

Organic Compounds of Arsenic. V. The Electrolytic Reduction of 3-nitro-4- hydroxyphenylarsinic acid.

By

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ABSTRACT.

The electrolytic reduction of 3-nitro-4-hydroxyphenylarsinic acid in an acid solution was studied with the object of obtaining the chemically pure organic compounds of arsenic related to salvarsan. The influence of the electrode material, current density, temperature, concentration of acid, etc., was investigated, and it was found that the cathode material and the concentration of acid have remarkable effects. Mercury, lead amalgam cathodes gave similar results which differ altogether from those given by the other cathodes. When mercury, lead, or lead amalgam was taken as the cathode, and a hydrochloric acid solution as the cathode solution, the strength of the hydrochloric acid showed such a noteworthy effect that so far as its strength was kept weaker than 4.7 normal, the reduction product was 3-amino-4-hydroxyphenylarsine while 3,3-diamino-4,4-dihydroxyarsenobenzene dihydrochloride was precipitated when the acidity became stronger. Sulphuric acid, however, showed no such influence of its strength, 3-amino-4-hydroxyphenylarsine having been always produced as its final product.

In the course of the studies on the synthesis of the organic compounds of arsenic for therapeutic purposes, it was found necessary to prepare the reduced compounds of 3-nitro-4-hydroxyphenylarsinic acid in chemically pure state. As one of the methods which were expected to meet such a demand electrolytic reduction was chosen.

As to the electrolytic reduction of 3-nitro-4-hydroxyphenylarsinic acid there are two patents, one in Germany and the other in America. The former¹ gives no precise description concerning the resulting products ;

1. H. Bart, D. R. P., 270568.

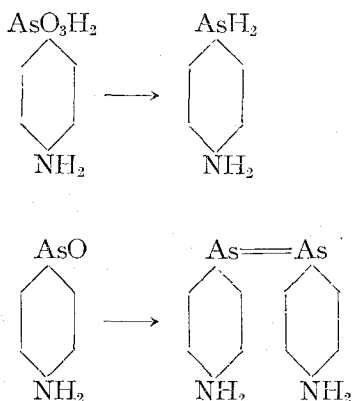
and the latter¹ averts the obtaining of 3-amino-4-hydroxyphenylarsinic acid in an alkaline solution.

As arsenic acid radical² is not reduceable in an alkaline medium, our experiments were conducted in an acidic medium. The following are the results obtained by reducing 3-nitro-4-hydroxyphenylarsinic acid with a mercury cathode in a hydrochloric acid solution.

The nitro group and the arsenic acid radical of 3-nitro-4-hydroxyphenylarsinic acid were both reduced energetically and 3-amino-4-hydroxyphenylarsine was produced. It was now found that the strength of the hydrochloric acid in the cathode solution has a remarkable influence upon the reduction, that is, when rather weak hydrochloric acid was used, 3-amino-4-hydroxyphenylarsine was the product, which remained dissolved in the cathode solution, while 3,3-diamino-4,4-dihydroxyarsenobenzene dihydrochloride (salvarsan) was produced as a yellow-coloured powder, when the strength of the hydrochloric acid was more than 4.7 normal.

3-amino-4-hydroxyphenylarsine thus electrochemically obtained was found to be purer than that ever obtained by chemical methods. So far as we know, there is no statement in chemical literature that salvarsan has ever been prepared electrolytically from 3-nitro-4-hydroxyphenylarsinic acid.

According to Fichter and Elkind's study³ of the electrolytic reduction of organic compounds of arsenic, 4-aminophenylarsinic acid is reduced to 4-aminophenylarsine, while more easily reduceable 4-aminophenylarsine oxide gives p-arsenoaniline which belongs to a less reduced stage than the corresponding arsine; thus,

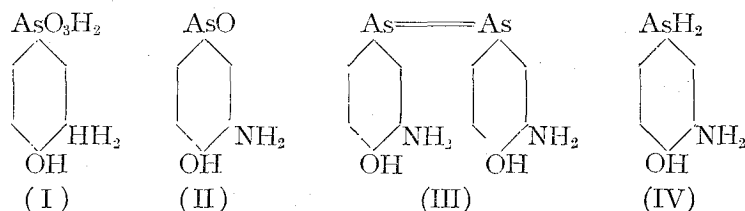


1. A. Mouneyrat, U. S. P., 1232373.

2. F. Fichter and E. Elkind, Ber., 49, 240 (1916)

3. loc. cit.

