

[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, HARVARD MEDICAL SCHOOL]

THE ARSONATION OF ORTHO- AND META-CRESOL¹

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Received November 17, 1922

In the course of the present research on arspenamine, it has been necessary to investigate some arsenical derivatives of *o*-cresol of which 3-methyl-4-hydroxyphenylarsonic acid was the parent substance. This compound has been made by treating *o*-cresol with arsenic acid.² As Jacobs and Heidelberger³ found that when arsenic acid acts on phenol the following substances are formed, *p*-HOC₆H₄AsO₃H₂, *o*-HOC₆H₄AsO₃H₂, *p,p'*-(HOC₆H₄)₂AsO₂H, and a compound probably having the formula *p,o'*-(HOC₆H₄)₂AsO₂H, it seemed as though analogous substances should result when *o*-cresol is used in place of phenol. This expectation has been realized and a series of compounds homologous with those mentioned above has been secured.

The action of arsenic acid on *o*-cresol results in the formation of a considerable amount of tar which renders the isolation of the products much more difficult than in the case of phenol; also, the yields are lower in this reaction. As the experimental conditions have not been subjected to detailed study, it may be possible by varying them to increase the yields. The products 3,4-CH₃-HOC₆H₃AsO₃H₂, 3,2-CH₃-HOC₆H₃AsO₃H₂, 3,4,3',4'-(CH₃-HOC₆H₃)₂AsO₂H, and 3,4,3',2'-(CH₃-HOC₆H₃)₂AsO₂H, are very similar to those obtained from phenol and the isomers can be distinguished by treatment with ferric chloride, as only those in which an hydroxyl group is *ortho* to the arsonic acid group give a purple color with this reagent.

Upon investigating the preparation of 2-methyl-4-hydroxyphenylarsonic acid from *m*-cresol and arsenic acid,² it has been possible to isolate by-products isomeric with those obtained from *o*-cresol, and the formation of such compounds appears to occur during the arsonation of phenols in general. The tar formation is very slight during the arsonation of *m*-cresol as compared with that occurring in the case of the *ortho* compound.

The experimental conditions are similar to those used by Jacobs and Heidelberger for the arsonation of phenol,³ and the arsenic determinations were made by Ewins' method.

¹ This is the tenth of a series of studies on the properties contributing to the toxicity of arspenamine being made under a grant from the United States Interdepartmental Social Hygiene Board to the Harvard Medical School; the work is under the general direction of Dr. Reid Hunt.

² Ger. pat., 205,616.

³ Jacobs and Heidelberger, THIS JOURNAL, 41, 1440 (1919).

Experimental Part

Arsonation of Ortho-cresol

3-Methyl-4-hydroxyphenylarsonic Acid.—After boiling 540 g. of sirupy arsenic acid (70–75% acid) in a beaker until the temperature reaches 150°, the acid is added to 224 g. of *o*-cresol (m. p., 31.2°) in a round-bottom flask and the material is heated under an air-cooled reflux condenser in an oil-bath at 155–160°. For 2 hours the contents of the flask boil gently; then tar gradually forms; after 5½ hours the reaction mass is cooled somewhat and diluted with 2 liters of water. The diluted material is filtered from the tar after some hours and the red filtrate, while being mechanically stirred, is gradually treated with powdered solid barium hydroxide until it is faintly alkaline to litmus in order to remove the excess arsenic acid. Although the use of solid barium hydroxide increases the time required to neutralize the acid, it does not increase the volume of the solution as much as the use of a solution of barium hydroxide. The barium arsenate is collected on a filter and the filtrate is treated with sulfuric acid until it is free from barium and sulfate ions. The barium sulfate is removed by filtration or the liquor may be siphoned off after the precipitate has settled.

The tar obtained above is extracted by boiling it 3 or 4 times with aqueous solution of caustic soda. The filtered extracts are acidified with hydrochloric acid and added to the filtrate from the barium sulfate. The material is evaporated as far as possible on a steam-bath and is then extracted thoroughly with acetone either by shaking the mixture in a machine or by refluxing it. After the acetone is distilled from the extracts a red sirup remains; this contains the aromatic arsonic acids.

