has collected, and though it does not cease to collect, it separates very slowly. One liter of the aqueous liquid is at this point collected separately instead of allowing it to return to the reaction flask, and the boiling continued as before. After boiling for another 8 hours, very little oil separates and the reaction is discontinued. The residue in the flask is distilled as far as possible, and the combined watery distillates distilled until no more oil separates in the condensed liquid. A total of 950 g. of wet oil is obtained; less than 200 g. of residue remains in the reaction vessel after the bulk of the watery acid has been distilled out.

The product is then fractionally distilled, the water being separated from the fore-runs, and the oily portions returned for distillation, until no more water is present. On repeated fractionation of the material thus dried 421 g. of pure trimethylene chlorohydrin boiling at 160° to 162° is obtained; the fore-runs yield 115 g. of trimethylene chloride boiling at 120° to 122°. The intermediate fractions amount to 75 g.; if fractionation were continued they could be resolved into further quantities of the chloride and chlorohydrin. A high boiling fraction of 129 g. was also obtained. This was not examined closely, but probably contains ethereal condensation products.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, HARVARD MEDICAL SCHOOL.]

INDIRECT REDUCTION OF 3-AMINO-4-HYDROXYPHENYL-ARSONIC ACID TO ARSPHENAMINE.

BY WALTER G. CHRISTIANSEN.[1]

Received December 1, 1920.

In a recent paper from this laboratory[2] a method was described for the preparation of arsphenamine by reduction of 3-amino-4-hydroxy-phenyl-arsonic acid with hypophosphorous acid followed by precipitation with hydrochloric acid. Although the product formed a gel with water at room temperature and could be dissolved easily only by warming to 55°, it was of low toxicity. It seems desirable that arsphenamine should dissolve readily in water without warming in order to simplify the technic required in administering the material in medical practise. When a similar reduction was carried out starting with the hydrochloride of 3-amino-4-hydroxy-phenyl-arsenious oxide instead of the arsonic acid, the product, still of low toxicity, was readily soluble in water at room temperature. Owing to the solubility of the oxide base in water[3] this substance is difficult to isolate in the pure state. However, it was found that a solution of the oxide obtained by reduction of the corresponding arsonic acid met our requirements just as well as the purified oxide. After reduction of

[1] This is the second of a series of studies on the properties contributing to the toxicity of arsphenamine being made under a grant from the United States Interdepartmental Social Hygiene Board to the Harvard Medical School; the work is under the general direction of Dr. Reid Hunt, who is also responsible for the biological tests reported in this paper. Additional aid has been received from the Committee of the Permanent Charity Fund, Incorp.

[2] Christiansen, THIS JOURNAL, 42, 2402 (1920).

[3] Ehrlich and Bertheim, *Ber.*, 45, 756 (1912).

the arsonic acid to the oxide in hydrochloric acid solution by means of hydriodic acid and sulfur dioxide[1] and after removal of the sulfur dioxide, hypophosphorous acid was added in order to reduce the oxide to arsphenamine which was then precipitated as the dihydrochloride by pouring into 1:1 hydrochloric acid. The material separated as a slightly orange powder which, after drying *in vacuo* over caustic soda, was readily soluble in water and was of quite low toxicity.

The removal and the method of removal of the sulfur dioxide from the oxide solution is of great importance. If it is not removed, the addition of hypophosphorous acid results in the production of hydrogen sulfide and the precipitation of sulfur. If it is expelled by boiling, the oxide decomposes, and when the next reducing agent is added a small yield of arsphenamine polyarsenide is obtained instead of arsphenamine. During the boiling out of the sulfur dioxide the arylarsenious oxide had been partially decomposed thereby liberating arsenious acid; the boiled solution gives a strong test for a trivalent inorganic arsenical. It is known that the reduction of primary arylarsenious oxides and arylarsonic acids in the presence of arsenites results in the formation of polyarsenides of the above type. However, removal of the sulfur dioxide by aeration gave a solution which was free from inorganic arsenic compounds and which, when reduced with hypophosphorous acid, gave arsphenamine of excellent quality. It was found that by adding sodium arsenite to the aerated oxide solution the same polyarsenide could be secured as from the boiled solution.

