[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

Amidino Arsenicals. II. Some Trivalent Arsenicals

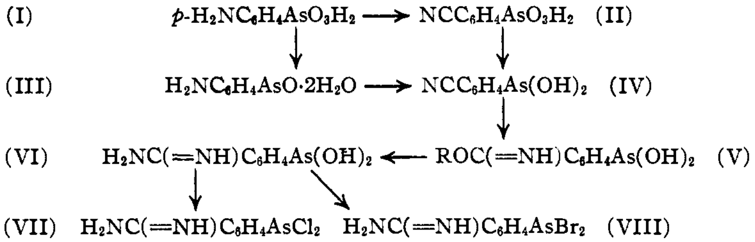
BY FRED LINSKER[1] AND MARSTON TAYLOR BOGERT

In a previous paper,[2] we have described the preparation and some of the properties of *p*-amidinophenylarsonic acid, 4,4′-diamidinoarsenobenzene, and a few intermediate or incidental compounds. The present communication records further progress in the study of the trivalent amidino arsenicals.

Mapharsen and Phenarsine are good examples of the generally recognized greater therapeutic efficiency of the trivalent as compared with the pentavalent arsenicals, the reasons for which need not be discussed here.

The Flow Sheet exhibits the various steps involved in this study.

FLOW SHEET



$$\begin{tikzcd}
\text{(I)} & p\text{-}H_2NC_6H_4AsO_3H_2 \arrow[r] \arrow[d] & NCC_6H_4AsO_3H_2 \arrow[d] & \text{(II)} \\
\text{(III)} & H_2NC_6H_4AsO\cdot 2H_2O \arrow[r] & NCC_6H_4As(OH)_2 \arrow[d] & \text{(IV)} \\
\text{(VI)} & H_2NC(=NH)C_6H_4As(OH)_2 \arrow[d] \arrow[dr] & ROC(=NH)C_6H_4As(OH)_2 \arrow[l] & \text{(V)} \\
\text{(VII)} & H_2NC(=NH)C_6H_4AsCl_2 & H_2NC(=NH)C_6H_4AsBr_2 & \text{(VIII)}
\end{tikzcd}$$

Acknowledgments.—This investigation, like its predecessor, was made possible by the generous action of Merck & Co., Inc., of Rahway, N. J., in establishing at Columbia University a research fellowship for the purpose of finding better medicaments for the treatment of various tropical diseases. The necessary microanalyses were carried out by Miss Frances E. Marx and Miss Lois E. May, of the Columbia University Department of Chemistry.

Experimental

***p*-Cyanophenylarsonous Acid (IV) (a) By Reduction of *p*-Cyanophenylarsonic Acid (II).**—To a solution of 14 g. of *p*-cyanophenylarsonic acid[2] in 220 cc. of water and 32 cc. of 2 *N* sodium hydroxide, there was added 3.2 g. of potassium iodide. The clear solution was acidified with 84 cc. of dilute (16% by volume) sulfuric acid, cooled to below 10°, and sulfur dioxide passed through the solution for three hours at the rate of 3 bubbles per second, while the temperature was not permitted to rise above 10°. A yellow precipitate soon began to separate, and gradually increased in amount. When the reduction was complete, the flask was removed, stoppered tightly and left in the refrigerator overnight. The yellow-brown crystalline precipitate was filtered out, and consisted of 11 g. (85% yield) of quite pure *p*-cyanophenylarsonous acid. It was further purified by solution in *N* sodium hydroxide and reprecipitation with 5 *N* ammonium chloride solution, washing the precipitate with water until it gave no test for chlorine ion, and then drying in a desiccator over calcium chloride. It formed pale yellow-brown small prisms, which softened at 230° and melted with decomposition at 234° (cor.).

Anal. Calcd. for $C_7H_6O_2AsN$: As, 35.5; N, 6.6. Found: As, 35.3; N, 6.6.

This process is preferable to the succeeding one in that it gives a purer product.

(b) **From *p*-Aminophenylarsine Oxide Dihydrate (III).**—The arsine oxide dihydrate was prepared from *p*-arsanilic acid by reduction with sulfur dioxide, as described by Ehrlich and Bertheim[3]; yield, 71%; melts with decomposition at 98° (literature, yield, about 71%; m. p. with decomposition, 100°).

