

UNITED STATES PATENT OFFICE.

HEINRICH BART, OF BAD DÜRKHEIM, GERMANY.

PROCESS OF PRODUCTION OF ORGANIC DERIVATIVES OF ARSENIC ACID.

1,061,587.

Specification of Letters Patent.

Patented May 13, 1913.

No Drawing.

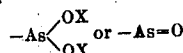
Application filed December 27, 1910. Serial No. 599,329.

To all whom it may concern:

Be it known that I, HEINRICH BART, a subject of the German Emperor, and resident of Bad Dürkheim, Germany, have invented certain new and useful Improvements in the Process of Production of Organic Derivatives of Arsenic Acid, of which the following is a specification.

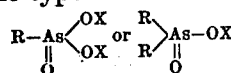
The arsenic compounds in which arsenic is bonded to organic radicals have created considerable interest on account of their application in the therapeutics of infectious diseases, and especially in connection with trypanosoma and spirochaetes. For therapeutic reasons, as large a number as possible of arsenic compounds with the greatest possible variation of the substituents are required to obtain valuable therapeutic preparations. It has consequently appeared desirable to find out syntheses for a simple, or multiple, introduction of arsenic into organic compounds, which would differ from the known process by being capable of general application so as to produce, for example, the important, but hitherto unknown, polyarsenic acids. By the process herein-after described which is capable of as large an application as the Sandmeyer and Gattermann reactions, such bodies can be obtained in a simple manner.

According to Schraube and Schmitt, *Report* 27,522, it is known that it is only at temperatures of over 100° centigrade that the normal benzene diazotates undergo the intramolecular change to the iso compounds, so that it is supposed that in this case normal diazotate entered into reaction. In the *Reports of the Deutsche Chemische Gesellschaft*, vol. 23, page 2672, Ann., it is stated that an alkaline solution of benzene diazotate can be changed by sodium arsenite partly into benzene and other reduction products of diazobenzene. In that case the arsenious acid acted only as reducing agent without any substituting action of the arsenious acid on benzene diazotate coming into play. Now the remarkable observation has been made that by the action of inorganic, or organic, bodies, containing the following group:

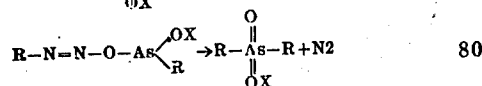
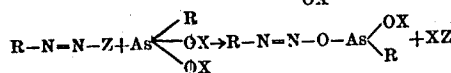
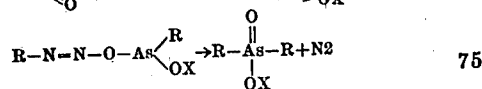
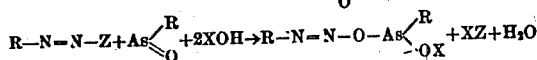
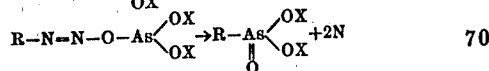
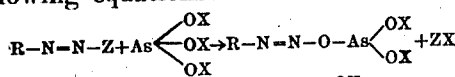


(wherein X denotes a group acting as a cation, or a radical), such for instance, as arsenious acid, or salts thereof, the organic aryl arsenic oxids, the aryl arsinious acids, or their salt-like compounds, and the like,

in suspension, or dissolved, on compounds having one, or more, aromatic nuclei, in which at least a diazo group is present, compounds of the type:



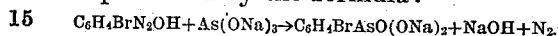
are formed, probably in accordance with the following equations:



Z denotes a negative, or positive, group, such, for instance, as halogen, $\text{--O--SO}_3\text{X}(\text{OX})_2$ and the like, or OX, X representing a cation such as Na, K, etc. It has been further shown that normal benzene diazotate possesses a very small capacity of reaction toward arsenic compounds as regards the substitution of the arsenic acid group, but that the corresponding iso compound reacts much better. If the nucleus undergoes a simple, or a multiple, substitution, the capacity for reaction is increased both in normal and iso compounds. Positive substituents here come into consideration, such, for instance, as NR_2 (R=alkyls, or acid radical), OC_2H_5 , HgR' (R'=OH or an acid radical as well as alkyls, or aryls), and, to a greater extent, the negative substituents, such, for instance, as NO_2 , $\text{AsO}(\text{OH})_2$, halogens, COOH , OR'' (R''=acid radical), SO_3H , and the like. The process is best carried out in alkaline, and if needs be also in neutral, solution, when diazonium salts, syn-, or anti-diazo bodies, are employed. When acid is present, the yields decrease as the concentration of the H-ions increases. The yields and the ease of execution insure the technical value of the process.

