

### Summary

1. The nitronic acid structure for the nitro-anilines is discussed. Evidence is given that is compatible with the assumption that, in alcoholic solution, the *o*- and *p*-nitro-anilines exist in two or more tautomeric forms. The fundamental difference between the mercury salts of the *o*- and *p*-nitro-anilines and that formed by the *meta* compound is pointed out.

2. The mercurization of the nitro-anilines is discussed.

3. The positions taken by the entering mercury in the nitro-anilines has been established as *ortho* or *para*, or *ortho-para*, to the amino group.

4. The preparation of the following compounds is described: *p*-quinone-imide-aci-nitro mercury salt, *o*-acetoxymercuri-*p*-nitro-aniline, *o*-chloromercuri-*p*-nitro-aniline, *o*-,*o'*-di-acetoxymercuri-*p*-nitro-aniline, quinone-(1)-imide-aci-(4)nitro-(2)-mercury, *o*-,*o'*-mercury-*bis-p*-nitro-aniline, *o*-acetoxymercuri-acetyl-*p*-nitro-aniline, quinone-(1)-imide-aci-(2)-nitro mercury salt, *p*-acetoxymercuri-*o*-nitro-aniline, *p*-chloro-mercuri-*o*-nitro-aniline, quinone-(1)-imide-aci-(2)nitro-(4)-mercury, *p*-acetoxymercuri-di-acetyl-*o*-nitro-aniline, *p*-acetoxymercuri-acetyl-*o*-nitro-aniline, *N*-*iso*-mercuric acetate *m*-nitrophenylammonium acetate, *p*-acetoxymercuri-*m*-nitro-aniline, *o*-,*p*-diacetoxymercuri-*m*-nitro-aniline, *p*-acetoxymercuri-acetyl-*m*-nitro-aniline.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]  
**ALIPHATIC ARSONIC AND ARSINIC ACIDS, AND ALIPHATIC-AROMATIC ARSINIC ACIDS<sup>1</sup>**

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Received December 26, 1921

The extensive development of aromatic arsenicals as compared with those of the aliphatic series is in part explained by the fact that the most active and most effective trypanocidal drugs belong to the aromatic series. Another cause for the unbalanced development is found in the ease and convenience with which aromatic arsenicals can be synthesized. The methods of preparation for the arsenic compounds belonging to the aliphatic series are very numerous,<sup>2</sup> but they are quite unsatisfactory.

The arsonic ( $\text{RAsO}_3\text{H}_2$ ) and, to a less extent, the arsinic acids ( $\text{R}_2\text{AsO}_2\text{H}$ ) are substances from which many different types of compounds may be made, so that the lack of a satisfactory method of preparation of these has limited development in this field. The object of this research was to find an easy method for preparing these compounds and to apply such a method

<sup>1</sup> This communication is an abstract of a thesis submitted by A. J. Quick in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

<sup>2</sup> See THIS JOURNAL, 28, 347 (1906) for a list of the known methods.

to the preparation of certain aliphatic-aromatic acids which might have therapeutic value.

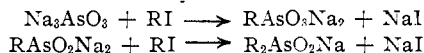
Of all methods available for preparing primary and secondary arsenic compounds, only one, namely the Meyer reaction, has any great importance. This consists in the treatment of sodium arsenite with an alkyl halide to give an arsonic acid, or the treatment of a sodium alkyl arsenite with an alkyl halide to give an arsinic acid.<sup>3</sup>

The reaction was first studied by G. Meyer<sup>4</sup> in 1883. Klinger and Kreutz<sup>5</sup> reinvestigated the reaction and developed it into a practical method for the preparation of sodium methyl arsonate. Auger<sup>6</sup> showed its application to the formation of dimethyl arsinic acid. Dehn<sup>7</sup> applied the method to the general synthesis of arsonic acids and obtained the salts of a number of the higher homologs in this way. It was necessary to use a rather uncertain and tedious procedure, however, for getting rid of the impurities and for the isolation of the product. Valeur and Delaby<sup>8</sup> reinvestigated the action of ethyl iodide on potassium arsenite, but added little to what was previously known so far as the isolation of the product was concerned.

The possibilities of the Meyer reaction were recognized to some extent in the preparation of toxic gases during the recent war. Ethyl dichloroarsine, which was used by Germany, was prepared by the action of ethyl chloride on sodium arsenite under pressure,<sup>9</sup> then subsequent reduction and treatment with hydrochloric acid. In this country methyl dichloroarsine was prepared by the action of dimethyl sulfate on sodium arsenite,<sup>10</sup> then subsequent reduction and treatment with hydrochloric acid. More recently methyl di-iodoarsine<sup>11</sup> has been made in an analogous manner except that methyl iodide was used in place of dimethyl sulfate. In none of these cases, however, was the arsonic acid isolated.

The greatest disadvantage at present in the Meyer method for making arsonic acids lies in the difficulty with which the products are isolated. The method, as it has been used, consists in the treatment of an aqueous alcoholic solution of sodium arsenite with an alkyl iodide until titration

<sup>3</sup> It is probable that the alkyl halide reacts with the tautomeric forms of the sodium arsenite or sodium alkyl arsonite in each instance ( $\text{Na}_2\text{O}_3\text{AsNa}$  and  $\text{RNaO}_2\text{AsNa}$ ) thus producing compounds with the alkyl radical attached to arsenic.



