in this reaction; commercial bisulfite suffices. Also, it is unnecessary to start with arsphenamine, that is, the dihydrochloride; equally good results can be secured by starting with dry arsphenamine base.

As the impurities present in the crude sulfarsphenamine have little bearing on the toxicity, it is unnecessary to purify the material.

Arsphenamine polyarsenide can be converted into a polyarsenide of sulfarsphenamine, but this substance is comparatively toxic.

Boston 17, Massachusetts

[Contribution from the Department of Pharmacology, Harvard Medical School]

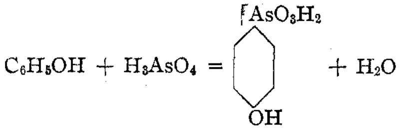
THE ARSONATION OF PHENOL[1]

By Walter G. Christiansen and Arthur J. Norton

Received July 9, 1923

In synthesizing arsphenamine from aniline or phenol by any of the common methods,[2] all of the reactions except that in which the arsenical group is introduced into the benzene nucleus progress smoothly, and excellent yields (75% or over) are easily obtained. Owing to the low yields obtained when aniline or phenol is arsonated with arsenic acid, the cost of production of the final product is greatly influenced by this reaction. Cheetham and Schmidt,[3] by modifying the conditions for arsonating aniline, secured recrystallized arsanilic acid in 26% yields, whereas the yields obtained by previous methods averaged approximately 15%. The arsonation of phenol with arsenic acid has been discussed in two papers; one by Conant[4] and the other by Jacobs and Heidelberger,[5] and in both cases the yield of hydrated sodium *p*-hydroxyphenylarsonate is given as approximately 20%. Conant suggests that by proper adjustment of the experimental conditions, it should be possible to raise the yield to about 30%.

For the production of sodium *p*-hydroxyphenylarsonate in this Laboratory, the method of Jacobs and Heidelberger was adopted but the yield averaged only 18% instead of 20. The main reaction is expressed by the equation



$$C_6H_5OH + H_3AsO_4 = C_6H_4(AsO_3H_2)(OH) + H_2O \qquad (1)$$

---

[1] This investigation was undertaken in connection with a study of arsphenamine which was made under a grant from the United States Interdepartmental Social Hygiene Board to the Harvard Medical School; the work was under the general direction of Dr. Reid Hunt.

[2] For a brief outline of these methods see Lythgoe, *Chem. Age,* **28,** 390 (1920).

[3] Cheetham and Schmidt, This Journal, **42,** 828 (1920).

[4] Conant, *ibid.,* **41,** 431 (1919).

[5] Jacobs and Heidelberger, *ibid.,* **41,** 1440 (1919).

By systematic modification of the reaction conditions the yield has gradually been raised until it is now possible to secure the product in 33% yields; although this is not a high yield, it is a very distinct improvement over an 18–20% yield.

Jacobs and Heidelberger mix sirupy arsenic acid (from which the excess of water has been removed by boiling to 150°) with phenol in a flask and heat the mixture under a reflux air condenser in an oil bath maintained at 155–160° for 7 hours. At first the substances remain as 2 distinct layers and the temperature inside the flask is approximately 145°, but as the reaction progresses the contents of the flask become homogeneous and the temperature falls steadily to about 130° due to the retention of the water eliminated by the reaction. Inasmuch as the reaction takes place, for some time at least, between 2 distinct phases, it seems advisable to stir the reacting materials as efficiently as possible. Also, the temperature of the reaction mixture should not be permitted to decrease to any great extent as it is accompanied by a marked decrease in the speed of reaction. This can be avoided by letting the water which is formed distil during the first part of the reaction. Since *p*-hydroxyphenylarsonic acid is hydrolyzed in water to a marked degree even at 130°[6] there is a tendency for the reverse of Reaction 1 to take place and it should probably be written as a reversible reaction. Owing, however, to the excess of arsenic acid and comparatively small amount of water the equilibrium would be far to the right. If the water is allowed to escape, the tendency toward reversal of the reaction will be diminished and the yield should be increased. Thus, to show clearly the extent to which water affects the reaction, when 200 g. of boiled arsenic acid, 100 g. of phenol and 20 cc. of water are heated and stirred under sufficient pressure to maintain the mixture at 140–150°, no reaction takes place.

All the detailed experiments that were made while the individual experimental conditions were being examined will be omitted in this report and only the method finally adopted will be carefully described.