A solution of 11 g. of the arsine oxide dihydrate (III) in 120 cc. of water and 13 cc. of hydrochloric acid (sp. gr. 1.12) was cooled to 5° and diazotized with 17 cc. of a 3 *N* sodium nitrite solution. During the diazotization a pale yellow precipitate formed but was not removed. The diazotized mixture was poured slowly into a cuprous cyanide solution prepared from 12.5 g. of copper sulfate pentahydrate, 14 g. of potassium cyanide, and 75 cc. of water. The mixture was warmed until the evolution of nitrogen ceased. After cooling for three hours in the refrigerator, the brown solid which had precipitated was removed, washed with dilute hydrochloric acid and dried; yield, 13 g. Since this crude product was contaminated by considerable copper, it was dissolved in 170 cc. of *N* sodium hydroxide solution, filtered, and the product reprecipitated from the red filtrate by the addition of 45 cc. of 5 *N* ammonium chloride solution; yield, 9 g. (80%) of pale yellow-brown copper-free *p*-cyanophenylarsonous acid (IV); m. p. 230-240° with decomposition; soluble in caustic or carbonated alkali solutions, or in hot alcohol; insoluble in water, cold alcohol, ether, acetone, or ammonium hydroxide solution. It evolved ammonia when heated with caustic alkalies. The product was identical in all respects with that obtained by the reduction of *p*-cyanophenylarsonic acid.

***p*-Arsonosobenziminoether Hydrochloride (V).**—The base of this compound appears in a list of amide-substituted phenylarsine oxides and their derivatives recently published by Eagle, Hogan, Doak and Steinman [as a note in THIS JOURNAL, **65**, 1236 (1943)] where its analysis is given, as well as its toxicity and treponemicidal activity, and where it is stated that "Experimental details for the preparation of this compound will be published in a separate paper."

As these details have not yet appeared, so far as we are aware, the details of our own experiments were as follows.

To a suspension of 7 g. of dry finely pulverized *p*-cyanophenylarsonous acid (IV) in 40 cc. of dry ether, there was added 3 cc. of absolute alcohol, the mixture was cooled to 0° and dry hydrogen chloride passed through it for thirty minutes. The cyano acid dissolved and the solution assumed a dark red color. The flask was stoppered tightly and placed in the refrigerator. After several hours, crystallization of the imino ether hydrochloride began, and was complete in five days. The grayish crystals were removed, washed with dry ether and excess of hydrogen chloride eliminated in a vacuum desiccator over solid potassium hydroxide. Dissolved in a little cold absolute alcohol and precipitated by dry ether, the hydrochloride separated in colorless prisms; yield, 9.3 g. (95%). This hydrochloride softened at 150° and melted at 152°, with decomposition and foaming, to a dark liquid. It was easily soluble in water or alcohol, insoluble in ether or acetone. Its aqueous solution precipitated silver chloride from a silver nitrate solution, and liberated ammonia when heated with caustic alkali.

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(2) Linsker and Bogert, THIS JOURNAL, **65**, 932 (1943).

(3) Ehrlich and Bertheim, *Ber.*, **43**, 917 (1910).

Anal. Calcd. for $C_9H_{13}O_3AsClN$: N, 4.7. Found: N, 4.7.

***p*-Amidinophenylarsonous Acid Hydrochloride (VI).**—Six grams of finely pulverized iminoether hydrochloride (V) was suspended in 60 cc. of a 10% solution of dry ammonia in absolute alcohol. The suspension was warmed in a closed vessel for four hours at 60°, with frequent shaking. The mixture was filtered, and to the filtrate there was added five times its volume of absolute ether. This threw down the amidine hydrochloride as a white voluminous precipitate, which was filtered out rapidly, to avoid prolonged contact with moist air, and placed immediately in a vacuum desiccator over calcium chloride; yield, 4 g., or 80%. It crystallized in colorless needles when its absolute alcohol solution was concentrated. When heated to 210°, it decomposed with foaming. It was very hygroscopic, soluble in water or alcohol, insoluble in ether or acetone. The sample used for analysis was dried at 60° and 20 mm.

Anal. Calcd. for $C_7H_{10}O_2AsClN_2$: As, 28.3; N, 10.6. Found: As, 28.1; N, 10.7.

Due to its great solubility in water, this acid could not be prepared satisfactorily by the reduction of *p*-amidinophenylarsonic acid with sulfur dioxide.

***p*-Amidinophenyldichloroarsine Hydrochloride (VII).**—A solution of 4 g. of *p*-amidinophenylarsonous acid hydrochloride (VI) in 12 cc. of ice-cold 2 *N* hydrochloric acid was filtered into 30 cc. of concentrated hydrochloric acid cooled to 0°. A crystalline precipitate formed and increased in amount on standing overnight in the icebox. The precipitate was collected, washed with ice-cold concentrated hydrochloric acid, and then left for twenty-four hours over solid sodium hydroxide in a desiccator; yield, 4 g. (89%). For further purification, the product was precipitated from its concentrated aqueous solution with cold concentrated hydrochloric acid, and dried over solid sodium hydroxide at 80° and 20 mm. It was easily soluble in water or alcohol, crystallizing from the latter in small colorless prisms. When heated, it sintered at 202°, and melted at 208° with decomposition.

