The temperature coefficients for an increase of ten degrees show very little variation. An exception is found in the case of the β,γ-dichloropropyl acetate between 25° and 35°, where the coefficient seems to be 2.9.[1]

Summary.

1. A convenient method of procedure is introduced for the treatment of allyl alcohol with phosphorus trichloride in the preparation of allyl chloride based upon the insolubility of allyl chloride and the solubility of the phosphorous acid produced in the process.

2. In preparing β-monochloroisopropyl alcohol, Oppenheim brought about the separation of this alcohol by saturating the distillate obtained from the solution of hydrolysis products with potassium carbonate. It was found in performing this operation that a more convenient and complete separation was effected by salting out the alcohol with sodium chloride, and extracting with ether.

3. Substitution of chlorine in the β-position of the alkyl radical of the ester produces a marked retardation of the rate of hydrolysis. Substitution of two chlorine atoms in the β,γ-position produces a greater and in the β,β'-position a still greater retardation.

4. Evidence is furnished to show that the iso-structure in the molecule of an ester produces a retarding influence on the rate of hydrolysis.

The writer is indebted to Professor W. A. Drushel for his coöperation in this work.

[CONTRIBUTION FROM THE COLOR LABORATORY, UNITED STATES BUREAU OF CHEMISTRY, WASHINGTON, D. C.]

THE PREPARATION OF SODIUM *p*-HYDROXYPHENYLARSONATE.

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Received November 22, 1918.

The importance of the aromatic arsenic acids is every day becoming more evident. Many of them have been found to be useful drugs. Their preparation is a necessary step in the synthesis of many other aromatic arsenic compounds which have the most valuable therapeutic properties, for example, the widely used Arsphenamine ("Salvarsan"). The reaction by which the arylarsenic acids may be prepared are, thus, of considerable practical interest. About seven different methods have been employed with more or less success, depending largely on the particular compound desired. Of these methods the most direct is the replacement of hydrogen by the arsenic acid group, a reaction which takes place when certain aromatic substances (phenols and amines) are heated with arsenic

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[1] See Table II.

acid. Very little has been published concerning this reaction of the phenols, the only reference being a German patent.[1] Because of this paucity of information about a rather important reaction it is perhaps worth while to record some preliminary experiments which were performed with phenol and arsenic acid.

This work was done in connection with a series of experiments undertaken for the purpose of studying the complete synthesis of arsphenamine from phenol and arsenic acid. Consequently it was particularly necessary to obtain the product of the reaction—parahydroxyphenylarsonic acid—in a form most suitable for carrying out the next step. This next stage is the preparation of nitrohydroxyphenylarsonic acid by nitration at low temperature with the equivalent amount of nitric acid. The procedure finally adopted involved the separation of the oxy acid as the sodium salt, contaminated with some sodium sulfate. This mixture was, however, well adapted for nitration and yielded the desired nitrohydroxy acid in a pure condition. It was necessary to know what portion of the crystalline material was the sodium salt of the organic acid, in order to determine the amounts of nitric and sulphuric acids used in the nitration. A method of analysis was evolved which was very rapid and gave sufficiently accurate results for this purpose.

The Interaction of Phenol and Arsenic Acid.

The patent specifications direct that equivalent amounts of phenol and crystalline arsenic acid be heated together for several hours at 150° C. It is further recommended that the reaction be carried out in an apparatus provided with a return condenser and a stirrer. Several difficulties were encountered when these directions were followed. The crystalline arsenic acid (the anhydrous ortho acid) is not appreciably soluble in phenol and it is very hard to prevent the solid from separating as a lump at the bottom of the flask. A great deal of tarry by-product was obtained and the yield of hydroxyphenylarsonic acid was small.

A number of experiments were performed in an effort to discover more favorable conditions for carrying out the reaction. The solid arsenic acid was discarded and the syrupy acid was employed. The substance as it comes on the market contains about 22% of H_2O; by distilling various amounts of water from it, a syrup of varying acid concentration was readily obtained. Besides varying the acid concentration in this way, different temperatures were also tried. Each experiment was continued for about 3 hours and at the end of that time the melt was dissolved in water. The amount of insoluble tarry material could then be roughly estimated and, after following the procedure described below, the hydroxyphenylarsonic acid was isolated as its sodium salt.

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[1] D. R. P. 205,616, *Chem. Zentr.*, 1, 807 (1909). H. F. Lewis, *J. Ind. Eng. Chem.*, 11, 141 (1919).

The results of this work may be summarized as follows: The best form of the acid to employ is a syrup containing an amount of water corresponding to H_3AsO_4; this is readily obtained by distilling 22 cc. of water from 100 g. of the 78% acid. Less concentrated solutions give poorer yields of the final product, while more dehydrated forms of the acid cause the formation of a very large amount of tar. The liquid condition of this acid makes it very easy to obtain a thorough mixing of the substances during the reaction by the use of a high-speed stirrer. The temperature of the reaction should be kept very near 150°; a thermometer immersed in the oil bath should not fall below 147° or rise above 157°. Lower temperatures cause the main reaction to go too slowly, while higher temperatures very quickly cause the whole mass to become a thick tar. When the best conditions are employed only a relatively small amount of water is vaporized during the reaction. It was found convenient to allow this vapor to distil away from the reaction and be condensed in the usual manner. In this way no reflux condenser was necessary. The small amount of phenol carried over by the steam was compensated for by starting with about a 10% excess of this substance. The maximum yield obtained in these experiments was 21.5%; however, by carefully controlling these conditions, it should be possible to obtain a yield of at least 30%.

Isolation of Sodium *p*-Hydroxyphenylarsonate.