<sup>4</sup> Meyer, *Ber.*, **16**, 1440 (1883).

<sup>5</sup> Klinger and Kreutz, *Ann.*, **249**, 147 (1903).

<sup>6</sup> Auger, *Compt. rend.*, **137**, 925 (1903).

<sup>7</sup> Dehn, *Am. Chem. J.*, **35**, 48 (1906); *THIS JOURNAL*, **28**, 357 (1906).

<sup>8</sup> Valeur and Delaby, *Bull. soc. chim.*, **27**, 370 (1920).

<sup>9</sup> *J. Ind. Eng. Chem.*, **11**, 817 (1919).

<sup>10</sup> *Ibid.*, **11**, 105 (1919).

<sup>11</sup> *J. Chem. Soc.*, **119**, 426 (1921).

shows that most of the arsenite has reacted. When methyl iodide has been used the reaction mixture is merely allowed to cool and the sodium methylarsonate being insoluble in dilute alcohol, precipitates in practically pure state. The isolation of the higher homologs, however, is not so simple since the sodium salts are soluble in the dilute alcohol. In these latter cases, the method that has been employed is to distil the alcohol and any ether that is formed in the reaction, to acidify to incipient precipitation, then to oxidize the excess of sodium arsenite to sodium arsenate by means of chlorine and at the same time to precipitate free iodine, to filter the iodine, to precipitate the sodium arsenate in the cold with magnesia mixture, to filter this and finally precipitate the magnesium salt of the arsonic acid by boiling with an excess of magnesia mixture. The difficulties that must arise in obtaining a product in this way, especially one that is pure, can readily be seen. Moreover, Valeur and Delaby found that in the presence of aqueous alcoholic sodium arsenite, over 50% of the ethyl iodide is converted to ether, thus necessitating a large excess of the alkyl halide. The ether formation undoubtedly occurs in the preparation of arsonic acids of higher molecular weight.

In order to make the Meyer reaction applicable for wider synthetic work the objectionable features pointed out were eliminated. Alkyl bromides or chlorides were used instead of the iodides so that the free arsonic acids might be isolated directly by acidification; this is not possible when an iodide is used, since the liberated hydriodic acid formed immediately reduces the arsonic acid. The use of dilute alcohol as a solvent was given up and water alone was used, thus eliminating to a great extent the formation of ether. Heating and stirring were employed to hasten the reaction. The speed of the reaction was determined by titrating from time to time 1 or 2 cc. of the reaction mixture with standard iodine in order to show the amount of sodium arsenite unchanged. The isolation of the arsonic acid is then simple since it is merely necessary to concentrate the solution, filter off the sodium halide and acidify. The arsonic acid is precipitated in such form that, after one crystallization from alcohol or water, it is perfectly pure. With the higher, less soluble homologs the method is even simpler in that the arsonic acid may be precipitated directly without concentration from the reaction mixture, by means of hydrochloric acid.

There is no general method for the preparation of aliphatic arsinic acids. Sodium dimethyl arsinic acid is made commercially by the Cadet cacodyl reaction, but this reaction is limited to this substance and at best is beset with experimental difficulties. The condensation of an alkyl halide with arsenious chloride by means of sodium to produce dialkyl chloro-arsines which can be converted to the corresponding arsinic acids by bromination or chlorination and then hydrolysis, has been used as often as any other re-

action for making aliphatic arsinic acids. The method is unsatisfactory, however, owing to the fact that the pure dialkyl chloro-arsines are difficult to obtain and the conversion to arsonic acid does not give large yields. The Meyer reaction gives very good results. The arsonic acid made by the Meyer method is readily reduced with sulfur dioxide in the presence of hydrochloric acid to give good yields of the alkyl dichloro-arsine. This latter product is separated, then dissolved in 4 moles of sodium hydroxide and treated with an alkyl halide under the same conditions used in the preparation of arsonic acids. The reactions take place rapidly, only 4 hours or less being required in order to prepare any of the arsinic acids studied. The isolation of some of the arsinic acids, however, is a little more difficult than the isolation of the arsonic acids, on account of the great solubility in water of the lower homologs. It is necessary to neutralize the solution, then to concentrate and filter out the inorganic salts, and finally to acidify in order to precipitate the arsinic acid. If a salt of the arsinic acid is desired, the copper dialkyl arsinates are readily precipitated from a neutral solution by means of copper sulfate.

In studying the action of various alkyl bromides or chlorides on sodium arsenite or sodium alkyl arsenites, the activity of the halogen in the alkyl halide and the solubility of the alkyl halide are very important factors in determining the speed of reaction. Benzyl chloride, allyl bromide and ethylene chlorohydrin react very rapidly, whereas ethyl bromide or more particularly *isopropyl* bromide react slowly. The three halides just mentioned which react rapidly, give practically a complete conversion in  $\frac{1}{5}$  to  $\frac{1}{10}$  the time necessary with the simple alkyl halides. It is noticeable that with a series of alkyl halides the speed of reaction diminishes as the molecular weight of the alkyl halide is increased. Aryl halides cannot be used in this reaction. It was found also that phenoxy alkyl bromides or ethylene dibromide do not react with sodium arsenite under the conditions used.

