time the dihydrochloride of the arsphenamine base has been prepared without organic or other solvents in combination or present in the final product.

[Contribution from the Division of Laboratories and Research of the New York State Department of Health, Albany.]

THE PREPARATION OF PRIMARY AND SECONDARY ARSANILIC ACIDS.[1]

By Philip Adolph Kober and Walter S. Davis.

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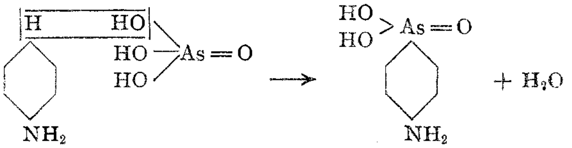
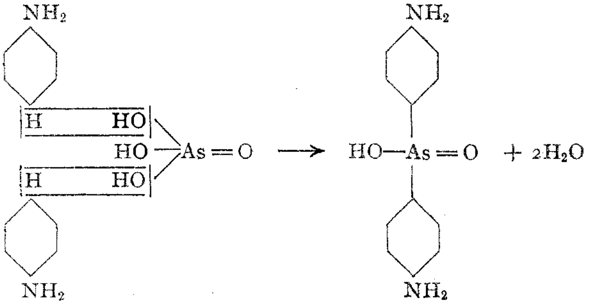
I. Introduction.

The preparation of what is now known as primary arsanilic acid, the starting point and the basis of Ehrlich's synthesis of arsphenamine or salvarsan, was first mentioned by Béchamp[2] in 1863. That Béchamp and others considered the substance an anilide until Ehrlich[3] and Bertheim proved it to be *p*-aminophenyl-arsonic acid is well known. Ehrlich,[4] however, started his work with a commercial source of arsanilic acid, namely, atoxyl, the sodium salt of the acid, and although his collaborators studied the Béchamp synthesis, the fact remains that the literature does not contain definite directions for making the primary arsanilic acid. Many laboratories have spent much time and money in trying to evolve



Aniline + Arsenic acid → (I) *p*-Aminophenylarsonic acid.



(II) Di-*p*-aminophenylarsinic acid.

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[1] A description of the preparation of the primary arsanilic acid was read before the Society of Experimental Biology and Medicine, New York City, November 20, 1918.

[2] *Compt. rend. soc. biol.*, 56, 1172 (1863).

[3] *Ber.*, 40, 3292 (1907).

[4] *Ibid.*

the synthesis of the primary acid for the purpose of making salvarsan, but without much success. It is usually understood that the process in its highest form is a trade secret.

As we have developed a simple and easy method for making not only the primary acid (I) free from the secondary, di-*p*-aminophenylarsinic acid, (II), but also the secondary free from the primary, it might be worth while to give and discuss the methods in detail.

II. Preparation of *p*-Aminophenylarsonic Acid from Aniline and Arsenic Acid.

Béchamp[1] stated that the "arsenanilid" (the primary acid) was a constant product of heating aniline arsenate. This aniline arsenate was given the formula $AsO_5.2C_{12}H_7N.3H_2O$, which is obviously the dianiline compound $H_3AsO_4(C_6H_5NH_2)2.3H_2O$. While he mentions temperatures from 140° to 200° C. it seems certain that according to his information the synthesis did not take place below 180° C. No mention of other quantities is made, of the amount of substance, of the nature of the apparatus, of the time of heating, and volume of solution, or their concentrations.

That Béchamp's method had as a by-product, the secondary acid, is substantiated by Pyman[2] and Reynolds, and Benda[3] and Kahn, as well as by Morgan.[4] Pyman and Reynolds heated the aniline arsenate with an excess of aniline at 180° C. without indicating in their published work the length of heating. Benda and Kahn heated a mixture of arsenic acid and aniline slowly to a temperature of 170–200° C. Parenthetically they state that aniline arsenate is less suitable, but in a subsequent communication, Benda[5] makes it clear that his mixture had an excess of aniline. In neither Benda's communication nor the article by Pyman and Reynolds are any details given as to the length of heating, nature of apparatus, volume of solution, or their concentrations.