In the case of *p*-amino-phenyl-arsenious oxide, heating in acid solution for a minute caused decomposition resulting in p^1,p^2,p^3-tri-aminotriphenyl-arsine and aniline.[2] Judging by analogy, $3^1,3^2,3^3$-tri-amino-$4^1,4^2,4^3$-trihydroxy-triphenyl-arsine and *o*-aminophenol might be expected to be formed during the decomposition of 3-amino-4-hydroxy-phenyl-arsenious oxide. From a solution which had been refluxed for 4 hours a good yield of *o*-aminophenol was obtained and no organic arsenic compound; the aminophenol was identified by conversion into its acetyl derivative. Therefore, de-arsenation continues until the arsenic has been completely removed from the molecule. By adding sodium carbonate to a solution which had been refluxed for 30 minutes an impure $3^1,3^2$-diamino-$4^1,4^2$-dihydroxy-diphenyl-arsenious oxide was obtained, which was reduced to $3^1,3^2,3^3,3^4$-tetramino-$4^1,4^2,4^3,4^4$-tetrahydroxy-tetraphenyl-diarsine tetrahydrochloride. When a solution which had been kept just under the boiling point for 50 minutes was diluted and then neutralized the secondary oxide was obtained in a pure form.

[1] *Ber.*

[2] Ehrlich and Bertheim, *Ber.*, **43**, 917 (1910).

Experimental.

I. Reduction of 3-Amino-4-hydroxy-phenyl-arsonious oxide.—Three g. of 3-amino-4-hydroxy-phenyl-arsenious oxide hydrochloride was dissolved in 40 cc. of water and treated with 10 cc. of 50% hypophosphorous acid. After the solution had stood at room temperature for $1^1/_2$ hours, it was poured into 100 cc. of 1:1 hydrochloric acid which had previously been cooled to 3°. The yellow precipitate was filtered, washed with hydrochloric acid and dried *in vacuo* over caustic soda. One and eight-tenths g. of arsphenamine was obtained which dissolved fairly readily in water, and which had a tolerated dose[1] of 130 mg./kg. body weight. On analysis, this substance gave 31.95% As, as against 31.58% as calculated for $C_{12}H_{14}O_2N_2Cl_2As_2.2H_2O$.

II. Indirect Reduction of 3-Amino-4-hydroxy-phenyl-arsonic Acid.—*a.* Two and a half g. of purified 3-amino-4-hydroxy-phenyl-arsonic acid was dissolved in 15 cc. of water and 5 cc. of hydrochloric acid (1.19), and 0.4 g. of potassium iodide was added. The solution was saturated with sulfur dioxide at room temperature, and after one hour the yellow solution was aerated until no odor of sulfur dioxide could be detected. After filtration from a small quantity of a yellow precipitate, probably the hydroiodide of the 3-amino-4-hydroxy-phenyl-arsenious iodide, the precipitate was washed with 8 cc. of water, and 10 cc. of 50% hypophosphorous acid was added to the filtrate. The pale yellow solution gradually became orange-yellow as the exothermic reaction progressed. When the solution had stood for $1^1/_2$ hours at room temperature it was cooled to 10° and poured into 100 cc. of 1:1 hydrochloric acid previously cooled to 2°; the acid was stirred well during the precipitation. The precipitate was washed and dried as in **I.** Yield, 2.2 g. (86.5%) of slightly orange-yellow arsphenamine which was readily soluble in water and which conformed to the qualitative tests for arsphenamine.[2] Five samples made according to this procedure averaged 31.47% As, and the tolerated dose varied between 130 and 140 mg./kg.

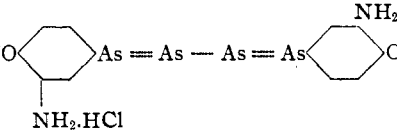
b. Five g. of the aminohydroxy acid was reduced as above to the oxide, and then the solution was boiled until the odor of sulfur dioxide could no longer be detected. After diluting to 80 cc. with water, 20 cc. of 50% hypophosphorous acid was added; an exothermic reaction occurred and the solution became yellow, orange, then red, and an orange-colored precipitate separated to some extent. After $1^1/_2$ hours at room temperature, the material was precipitated by pouring into 225 cc. of 1:1 hydrochloric acid as above. A very finely divided solid separated. After drying *in vacuo* over caustic soda, the product, which was free from arsphenamine, was red, weighed 0.5 g. and had a tolerated dose of 140 mg./kg. On analysis, 50.81% As was found, as against 50.93% as calculated for $C_{12}H_{14}O_2N_2Cl_2As_4$.[3]

The solid dissolved readily in water forming a deep red solution from which sulfuric acid precipitated the hydrosulfate as an orange-colored solid. With sodium acetate an orange-colored precipitate of the free base was formed which was readily soluble in sodium hydroxide. A very dilute solution when diazotized and then added to alcoholic α-naphthylamine hydrochloride produced a deep purple color. Evidently,

[1] Determined by intraveneous injection into albino rats.

[2] Myers and Du Mez, *Pub. Health Reports*, **33**, 1004 (1918).