The investigation on the arsinic and arsonic acids which has just been described was undertaken in connection with other researches, carried out with funds furnished by the Interdepartmental Social Hygiene Board, which had as their object the discovery of arsenic compounds of low toxicity and high trypanocidal action. All such active substances which have so far been discovered contain nitrogen. Moreover, this nitrogen has been in the form of an amino or substituted amino group in a benzene ring which holds the arsenic either in the form of an arsonic acid group or arseno group. A number of new arsenic compounds belonging to the class of aromatic-aliphatic arsinic acids have been prepared in some of which the nitrogen is substituted in the aliphatic group which is attached to the arsenic, and in others of which the nitrogen is both in the benzene ring holding the arsenic as well as in the aliphatic group. These substances may be represented by the compound formed between sodium phenyl arsenite and chloro-acetanilide.

$C_6H_5AsO_2Na_2 + ClCH_2CONHR \longrightarrow C_6H_5As(O_2Na)CH_2CONHR + NaCl$ .  
Compounds of this general structure are extremely easily produced by using practically the same conditions which are described for the preparation of the dialkyl arsinic acids. Because of the slight solubility in water of the reaction products, they are very readily isolated as the free acids. The reactions in practically every instance take place within a very few hours, and the yields are very nearly quantitative. The preliminary pharmacological results<sup>12</sup> show that these substances have a low toxicity, the lethal dose for rabbits varying from 250 to over 600 mg. per kg. of body weight. At the same time, however, the trypanocidal action is nil in some of the compounds, or low in most of the compounds, even though administered in relatively large amounts.

The reactions between sodium phenyl arsenite and various halogen compounds run just as smoothly as the sodium alkyl arsenites and much more readily than with the sodium arsenite. Whereas the phenoxyalkyl halides or ethylene dibromide do not react with sodium arsenite, they do react with the sodium alkyl or aryl arsenites to give the expected condensation products. The simple alkyl halides peculiarly, when condensed with sodium phenyl arsenite, give oily reaction products, although these substances when pure are crystalline solids.<sup>13</sup> A number of other condensations that were attempted yielded oily products and a method has not yet been developed by which these oils may be obtained as crystalline solids.

### Experimental

#### Synthesis of Arsonic Acids

**General Procedure.**<sup>14</sup>—One mole of arsenious oxide is dissolved in sufficient 10 *N* sodium hydroxide solution to produce tri-sodium arsenite. This is placed in a round-bottom flask fitted with an efficient mechanical stirrer and a reflux condenser. Slightly more than a mole of alkyl halide is added and the mixture stirred and refluxed until a cubic centimeter withdrawn from the reaction mixture and titrated with standard iodine shows that most of the sodium arsenite (80 to 90%) has reacted. The method of isolation is slightly different in each case and will be described under the individual compounds. In every case acidification with hydrochloric acid is involved. Excess acid must be avoided, as it tends to dissolve the arsonic acids.

**Sodium Methyl Arsonate,**<sup>15</sup>  $CH_3AsO_2Na_2$ .—The reaction between 99 g. of arsenious oxide, 300 cc. of 10 *N* sodium hydroxide solution and 150 g. of methyl iodide on warming

<sup>12</sup> Detailed pharmacological results will be published by Dr. A. S. Loevenhart of the University of Wisconsin when the investigation is completed.

<sup>13</sup> *Ber.*, **48**, 350 (1915).

<sup>14</sup> All analyses for arsenic were done by the method described by Robertson, *This Journal*, **43**, 182 (1921).

<sup>15</sup> *Ann.*, **249**, 147 (1903).

is complete in about 2 hours. An equal volume of alcohol is added to the mixture and the sodium methyl arsonate precipitates in very good yields. The product may be purified by dissolving in a small amount of water and reprecipitating with alcohol.

**Ethyl Arsonic Acid,  $C_2H_5AsO_3H_2$ .**—The reaction between 198 g. of arsenious oxide, 300 cc. of 10 *N* sodium hydroxide solution and 175 g. of ethyl bromide (110 g. is added at the beginning and 50 to 65 g. added gradually during the course of the reaction to compensate any loss due to volatilization), requires 24 to 48 hours before it is 90% complete. The reaction mixture is concentrated to a little less than half of its original volume and filtered to remove the sodium bromide which separates. The filtrate is now made neutral to phenolphthalein with hydrochloric acid, again concentrated to  $1/2$  or  $2/3$  its volume and filtered from sodium halide. It is next acidified with hydrochloric acid till congo red just commences to turn blue, once more concentrated to  $1/2$  or  $2/3$  its volume and filtered from sodium halide while still *hot*. On cooling, about 80 g. of needle-like crystals separates, together with a small quantity of sodium chloride. The filtrate will yield a larger quantity of ethyl arsonic acid if it is concentrated, filtered hot from the sodium halide and allowed to cool. This last treatment is repeated and from these two concentrations about 40 g. more of arsonic acid is obtained. The total yield of 120 g. is best purified from traces of salts by crystallizing from a small amount of water. The product then melts at  $95-96^\circ$  which is the same melting point as was found by La Coste.<sup>16</sup>

***n*-Propyl Arsonic Acid,  $C_3H_7AsO_3H_2$ .**—The reaction between 99 g. of arsenious oxide, 300 cc. of 10 *N* sodium hydroxide solution and 123 g. of *n*-propyl bromide requires 24 to 48 hours for 90% completion. The reaction mixture is treated exactly as with the ethyl arsonic acid. The propyl arsonic acid separates as small plates. As the acid is less soluble than the ethyl compound, it is obtained more readily and in better yields. The product is easily purified by recrystallization from a small amount of water and then has a melting point of  $126-7^\circ$  which agrees with that recorded in the literature.<sup>17</sup>

