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DICARBOXYPHENYLARSONIC ACIDS. II
3,4-DICARBOXYPHENYLARSONIC ACID AND SOME OF ITS DERIVATIVES

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Previous to this time, only three dicarboxyphenylarsonic acids have been prepared. Isophthalarsonic acid, or 2,4-dicarboxyphenylarsonic acid, was prepared by Michaelis from 2,4-dimethylphenylarsonic acid by oxidation with potassium permanganate in alkaline solution.[1] According to the German patents, 4-acetylamino-2,5-dicarboxyphenylarsonic acid was prepared by oxidation of 4-acetylamino-5-carboxy-2-methylphenylarsonic acid with potassium permanganate in alkaline solution.[2] 2,3-Dicarboxyphenylarsonic acid, the first dicarboxyphenylarsonic acid with the carboxyl groups ortho to each other, was prepared by Hamilton and Frazier[3] by first nitrating *o*-phthalic acid, then reducing the nitro compound to 3-amino-*o*-phthalic acid and finally introducing the arsonic acid group by means of Bart's reaction.[4]

As a further contribution to the study of dicarboxyphenylarsonic acids, 3,4-dicarboxyphenylarsonic acid and some of its derivatives have been prepared. This is the first dicarboxyphenylarsonic acid to be obtained by the introduction of the arsonic group into the neutral ester of an aromatic dicarboxy acid. 4-Nitro-*o*-phthalic acid was first obtained by preparing phthalimide from phthalic anhydride and urea, reducing phthalimide to phthalide, nitrating phthalide and oxidizing 5-nitrophthalide to 4-nitro-*o*-phthalic acid. On direct reduction of 4-nitro-*o*-phthalic acid with tin and hydrochloric acid, Bogert[5] and Miller[6] found that carbon dioxide was evolved, forming *m*-aminobenzoic acid. Thus to prepare 4-amino-*o*-phthalic acid, it was necessary to esterify 4-nitro-*o*-phthalic acid before reduction in order to protect the carboxyl groups. The dimethyl-4-nitrophthalate was then reduced with zinc dust and hydrochloric acid in the presence of alcohol.

The arsonic acid group was introduced directly into dimethyl-4-aminophthalate following the method used by Bart to prepare 2-carboxyphenylarsonic acid.[4b] Bart observed that substitution of the arsonic acid group did not occur when benzene diazonium chloride was treated with arsenious acid in weakly or strongly acid solution, the diazo compound

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[1] Michaelis, *Ann.*, **320**, 335 (1902).

[2] Farbwerke vorm. Meister, Lucius and Bruning, Ger. pat. 203,717 (1907).

[3] Hamilton and Frazier, THIS JOURNAL, **48**, 2414 (1926).

[4] (a) Bart, Ger. pat. 250,264 (1910); (b) *Ann.*, **429**, 55 (1922).

[5] Bogert and Renshaw, THIS JOURNAL, **30**, 1136 (1908).

[6] Miller, *Ber.*, **11**, 992 (1878); *Ann.*, **208**, 223 (1881).

behaving exactly the same as if arsenious acid were not present. The diazonium compound gave off nitrogen, gradually changing to phenol. However, when the reaction was carried out in the presence of hydroxyl ion of not too high concentration, the diazo compound reacted with the arsenious acid to form phenylarsonic acid. The failure to form the arsonic acid after treatment of the diazonium chloride with arsenious acid in the presence of hydrogen ion, led Bart to conclude that the diazonium group could not be replaced by the arsonic acid radical. Because of the favorable effect of hydroxyl ion on the formation of arsonic acids, Bart concluded that the reaction took place only after the transformation of the diazonium to the diazohydrate form, which is stable only in alkaline solution. Further investigation by Bart showed that hydroxyl ion in high concentration had a negative influence on the course of arsonic acid formation. It was not known whether this phenomenon depended on the fact that the diazotate, which is formed by increasing the hydroxyl-ion concentration, had a lower tendency to react with arsenious acid, or whether the activity of arsenious acid as a reducing agent was decreased. It was certain, according to Bart, that the best reaction took place when the hydroxyl-ion concentration was just sufficient for the formation of the *syn*-diazohydrate from the diazonium compound.

Bart also found that if the diazo compound contained a strongly negative group such as nitro or carboxyl, a good reaction with arsenious acid occurred even with a small hydroxyl-ion concentration, due to the great tendency of such diazonium compounds to form the diazohydrate. If the negative group was meta or para to the arsonic acid group, a somewhat stronger alkalinity was found to be necessary than for a compound containing the negative group in the ortho position. This was thought to be due, probably, to the further distance of the negative group from the diazonium group, a slightly higher alkalinity being required to form the *syn*-diazo compound.