[3] The statement occurs in the literature that this polyarsenide is more toxic than arsphenamine and if present may contribute to the toxicity of commercial products. However, the average tolerated dose of the arsphenamine of 6 manufacturers was found by Schamberg, Kolmer and Raiziss, *Am. J. Med. Sci.*, **160**, 188 (1920), to be 105 mg./kg. rat; that is, these products were more toxic than the polyarsenide itself. Hence, it is improbable that the latter is a factor in the toxicity of commercial preparations of arsphenamine.

the product was a polyarsenide of arsphenamine. If the arrangement of the 4 arsenic atoms in these polyarsenides proposed by previous experimenters is accepted, the red solid had the structure  The small yield

was due to the fact that most of the oxide had been decomposed during the boiling.

III. Action of Hypophosphorous acid on a Solution of 3-Amino-4-hydroxy-phenyl-arsenious Oxide Hydrochloride and Arsenious Acid.—One and seven-tenths g. of the arsonic acid was reduced to the oxide and the sulfur dioxide removed as in **II** *a*. The filtered solution was diluted to 27 cc., mixed with one g. (one mol.) of sodium arsenite dissolved in 27 cc. of water, and 14 cc. of 50% hypophosphorous acid was added. The experiment was completed as in **II** *b*, yielding 2 g. (93.5%) of arsphenamine polyarsenide. All the phenomena and all the properties of the red product were the same as those noted in **II** *b*, but the arsenic content was only 47.31%.

When a similar experiment was performed using 1.6 molecules of sodium arsenite, the polyarsenide contained 53.72% As, gave no test for inorganic arsenic with hydrogen sulfide, and was tolerated in doses of 140 mg./kg.

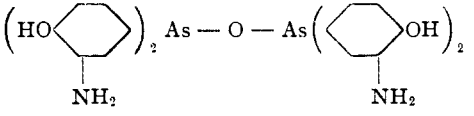
When a mixture of 3-amino-4-hydroxy-phenyl-arsenious oxide and inorganic arsenic is reduced with hypophosphorous acid, the arsenic content of the resulting polyarsenide varies with the ratio of inorganic to organic arsenic present before reduction.

IV. Decomposition of 3-Amino-4-hydroxy-phenyl-arsenious Oxide in Hot Acid Solution.—One and seven-tenths g. of the arsonic acid was reduced to the oxide as in **II** *a* and the solution was boiled for 55 minutes, then diluted to 27 cc. The solution gave an immediate yellow precipitate with hydrogen sulfide; a similar experiment in which the sulfur dioxide was removed by aeration was free from inorganic arsenicals. When neutralized with sodium carbonate the solution gave a white curdy precipitate which, washed with water and dried *in vacuo* over sulfuric acid, was insoluble in water, but dissolved in dil. hydrochloric acid, and this solution reduced iodine immediately.

0.0097 g. dissolved in 10 cc. of water plus one cc. of *N* hydrochloric acid decolorizes 0.71 cc. of 0.0940 *N* iodine solution (starch as indicator).

Calc. for $C_{24}H_{24}O_5N_4As_2$: As 25.1. Found: 25.8.

The properties and analysis indicate that the solid was the secondary oxide

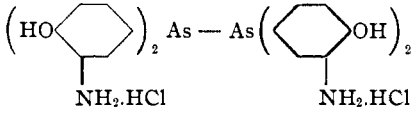


One-tenth g. of crude secondary oxide was dissolved in 1.5 cc. of water and 0.1 cc. of 1:1 HCl, and the filtered solution was reduced with 0.5 cc. of 50% hypophosphorous acid. The solution did not become bright yellow as when the primary oxide is reduced to arsphenamine, and when it was poured into cold hydrochloric acid 1:1, a white gelatinous precipitate was formed. After washing with hydrochloric acid and drying *in vacuo* over caustic soda a flaky white solid was left which was very readily soluble in water. The colorless aqueous solution gave a white curdy precipitate with sodium carbonate which dissolved upon the addition of caustic soda. Hydrochloric acid was added to the alkaline solution until the precipitate first formed redissolved; the resulting colorless solution decolorized iodine instantly.

Subs., 0.0113: 0.61 cc. 0.1105 *N* $Na_2S_2O_3$.

Calc. for $C_{24}H_{28}O_4N_4Cl_4As_2$: As, 20.6. Found: 22.4.

The preparation from the secondary arsenious oxide and analysis indicate that the flaky solid was



A substance with this structure would be colorless due to the absence of the arseno linkage.