***n*-Butyl Arsonic Acid,  $C_4H_9AsO_3H_2$ .**—The reaction between 275 g. of *n*-butyl bromide, 198 g. of arsenious oxide and 600 cc. of 10 *N* sodium hydroxide solution requires 40 to 60 hours before 90% of the arsenious oxide has reacted. Small amounts of butyl bromide and butyl alcohol which have formed by hydrolysis are distilled and the solution is then neutralized to phenolphthalein with hydrochloric acid, concentrated to about half its volume and filtered. Upon adding hydrochloric acid till congo red just commences to turn blue, butyl arsonic acid separates as a thick crystalline paste. About 300 g. of the crude material is thus obtained. It is readily purified by a crystallization or two from hot water. It may also be recrystallized from alcohol. Butyl arsonic acid melts at  $159-160^\circ$  and in its general properties resembles the other arsonic acids. It forms an insoluble magnesium salt with magnesia mixture.

*Analyses.* Subs., 0.2000, 0.2000: required 21.2, 21.2 cc. of 0.1038 *N* I. Calc. for  $C_4H_9O_3As$ : As, 41.2. Found: 41.2, 41.2.

**Allyl Arsonic Acid,  $CB_2=CHCH_2AsO_3H_2$ .**<sup>18</sup>—The reaction between 250 g. of allyl bromide, 198 g. of arsenious oxide and 600 cc. of 10 *N* sodium hydroxide solution is 90% complete in 2 to 3 hours. The reaction mixture is neutralized to phenolphthalein with hydrochloric acid, concentrated to about  $1/2$  of its original volume and filtered. On acidifying the filtrate till congo red just commences to turn blue, the allyl arsonic

<sup>16</sup> La Coste, *Ann.*, **208**, 34 (1881).

<sup>17</sup> THIS JOURNAL, **28**, 352 (1906).

<sup>18</sup> During the preparation of this communication, an abstract of an English patent has appeared which describes the production of allyl arsonic acid and its salts. The procedure is somewhat different from the one used in this investigation. Brit. pat. 167,157; *Zentr.*, 1921, II, 1065.

acid precipitates in needle-like crystals, with a small amount of sodium chloride. The mixture is heated to boiling and filtered hot, thus removing most of the salt. The filtrate deposits crystals on cooling. These weigh 270 g., are pure after one recrystallization from water, and then melt at 128–9°.

*Analysis.* Subs., 0.2000: required 26.4 cc. of 0.09205 *N* I. Calc. for  $C_6H_5O_3As$ : As, 45.2. Found: 45.4.

**Benzyl Arsonic Acid,**<sup>19</sup>  $C_6H_5CH_2AsO_3H_2$ .—The reaction between 126 g. of benzyl chloride, 99 g. of arsenious oxide and 300 cc. of 10 *N* sodium hydroxide solution is more than 90% complete within 2 hours. An oily layer consisting of benzyl alcohol and a slight excess of benzyl chloride is always present at the end of the reaction. This is removed and the solution carefully neutralized to litmus with hydrochloric acid, then just a little more is added. On standing for about an hour, a small amount of flocculent material separates. This is filtered and the filtrate acidified till congo red commences to turn blue. Benzyl arsonic acid separates and is immediately filtered. It is washed with water and dried at 90°. The yields vary from about 130 to 135 g. After a crystallization from alcohol or water it melts at 167–8°.

**Attempts to Prepare Other Arsonic Acids.**—Ethylene chlorohydrin reacts very rapidly with sodium arsenite and in 10 minutes over 80% of the arsenious oxide has disappeared. The product, however, does not precipitate when treated in the way described for the alkyl arsonic acids. The solution is evaporated to an extremely small volume, the sodium halide filtered from time to time, and the residue is treated with absolute alcohol; practically all of the sodium halide separates and is filtered off. Upon evaporation of the filtrate an oil is obtained which is presumably the desired product, but as no method of purification was found it was not analyzed.

Similar results are obtained with trimethylene bromide, using two moles of sodium arsenite. The reaction takes place slowly. The product in this case is a thick oil which does not solidify.

Phenoxy-propyl bromide, phenoxy-ethyl bromide, isopropyl bromide and ethylene bromide react only very slowly with sodium arsenite and no products were isolated.

**General Procedure for Aliphatic Arsinic Acids.**—The conditions for the preparation of the arsinic acids are almost the same as those required for the preparation of arsonic acids. One mole of alkyl dichloro-arsine is dissolved in sufficient 10 *N* sodium hydroxide solution to produce the disodium alkyl arsenite. This is placed in a round-bottom flask fitted with an efficient mechanical stirrer and reflux condenser. Slightly more than a mole of alkyl halide is added and the mixture stirred and refluxed till titration shows that more than 90% of the disodium alkyl arsenite has reacted. Wherever the final products are only slightly soluble in water, direct acidification of the reaction mixture till congo red just commences to turn blue will cause the product to separate; where they are very soluble in water, it is necessary to proceed in a manner somewhat similar to that used for the isolation of the alkyl arsonic acids. Excess of acid causes the arsinic acids to become oily, so must be avoided.

