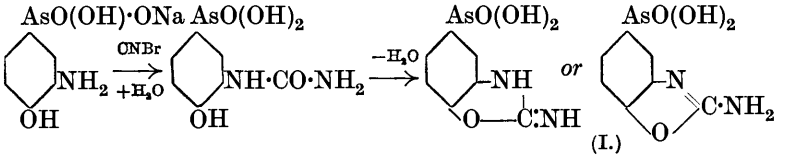
IN an attempt to prepare some guanidine derivatives of aromatic arsinic acids, the well-known reaction between a primary amine and a cyanogen halide was employed :

$$R{\cdot}NH_2 + CNBr \longrightarrow R{\cdot}NH{\cdot}CN + HBr.$$
$$R{\cdot}NH{\cdot}CN + R{\cdot}NH_2,HBr \longrightarrow (R{\cdot}NH)_2C{:}NH,HBr.$$

p-Arsanilic acid and cyanogen bromide, however, would not react in presence of benzene, even when boiling. Sodium *p*-arsanilate reacted rapidly with an aqueous suspension of cyanogen bromide in the cold, yielding, not a guanidine derivative, but p-*carbamidophenylarsinic acid*; of the two g.-mols. of arsanilate employed, one was recovered unchanged :

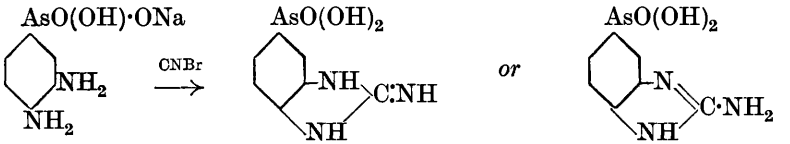
$$NH_2{\cdot}C_6H_4{\cdot}AsO(OH){\cdot}ONa + CNBr + H_2O = NH_2{\cdot}CO{\cdot}NH{\cdot}C_6H_4{\cdot}AsO(OH)_2 + NaBr.$$

No intermediate cyanamide derivative could be isolated, and it was subsequently found that this reaction was a general one with aminoarylarsinic acids. In cases where the primary amino-group is in the ortho-position to another reactive constituent group, *e.g.*, (OH) or (NH_2), the reaction proceeds further with ring formation :



(I.)

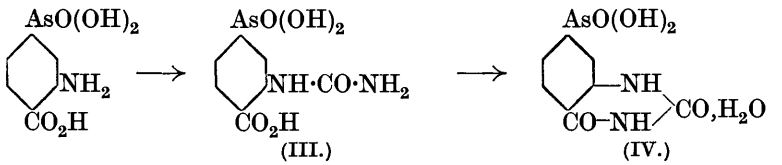
Similarly



(II.)

These heterocyclic compounds are soluble in mineral acids and in alkalis. They probably contain a primary amino-group, since, on diazotisation and boiling, the compound (I) yields a hydroxy-derivative. With compound (II), however, the reaction appeared to go further, the only product isolated being the original diaminophenylarsinic acid.

If the parent arsinic acid contains a carboxyl group ortho to the amino-group, a compound is produced by the action of cyanogen bromide and water which has the properties of a diketotetrahydroquinazoline. It is insoluble in mineral acids, is not decomposed by prolonged heating with concentrated sodium hydroxide solution or 50% sulphuric acid, and on reduction with sodium hydrosulphite gives an arseno-compound insoluble in sodium hydroxide solution. On the other hand, analysis gives figures which indicate the presence of an extra molecule of water, which cannot be removed by prolonged drying in a vacuum at 110°. It appears, therefore, that this molecule of water is attached to one of the carbonyl groups in the heterocyclic nucleus and that the reaction may be represented thus :

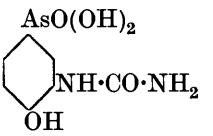


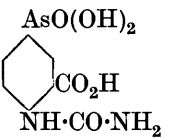
(III.) (IV.)

It is inconceivable that prolonged boiling with concentrated alkali solution or acid would fail to liberate ammonia and carbon dioxide from a substituted carbamide of the type (III).

Methods (Farbwerke vorm. Meister, Lucius, & Brüning, U.S.P. 1077462, D.R.-P. 213155) for the preparation of carbamidoarylarsinic acids by the potassium cyanate method lead, according to their authors, to simple carbamide derivatives such as (V) and (VI).

(V.)





(VI.)

This work has been confirmed in the case of (V); the compound isolated differs in properties, as would be expected, from the condensation product (I) obtained by means of cyanogen bromide.

Further work is in progress to elucidate the course of the reaction which produces these heterocyclic arsinic acids, as it has been found difficult to convert (V) into (I) by formation of the heterocyclic nucleus. An attempt is also being made to synthesise (IV) by introducing the arsinic acid group at the final stage by the Bart method.

The trypanocidal action of these compounds and of further derivatives thereof has been studied and will be reported elsewhere.