Experimental Part

Three hundred and sixty g. of sirupy arsenic acid (75–80%) is boiled in a beaker until the temperature of the acid is 150°; about 60 g. of water is driven off leaving a sirup containing approximately 95% of orthoarsenic acid which is then added to 150 g. of phenol in a 500cc. round-bottom short-neck flask. By means of a 3-hole stopper, an efficient, jacketed stirrer and a thermometer are introduced into the flask and a connection is established with a downward condenser. The flask is set in an oil-bath which is heated at once to 155–160°, and the stirrer is run at a rate high enough to insure thorough mixing of the contents of the flask. When the inside temperature reaches 140° boiling commences, and water plus a very little phenol begins to distil. The distillation is allowed to continue until 30 cc. (1 molecular equivalent) of water has been collected; this usually requires 1 to 1.5 hours, and the inside temperature rises to 146°. The downward

---

[6] Schmitz, *Ber.*, **47**, 370 (1914).

condenser is then replaced by a return air condenser, and the reaction is allowed to continue until a total of 7 hours has elapsed from the time the contents of the flask first reached 140°. After the return condenser has been attached, the inside temperature declines slowly to 141° or 142°, and the reaction mixture becomes thicker and somewhat tarry. After the contents of the flask have been partially cooled, they are poured into 2 liters of water and mechanically stirred; the agitation is continued for a short time in order to break up the tarry material and enable the water to dissolve the hydroxyphenyl arsonic acids completely.

The reaction mixture is worked up by the method employed by Jacobs and Heidelberger, with a few modifications. Finely ground, fresh barium hydroxide is added gradually to the well-stirred water solution until the material is slightly alkaline to litmus, in order to remove the excess of arsenic acid; when this point is reached the solution becomes pink. If the procedure is carried out properly, 350–400 g. of $Ba(OH)_2.8H_2O$ should suffice. The time required by this method is greater than when a hot solution of barium hydroxide is used, but the method is more convenient and does not cause such a great increase in volume. After removal of the barium arsenate[7] by filtration, the mother liquor and washings are treated with sulfuric acid until the solution contains neither barium nor sulfate ions. When the barium sulfate has been separated[8] and thoroughly washed, the filtrate is concentrated on a steam-bath to about 1.5 liters, neutralized to litmus with sodium hydroxide, filtered, evaporated until the solution becomes well coated with crystals and then treated with 2.5 volumes of alcohol. After the mixture has cooled in an ice box the sodium *p*-hydroxyphenylarsonate is separated, washed with alcohol and dried in an oven at 80°. A second crop may be secured from the filtrate by concentrating it further and precipitating with alcohol. The total yield of anhydrous sodium *p*-hydroxyphenylarsonate is 126 g. (33%). By proper manipulation it is possible to obtain as much as 122 g. in the first crop and to have it free from sulfate, arsenate and sodium *o*-hydroxyphenylarsonate, which is one of the by-products formed in this reaction.[5]

When the downward condenser is not replaced by a return condenser, the total volume of water that distils is 55–60 cc., whereas the arsonation of phenol should liberate only 1 molecular equivalent (30 cc.) of water. Moreover, when all of the water is removed from the reaction chamber in this way, the mass becomes very tarry; the tar formation was so extensive in one experiment that the reaction had to be discontinued after 5.5 hours. The oxidation of organic matter to tarry material by the arsenic acid is the source of the excess of water that distils. To determine whether the reaction product is destructively oxidized, 20 g. of anhydrous sodium *p*-hydroxyphenylarsonate and 57 g. of boiled arsenic acid were heated and stirred so that the inside temperature was 145–150° for 3.5 hours. During this time, no water distilled, there was not the slightest trace of tar formation, and 15 g. of pure, anhydrous sodium *p*-hydroxyphenylarsonate was recovered from the material by working as described above. As there are slight, unavoidable mechanical losses incident to the use of the long process required to isolate the product, and as the original material was not exceptionally pure, the recovery of 15 g. is very good. This experiment proves conclusively that the reaction product is not destroyed when subjected to the action of hot arsenic acid and that the tar must be formed either from phenol that has not been acted on or from an intermediate substance formed in the reaction. It is

---

[7] Carefully washed barium arsenate proved just as efficient as lead arsenate as an insecticide when sprayed on potato plants and, when suspended in water, could be used in a spraying machine without difficulty.

[8] The filtration of large quantities of barium sulfate is usually tedious, but if filtering carbon is added to the suspension to be filtered and if a mat of this carbon is prepared on the filter by filtering an aqueous suspension of carbon, the barium sulfate may be removed rapidly and completely even when it is precipitated from cold solutions.

possible that the first step in the reaction is the formation of a phenyl ester of arsenic acid analogous to the known phenyl esters of sulfuric and phosphoric acids[9,10,11] and that this then rearranges to the *p*- and *o*-hydroxyphenylarsonic acids.

It has been frequently noted that the second crops of sodium *p*-hydroxyphenylarsonate contain some material insoluble in water and that the amount of this material varies directly with the degree of tar formation during the reaction. Examination of the insoluble matter showed that it is chiefly arsenious oxide which must be formed when the arsenic acid acts as an oxidizing agent. A few catalysts, such as copper arsenate, iodine or a dehydrated clay, were introduced but in each case the yield decreased instead of increased. It was hoped that the finely divided, dehydrated clay would provide a surface on which the two liquids might react and would facilitate the removal of water.

