CXXIV.—*Heterocyclic Compounds containing Arsenic. Part I. The Action of Chloroacetamide on* 3 : 4-*Diaminophenylarsinic Acid.*

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In the course of investigations in connexion with the chemotherapy of organic arsenical derivatives, our attention was recently directed to a communication by Lewis and Bent (*J. Amer. Chem. Soc.*, 1926, **48**, 949) in which the action of chloroacetamide on 3 : 4-diaminophenylarsinic acid (I) is discussed. These authors consider

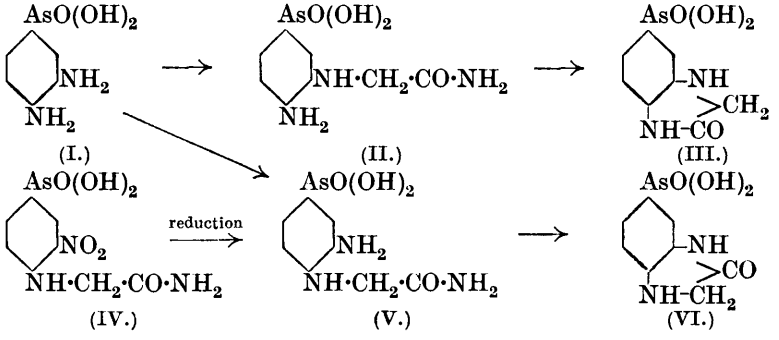
that under their conditions of experiment chloroacetamide reacts preferentially with one amino-group with the production of 3-aminophenylarsinic acid 4-glycineamide (V). They state also that, if the reaction be not carefully controlled, ring closure takes place with elimination of water and the formation of a quinoxaline derivative, $(HO)_2OAs{\cdot}C_6H_3{<}\begin{matrix}N{=}C{\cdot}NH_2\\ NH{\cdot}CH_2\end{matrix}$, the reaction being analogous to the formation of a phenylquinoxaline from ω-bromoacetophenone and *o*-phenylenediamine (Fischer and Romer, *Ber.*, 1908, **41**, 2350). The reaction is suggested as a new method of preparing quinoxalines containing an amino-group.

The production of 3-aminophenylarsinic acid 4-glycineamide is of interest, as this compound is a derivative of tryparsamide, phenylarsinic acid 4-glycineamide, which is a product of considerable therapeutic value.

One of us (R. W. E. S.) had already attempted the preparation of the amino-derivative of tryparsamide by reduction of the corresponding nitro-compound (IV), but the experiments invariably resulted in the production of what we were able to show was 3-*hydroxy*-1 : 4-*dihydroquinoxaline*-6-*arsinic acid* (VI).

We were therefore led to repeat the work of Lewis and Bent (*loc. cit.*) and we were unable to confirm their conclusions. Following the directions given on p. 955 of their paper, we obtained a product which we were able to show consisted of a mixture of two isomeric hydroxydihydroquinoxalinearsinic acids, one of which was identical with that produced by the reduction of 3-nitrophenylarsinic acid 4-glycineamide.

It seems obvious, therefore, that chloroacetamide reacts with both amino-groups of 3 : 4-diaminophenylarsinic acid, ring closure taking place in each case with elimination of ammonia and formation of a quinoxaline derivative according to the following scheme, the intermediate amino-derivatives (II and V) being unstable.



The formation of these quinoxalines has been confirmed by analysis. Lewis and Bent apparently only determined the percentage of arsenic in their product. Determination of nitrogen would have undoubtedly shown them the true nature of the compound produced.

The constitution of 3-hydroxy-1 : 4-dihydroquinoxalinearsinic acid (VI) is established by its identity with the product obtained by reduction of 3-nitrophenylarsinic acid 4-glycineamide (IV). It is therefore highly probable that (III) has the constitution denoted, and experiments are in progress to establish this by synthetic methods also.

EXPERIMENTAL.

Action of Chloroacetamide on 3 : 4-Diaminophenylarsinic Acid.—Following the procedure outlined by Lewis and Bent (*loc. cit.*), 25 g. of 3 : 4-diaminophenylarsinic acid were dissolved in a solution of 4·1 g. of sodium hydroxide in 105 c.c. of water, 19·4 g. of chloroacetamide were added, and the mixture was boiled under reflux for 45 minutes. Concentrated hydrochloric acid (7·8 c.c.) was added to the cooled solution. A crystalline solid readily separdate which was seen under the microscope to consist of a mixture of long, fine needles and tetrahedra. The product was in part somewhat readily soluble in hot water, completely soluble in dilute alkali solution, and insoluble in dilute mineral acids. Treatment with caustic soda solution produced only a trace of ammonia. The crude product was purified by reprecipitation from dilute sodium carbonate solution after treatment with charcoal (yield, 15 g.) (Found : As, 27·5; N, 10·5. $C_8H_9O_4N_2As$ requires As, 27·6; N, 10·3%).