Recently Morgan in his book gives a little more detail. He states that approximately two molecules of aniline and one molecule of arsenic acid are heated to 170–200° C. at the start. He then recommends heating to 190–200° C. for an hour or two. But Morgan as well as Benda and Pyman and Reynolds, find it necessary to purify their primary acid free from the secondary, by the precipitation of the sodium salt with alcohol. A careful review of the literature, in the light of our experiments, shows that either an excess of aniline was used or the mixtures were heated too high or that both of these errors were made.

After making many experiments varying one factor after another, we

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[1] *Loc. cit.*

[2] *Trans. Chem. Soc.* (*London*), **93**, 1184 (1908).

[3] *Ber.*, **41**, 1672 (1908).

[4] Longmans, "Organic Compounds of Arsenic and Antimony," **1918**, p. 156.

[5] *Ber.*, **41**, 2367 (1908).

finally found that the secondary acid formation did not take place to any appreciable extent when less than two molecules of aniline were heated with one molecule of arsenic acid. We also found that one could use two molecules of aniline to one molecule of arsenic acid if the temperature was not allowed to go above 180° C. Below this temperature it seems that the second molecule of aniline does not enter into the synthesis.

Method.—One thousand cc. of crude arsenic acid (76 per cent.) are heated in an open beaker placed in an oil or "crisco" bath at 120 to 140° C. for twelve to fifteen hours. This should concentrate the acid to practically 100 per cent.

Fourteen hundred cc. of dry aniline oil are cooled with an ice mixture to 0° C. or lower, and the cooled arsenic acid is added with vigorous stirring, slowly. The mixture soon becomes thick and then granular, after which it is finally ground and thoroughly mixed.

This powder has roughly the composition of (aniline)$_3$(H_3AsO_4)$_2$. Two hundred (200) grams of this powder are heated in an Erlenmeyer flask, by means of a "crisco" bath to 160° C., when the arsenate begins to melt. The substance is stirred continually and when it has all melted, a reflux condenser is then attached; for about one and one-half hours it is heated from 160–170° C. and then one hour from 180 to 185° C. After allowing the mixture to cool somewhat 225 cc. of six normal hydroxide and 225 cc. of water are added, which causes the substance to dissolve and separates out the aniline oil that is left uncombined.

When cooled the aqueous layer is drawn off, with the aid of a separatory funnel, and after shaking with 15 to 20 grams of infusorial earth or kaolin, it is filtered with suction. To the clear filtrate is added 100 cc. of six normal hydrochloric acid. By means of 25 cc. portions and further additions of 0.5 cc., 1.0 cc., 2.00 cc., etc., of six normal hydrochloric acid one finds out, if further additions of acid to the whole filtrate will give a larger yield or not. After waiting for a few moments to allow the crystallization to take place in these tests and when the best medium has been determined, an equivalent amount of acid is added to the whole filtrate and stirred. As a rule in a few moments the crystals fill the entire solution to such an extent as to give the appearance that the solution has solidified. The yield is about 30%, of the theory, while 10% seems to be the average obtained heretofore.

After standing for an hour or longer, the precipitate, which is practically white and crystalline, is filtered with suction. It is then washed by suspending in 200 cc. of water and again filtering with suction. After drying by fanning or by any other suitable means the substance is ready for further use or for recrystallization.

For this purpose the arsanilic acid may be suspended in water and dissolved in the least quantity of alkali. Then a sufficient amount of hydrochloric or sulfuric acid in dilute solution is added to make a faint precipitation. After allowing the mixture to stand, or upon heating until the precipitate has dissolved, and allowed to cool again, it is filtered with suction and completely precipitated with acid.

The substance can also be purified by dissolving it in the least quantity of boiling water, filtering with or without the usual color absorbents, and allowing the solution to cool.

The crystals from either of these purifications are the typical pearly scales. The analysis of the crude product, once purified by hot water crystallization and dried in a vacuum desiccator gave:

	% As.	% N.
Product Sample A	34.20	6.02
Product Sample A	34.50	6.16
Product Sample B	33.20	6.79
Product Sample B	33.40	6.81
Product Sample B	34.50	..
Average	33.96	6.44
Theory for primary	34.60	6.45
Theory for secondary	25.65	9.65

Arsenic estimations were made by Ewins' method and nitrogen by the modified Kjeldahl-Gunning method.