**Diethyl Arsinic Acid,**<sup>20</sup>  $(C_2H_5)_2AsO_2H$ .—The reaction between 55 g. of ethyl bromide, 90 g. of ethyl dichloro-arsine and 210 cc. of 10 *N* sodium hydroxide requires from 4 to 6 hours before it is 90% complete. It is desirable to add 20 g. more of ethyl bromide

<sup>19</sup> THIS JOURNAL, 28, 347 (1906).

<sup>20</sup> *J. prakt. Chem.*, 63, 283 (1854).

toward the end of the reaction in order to replace that lost by volatilization. The excess of ethyl bromide is boiled away, the solution neutralized to phenolphthalein with hydrochloric acid, concentrated to half its volume and filtered from the salt which separates. The filtrate is acidified with hydrochloric acid till congo red just commences to turn blue, and concentrated once more to about  $\frac{2}{3}$  of its original volume when 50 g. of crude diethyl arsenic acid separate in plates. After two crystallizations from alcohol, the product is entirely free from a small amount of sodium chloride.

***n*-Butyl Dichloro-arsine,  $C_4H_9AsCl_2$ .**—A solution of 150 g. of crude *n*-butyl arsenic acid in 300 cc. of conc. hydrochloric acid is prepared. A few crystals of potassium iodide are added as a catalyst and then the solution is saturated with sulfur dioxide (about 2 hours is required). By this procedure, 100 g. of crude butyl dichloro-arsine separates. It is removed and the aqueous liquors are saturated with salt, thus yielding an additional quantity of the dichloride. The product is fractionated under diminished pressure and when pure consists of a colorless oil boiling at  $192-4^\circ$ .

*Analysis.* Subs., 0.5035:  $AgNO_3$ , 0.8426. Calc. for  $C_4H_9Cl_2As$ : Cl, 34.9. Found: 34.9.

***n*-Propyl *n*-Butyl Arsenic Acid,  $C_4H_9(C_3H_7)AsO_2H$ .**—The reaction between 25 g. of *n*-butyl dichloro-arsine, 60 cc. of 10 *N* sodium hydroxide solution and 20 g. of *n*-propyl bromide requires 3 to 5 hours for completion. The reaction mixture is made neutral to phenolphthalein with hydrochloric acid and then concentrated to half its volume. The salt which separates is filtered and the filtrate carefully acidified. The crystalline precipitate of arsenic acid is filtered and dried, and weighs 16 g. The filtrate is further concentrated to about  $\frac{2}{3}$  of its volume, filtered hot to remove the salt which separates, and then cooled to obtain a further amount of arsenic acid. The crude product must be crystallized once or twice from water to free it from sodium chloride, and then melts at  $127-8^\circ$ .

*Analyses.* Subs., 0.2000, 0.2000: required 21.1, 21.0 cc. of 0.09205 *N* I. Calc. for  $C_7H_{17}O_2As$ : As, 36.0. Found: 36.2, 36.1.

**Di-*n*-butyl Arsenic Acid,  $(C_4H_9)_2AsO_2H$ .**—The reaction between 61 g. of *n*-butyl bromide, 90 g. of butyl dichloro-arsine and 180 cc. of 10 *N* sodium hydroxide solution requires 3 hours for completion. The solution is neutralized, concentrated, and the salt filtered as described in the previous experiments. The filtrate is carefully acidified till congo red just commences to turn blue, and the crystalline dibutyl arsenic acid separates. After washing and drying it weighs 85 g. and after one crystallization from water it is perfectly pure and melts at  $137-8^\circ$ . Considerable care should be taken in acidifying the solution in order to precipitate the arsenic acid, since excess of acid causes the product to become oily.

*Analysis.* Subs., 0.2000: required 19.65 cc. of 0.09205 *N* I. Calc. for  $C_8H_{18}O_2As$ : As, 33.8. Found: 33.8.

The light-blue COPPER SALT,  $[(C_4H_9)AsO_2]_2Cu$ , is readily precipitated from a solution of dibutyl arsenic acid which has been just neutralized to phenolphthalein with sodium hydroxide by adding copper sulfate solution. The product is filtered, washed and dried for 2 hours at  $90^\circ$  in a vacuum. The yield is nearly quantitative.

*Analysis.* Subs., 0.2000: required 17.0 cc. of 0.09205 *N* I. Calc. for  $C_8H_{18}O_4As_2Cu$ : As, 29.6. Found: 29.2.

**General Procedure for Aliphatic-aromatic Arsenic Acids.**—One mole of the dichloro-arsine is dissolved in 4 moles of alkali in the usual way and 1 mole of the halogen compound added gradually, generally at room temperature. The reactions take place rapidly enough so that with the



sodium aromatic arsenites neither heating nor stirring are necessary in most cases to give excellent results. To isolate the products which for the most part are not very soluble in water, the reaction mixture is made neutral to phenolphthalein with hydrochloric acid. This causes the precipitation of a small amount of unchanged aromatic arsine oxide which is filtered. The filtrate is made acid with hydrochloric acid until congo red just commences to turn blue, to precipitate the product. If the product contains an amino group the final acidification must be done with care, not enough acid being added to redissolve the precipitate.

The majority of these compounds have decomposition points and not melting points. It was found that the decomposition points may vary considerably with the speed at which the temperature of the bath is raised.