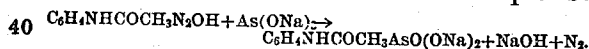
Example I: 1 part of parabromanilin is dissolved with 2 parts of concentrated hydrochloric acid (specific gravity 1.16) and 10 parts of water, and diazotized in the

usual manner. 3 parts of sodium arsenite are introduced into the diazo solution thus obtained, the sodium arsenite being dissolved in water; the alkali is added and the solution is heated. When the evolution of nitrogen is over, it is filtered from the separated oil and the addition of hydrochloric acid precipitates the para-bromo-phenyl-arsinic acid. The latter crystallizes in white needles, dissolves with difficulty in water, but more readily in methyl and ethyl alcohol from which it can be re-crystallized. The reaction of this example of the invention is represented by the formula:



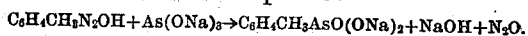
The other halogen substitution products behave in a similar manner.

Example II: 1.5 parts of para-mono-acetylphenylene diamine are mixed with 3.5 parts of concentrated hydrochloric acid and 20 parts of water, and diazotized in the usual manner. To this solution are added 2.5 parts of sodium arsenite, dissolved in 5 parts of water. Care is taken that the reaction mixture shows no acid reaction, this being insured if necessary by neutralizing with dilute soda lye. The solution is then heated slowly until the nitrogen ceases to be evolved, then separated from by products and filtered. The filtrate is evaporated down to $\frac{1}{4}$ of its original volume and on cooling, the sodium salt of the para-mono-acetylaminophenyl arsenic acid crystallizes out in the form of needles. It can be re-crystallized from methyl alcohol, from which it is precipitated in white needles; it can also be re-crystallized from water. The formula of the reaction of this example is:



The other diazo compounds in which the amino groups contain substituents, such, for instance, as CH_2COOH , NHCONH_2 , C_6H_5 , alkyls and the like, behave in a similar way.

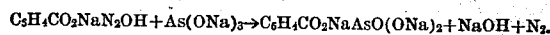
Example III: 1 part of para-toluidine is dissolved in a mixture of 10 parts of water and 2 parts of concentrated hydrochloric acid and converted into the diazo compound. It is neutralized with the equivalent quantity of sodium hydroxid and a solution of 2.5 parts of sodium arsenite in 5 parts of water is added. The reaction is completed by heating. After filtering off the insoluble substances, formed as by products, it is possible, by adding to the filtrate hydrochloric acid, to precipitate the resulting para-tolyl-arsinic acid in white crystals which are almost chemically pure. The acid is difficultly soluble in cold water, but readily soluble in hot water, crystallizing out in long white needles. The formula of the reaction of this example is:



The properties are described by La Coste

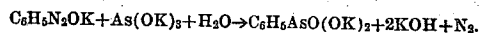
and Michaelis, A. 201, page 255. The isomeric toluidins behave in an analogous manner.

Example IV: 1 part of ortho-amino benzoic acid is neutralized with 15 parts of water and the equivalent quantity of sodium carbonate, and carefully mixed with 2 parts of concentrated hydrochloric acid (specific gravity 1.190) and diazotized. 3 parts of sodium arsenite dissolved in 5 parts of water are added, care being taken to insure a neutral, or alkaline, reaction. The reaction mixture is heated until the reaction is completed. The neutral solution is evaporated to dryness and the by products are extracted with methyl alcohol and then the residue is again dissolved in water, acidified with hydrochloric acid, separated from the by products by filtration and evaporated to dryness. The ortho-benzarsinic acid can now be extracted with methyl alcohol. It is thus obtained almost free from salicylic acid and benzoic acid. It crystallizes out of water in fine white needles. The sodium salt is more readily soluble in water than the free acid. The formula of the reaction of the foregoing example is represented as follows:



The isomeric amino-benzoic acids behave in an analogous manner.

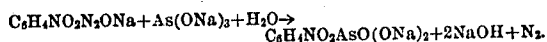
Example V: 1.61 parts of iso-diazo-benzene-potassium are dissolved in 6 parts of water and 2 parts of potassium arsenite are added; the whole is well stirred and heated until the evolution of nitrogen ceases. Neutralization is then effected with acid, the by products are removed, the solution evaporated to dryness and the residue extracted with alcohol. The potassium phenylarsinate thus obtained is dissolved in water and converted into the free acid by the addition of hydrochloric acid. Its properties are described by La Coste and Michaelis A. 201, page 203. The reaction of this example is represented as follows:



The homologous iso-diazo compounds behave in an analogous manner.