Now the successive reduction stages of 3-amino-4-hydroxyphenylarsinic acid traced by ordinary chemical reaction are as follows :



In our electrolytic experiments compounds (III) and (IV) were obtained from 3-nitro-4-hydroxyphenylarsinic acid. Consequently we regarded at first the electrolytic reduction of 3-nitro-4-hydroxyphenylarsinic acid to have taken place similarly, passing from (I) to (IV) successively and 3,3-diamino-4,4-dihydroxyarsenobenzene to be an intermediate reduction product. The fact that 3,3-diamino-4,4-dihydroxyarsenobenzene dihydrochloride is separated as precipitates in a hydrochloric acid solution more concentrated than 4.7 normal was also deemed to be due to its difficult solubility in concentrated hydrochloric acid.

By closer study, however, many contradictory facts were found out. First, when hydrochloric acid was added to 0.25 % solution of 3,3-diamino-4,4-dihydroxyarsenobenzene dihydrochloride the precipitation of the dihydrochloride took place as soon as the strength of the hydrochloric acid in the solution just reached 2.5 normal. In our electrolytic experiment the precipitation of the dihydrochloride was observed to occur only when the concentration of hydrochloric acid was more than 4.7 normal, (the concentration of 3-nitro-4-hydroxyphenylarsinic acid at that moment was 1.6%). Secondly, when dilute sulphuric acid was used instead of hydrochloric acid, no precipitation was recognized during the electrolysis, and no reduction product other than 3-amino-4-hydroxyphenylarsine was found in the solution. If 3,3-diamino-4,4-dihydroxyarsenobenzene were produced in the course of reduction, it must have been instantly precipitated as the sulphate, for it is practically insoluble in water. Thirdly, when 3-nitro-4-hydroxyphenylarsinic acid, dissolved in a 2.5 normal solution of hydrochloric acid, was reduced by passing exactly the theoretical quantity of electricity necessary to reduce it to diamino dihydroxyarsenobenzene, and the resulting product was precipitated by neutralising the cathode solution with sodium bicarbonate, nothing but 3-amino-4-hydroxyphenylarsine could be isolated.

These facts indicate that 3,3-diamino-4,4-dihydroxyarsenobenzene can not be regarded necessarily as the intermediate product which precedes the

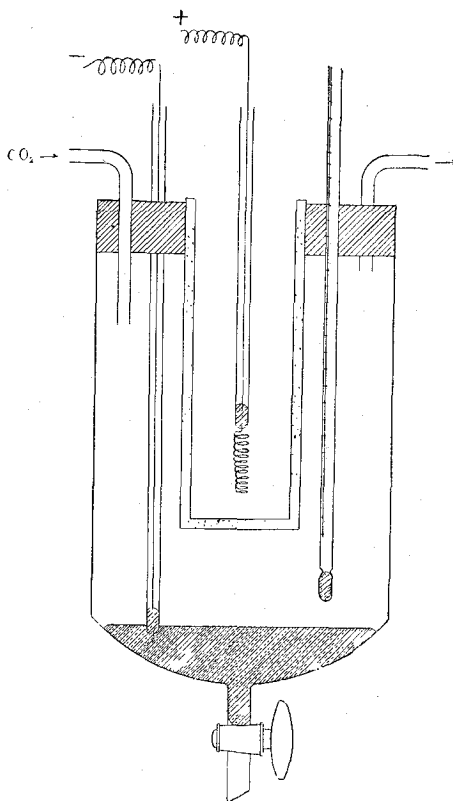
formation of 3-amino-4-hydroxyphenylarsine by the electrolytic reduction of 3-nitro-4-hydroxyphenylarsinic acid. The oxidation of 3-amino-4-hydroxyphenylarsine in the cathode solution to the corresponding arseno-compound by atmospheric oxygen is hardly imaginable, as the cathode chamber was entirely filled with carbon dioxide.