**Phenylarsino Acetic Acid**,  $C_6H_5As(O_2H)CH_2CO_2H$ .—A mixture of 180 g. of phenyl dichloro-arsine and 365 cc. of 10 *N* sodium hydroxide solution is cooled and to this solution is added gradually with stirring 121 g. of sodium chloro-acetate in 150 cc. of water. An immediate reaction takes place and is complete within about 30 minutes, but it is best to allow the mixture to stand for 2 to 3 hours longer. The yield of product is 120 g. The substance may be purified by crystallization from hot water and then melts at  $141-2^\circ$  with decomposition.

*Analysis.* Subs., 0.2000: required 17.8 cc. of 0.09205 *N* I. Calc. for  $C_6H_5O_4As$ : As, 30.7. Found: 30.6.

**Phenyl Chloro-arsine Acetic Acid**,  $C_6H_5AsClCH_2CO_2H$ .—A solution is made of 60 g. of phenylarsino acetic acid in 180 cc. of conc. hydrochloric acid to which a few crystals of potassium iodide have been added. Sulfur dioxide is passed through to saturation and the phenyl chloro-arsine acetic acid separates in the form of plates. The yield is practically quantitative. The product is purified by crystallization from chloroform and then melts at  $102-3^\circ$ . Phosphorus pentachloride in chloroform solution converts the substance into phenyl dichloro-arsine.

*Analyses.* Subs., 0.2000: required 15.8 cc. of 0.09205 *N* I. Calc. for  $C_6H_5O_2ClAs$ : As, 30.4. Found: 30.7.

Subs., 0.5000:  $AgNO_3$ , 0.3430. Calc. for  $C_6H_5O_2ClAs$ : Cl, 14.4. Found: 14.3.

**Phenyl Bromo-arsine Acetic Acid**,  $C_6H_5AsBrCH_2CO_2H$ .—This is produced in a manner analogous to that for the chloro compound and after recrystallization from chloroform melts at  $113-4^\circ$ .

*Analysis.* Subs., 0.5000:  $AgNO_3$ , 0.2880. Calc. for  $C_6H_5O_2BrAs$ : Br, 27.5. Found: 27.1.

**Phenylarsino Acetanilide**,  $C_6H_5As(O_2H)CH_2CONHC_6H_5$ .—A solution of 35 g. of phenyl dichloro-arsine in 65 cc. of 10 *N* sodium hydroxide solution is made and with mechanical stirring 28 g. of chloro-acetanilide<sup>21</sup> is added. After 3 hours, when the reaction is complete, the solution is diluted with an equal volume of water before proceeding in the usual way. The product weighs 50 g. after washing with water and drying. It is purified by crystallization from water and then forms small needles melting at  $182-3^\circ$  with evolution of gas.

*Analysis.* Subs., 0.2000: required 12.2 cc. of 0.09205 *N* I. Calc. for  $C_{14}H_{14}O_2NAs$ : As, 23.5. Found: 23.7.

<sup>21</sup> THIS JOURNAL, 39, 1439 (1917).

**Phenyl Bromo-arsine Acetanilide**,  $C_6H_5AsBrCH_2CONHC_6H_5$ .—This product is made in a manner similar to that for phenyl bromo-arsine acetic acid, using 20 g. of phenylarsino acetanilide, 10 cc. of glacial acetic acid, 20 cc. of constant-boiling hydrobromic acid and 30 cc. of water containing a few crystals of potassium iodide. After saturation with sulfur dioxide, an oil separates which solidifies on standing. The compound is crystallized from methyl alcohol, and then melts at 108–110°.

*Analysis.* Subs., 0.4000:  $AgNO_3$ , 0.1900. Calc. for  $C_{14}H_{13}ONBrAs$ : Br, 21.9. Found: 22.4.

**Phenylarsino Acetphenetidine**,  $C_6H_5As(O_2H)CH_2CONHC_6H_4OC_2H_5(p)$ .—The reaction between 18 g. of chloro-acetphenetidine<sup>22</sup> and 19 g. of phenyl dichloro-arsine in 35 cc. of 10 *N* sodium hydroxide solution takes place and is complete in a few hours. The product crystallizes from alcohol in needles which melt at 175° with decomposition.

*Analyses.* Subs., 0.2000, 0.2000: required 10.70, 10.75 cc. of 0.1038 *N* I. Calc. for  $C_{16}H_{15}O_4NAs$ : As, 20.6. Found: 20.8, 20.9.

**Phenylarsino Aceto-arsanilic Acid**,  $C_6H_5As(O_2H)CH_2CONHC_6H_4AsO_3H_2(p)$ .—A solution of 31 g. of sodium chloro-acetoarsanilate<sup>23</sup> in 50 cc. of water is added gradually to 22 g. of phenyl dichloro-arsine in 45 cc. of 10 *N* sodium hydroxide solution. The reaction is complete in 2 hours. The chalky white material is extracted with a large amount of hot water, then with hot alcohol, and finally dried at 110°. As it is insoluble in water or the common organic solvents, it cannot be recrystallized. It may be dissolved in alkali, however, and reprecipitated by acidification. It does not melt below 250°.

*Analyses.* Subs., 0.2000, 0.2000: required 17.4, 17.4 cc. of 0.1038 *N* I. Calc. for  $C_{14}H_{13}O_6NAs_2$ : As, 33.8. Found: 33.8, 33.8.