As Jacobs and Heidelberger[5] state that, after the removal of the barium sulfate, it is preferable to concentrate the solution in a vacuum, it seemed advisable to determine the extent to which the product is hydrolyzed in boiling water.

This was done by distilling 100 cc. of a 5% aqueous solution with steam so that 20 cc. of distillate collected every 5 minutes and analyzing the distillate for phenol by the bromine method, that is, by addition of an excess of bromine water of known strength, the determination of the excess of bromine by the addition of potassium iodide and titration of the liberated iodine with thiosulfate solution. When solutions of pure *p*-hydroxyphenylarsonic acid prepared either from the acid itself or by addition of hydrochloric acid to a solution of the purified sodium salt are examined in this way, the distillate is found to contain only 0.1 to 0.5 mg. of phenol in each 20 cc. After a slight excess of sodium carbonate has been added to the solution being distilled, the phenol content of the distillate is found to be approximately 1.0 mg. in 20 cc. The steam-distilled solution gives a very slight reaction for arsenic acid when tested with hydrogen sulfide. When 250 cc. of a 0.5% solution of phenol in water is distilled with steam, the distillate at first contains 156 mg. in each 20 cc. and it is only after prolonged distillation, namely, when the concentration of the phenol solution has become very low that the distillate contains only 1 mg. of phenol in 20 cc. Consequently, the hydrolysis of *p*-hydroxyphenylarsonic acid and its sodium salt is practically nil at 100°. This agrees with Schmitz'[12] conclusion which was arrived at by another method. These results indicate clearly the absence of any necessity for concentrating the solutions in a vacuum.

The modifications of Jacobs and Heidelberger's method of arsonating phenol outlined in this paper have been applied to large-scale production in the Arsphenamine Laboratory of the Massachusetts State Department

---

[9] Baumann, *Ber.*, **11**, 1907 (1878), isolated the phenyl ester of sulfuric acid as its potassium salt which, when heated, rearranged mainly to potassium *p*-phenolsulfonate. Similar results were obtained with other phenols.

[10] Heymann and Koenigs, *ibid.*, **19**, 3304 (1886), obtained the potassium salt of phenylphosphoric acid.

[11] A phenyl ester of arsenious acid is known. Lang, Mackey, and Gortner, *J. Chem. Soc.*, **93**, 1364 (1908).

[12] Ref. 6, p. 368.

of Health, and the yields have increased very greatly over those that were obtained prior to the institution of these changes.

Summary

By vigorous agitation of the reacting substances and partial removal of the water produced during the arsonation of phenol by arsenic acid, it is possible to secure a 33% yield of anhydrous sodium *p*-hydroxyphenylarsonate instead of the 20% yield obtained by previous methods.

It is suggested that a phenyl ester of arsenic acid may be an intermediate in the formation of hydroxyphenylarsonic acids by this reaction.

By distillation of aqueous solutions of *p*-hydroxyphenylarsonic acid, with steam, it is shown that at 100° this substance hydrolyzes scarcely at all into phenol and arsenic acid. This confirms Schmitz' results obtained by another method.

Boston 17, Massachusetts

[Contribution from the Department of Pharmacology, Harvard Medical School]

N-METHYL-PARA-AMINO-ORTHO-CHLOROPHENOL SULFATE, A NEW PHOTOGRAPHIC DEVELOPER

By Walter G. Christiansen

Received July 9, 1923

For a number of years N-methyl-*p*-aminophenol sulfate (Metol) has been the outstanding member of the aminophenol class of photographic developing agents, but analogous substances with additional groups attached to the benzene ring have not been investigated to determine the effect of these groups on the photographic developing properties of Metol. In this Laboratory the hydrochloride of *p*-amino-*o*-chlorophenol and the sulfate of its N-monomethyl derivative have been prepared. These compounds possess excellent developing properties when tested on both plates and paper but the methyl derivative is the superior; the finished plates and prints obtained by use of the latter substance are indistinguishable from those secured when Metol is used, but this material shows no marked advantages over Metol. Consequently, it may be concluded that the presence of a nuclear chlorine atom has little influence on the ability of Metol to function as a photographic developer. The amine is methylated by a well-known method, namely, condensation with formaldehyde and reduction of the condensation product.

Experimental Part

***p*-Nitro-*o*-chlorophenol.**[1]—A mixture of 10 g. of c. p. *p*-nitrophenol with 200 cc. of concd. hydrochloric acid is heated in a tall, narrow beaker until solution is complete.

---

[1] The method herein described is a modification of that used by Kollrepp, *Ann.*, **234,** 3 (1886).