EXPERIMENTAL PART

Preliminary Experiment.

As almost all the reduction products of 3-nitro-4-hydroxyphenylarsinic acid hitherto known are easily oxidizable, the electrolytic reduction of the acid was performed in the atmosphere of carbon dioxide. This was effected by the aid of the apparatus sketched below. A porous cell containing hydrochloric acid and a platinum anode was used as the anode compartment, and it was tightly inserted into a cathode cell by means of a cork provided with a glass tube holding a platinum wire connected with the cathode, and a thermometer and two delivery tubes for the passage of the carbon dioxide. The cathode cell consisted of a glass vessel containing mercury which served as the cathode. As the catholyte a hydrochloric acid solution of 3-nitro-4-hydroxyphenylarsinic acid was taken.

1. The cathode solution was prepared by suspending 5 grms. of 3-nitro-4-hydroxyphenylarsinic acid in a mixture of 100 c. c. of water and 30 c. c. of hydrochloric acid (1.19), and as the anode solution a 20 % solution of hydrochloric acid was taken; the



surface area of the mercury cathode was 12.5 sq. cm.. Keeping the temperature at 30°-35° a current of 2.6 amperes was passed. During the electrolysis some arsine gas was always observed to evolve from the cathode though the contrary is stated in the German patent¹. At the end of the electrolysis, that is, after about two hours from the beginning, the cathode solution became clear and colourless. When it was kept in the atmosphere of carbon dioxide over night, fine needle crystals (i) separated out. These were separated and dried in vacuo over sulphuric acid. On neutralizing the filtrate with sodium bicarbonate white precipitates (ii) were obtained which were also collected and dried.

The crystals (i) were observed to decompose at about 180° and were soluble in water, alcohol and dilute mineral acid, but insoluble in ether and concentrated hydrochloric acid. Their aqueous solution reacted acidic to litmus, and on neutralizing the solution with an alkali, white precipitates were formed which redissolved in an excess of the precipitant. It became black on standing in the air. From these properties and the following analytical results the substance was recognized to be 3-amino-4-hydroxyphenylarsine hydrochloride. Arsenic was estimated by Ewins' method.²

0.1182gram. subst. required 9.85 c. c. N/10 iodine solution.
 0.1227gram. subst. gave 0.0513gram. H₂O and 0.1360gram CO₂.
 0.2449gram. subst. required 11.19 c. c. N/10 H₂SO₄.
 0.1431gram. subst. gave 0.0855 gram. AgCl.

	Found	Calc. for C ₆ H ₉ ONAsCl, H ₂ O
As	31.25	31.29
C	30.23	30.07
H	4.68	4.63
N	6.40	5.85
Cl	14.78	14.80

To verify that the arsenic was in the form -AsH₂, the substance was titrated with an iodine solution which oxidizes the former into the corresponding arsinic acid. During the titration a sodium bicarbonate solution was constantly dropped to keep the solution slightly acidic. The amount of the iodine required was found exactly to coincide with that of the theoretical: 0.1619 gram. subst. required 40.96 c.c. N/10 iodine solution. (Calc. 40.56 c.c.)

1. loc. cit.

2. A. J. Ewins, J. Chem. Soc., 109, 1355 (1916).

The precipitates (11) decompose at 140° - 150° and were soluble in alcohol, ether, dilute mineral acid and alkali, but sparingly so in water. When a dilute hydrochloric acid solution of the substance was dropped into concentrated hydrochloric acid fine needle crystals identical with crystals (1) separated. Thus the substance was confirmed to be free 3-amino-4-hydroxyphenylarsine. The result of the estimation of arsenic was as follows:—

0.1330 grm. subst. required 14.30 c.c. N/10 iodine solution.

	Found	Calc. for C_6H_5ONAs .
As	40.32	40.51

The total yield of 3-amino-4-hydroxyphenylarsine was found to be 80 %.