Separation of the Isomeric Quinoxalines.—The product (12 g.) was boiled with successive quantities (50, 25, 25, 25 c.c.) of water, the hot extracts were combined, and the crystalline product obtained on cooling was repeatedly crystallised from water, being finally obtained in long, nearly white, prismatic needles, which did not decompose at 260°. Analysis indicated it to be 3-*hydroxy*-1 : 4-*dihydroquinoxaline*-6-*arsinic acid* (VI) (Found : As, 27·4; N, 10·35%).

A *monobenzoyl* derivative was obtained by the Schotten–Baumann method. It crystallised from 50% alcohol, in which it was readily soluble, in lustrous, hexagonal plates, which did not decompose below 290° (Found : As, 19·85; N, 7·45. $C_{15}H_{13}O_5N_2As$ requires As, 20·0; N, 7·4%).

3-Hydroxy-1 : 4-dihydroquinoxaline-6-arsinic acid was readily obtained again on boiling the monobenzoyl derivative with 5% sodium hydroxide solution for 15 minutes.

2-*Hydroxy*-1 : 4-*dihydroquinoxaline*-6-*arsinic acid* (III) was ob-

tained by purification of the less soluble fraction (about 6·8 g.) left after extraction of the original mixture with hot water. Owing to the general insolubility of the compound in neutral solvents, purification was effected by means of the sodium salt. The acid was dissolved in just sufficient sodium carbonate solution to produce a neutral or faintly alkaline solution. To the hot filtered solution alcohol was added gradually until crystallisation of the sodium salt commenced. On standing, a semi-solid crystalline mass of needles was obtained. The crystals were filtered off, washed with a little alcohol, and dissolved in hot water, and the hot solution was made just acid to Congo-red. On standing, the *acid* separated in diamond-shaped plates, m. p. 258° (decomp.) (Found : As, 27·7; N, 10·4%).

A *monobenzoyl* derivative was obtained in the usual way. The alkaline reaction product was made just acid to Congo-red with dilute hydrochloric acid, and the precipitated benzoic acid removed in ether. The aqueous solution slowly deposited the *benzoyl* derivative, which crystallised from water in stout, hexagonal plates, m. p. 251—252° (Found : As, 20·1; N, 7·8%).

Nitration of Phenylarsinic Acid 4-Glycineamide.—A solution of 220 g. of the sodium salt of phenylarsinic acid 4-glycineamide in 800 c.c. of concentrated sulphuric acid was cooled to 0° and slowly treated with a mixture of 46 c.c. of nitric acid (*d* 1·42) and 46 c.c. of concentrated sulphuric acid, the temperature being maintained below 5°. After being kept for 30 minutes, the reaction mixture was poured on 1 kg. of ice, 4 litres of water were added, and the whole was stirred; crystallisation then started. After cooling to 0°, the crystals were filtered off, washed free from mineral acid, and dried. The product was an intensely yellow, crystalline substance (yield, 155 g.) soluble in alkalis to a dark red solution (Found : As, 23·4; N, 13·2. $C_8H_{10}O_6N_3As$ requires As, 23·5; N, 13·2%).

Reduction of 3-Nitrophenylarsinic Acid 4-Glycineamide with Ferrous Hydroxide. Production of 3-Hydroxy-1 : 4-dihydroquinoxaline-6-arsinic Acid.—3-Nitrophenylarsinic acid 4-glycineamide (100 g.) was dissolved in 800 c.c. of saturated sodium carbonate solution, and added to a cooled precipitate of alkaline ferrous hydroxide produced by pouring a solution of 300 g. of caustic soda in 400 c.c. of water into a cooled solution of 800 g. of ferrous sulphate in 800 c.c. of water. The temperature of the reduction was maintained at 30° for 1 hour, with occasional stirring, during which a strong smell of ammonia was noticed. The reaction mixture was then filtered, and the yellow filtrate was acidified to Congo-paper by addition of 50% sulphuric acid, crystallisation commencing immediately. After 10 minutes, the crystals were filtered off, washed, and purified by solution in dilute aqueous sodium

carbonate and reprecipitation with excess of mineral acid. The product so obtained was a yellowish-white, crystalline substance, soluble in alkalis and insoluble in mineral acids. No ammonia was evolved on warming it with excess of caustic soda solution. It was moderately easily soluble in boiling water, from which it crystallised in long, prismatic needles which did not decompose below 260° (yield, 45 g.) (Found: As, 27·5; N, 10·4. Calc. for $C_8H_9O_4N_2As$: As, 27·5; N, 10·3%). This substance was identified with the compound (VI) by its crystalline form, solubility, and analysis and also by comparison of the monobenzoyl derivatives.

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