The acids are converted into the sodium salts by diluting the sirup with water and adding caustic soda until the material is slightly alkaline to litmus. After separating a small gummy residue by filtration, the red solution is evaporated on a steam-bath until crystals appear on the surface. Three volumes of alcohol are added and the material is allowed to stand overnight in the ice-box.

After collecting the crystals on a filter and washing them with alcohol, the alcohol is distilled from the filtrate and the liquor is again evaporated to crystallization on a steam-bath. When alcohol is added and the solution is cooled, a second crop of material precipitates. The 2 crops of crystals are combined and dried at 80° overnight; yield, 41 g.

The product, thus obtained, is monosodium 3-methyl-4-hydroxyphenylarsonate and is a nearly white powder. By recrystallization of this powder from water and drying it in air, white crystals are obtained which are readily soluble in water to give a colorless solution. An aqueous solution, acidified with hydrochloric acid, gives no coloration with ferric chloride, but it forms a white precipitate when treated with bromine water.

Analysis. Calc. for $C_7H_8O_4AsNa \cdot 2.5H_2O$: As, 25.07; H_2O , 15.05. Found: As, 25.07; H_2O , 15.19.

To obtain the free acid, 4 g. of crude sodium salt is dissolved in water and acidified with hydrochloric acid. A little decolorizing carbon is added; after this mixture has been heated to boiling, the solution is filtered and the filtrate is evaporated to dryness on a steam-bath. The residue is extracted thrice with boiling acetone. By evaporation of the extract a sirup is obtained which solidifies when it is rubbed with a glass rod. After this product has been dried at 90°, 2.3 g. of a slightly pink solid is obtained which softens at 146° and melts at 170°,² and in aqueous solution gives no red coloration with ferric chloride.

Analysis. Calc. for $C_7H_8O_4As$: As, 32.33. Found: 32.08.

2-Hydroxy-3-methylphenylarsonic Acid.—The alcohol is distilled from the alcoholic filtrate from the second crop of sodium salt obtained above and the deep red

residue is diluted with 650 cc. of water and made distinctly alkaline to phenolphthalein with caustic soda. After this mixture has been heated to boiling, an aqueous solution of barium chloride is added. The solution is cooled overnight in the ice box and the precipitate which forms is collected on a filter, washed and dried in air. By heating the filtrate to boiling, an additional small quantity of precipitate forms which is removed and added to the first crop. The total yield of crude barium salt is 11.8 g.

To obtain the free acid, the crude salt is suspended in hot water and treated with sulfuric acid until the solution contains neither barium nor sulfate ions. By evaporation of the filtrate from the barium sulfate, stout white needles are obtained. The yield of free acid is very poor, amounting to only 1.3 g. The product melts at 198–200° and contains 32.03% of arsenic as compared with 32.33, the calculated percentage. An aqueous solution of the product gives a very deep purple color with ferric chloride.

4,4'-Dihydroxy-3,3'-dimethyl-diphenylarsinic Acid.—Acidification of the mother liquor from the crude barium salt obtained above with hydrochloric acid gives a reddish-brown flocculent precipitate which is separated by filtration immediately and, after drying, weighs 1.7 g. After extracting this material thrice with 5cc. portions of boiling 50% acetic acid, there remains 0.8 g. of a light brown solid melting at 249°, containing 22.6% of arsenic (calc., 23.3%) and giving no color when treated in aqueous suspension with ferric chloride either cold or warm. Benda⁴ prepared this substance from 4,4'-diamino-3,3'-dimethyldiphenyl-arsinic acid and found a melting-point of 247°.

3,3-Dimethyl-2,4-dihydroxy-diphenylarsinic Acid.—Upon standing, the mother liquor from the crude secondary acid obtained above deposits a precipitate which is collected on a filter after the liquor has been cooled in an ice-bath for 3 hours. After air drying, the solid (1.4 g.) is extracted by boiling it with two 5cc. portions of 50% acetic acid. The residue, 0.8 g., is the symmetrical secondary acid obtained above; it melts at 249° and gives no color with ferric chloride. The extracts deposit 0.03 g. of white solid which melts at 208–210° and which contains 23.9% of arsenic (calc., 23.3%). Addition of ferric chloride to an aqueous suspension of the solid gives a light purple color which becomes very deep when the mixture is warmed.