III. Preparation of Di-*p*-Aminophenylarsinic Acid.

Benda[1] seems to be the first to call attention to the presence of this substance in the Béchamp synthesis. Benda obtained the substance by means of the sodium salt which is soluble in ethyl alcohol in distinction to the primary salt which is insoluble. Pyman[2] and Reynolds, a little later, published some work about the same subject in which they also found that the secondary acid was a by-product in the Béchamp synthesis. Their separation of the secondary from the primary depended on the difference in acidity between the primary and the secondary arsanilic acids, and the purification of the secondary by means of barium salt. Their yield of the purified product was 2 to 3% of the theoretical. The yields of the method to be described vary from 20 to 30% of a fairly pure product.

Method.—After making many experiments, varying each factor step by step, we were able to obtain substantial yields of the secondary arsanilic acid by the following procedure:

Fifty-six and four tenths (56.4) cc. of commercial arsenic acid (specific

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[1] *Ber.*, **41**, 1672, 2367 (1908).

[2] *Trans. Chem. Soc.* (*London*), **93**, 1184 (1908).

gravity 1.88; 75.5% H_3AsO_4) are added with 1500 cc. of commercial aniline oil to a round bottom two-liter flask in an oil-bath. Into this are tightly fitted an inlet tube extending nearly to the bottom of the flask and a bent delivery tube fitted at its other end into a receiver. An outlet tube which can be connected with a pump is also fitted tightly to the receiver. The bath is slowly but constantly heated to 230° C. When the bath reaches a temperature of about 100° C. the aeration is begun by turning on the suction pump or negative pressure.

The object of aeration is to mix the aniline arsenic acid compound (formed as an insoluble precipitate on adding the acid to the oil) intimately with a large excess of aniline oil, so as to dissolve it rapidly as the temperature rises. If it remains unmixed it tends to decompose or reduce at the bottom of the flask. Furthermore, the aeration prevents superheating of the aniline oil, and effects a rapid distillation of the oil or a recovery of it.

When about 1200 cc. of aniline oil has been collected in the receiver, the process is stopped and the apparatus disconnected. After allowing the arsenic acid-aniline oil mixture to cool, 200 cc. of about three normal sodium hydroxide are added and well shaken. After standing for some time in a separatory funnel, the aqueous layer is drawn off. A second portion of 100 cc. of three normal sodium hydroxide is then added to the residue and in a like manner extracted.

The combined extracts are then thoroughly shaken with about five to ten grams of infusorial earth and filtered through hard filter paper.

To the combined filtrate (about 300 cc.) is added an equivalent amount of three normal acetic acid. Acetic acid is used instead of a mineral or strong acid as its salts are weak and easily hydrolyzed. It therefore allows an excess of the acid without much loss due to acid salt formation, and at the same time gives a buffer action. On adding the acetic acid crude arsanilic acid separates out as a more or less colored gum. It contains beside the crude acid, aniline oil, and various colored and humus matter. The mother liquor, after standing some time, is decanted, which, after a time often gives on slow crystallization a second yield of colorless and fairly pure secondary arsanilic acid.

Purification.—The crude product, containing much coloring matter and aniline oil, is dissolved in the least quantity of three normal sodium hydroxide and subjected to steam distillation, or aeration while boiling, to remove the aniline oil.[1]

The alkaline residue is then extracted with water and acidified with three normal acetic acid until the first permanent precipitate is produced.

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[1] By dissolving the gum in boiling hot water, allowing the solution to cool, the same object seems to be obtainable.

This precipitate, which contains most of the coloring matter and a little of the secondary arsanilic acid, is filtered off and discarded and the filtrate then completely precipitated by a slight excess of the three normal acetic acid. After allowing the mixture to stand for 12 hours, the supernatant liquid is poured off and the residue is extracted with hot acetone. The acetone extraction, on standing for 12 hours in a cold place precipitates out a fairly pure arsanilic acid. The residue is dissolved in three normal sodium hydroxide, filtered, and again reprecipitated with the acetic acid. Finally, it is washed with acetone and dried. Such a product will undoubtedly be sufficiently pure for most purposes. As mentioned before yields average from 20 to 30%.