**Phenylarsino *o*-Aceto-amino Benzoic Acid**,  $C_6H_5As(O_2H)CH_2CONHC_6H_4CO_2H(o)$ .—A solution of 22.5 g. of sodium *o*-chloro-aceto-amino benzoate<sup>24</sup> in 50 cc. of water is added to 22 g. of phenyl dichloro-arsine in 40 cc. of 10 *N* sodium hydroxide solution. The reaction takes only a short time for completion. (The sodium *o*-chloro-aceto-amino benzoate is prepared in a similar manner to the preparation of *p*-chloro-aceto-amino benzoic acid described below.) The product is purified by boiling the alkaline solution with animal charcoal, filtering and reprecipitating with hydrochloric acid. It melts at 198–200° with decomposition.

*Analysis.* Subs., 0.2000: required 11.9 cc. of 0.09205 *N* I. Calc. for  $C_{15}H_{14}O_6NAs$ : As, 20.6. Found: 20.4.

**$\beta$ -Phenoxy-ethyl Phenyl-arsinic Acid**,  $C_6H_5As(O_2H)CH_2CH_2OC_6H_5$ .—The reaction between 45 g. of  $\beta$ -phenoxy-ethyl bromide, 45 g. of phenyl dichloro-arsine and 80 cc. of 10 *N* sodium hydroxide solution requires 4 to 6 hours for completion. Heating and mechanical stirring are necessary to get good results. The small excess of unchanged halide is removed first before isolating the product. The substance separates as an oil which soon crystallizes. After recrystallization from water it melts at 122–3° and weighs about 20 g.

*Analysis.* Subs., 0.2000: required 14.3 cc. of 0.09205 *N* I. Calc. for  $C_{14}H_{13}O_3As$ : As, 24.5. Found: 24.6.

**Ethylene Diphenyl-diarsinic Acid**,  $C_2H_4(C_6H_5AsO_2H)_2$ .—The reaction between 32 g. of phenyl dichloro-arsine, 120 cc. of 10 *N* sodium hydroxide solution and 60 g. of ethyl-

<sup>22</sup> THIS JOURNAL, 41, 1453 (1919).

<sup>23</sup> *Ibid.*, 41, 1810 (1919).

<sup>24</sup> *Ber.*, 38, 1684 (1905).

ene bromide requires 4 to 8 hours for completion. Heating and mechanical stirring are necessary. The product separates as an oil. On dissolving in dil. ammonium hydroxide, filtering and again precipitating by careful acidification with hydrochloric acid, an oil is formed which gradually solidifies. The product may be recrystallized from hot water or alcohol and melts at 209–11°.

*Analysis.* Subs., 0.2000: required 21.7 cc. of 0.09205 *N* I. Calc. for  $C_{14}H_{16}O_4As_2$ : As, 37.7. Found: 37.3.

Subs., 0.2000: required 8.8 cc. of 0.135 *N* NaOH. Found: 8.4 cc.

*p*-Amino-phenyl Dichloro-arsine Hydrochloride,<sup>25</sup>  $(p)Cl_2AsC_6H_4NH_2HCl$ .—This product is precipitated in practically quantitative yields when a stream of sulfur dioxide is passed into a solution of one part of arsenic acid dissolved in 3 parts of conc. hydrochloric acid. A crystal or two of potassium iodide is added as a catalyst.

*p*-Amino-phenylarsino Acetanilide,  $(p)H_2NC_6H_4As(O_2H)CH_2CONHC_6H_5$ .—This substance is prepared in the usual way from 58 g. of *p*-amino-phenyl dichloro-arsine hydrochloride in 100 cc. of 10 *N* sodium hydroxide solution and 34 g. of chloro-acetanilide. The reaction is complete in about an hour but is allowed to stand for several hours. The product may be purified by crystallizing from either water or alcohol. It melts at 181–2° with decomposition.

*Analysis.* Subs., 0.2000: required 13 cc. of 0.09205 *N* I. Calc. for  $C_{14}H_{16}O_3N_2As$ : As, 22.4. Found: 22.4.

*p*-Aceto-amino-phenylarsino Acetanilide,  $(p)CH_3CONHC_6H_4As(O_2H)CH_2CONHC_6H_5$ .—This compound is made from the one just described by warming for 15 minutes after the initial reaction has taken place, with a slight excess of acetic anhydride. The compound which separates upon diluting with water is washed with dil. hydrochloric acid, then with water, and finally dried. It crystallizes from hot water in plates which melt at 205–6° with decomposition.

*Analyses.* Subs., 0.2000, 0.2000: required 11.65, 11.65 cc. of 0.09205 *N* I. Calc. for  $C_{16}H_{17}O_4N_2As$ : As, 19.9. Found: 20.0, 20.0.

*p*-Glycyl-aminophenylarsino Acetanilide,  $HO_2CCH_2NHC_6H_4As(O_2H)CH_2CONHC_6H_5$ .—This compound is prepared from *p*-amino-phenylarsino acetanilide by heating 10 g. in 30 cc. of 4% sodium hydroxide solution, with 7 g. of chloroacetic acid. After refluxing for 3 to 4 hours and allowing to cool, an oil separates which solidifies on standing, or sometimes a solid separates directly. The compound after crystallization from methyl alcohol melts at 199° with decomposition.