2. The cathode solution was prepared by dissolving 2 grms. of 3-nitro-4-hydroxyphenylarsinic acid in a mixture of 60 c.c. of water and 60 c.c. of hydrochloric acid (1.19), and 6 N. hydrochloric acid was used as the anode solution. Keeping the temperature at 20° - 25° , a current of 2 amperes was passed, and then yellow precipitates were gradually deposited. After about one hour and a half, when the precipitates ceased to increase, the current was cut off, and the yellow precipitates were collected on a filter and dried in vacuo over sulphuric acid.

The yellow substance was seen to be soluble in water, methyl alcohol and dilute hydrochloric acid, insoluble in ether and conc. hydrochloric acid. Its aqueous solution reacted acidic to litmus. On neutralizing its solution with alkali, yellow precipitates were produced which redissolved in an excess of the precipitant. From the aqueous solution yellowish-white precipitates were formed by the addition of dilute sulphuric acid. This yellowish substance was easily oxidizable, and on exposing it in the air its colour slowly turned red and then black. It had no distinct melting point and decomposed at 180° - 190° . These properties indicate that the substance is 3,3-diamino-4,4-dihydroxyarsenobenzene dihydrochloride, and this was confirmed by the following results of the analysis:

0.1749 grm. subst. gave 0.1053 grm. AgCl.

0.1294 grm. subst. required 10.95 c.c. N/10 iodine solution.

	Found	Calc. for $C_{12}H_{14}O_2N_2As_2Cl_2 \cdot 2H_2O$
Cl	14.89	14.93
As	31.73	31.56

The yield was about 25 %.

The mother liquor having a yellow colour was diluted, and one part of it was titrated with an iodine solution in the presence of sodium bicarbonate, and the arsenic content was determined by Newbery's method¹. The quantity of N/10 iodine solution required for the whole solution was found to be 197.5 c.c. and the amount of arsenic was estimated to be 0.3725 gm. The quantity of N/10 iodine solution required for 0.3725 gm. arsenic is calculated to be 198.7 c.c. if the arsenic be in the form $-\text{As}=\text{As}-$, but 298.14 c.c. if it be in the form $-\text{AsH}_2$. Thus it is clear that the 3-nitro-4-hydroxyphenylarsinic acid used was entirely reduced to 3,3-diamino-4,4-dihydroxyarsenobenzene.

3. Two grms. of 3-nitro-4-hydroxyphenylarsinic acid were dissolved in 125 c.c. of 2.5 N. sulphuric acid, and treated in the same way as in experiment 1, dilute sulphuric acid having been taken as the anode solution. On passing a current of 2 amperes for one hour and a half, the yellow-coloured cathode solution became quite colourless. It was neutralized with sodium bicarbonate, and 3-amino-4-hydroxyphenylarsine was obtained as white precipitates, the yield being 58 %.

Quantitative Investigation.

1. Influence of the Quantity of Electricity.

Cathode : mercury. (12.56 sq. cm.)

Anode : platinum.

Cathode solution : $\left\{ \begin{array}{l} 2\text{grms. of 3-nitro-4-hydroxyphenylarsinic acid.} \\ 100\text{ c.c. of water.} \\ 25\text{ c.c. of hydrochloric acid (1.19).} \end{array} \right.$

Anode solution : dilute hydrochloric acid.

Current : 2.6 amperes.

Time (hour)	Current quantity (amp-hour)	3-amino-4-hydroxyphenylarsine produced (gm)	Material yield (%)
1	2.6	1.26	89.6
1 $\frac{1}{6}$	3.0	1.29	91.4
1 $\frac{1}{3}$	3.5	1.33	94.8
2	5.2	1.32	93.9*

* 3-amino-4-hydroxyphenylarsine seems to decompose owing to a prolonged electrolysis.

1. G. Newbery, J. Chem. Soc., **127**, 1751 (1925).

Temperature: 30°,

Treatment after electrolysis—The cathode solution was diluted with water to 500 c.c., and 20 c.c. of it was titrated with N/10 iodine solution in the presence of sodium bicarbonate.

2. *Influence of temperature.*

Current: 2.5 amperes.

Time: 1 1/5 hours.

The other conditions were the same as in the previous case. Treatment after electrolysis—The cathode solution was neutralized with sodium bicarbonate, and the precipitates of 3-amino-4-hydroxyphenylarsine were collected and weighed.