EXPERIMENTAL.

p-*Carbamidophenylarsinic Acid* (compare D.R.-P. 213155).—A solution of 108 g. of *p*-arsanilic acid in aqueous sodium hydroxide (20 g. in 500 c.c. of water) and a freshly prepared suspension of 106 g. of cyanogen bromide in 300 c.c. of water were mixed and stirred; a crystalline precipitate gradually formed and the odour of cyanogen bromide disappeared. Next day, the mixture was acidified to Congo-red with concentrated hydrochloric acid. The precipitate was collected, redissolved in aqueous sodium hydroxide, and, after the solution had been made neutral and treated with charcoal, re-precipitated with hydrochloric acid; yield, 89 g. (Found: As, 28·7; N, 10·8. $C_7H_9O_4N_2As$ requires As, 28·8; N, 10·8%). The product crystallised from hot water in glistening needles. It was sparingly soluble in cold water or organic solvents, insoluble in dilute mineral acids, and readily soluble in hot water and in caustic alkali or alkali carbonate solutions. Warming with sodium hydroxide solution liberated ammonia, and the solution on acidification with acetic acid gave carbon dioxide and *p*-arsanilic acid.

5-*Carbamido*-2-*hydroxyphenylarsinic Acid*.—5-Amino-2-hydroxyphenylarsinic acid (Fourneau, Tréfouel, and Bénoit, *Bull. Soc. chim.*, 1927, **41**, 449) (117 g.) was treated exactly as described above with 106 g. of cyanogen bromide. The product obtained on acidification was decolorised by isolation of the sodium salt and regeneration of the acid. Yield, 64 g. of white, needle-shaped crystals, soluble in hot water and in alkalis, insoluble in mineral acids (Found: As, 27·0; N, 10·3. $C_7H_9O_5N_2As$ requires As, 27·2; N, 10·1%).

1-*Aminobenzoxazole*-4-*arsinic Acid* (I).—The reaction between 3-amino-4-hydroxyphenylarsinic acid (117 g., dissolved in a solution of 20 g. of sodium hydroxide in 500 c.c. of water) and 120 g. (excess) of cyanogen bromide was complete in about 1 hour. After the addition of 10 c.c. of glacial acetic acid, the rather dark precipitate was collected and dissolved in 20% sodium hydroxide solution, which was then cooled and treated with an excess of sodium chloride. Next day, the thick mass of crystals obtained was washed with brine and decolorised in 400 c.c. of hot water with charcoal. Acidification with excess of acetic acid gave 88 g. of white prismatic needles (Found: As, 28·9; N, 10·7. $C_7H_7O_4N_2As$ requires As, 29·1; N, 10·8%).

The new *acid* is soluble in dilute mineral acids and in alkalis and sparingly soluble in hot or cold water. It is only slowly decomposed by boiling concentrated aqueous caustic alkali.

2-*Aminobenziminazole*-5-*arsinic Acid* (II).—3 : 4-Diaminophenyl-

arsinic acid (Bertheim, *Ber.*, 1911, **44**, 3095) (116 g.) was treated exactly as described in the preceding preparation. The *product*, also purified in the same way, formed white, slender needles (55 g.), moderately easily soluble in hot water and readily soluble in dilute mineral acids or alkalis (Found : As, 29·0; N, 16·1. $C_7H_8O_3N_3As$ requires As, 29·2; N, 16·3%).

1-*Amino*-6-*acetamidobenzoxazole*-4-*arsinic Acid*.—A neutral solution of 28 g. of 3-amino-5-acetamido-4-hydroxyphenylarsinic acid (this vol., p. 2376) in dilute aqueous sodium hydroxide was diluted to 150 c.c. and added rapidly to an aqueous suspension of cyanogen bromide freshly made from 18 g. of bromine, and the whole was well stirred. After 1 hour, the product was acidified with acetic acid in excess and the brown crystals obtained were treated in alkali solution with charcoal and reprecipitated as white, prismatic needles (20 g.), readily soluble in dilute mineral acids and in alkalis (Found : As, 23·2; N, 13·2. $C_9H_{10}O_5N_3As$ requires As, 23·8; N, 13·3%).

2 : 4-*Diketo*-1 : 2 : 3 : 4-*tetrahydro*-1 : 3-*quinazoline*-7-*arsinic Acid* (IV).—3-Amino-4-carboxyphenylarsinic acid (26 g.) in neutral solution was similarly treated with cyanogen bromide (from 15 g. of bromine) and left for 1 hour in a warm place. The crystalline precipitate obtained on acidification (to Congo-red) with hydrochloric acid was recovered, after the usual purification with charcoal, in white prisms (18 g.), which were dried at 110° (Found : As, 24·4; N, 9·3. $C_8H_7O_5N_2As$ requires As, 26·2; N, 9·8%. $C_8H_7O_5N_2As,H_2O$ requires As, 24·7; N, 9·2%).

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