*Analyses.* Subs., 0.2000, 0.2000: required 11.15, 11.2 cc. of 0.09205 *N* I. Calc. for  $C_{16}H_{18}O_5N_2As$ : As, 19.1. Found: 19.2, 19.2.

*p*-Amino-phenylarsino Acetphenetidine,  $(p)H_2NC_6H_4As(O_2H)CH_2CONHC_6H_4O-C_2H_5(p)$ .—The reaction between 21 g. of chloro-acetphenetidine and 29 g. of *p*-amino-phenyl dichloro-arsine hydrochloride in 50 cc. of 10 *N* sodium hydroxide solution is complete in 3 hours. The product is crystallized from alcohol, then melts at 211.5–212.5°.

*Analyses.* Subs., 0.2000, 0.2000: required 11.5, 11.5 cc. of 0.09205 *N* I. Calc. for  $C_{16}H_{19}O_4N_2As$ : As, 19.8. Found: 19.8, 19.8.

*p*-Aceto-amino-phenylarsino Acetphenetidine,  $(p)CH_3CONHC_6H_4(AsO_2H)-CH_2CONHC_6H_4OC_2H_5(p)$ .—The product is made from the one just described by using the directions given under *p*-aceto-amino-phenylarsino acetanilide. On crystallization from alcohol it melts at 214–215° with decomposition.

*Analyses.* Subs., 0.2000, 0.2000: required 10.3, 10.3 cc. of 0.09205 *N* I. Calc. for  $C_{18}H_{21}O_5N_2As$ : As, 17.8. Found: 17.7, 17.7.

<sup>25</sup> *Ber.*, 43, 917 (1910).

*p*-Amino-phenylarsino Acetoarsanilic Acid,  $(p)H_2NC_6H_4As(O_2H)CH_2CONHC_6H_4AsO_3H_2(p)$ .—The reaction between 29 g. of chloro-aceto-arsanilic acid in 20 cc. of 10 *N* sodium hydroxide solution and sodium *p*-amino-phenyl arsenite made by dissolving 29 g. of *p*-amino-phenyl dichloro-arsine hydrochloride in 50 cc. of 10 *N* sodium hydroxide solution, is complete within 3 hours. The product is purified by crystallization from hot water. It does not melt below 350°.

*Analyses.* Subs., 0.2000, 0.2000: required 18.8, 18.9 cc. of 0.09205 *N* I. Calc. for  $C_{14}H_{16}O_6N_2As_2$ : As, 32.7. Found: 32.3, 32.5.

*p*-Aceto-amino-phenylarsino Aceto-arsanilic Acid,  $(p)CH_3CONHC_6H_4As(O_2H)CH_2CONHC_6H_4AsO_3H_2(p)$ .—This compound is made by the general procedure already described under the other aceto compounds. It forms in poor yields. It is purified by crystallization from hot water. It does not melt below 250°.

*Analyses.* Subs., 0.2000, 0.2000: required 17.3, 17.3 cc. of 0.09205 *N* I. Calc. for  $C_{16}H_{18}O_7N_2As_2$ : As, 30.0. Found: 29.7, 29.9.

*p*-Chloro-aceto-amino Benzoic Acid,  $(p)ClCH_2CONHC_6H_4CO_2H$ .—A suspension of 10 g. of *p*-amino benzoic acid in a mixture of 50 cc. of glacial acetic acid and 50 cc. of saturated sodium acetate solution is treated slowly, with vigorous stirring, with chloroacetyl chloride. A white amorphous solid precipitates, is filtered, washed and dried. For subsequent work the crude material is satisfactory, but it may be purified by crystallization from alcohol and then has a melting point of 239°.

*Analysis.* Subs., 0.2000:  $AgNO_3$ , 0.1575. Calc. for  $C_8H_8O_3NCl$ : Cl, 16.61. Found: 16.5.

*p*-Amino-phenylarsino *p*-Aceto-amino Benzoic Acid,  $(p)H_2NC_6H_4As(O_2H)CH_2CONHC_6H_4CO_2H(p)$ .—This reaction between 42 g. of *p*-chloro-aceto-amino benzoic acid in 10 cc. of 10 *N* sodium hydroxide solution and 58 g. of *p*-amino-phenyl dichloro-arsine hydrochloride in 100 cc. of 10 *N* sodium hydroxide solution is complete in a few hours. It forms needles from hot water, melting at 217° with decomposition.

*Analysis.* Subs., 0.2000: required 11.4 cc. of 0.09205 *N* I. Calc. for  $C_{14}H_{18}O_6N_2As$ : As, 19.8. Found: 19.6.

### Summary

1. It has been shown that aliphatic arsonic acids, aliphatic arsinic acids and aliphatic-aromatic arsinic acids may be very readily prepared by the action of various halogen compounds upon an aqueous solution of sodium arsenite, sodium alkyl arsenite or sodium aryl arsenite.

2. This method has been applied to the preparation of several alkyl arsonic acids, as well as to allyl and benzyl arsonic acids; also to simple and mixed alkyl arsinic acids.

3. This method has also been applied to the preparation of many compounds of the general formula  $RA_s(O_2H)CH_2CONHR'$  where R is a phenyl, *p*-amino-phenyl or *p*-aceto-amino-phenyl group and R' is a phenyl or substituted phenyl group. The compounds dissolve readily in aqueous alkalis, giving solutions which possess relatively low toxicity but at the same time only a slight trypanocidal action.