Arsonation of Meta-Cresol

2-Methyl-4-hydroxyphenylarsonic Acid.—After boiling 720 g. of sirupy arsenic acid (75%) in a beaker at 160°, it is added to 300 g. of *m*-cresol in a round-bottom flask and the reagents are mechanically stirred and heated under an air reflux condenser for 7 hours in an oil-bath. The inside temperature is kept between 140° and 146°. The reaction mixture is diluted with 2.6 liters of water and the small amount of tar is separated from the aqueous solution.

To remove the excess of arsenic acid the solution is stirred while powdered barium hydroxide is gradually added until the mixture is slightly alkaline to litmus. The filtrate from the barium arsenate is treated with sulfuric acid until it is free from barium and sulfate ions and, after removal of the barium sulfate, the colorless solution is evaporated to about 3 liters, neutralized to litmus with caustic soda and evaporated to approximately 250 cc. Upon the addition of 2.5 volumes of alcohol to this solution and cooling in an ice box overnight, a white precipitate of $2\text{-CH}_3\text{-4-OH-C}_6\text{H}_3\text{AsO}_3\text{-HNa}\cdot x\text{H}_2\text{O}$ is obtained which is collected and washed with alcohol. After drying it at room temperature and then at 80°, 89.5 g. of the anhydrous salt is obtained.

By evaporation of the mother liquor to crystallization and a second treatment with alcohol another crop of crystals is secured which, after drying, weighs 49.3 g.

The sodium salt can readily be purified by dissolving it in a small amount of hot

⁴ Benda, *Ber.*, **41**, 2372 (1908).

water, clarifying the solution with carbon and adding 2.5 volumes of alcohol. From 20 g. of the crude anhydrous salt 19.2 g. of air-dried, purified material is obtained.

Analysis. Calc. for $C_7H_5O_4AsNa \cdot 5H_2O$: H_2O , 26.2. Found: 25.3. Calc. for $C_8H_5O_4AsNa$: As, 29.5. Found: 30.00.

The mother liquor from the purified sodium salt is evaporated to remove the alcohol and a solution of 10 g. of crude sodium salt in 70 cc. of water is added. After filtering the solution, it is made acid to congo red with hydrochloric acid and evaporated until crystallization starts. The solution is cooled in an ice-box and the crystals are collected and washed with cold water. After these are dried in air, 10.9 g. of 2-methyl-4-hydroxyphenylarsonic acid is obtained.

Analysis. Calc. for $C_7H_9O_4As \cdot H_2O$: H_2O , 7.2. Found: 7.1. Calc. for $C_7H_9O_4As$: As, 32.33. Found: 32.13.

This acid is soluble in hot water and crystallizes in white needles when a hot aqueous solution is cooled. It dissolves readily in dil. aqueous solutions of alkali. A dil. water solution gives a heavy white precipitate with bromine water and no coloration with ferric chloride. When heated gradually the solid melts at 194–195°; the melting-point recorded in the patent² is 183–185°.

1-Methyl-3-hydroxy-benzene-(2- or 4-)-arsonic Acid.—By following the procedure described for the isolation of 3-methyl-2-hydroxyphenylarsonic acid, 2.5 g. of an arsonic acid derivative of *m*-cresol is obtained in which the arsonic acid group is *ortho* to the hydroxyl group.

Analysis. Calc. for $C_7H_9O_4As \cdot 2H_2O$: H_2O , 13.4. Found: 12.8. Calc. for $C_7H_9O_4As$: As, 32.33. Found: 32.31.