In the first experiments an attempt was made to isolate the oxyphenylarsonic acid in the way described in the patent. In this process the melt is dissolved in water, the aqueous solution is filtered and evaporated to dryness and the residue is extracted with acetone. The acetone solution on evaporating leaves the free acid which may then be recrystallized from glacial acetic acid. Only thick unworkable syrups were obtained by this method. A modification was tried next in which the final syrup (presumably the acid and impurities) was converted into the sodium salt with sodium hydroxide and the sodium salt crystallized from water and alcohol. While a crystalline salt could be readily isolated in this way, tests showed that it is very impure being contaminated with large amounts of salts of arsenic acid. Besides this difficulty the process seemed needlessly complicated. An entirely different procedure was finally decided upon which is as follows:

The aqueous solution of the melt is filtered from any tarry material. Barium hydroxide is now stirred into the solution until the original brown color begins to show a pink tint. At this point the solution is filtered and extracted several times with ether, thus removing a considerable amount of tarry impurity which is rather soluble in both acid and alkalies and can hence be extracted with success only when the acid concentration of the solution is suitable. The color change of this substance acts as an indicator for this point. More barium hydroxide is now added to the aqueous solution until a small portion, after being made alkaline and filtered, gives a test for barium ions. The entire solution is then made just alkaline to litmus with sodium hydroxide and filtered. The excess of barium is now removed by sodium sulfate and the solution filtered again. On evaporating to a small volume, a thick, red syrup is obtained from which the sodium salt begins to crystallize. If the extraction with ether has been successful in eliminating the greater part of the impurities a large part of the sodium hydroxyphenylarsonate can now be obtained by the addition of alcohol. More or less impurity always escapes the extraction and is present at this later stage as a sodium salt which is very soluble in water and prevents the crystallization of the other material. This difficulty may be very readily overcome by acidifying the syrup with dilute sulfuric acid until the solution is yellow and the impurities have separated as a thick, brown oil. This tarry material can then be readily separated from the solution which, on again neutralizing and evaporating, completely solidifies. The crystalline solid thus obtained is a mixture of sodium sulfate and sodium oxyphenylarsonate. The sodium sulfate seems to facilitate greatly the crystallization of the products from concentrated solutions. As will be shown later, the presence of sodium sulfate does not interfere with the nitration of the organic molecule. The mixture may be readily crystallized from dilute alcohol. One recrystallization of the mixture containing 33% of sodium sulfate gave a product containing less than 4% of sodium sulfate. The salt, when it separates from an aqueous or dilute alcoholic solution crystallizes with varying amounts of water which it readily loses on heating to 80° or 100°.

Method of Analysis of Mixtures of Sodium *p*-Hydroxyphenylarsonate and Sodium Sulfate.

The chief objection to working with the sodium salt rather than the free acid is that there is no simple criterion of purity, such as a melting point determination. This objection is particularly significant when the product is known to be contaminated with other substances such as sodium sulfate, and an exact amount must be taken for a subsequent step, as in the nitration. To circumvent this difficulty a method of analysis was devised. The procedure adopted resembles the bromine titration method for phenol determinations. When an aqueous solution of *p*-hydroxyphenylarsonic acid or its salts is treated with an excess of bromine water a precipitate of tribromophenol is at once formed.[1] On adding potassium iodide the excess bromine liberates iodine and any tribromophenol bromide also liberates bromine; the organic substance is thus all present as tribromophenol. The method actually employed was as follows: About a tenth of a gram of the substance dried at 100° was weighed into a small glass

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[1] Bertheim, Stuttgart, *Handbuch der Organischen Arsenverbindungen,* 1913, p. 113.

stoppered flask and dissolved in a little water. Fifteen cubic centimeters of an approximately normal solution of bromine and potassium bromide was now run in from a buret. The flask was stoppered and shaken several minutes. An excess of potassium iodide was now added, the flask shaken again and the solution titrated with $N/10$ sodium thiosulfate. The bromine solution was compared with the thiosulfate before each determination. This method was rapid and sufficiently accurate for the work at hand; it was checked by an analysis of pure phenol. Several determinations on the same substance usually varied from each other by two or three per cent.

Nitration of the Crude Salt.

A mixture of sodium sulfate and sodium *p*-hydroxyphenylarsonate obtained as the crude product of the process just described can be readily nitrated. From the analysis of the dried mixture the equivalent amount of nitric acid can be readily calculated. This amount of nitric acid is mixed with an equal amount of sulfuric acid and employed in the nitration as described in the literature. The crude salt is dried at 100°, finely powdered and slowly stirred into sulfuric acid and kept at 0°. The amount of sulfuric acid should be about half the weight of the salt used. The nitrating acids are now slowly introduced into the mixture which is well stirred and kept at 0° C. The temperature is then allowed to rise slowly to 10° C. and the product diluted with five times its volumes of water, the nitrohydroxyphenylarsonic acid separating out on standing 24 hours.

By this procedure a mixture containing 29% of sodium sulfate was readily nitrated and pure nitrohydroxyphenylarsonic acid obtained in a 75% yield.

Summary.

1. The reaction between phenol and arsenic acid has been studied and the optimum condition for the production of *p*-hydroxyphenylarsonic acid determined. A yield of 20% can be obtained.

2. A method has been devised for isolating the product of this reaction in the form of its crystalline sodium salt contaminated with some sodium sulfate. The tarry material formed in the reaction can be wholly eliminated.

3. A rapid method has been found for analyzing such a mixture of sodium sulfate and sodium hydroxyphenylarsonate.

4. The sodium hydroxyphenylarsonate may be readily obtained pure by recrystallizing the crude salt from dilute alcohol.

5. The crude salt may be directly nitrated with the production of nitrohydroxyphenylarsonic acid with good yields.