Temperature	3-amino-4-hydroxyphenylarsine obtained (gram)	Material yield (%)	Current efficiency (%)
2-7°	0.88	62	51.0
25°	0.96	68	54.4
50°	0.90	64	52.2

Thus the most favorable temperature was found to be 25°.

3. *Influence of current density.*

Temperature: 25°

Current: 2 amperes.

Time: 1 1/3 hours.

The other conditions were the same as in the foregoing case.

Area of cathode. (sq. cm.)	Cur. density (amp/sq. cm)	3-amino-4-hydroxyphenylarsine (gram)	Material yield (%)	Cur. eff. (%)
7.16	0.28	1.08	76.0	76.5
12.56	0.16	1.02	72.5	73.0
25.00	0.08	0.95	67.5	67.9

4. *Influence of the concentration of mineral acid.*

Cathode solution: { 2 grms. of 3-nitro-4-hydroxyphenylarsinic acid.
125 c.c. of hydrochloric or sulphuric acid

Anode solution: { hydrochloric or sulphuric acid of the same concentration as the cathode solution.

Time: 1 1/2 hours.

The other conditions were the same as in the preceding case.

Normality of hydrochloric acid	3-amino-4-hydroxyphenylarsine (gm)	3,3-diamino-4, 4-dihydroxyarseno-benzene dihydrochloride (gm)
2.4	0.94	0
4.2	0.92	0
4.7	0.90	0
5.1	0.22
6.2	0.40
Normality of sulphuric acid	3-amino-4-hydroxyphenylarsine (gm)	3,3-diamino-4, 4-dihydroxyarseno-benzene dihydrochloride (gm)
2.5	0.81	0
5.0	0.55	0
8.0	0.20	0

The number for 3-amino-4-hydroxyphenylarsine shows the quantity precipitated by neutralization with sodium bicarbonate, and that for 3,3-diamino-4,4-dihydroxyarsenobenzene dihydrochloride shows the amount actually precipitated during the electrolysis.

To confirm what substance would result when weak hydrochloric acid was used, and the calculated quantity of electrocity for 3,3-diamino-4,4-dihydroxyarsenobenzene was passed, the following experiment was carried out.

Two grms. of 3-nitro-4-hydroxyphenylarsinic acid dissolved in a 2.5 normal solution of hydrochloric acid were reduced by passing a 2 ampere current for one hour (2.0 ampere-hours). The resulting solution was treated with sodium bicarbonate, and 0.36 gm. of a substance was obtained whose properties coincided with those of 3-amino-4-hydroxyphenylarsine. The content of arsenic estimated by Ewins' method was 36.91 %, the theoretical amount being 40.51. To confirm whether the arsenic was in the form $-\text{AsH}_2$, or $-\text{As}=\text{As}-$, it was directly titrated with an N/10 iodine solution, and 0.1138 gm. of the substance required 32.70 c.c., the theoretical amounts of iodine required for the form $-\text{AsH}_2$ and the form $-\text{As}=\text{As}-$ being 33.62 c.c. and 22.30 c.c. respectively. Thus it was known to be impure 3-amino-4-hydroxyphenylarsine.

* Described in experiment 7.

5. *Influence of the cathode material.*

The influence of the cathode material is remarkable. When mercury, lead, or lead amalgam was used as the cathode, 3-amino-4-hydroxyphenylarsine was obtained, while other materials, such as copper, nickel, platinum gave entirely different results. The results of reduction with mercury, lead, and lead amalgam were as follows:—

Cathode: mercury, lead, or lead amalgam. 25 sq. cm.

Anode: platinum spiral.

Cathode solution: $\left\{ \begin{array}{l} 2 \text{ grms. of 3-nitro-4-hydroxyphenylarsinic acid.} \\ 100 \text{ c.c. of water.} \\ 25 \text{ c.c. of hydrochloric acid (1.19).} \end{array} \right.$

Anode solution: 2.5 normal solution of hydrochloric acid.

Current: 2.5 amperes.

Time: 1 1/5 hours.

Temperature: 23°–25°

After electrolysis the cathode solution was titrated with an N/10 iodine solution.