Anal. Calcd. for $C_7H_8AsCl_3N_2$: N, 9.3. Found: N, 9.2.

***p*-Amidinophenyldibromoarsine Hydrobromide (VIII).**—Two g. of *p*-amidinophenylarsonous acid hydrochloride (VI) was dissolved in 4 cc. of dilute cold hydrobromic acid (2 cc. of concentrated hydrobromic acid to 30 cc. of water). The filtered solution was added to 8 cc. of ice-cold concentrated hydrobromic acid. After the mixture had been standing for several hours at 0°, the pale yellow precipitate was collected and purified by a series of precipitations of its aqueous solution by concentrated hydrobromic acid. The pure salt formed starry clusters of elongated prisms, melting with decomposition at 219°; soluble in water, alcohol, or dilute mineral acids; yield, nearly that calculated. The sample for analysis was dried over solid sodium hydroxide at 80° and 20 mm., in an Abderhalden pistol.

Anal. Calcd. for $C_7H_8AsBr_3N_2$: N, 6.4. Found: N, 6.4.

The compound was soluble in water, alcohol, or dilute mineral acids, and was hygroscopic.

***p*-Arsonobenziminoether Hydrochloride, $ROC(=NH)$-$C_6H_4AsO_3H_2$.**—In our previous article,[2] the formation of this compound from *p*-cyanophenylarsonic acid was described, but the crude product was converted immediately into the corresponding amidino compound.

We have since purified this crude product by drying it *in vacuo* over solid caustic soda, and crystallizing it by concentration of its alcoholic solution. It formed colorless prisms which decomposed at 130° with strong effervescence.

Anal. Calcd. for $C_9H_{13}O_4AsClN$: N, 4.5. Found: N, 4.3.

Summary

1. *p*-Cyanophenylarsonous acid has been prepared by reduction of *p*-cyanophenylarsonic acid, and also from *p*-aminophenylarsine oxide dihydrate by the diazo reaction.

2. This cyano arsonous acid has been converted, through its imino ether, into the *p*-amidinophenylarsonous acid and, from the latter, the *p*-amidinophenyldihalo arsines have been prepared.

3. Certain of these new products are now being tested pharmacologically.

NEW YORK, N. Y. RECEIVED OCTOBER 15, 1943

[CONTRIBUTION FROM VENEREAL DISEASE RESEARCH AND POSTGRADUATE TRAINING CENTER, UNITED STATES PUBLIC HEALTH SERVICE, JOHNS HOPKINS HOSPITAL]

p-Arsenosobenzoylurea and Related Compounds[1]

BY H. G. STEINMAN, G. O. DOAK AND HARRY EAGLE

In previous papers of this series[2] we have described various amide-substituted aromatic arsenoso compounds.[3] Because of the interesting effect of the amide group in modifying the pharmacologic properties of arsenoso compounds we have extended the study to include compounds in which two or more amide groups were connected on a single side chain.

Two methods were used for the preparation of these compounds: namely, (1) the customary Bart reaction or the Scheller modification[4] with the corresponding amines and (2) the coupling of the appropriate dichloroarsinoacyl chlorides with the desired aliphatic amino acids or directly with the amino acid amides when available. All nitro compounds were reduced catalytically to the corresponding amines by the method of Stevinson and Hamilton.[5]

Experimental Part

***p*-Arsenosobenzoylurea.**—*p*-Aminobenzoylurea[6] yielded ***p*-arsonobenzoylurea** with the customary Bart reaction. *p*-Arsenosobenzoylurea was obtained on reduction with

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[1] Paper VI in the Series Entitled "The Preparation of Phenylarsenoxides."

[2] Doak, Steinman and Eagle, THIS JOURNAL, **62**, 3012 (1940); **63**, 99 (1941).

[3] In this and succeeding papers from this Laboratory, wherever practicable, new arsenicals will be named according to the system of nomenclature used in *Chemical Abstracts*.

[4] Scheller, French Patent 624,028, *Chem. Zentr.*, **98**, II, 2229 (1927); Doak, THIS JOURNAL, **62**, 167 (1940).

[5] Stevinson and Hamilton, *ibid.*, **57**, 1298 (1935).

[6] Jacobs and Heidelberger, *ibid.*, **39**, 2418 (1917).