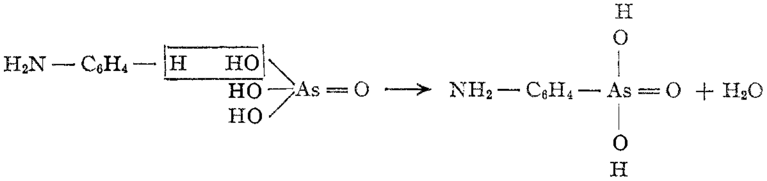
In most of the filtrations a Buchner funnel with hard filter paper was found most convenient and most efficient. The analyses of various purified samples gave the following results:

Lab. No.	Ash. %.	As air dried. %.	H_2O driven off, 105° C. %.	As dried, 105° C. %.	N dried, 105° C. %.
163	0.6	...	0.53	25.25	..
164	0.02	...	0.37	25.35	..
174	...	25.02	2.13	25.50	..
184	Trace	25.86	2.00	26.30	9.5
185	0.26	25.50	0.58	25.65	9.1
186	Trace	...	0.20	26.20	9.2
190	Trace	25.40	2.10	25.90	..
Average....................................				25.73	9.3
Theory......................................				25.65	9.65

The arsenic estimations were made by Ewins' method, and the nitrogen estimations were made by the modified Kjeldahl-Gunning method.

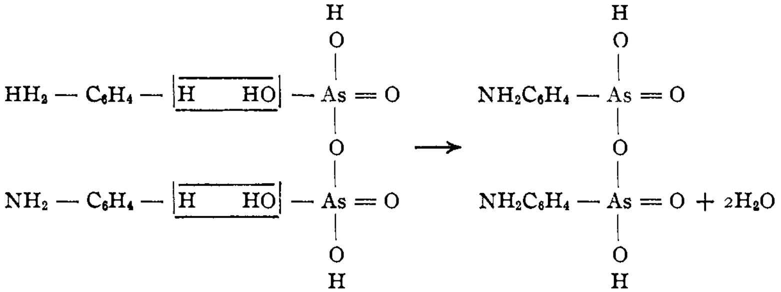
IV. General Discussion.

In the synthesis of the primary acid, anhydrous conditions at the start seem necessary, while in the process of making the secondary acid, any moisture present is speedily eliminated by the aeration. The question of the best form of the arsenic acid is of course an important one. The ortho-acid is presumed to act as follows:



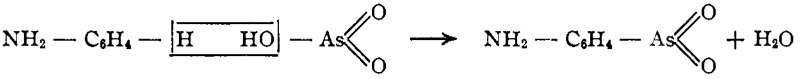
$$H_2N-C_6H_4-\boxed{H \quad HO}\begin{array}{l} \\ HO \\ HO \end{array}\!\!>\!As=O \longrightarrow NH_2-C_6H_4-\underset{\underset{H}{\overset{|}{O}}}{\overset{\overset{H}{\underset{|}{O}}}{As}}=O + H_2O$$

The pyro-acid, which is formed at 140 to 180° C. from the ortho-acid may act as follows:



$$\begin{array}{rclcrcl}
 & \text{H} & & & & \text{H} & \\
 & \text{O} & & & & \text{O} & \\
 & | & & & & | & \\
\text{HH}_2 - \text{C}_6\text{H}_4 - \boxed{\text{H} \quad \text{HO}} - & \text{As} & = \text{O} & & \text{NH}_2\text{C}_6\text{H}_4 - & \text{As} & = \text{O} \\
 & | & & & & | & \\
 & \text{O} & & \longrightarrow & & \text{O} & \\
 & | & & & & | & \\
\text{NH}_2 - \text{C}_6\text{H}_4 - \boxed{\text{H} \quad \text{HO}} - & \text{As} & = \text{O} & & \text{NH}_2\text{C}_6\text{H}_4 - & \text{As} & = \text{O} + 2\text{H}_2\text{O} \\
 & | & & & & | & \\
 & \text{O} & & & & \text{O} & \\
 & \text{H} & & & & \text{H} &
\end{array}$$