Cathode material	3-amino-4-hydroxyphenylarsine (gm)	Material yield (%)	Current efficiency (%)
lead	0.73	51.9	42.3
lead amalgam	1.08	76.7	61.7
mercury	1.24	88.1	72.0

6. *Influence of solvent*

The influence of the solvent used for the cathode solution was not noticeable.

Cathode: mercury.

Anode: platinum.

Cathode solution: $\left\{ \begin{array}{l} 2 \text{ grms. of 3-nitro-4-hydroxyphenylarsinic} \\ \text{acid dissolved in the solvent described below.} \end{array} \right.$

Anode solution: $\left\{ \begin{array}{l} \text{hydrochloric acid of the same strength as that} \\ \text{in the cathode solution.} \end{array} \right.$

Current: 2 amperes.

Temperature: 25°.

Time: 1 1/2 hours.

Solvent used for cathode solution	Normality of acid	3-amino-4-hydroxy-phenylarsine (gm)	3,3-diamino-4,4-dihydroxyarsenobenzene dihydrochloride(gm)
60 c.c. of ethyl alcohol 25 c.c. of HCl(sp. gr. 1.19) 35 c.c. of water	2.6	0.70 ¹	0
60 c.c. of ethyl alcohol 40 c.c. of HCl (sp. gr. 1.19) 20 c.c. of water	4.2	0.48 ¹	0
60 c.c. of ethyl alcohol 50 c.c. of HCl (sp. gr. 1.19) 10 c.c. of water	5.1		0.48 ²
60 c.c. of ethyl alcohol 60 c.c. of HCl (sp. gr. 1.19)	6.2	0.75 ³
60 c.c. of methyl alcohol 60 c.c. of HCl (sp. gr. 1.19)	6.2	0.55 ³

7. Study of a prolonged electrolysis

As stated before (Exp. 4), the concentration of hydrochloric acid used in the cathode solution has an important bearing upon the reduction, 3,3-diamino-4,4-dihydroxyarsenobenzene dihydrochloride being the main reduction-product when hydrochloric acid is stronger than 4.7 normal, and 3-amino-4-hydroxyphenylarsine, when it is weaker.

As, however, it was considered beyond doubt that arsenobenzene would be more or less reduced to the corresponding arsine compound by a prolonged electrolysis, the following two experiments were carried out using 2.4 N-hydrochloric acid in the one, and 6.2 N-acid in the other.

Cathode: mercury.

Anode: platinum.

Cathode solution: $\left\{ \begin{array}{l} 2 \text{ grms. of 3-nitro-4-hydroxyphenylarsinic} \\ \text{acid.} \\ 120 \text{ c.c. of hydrochloric acid} \end{array} \right.$

Anode solution: hydrochloric acid.

Current: 2 amperes.

Temperature: 25°

1. Quantities obtained by neutralising the cathode solution with sodium bicarbonate.
2. The same as above. Titration with iodine solution showed it to be a mixture of 3-amino-4-hydroxyphenylarsine and 3,3-diamino-4,4-dihydroxyarsenobenzene in the ratio of 7:3.
3. Quantities precipitated in the course of electrolysis.

During the electrolysis, a portion of the cathode solution was taken out at some interval and titrated with an N/10 iodine solution.

Time.	The quantity of iodine required for the whole cathode solution.	
	(2.4 normal solution)	(6.2 normal solution)
1 $\frac{1}{4}$ h	332.0 c.c.	287.5 c.c.
1 $\frac{1}{2}$ h	392.0 c.c.	315.0 c.c.
2 $\frac{1}{2}$ h	397.5 c.c.	365.0 c.c.

The theoretical amounts of the N/10 iodine solution required are calculated as follows:

When reduced to the arsine stage	When reduced to the arseno stage
461.5 c.c.	307.7 c.c.

It is therefore, clearly to be seen that in the 6.2 normal acid solution 3-nitro-4-hydroxyphenylarsinic acid is completely reduced to 3,3-diamino-4,4-dihydroxyarsenobenzene after electrolysis for 1 $\frac{1}{2}$ hours, and when the electrolysis is further prolonged the reduction goes on still further to produce 3-amino-4-hydroxyphenylarsine.