The anhydrous material melts at 165–167°. The acid is slightly soluble in cold water but readily soluble in alkalies and hot water. An aqueous solution becomes very deep red when treated with ferric chloride; this property is characteristic of compounds containing hydroxyl and arsonic acid groups *ortho* to each other. An ammoniacal solution gives a gelatinous precipitate, with calcium chloride, a crystalline precipitate when heated with barium chloride, and a gelatinous precipitate when heated with magnesia mixture; the latter precipitate partly redissolves as the liquid cools. When the substance is reduced in a warm aqueous solution with hypophosphorous acid and potassium iodide, a pale yellow arseno compound separates.

Evidently, the product is an arsonic acid with the hydroxyl group *ortho* to the acid group, but it has not been determined whether the methyl group is *ortho* or *para* to the arsonic acid group.

Secondary Acids.—Acidification of the filtrate from the crude barium salt of the *o*-hydroxy acid with hydrochloric acid produces a precipitate which partly redissolves when the solution becomes acid to congo red. The gummy insoluble material is separated by filtration and the colorless filtrate is treated with a concentrated solution of sodium acetate until it is no longer acid to congo red; a white precipitate forms which is separated after the solution has been thoroughly cooled. The precipitates are dissolved separately in small amounts of hot 50% acetic acid, but the filtered solutions, when cool, deposit nothing. By dilution with water the material is thrown out of solution as a gummy substance which solidifies upon manipulation. The filtered, washed and air-dried solids weigh 2.5 g. and 0.7 g., respectively. Qualitatively, they are very similar and appear to be mixtures of a number of secondary arsonic acids derived from *m*-cresol. In aqueous suspension they give deep purple colorations with ferric chloride. They are insoluble in water and ether but readily soluble in alkalies and alkali carbonates. A sodium carbonate solution gives a precipitate which is soluble in ether when treated with an acetic acid solution of bromine. An ammoniacal solution deposits a crystalline

precipitate when treated with calcium chloride, and a magnesium salt when heated with magnesia mixture.

Attempts to fractionate the mixture in acetic acid failed, but a partial separation was obtained by means of the calcium salts. To a solution of 1.5 g. of the acids in 10 cc. of water and 0.7 cc. of ammonia water is added a solution of 1 g. of calcium chloride and 2.5 g. of ammonium chloride in 9 cc. of water and 2 cc. of ammonia water. After the material has stood in the ice box it is centrifuged and the red liquor is decanted from the white solid which is washed with dil. aqueous ammonia and again centrifuged. The calcium salt is suspended in water and decomposed with acetic acid, thereby changing it to a curdy, white solid. The material is centrifuged, washed twice with water and dried in a vacuum over caustic soda. This constitutes Fraction 1. Fractions 2 and 3 are obtained by acidifying the washings (from the calcium salt) and mother liquor, respectively. Upon standing for several weeks, the mother liquor and washings from Fractions 2 and 3 deposit an additional quantity of material which is Fraction 4. All gave a reddish-purple with ferric chloride.

No.	Yield G.	As %	Melting range °C.
1	0.2	22.5	78-140
2	0.05	..	88-170
3	0.3	22.8	132-200
4	0.2	22.7	150-205

Calc. for $C_{14}H_{13}O_4As$: As, 23%.

Summary

In the arsonation of *o*-cresol the tar formation is much greater, the isolation of the products is more difficult and the yield is less than in the case of phenol. In addition to the main product, 3-methyl-4-hydroxyphenylarsonic acid, by-products are formed as in the arsonation of phenol, and 3 arsenicals can be isolated from the reaction mixture after the removal of the above compound. These substances appear to be 2-hydroxy-3-methylphenylarsonic acid, 4,4'-dihydroxy-3,3'-dimethyl-diphenylarsonic acid and 2,4'-dihydroxy-3,3'-dimethyl-diphenyl-arsinic acid.

The arsonation of *m*-cresol proceeds similarly but with much less tar formation. In addition to the main product, 2-methyl-4-hydroxyphenylarsonic acid, by-products similar to those formed from phenol and *o*-cresol can be isolated.

In the arsonation of phenols the production of by-products of this type seems to be a fairly general phenomenon.

The writer wishes to acknowledge his indebtedness to Dr. Reid Hunt for his interest in this research and to Mr. Arthur J. Norton for assisting with some of the analytical work.

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