The meta-acid, which is formed at about 200 to 205° C. from the ortho-, or pyro-acid, might possibly act as follows:



The pyro- and meta-arsanilic acid compounds, of course, hydrolyze when subsequently treated with water into the ortho- and stable form. Theoretically, the pyro- and meta- forms of arsenic acid might prevent the reverse action by taking up the water liberated as the result of the reaction, but the temperature necessary to keep the reaction mixture in a liquid condition may prevent the hydrolysis of the pyro- or meta- acid. Furthermore, the reactivity of these forms with aniline may be much smaller than that of the ortho- form. This difficulty, however, could be circumvented by having a mixture of the ortho- and other forms. Thus far a few preliminary experiments made to obtain primary arsanilic acid, with a pyro- form or a mixture of the pyro- and ortho- form, have not yet given any increased yield.

The use of an inert gas as a substitute for aeration has thus far not given any increased yields nor decreased the coloring matter due to oxidation.

The use of an indicator like congo-red for regulating the amount of hydrochloric acid necessary to precipitate the free primary arsanilic acid without redissolving it as an acid salt, has been suggested by Dr. Michael Heidelberger, but not yet tried.

Our thanks are due to Mr. Leonard M. Wachter, for supervising all the analytical work, and to Mr. F. W. Gilcreas, for careful and painstaking analytical work.

V. Summary.

I. A method has been described for the preparation of primary arsanilic acid, *p*-aminophenylarsonic acid. It has the following advantages:

1. The product is practically free from the secondary arsanilic acid.
2. (*a*) No distillation of unused aniline oil is necessary.
   (*b*) No concentration of the mother liquid is required, and
   (*c*) no expensive apparatus or materials are needed.

3. It gives a practically pure product, in large yields, with ease.

II. A method has also been described for the preparation of secondary arsanilic acid, di-*p*-aminophenylarsinic acid. It has the following advantages:

1. It is practically free from the primary arsanilic acid.
2. (*a*) No concentration of the mother liquid is required, and
   (*b*) no expensive apparatus nor materials are needed.
3. It gives a practically pure product, in large yields, with ease.

III. The theoretical considerations have been briefly described.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH.]

ON CERTAIN AROMATIC AMINES AND CHLOROACETYL DERIVATIVES.

BY WALTER A. JACOBS, MICHAEL HEIDELBERGER AND IDA P. ROLF.

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The compounds described in the present paper represent intermediates in the preparation of a number of aromatic arsenic compounds which are included in a series of papers now being prepared for publication. It is desired to record these intermediates separately in order not to encumber the final papers with descriptions of non-arsenical compounds. It is also hoped that many of these substances, as well as the methods employed in their preparation, may prove of sufficient intrinsic interest to justify the present paper on general grounds.

Experimental.

o-**Chloroacetylaminophenol.**—This substance was first obtained by Aschan[1] and later by the present authors.[2] More recent experiments have shown the following method to be most suitable for the preparation of this compound: 22 g. *o*-aminophenol are dissolved in 250 cc. of dry acetone, the solution is then chilled, and treated drop by drop, with stirring, with 8.5 cc. (1 mol.) chloroacetyl chloride. 75 cc. 2 *N* aqueous sodium hydroxide are then added in one portion and the mixture further treated with 8.5 cc. chloroacetyl chloride. After acidifying to congo-red with hydrochloric acid the mixture is concentrated to dryness *in vacuo* and the residue suspended in water, filtered off, washed with water, and recrystallized from 50% alcohol. The yield was 31 g., melting at 138–40°.

o-**Chloroacetylaminophenyl Acetate.**—On adding a drop of concentrated sulfuric acid to a mixture of 2.5 g. *o*-chloroacetylaminophenol and 5 cc. acetic anhydride a clear solution was at once obtained. After warming on the water bath for ten minutes the solution was cooled, treated

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[1] *Ber.*, **20**, 1524 (1887).

[2] *J. Biol. Chem.*, **21**, 131 (1915).