Two and eight-tenths g. of the aminohydroxy-arsonic acid was reduced to the oxide. The sulfur dioxide was removed by aeration, and after refluxing 4½ hours the solution was allowed to stand overnight. A small quantity of white solid was filtered out, and the filtrate was treated with an excess of sodium carbonate solution; a white crystalline precipitate separated which, after washing and air drying, weighed 0.45 g. and melted at 169° to 175°, was insoluble in water but readily soluble in dil. hydrochloric acid. The solution was oxidized by iodine and ferric chloride to a brown solution which deposited a brown precipitate. If the substance had contained trivalent arsenic, addition of iodine would have resulted in decolorization of the iodine without the production of the brown color. The substance was apparently *o*-aminophenol. m. p. 170°.

The mother liquor from the sodium carbonate precipitate was extracted with ether; the extract, after drying with calcium chloride, was evaporated to dryness, leaving 0.3 g. of shiny light brown plates, m. p. 170°–174°. The product gave the same reactions as above, and was also *o*-aminophenol.

The total yield of *o*-aminophenol was 60%.

Some of the *o*-aminophenol secured in this way was treated with acetic anhydride and then diluted with water. A brown solid separated slowly, and after air drying, it melted at 199° to 204° and was insoluble in water and dilute hydrochloric acid. The product was acetyl-*o*-aminophenol, m. p. 201°.

Therefore, when 3-amino-4-hydroxy-phenyl-arsenious oxide is boiled in acid solution, it decomposes into *o*-aminophenol, and 3,3¹-diamino-4,4¹-dihydroxy-phenyl-arsenious oxide is an intermediate in the process.

In determining the rate at which the oxide decomposes advantage was taken of the action of hypophosphorous acid on mixtures of arylarsenious oxides and inorganic arsenicals. As the decomposition progresses and the quantity of inorganic arsenic increases, reduction with hypophosphorous acid gives a mixture of arsphenamine and its polyarsenide, and the color changes from the bright yellow of an arsphenamine solution to the deep red of an arsphenamine polyarsenide solution as the percentage of the latter compound increases. When 50% of the oxide has been decomposed the maximum amount of the polyarsenide will be formed and the deep red solution will deposit an orange-colored precipitate. From this point on there is an excess of inorganic arsenic over that required by the remaining oxide for polyarsenide formation. Consequently, upon reduction a mixture of the polyarsenide and metallic arsenic results; the color of the solution becomes paler and paler and the precipitate becomes darker and darker as the quantity of metallic arsenic increases. Therefore, by noting the color changes and determining the arsenic content of

the reduction products an approximate idea of the rate of decomposition may be obtained.

When a solution of the oxide obtained by partial reduction of the acid was refluxed and the decomposition followed as outlined above by removing test portions, it was found that the decomposition progresses very rapidly at first so that 50% of the oxide has been decomposed after 40 minutes. At the end of 3 hours the reaction was 75% complete and had become very slow.

The arsenic determinations were made according to Lehmann's method.

Summary.

1. The indirect reduction of 3-amino-4-hydroxy-pheny-larsonic acid to arsphenamine has been investigated and a method developed for the preparation of a relatively nontoxic arsphenamine which is readily soluble in water.

2. Like the direct reduction of 3-amino-4-hydroxy-phenyl-arsonic acid this procedure avoids the isolation of arsphenamine base and has the additional advantage of producing the substance in a readily soluble condition.

3. The rate of decomposition of 3-amino-4-hydroxy-phenyl-arsenious oxide in boiling acid solution has been followed; the final product identified as *o*-aminophenol and 3,3^1-diamino-4,4^1-dihydroxy-diphenyl-arsenious oxide was found to be an intermediate.

4. The formation of arsphenamine polyarsenide has been investigated and some of the properties of this compound have been recorded.

The writer wishes to express his appreciation to Dr. Reid Hunt for testing the products biologically and to Mr. Lewis I. Nurenberg of the Arsphenamine Laboratory of the Massachusetts Department of Health, for preparing several lots of arsphenamine by this method.

BOSTON, MASS.

[CONTRIBUTION FROM THE LABORATORY OF THE G. SIEGLE CORPORATION OF AMERICA.]

5-NITRO-4-HYDROXY-3-METHYL-BENZOIC ACID.

BY K. PFISTER.

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In the course of an investigation the chance presented itself of correcting an error in the older chemical literature which appears to have passed unnoticed; at least no criticism regarding it could be found in the more recent literature.

In 1882 R. W. Mahon nitrated at a high temperature the so-called *p*-hydroxy-*m*-toluic acid (4-hydroxy-3-methyl-benzoic acid) and obtained another acid which he regarded as a mononitro derivative.[1] That such

[1] Mahon, *Am. Chem. J.*, **4**, 186 (1882).