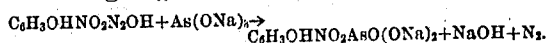
Example VI: 1.8 parts of ortho-nitro-iodiazo-benzene sodium and 2 parts of sodium arsenite are dissolved in 4 parts of water and heated until the evolution of nitrogen ceases. The mixture is acidified, evaporated to dryness and the reacting ortho-nitrophenylarsinic acid is extracted with alcohol. In this way an almost chemically pure acid is obtained. To more completely purify it, it is re-crystallized out of absolute alcohol, or water. It crystallizes in white needles which are difficultly soluble in water and alcohol, but insoluble in ether. At a high temperature the acid decrepitates without first melting. The reaction of this

example of the invention is represented by the formula:



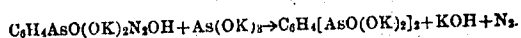
5 The isomeric nitrophenol arsinic acids react in a similar manner.

Example VII: 1.54 parts of 4-nitro-2-aminophenol are dissolved with 6 parts of water and 2 parts of concentrated hydrochloric acid (specific gravity 1.16) and diazotized in the usual manner. To this solution is added, at a temperature which should not be too low, a mixture of about from 8 to 10 parts of sodium hydroxid and 1.5 parts of sodium arsenite in 6 parts of water, and the whole heated without giving too strongly an alkaline reaction until the nitrogen has ceased to evolve. The reaction mixture is neutralized, filtered from the insoluble parts, and the filtrate with an excess of hydrochloric acid is evaporated to dryness. The residue of this evaporation is extracted with ethyl alcohol. The extract is boiled with animal charcoal and filtered. The new nitrophenolarsenic acid crystallizes out of the filtrate in light yellow crystals. It decomposes briskly when heated, it is soluble in alcohol, acetone, acetic acid and in hot water, but difficultly soluble in cold water. The aqueous solution of the alkali salts is of a yellow color. The reaction of the foregoing example has the formula:



35 The isomeric nitrophenol-arsinic acids can be obtained in an analogous manner.

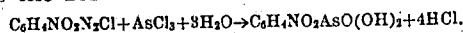
Example VIII: 2 parts of sodium meta-aminophenylarsinate are dissolved in 6 parts of water and 2 parts of hydrochloric acid (specific gravity 1.19) and diazotized. This solution is united with a mixture of about 8 to 10 parts of potassium hydroxid and 2 parts of potassium arsenite dissolved in 5 parts of water. The mixture is heated until the evolution of nitrogen ceases, neutralized and filtered. The filtrate is evaporated to dryness with a slight excess of mineral acid and extracted with methyl alcohol. In this way the benzene-meta-di-arsinic acid is obtained which is difficultly soluble in cold water and can be re-crystallized therefrom. To completely purify the product, it is treated with animal charcoal. Its alkali salts are readily soluble. The formula of the reaction of this example of the invention is:



The isomeric di-arsinic acids are obtained in an analogous manner. Other diazo arsinic acids which contain also substituents, such, for instance, the amino group NH_2OH , halogens, SO_3H , $\text{AsO}(\text{OH})_2$ and the like, react in the same way.

Example IX: 1.38 parts of para-nitranilin are dissolved in 8 parts of water and 2 parts

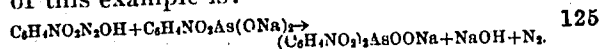
of hydrochloric acid (specific gravity 1.16) and diazotized in the usual way. The mixture is then mixed with a solution of 1.5 parts of arsenious acid in 2 parts of hydrochloric acid (specific gravity 1.16) as solvent (oxalic acid and tartaric acid may be used with equal success) and heated until the evolution of nitrogen ceases. The undissolved part is filtered off and the filtrate is evaporated to dryness. By crystallizing out of water it is possible to separate out the resulting by products. In this way the para-nitrophenyl-arsinic acid is obtained which can be crystallized out of water. It is readily soluble in alcohol. The reaction of the example of the invention just described has the formula:



Example X: 1.45 parts of 4-nitro-2-aminophenol are dissolved in 6 parts of water and 2 parts of hydrochloric acid (specific gravity 1.16) and diazotized in the usual manner and mixed with the equivalent quantity of sodium hydroxid until a slight alkaline reaction is shown. Thereupon 1.5 parts of magnesium arsenite suspended in 6 parts of water are added and the whole heated until the evolution of nitrogen ceases. The product is acidified with hydrochloric acid and boiled, the undissolved portion filtered off and the solution evaporated to dryness. From the residue of the evaporation the nitrophenolarsenic acid is removed by ethyl alcohol and preferably re-crystallized out of water. It is identical with the nitrophenol-arsinic acid obtained in accordance with Example VII. The reaction of this example of the invention has the formula:

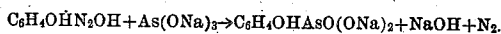


Example XI: 1.38 parts of para-nitranilin are dissolved in 6 parts of water and 8 parts of hydrochloric acid (specific gravity 1.19) and diazotized in the usual manner. The diazo solution thus obtained is neutralized with the equivalent quantity of sodium hydroxid and mixed with 2.5 parts of the sodium salt of para-nitro-phenyl-arsenious acid. A brisk evolution of nitrogen takes place at once, the cessation of which indicates that the reaction is at an end. The mixture is then filtered off and the filtrate is acidified with hydrochloric acid. Para-dinitro-di-phenyl-arsinic acid separates out as a whitish-yellow filtrate. This acid is difficultly soluble in water and in alcohol and the aqueous solution of the alkali salts is of a yellow color. The formula of the reaction of this example is:



Compounds with positive substituents, such, for instance, as meta-acetyl-amino-phenylarsenic acid, and the like, behave in a similar manner.

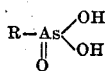
Example XII: 1.09 parts of para-aminophenol are dissolved in 6 parts of water and 2 parts of concentrated hydrochloric acid (specific gravity 1.16) and diazotized in the usual way. To this mixture is added, at a temperature which should not be too low, a solution of about from 8 to 10 parts of sodium hydroxid and 1.5 parts of sodium arsenite in 6 parts of water and the whole heated without giving too strong an alkaline reaction until the evolution of nitrogen is at an end. The reaction mixture is neutralized, the insoluble products filtered off, and the filtrate is concentrated under neutral reaction, preferably with animal charcoal. The sodium salt of the para-phenol-arsinic acid crystallizes out from the solution thus obtained. It can be re-crystallized out of alcohol for the purpose of purifying it. The reaction of this example of the invention has the formula:



The isomeric animophenols behave in the same fashion. If the OH group be etherified, or esterified, the corresponding yields of ethers or ester phenol arsenic acids are improved. Diazo phenols with several OR groups (R being hydrogen, alkyl, aryl, or acyl), such as, for instance, diazo-guaiacol, react analogously.

What I claim is:—

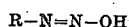
1. Process for the production of aryl-substitution products of the arsenic acid having the following general formula:



which process consists in causing compounds which contain the group



to react on aryl-diazo-compounds having the general formula



wherein R denotes an aryl-radical.

2. Process of producing aromatic arsenic compounds which comprises heating an aromatic diazo compound with an arsenic compound, until the arsenic compound has been combined with the aromatic nucleus.

3. Process of producing aromatic arsenic compounds which comprises heating an aromatic diazo compound with an arsenic compound in the presence of an alkali, until the arsenic compound has been combined with the aromatic nucleus.

4. The process of producing aromatic arsenic compounds which comprises heating

an aromatic diazo compound with an alkaline arsenite until the arsenic is combined with the aromatic nucleus.

5. The process of producing aromatic arsenic compounds which comprises heating an aromatic diazo compound with sodium arsenite until the arsenic is combined with the aromatic nucleus.

6. The process of producing aromatic arsenic compounds which comprises heating an aromatic diazo compound in the presence of an alkali with an alkaline arsenite until the arsenic is combined with the aromatic nucleus.

7. The process of producing aromatic arsenic compounds which comprises heating an aromatic diazo compound in the presence of an alkali with sodium arsenite until the arsenic is combined with the aromatic nucleus.

8. Process of producing aromatic arsenic compounds which comprises heating a substituted aromatic diazo compound with an arsenic compound, until the arsenic compound has been combined with the aromatic nucleus.

9. The process of producing aromatic arsenic compounds which comprises heating a substituted aromatic diazo compound with an alkaline arsenite until the arsenic is combined with the aromatic nucleus.

10. The process of producing aromatic arsenic compounds which comprises heating a substituted aromatic diazo compound in the presence of an alkali with an alkaline arsenite until the arsenic is combined with the aromatic nucleus.

11. The process of producing a nitrophenol-arsinic acid which comprises reacting on an aromatic nitro-diazo compound with an alkaline arsenite.

12. The process of producing a nitrophenol-arsinic acid which comprises reacting on a diazo-nitro-phenol with an alkaline arsenite.

13. The process of producing 4-nitrophenol-2-arsinic acid which comprises reacting on 4-nitro-2-diazo-phenol with an alkaline arsenite.

14. As a new product 4-nitrophenol-2-arsinic acid, being in its free form a yellow crystalline body, soluble in alcohol, difficultly soluble in water, but soluble in water in the form of its alkali salts.

In testimony whereof I have signed my name to this specification in the presence of two subscribing witnesses.

HEINRICH BART.

Witnesses:

FRANZ HASSLACHER,
ERWIN DIPPFL.