Thus, in preparing the dimethyl ester of 3,4-dicarboxyphenylarsonic acid, the diazonium mixture, before being added to the sodium arsenite solution, was just neutralized with sodium hydroxide solution in order to form the *syn*-diazohydrate. This change was apparent, for just at the neutral point an orange precipitate separated from the clear diazonium solution. Because of the presence of the negative carboxyl groups, a very low hydroxyl-ion concentration was used. The diazonium solution was just neutralized with sodium hydroxide solution, but none was added to the sodium arsenite solution, a sufficient hydroxyl-ion concentration resulting from the hydrolysis of the sodium arsenate. The neutral methyl ester of 3,4-dicarboxyphenylarsonic acid was hydrolyzed with metallic sodium and alcohol, forming the sodium salt, which was converted into the silver salt. From the silver salt pure 3,4-dicarboxyphenylarsonic acid was obtained

Experimental Part

Preparation of Phthalimide.—The phthalimide used in the synthesis of 3,4-dicarboxyphenylarsonic acid was prepared according to the method of Herzog;[7] yield 97%.

Preparation of Phthalide.—Phthalide was prepared readily by the method of Reissert.[8] The yield from 1130 g. of phthalimide was 743 g. of phthalide (73%); m. p. 71–73°.

Nitration of Phthalide.—Hoenig nitrated phthalide with potassium nitrate and concd. nitric acid and believed that the product was 4-nitrophthalide.[9] Teppema showed that Hoenig's product was 5-nitrophthalide instead of the 4-nitro derivative.[10] 5-Nitrophthalide was prepared very satisfactorily by the method of Hoenig. From 743 g. of phthalide, 704 g. of crude 5-nitrophthalide was obtained. On recrystallization from ethyl alcohol, the nitrophthalide melted at 132–134°.

Oxidation of 5-Nitro-phthalide.—By following the method of Bogert and Boroschek,[11] 90% yields of 4-nitro-*o*-phthalic acid melting at 162–163° were obtained.

Preparation of the Dimethyl Ester of 4-Nitro-*o*-phthalic Acid.—Dimethyl-4-nitrophthalate was prepared by the method of Bogert and Renshaw,[12] which involved the sulfuric acid method of esterification. Four hundred g. of pure 4-nitro-*o*-phthalic acid yielded 448 g. of the ester melting at 69–71°; yield, 86%.

Reduction of Dimethyl-4-nitrophthalate to Dimethyl-4-aminophthalate.—Dimethyl-4-nitrophthalate was reduced with alcoholic hydrochloric acid and zinc dust according to the method of Bogert and Rensahw.[12] Tan-colored, glistening plates of dimethyl-4-aminophthalate melting at 80–84° were obtained in 75% yield.

Arsonation of Dimethyl-4-aminophthalate.—The method which was used by Bart[13] to prepare 2-carboxyphenylarsonic acid was modified and employed in the arsonation of dimethyl-4-aminophthalate. Sixty-two g. of dimethyl-4-aminophthalate was dissolved in a three-liter beaker containing 1200 cc. of water and 105 cc. of hydrochloric acid (sp. gr. 1.18). The beaker was surrounded by a freezing mixture and the solution was cooled below 0° by the aid of a motor-driven stirrer. With constant stirring and keeping the temperature below 0°, a solution of 24 g. of sodium nitrite in 300 cc. of water was added drop by drop by means of a separatory funnel until starch iodide paper indicated an excess of nitrous acid. After stirring for fifteen minutes, the excess hydrochloric acid was carefully neutralized with sodium hydroxide solution, care being taken to keep the temperature below 0°. At the neutral point, as indicated by Congo Red paper, an orange precipitate separated. The diazo mixture, kept at 0°, was added slowly with constant stirring to a three-gallon crock containing a solution of 1500 cc. of water, 150 g. of sodium arsenite, and 15 g. of copper sulfate. The purpose of the copper sulfate was to serve as a catalyst. After each addition of the diazo mixture, nitrogen was evolved. A red coloration, spoken of by Bart,[14] when the diazo solution was first poured into the sodium arsenite solution, was not noticed. Since a good yield of the arsonated product was obtained, this indicated that the red coloration was not necessary for a good reaction. After the diazo solution had all been added, the mixture was stirred for one hour. The resulting brown material was then heated to insure com-

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[7] Herzog, *Z. angew. Chem.*, **32**, 301 (1919).

[8] Reissert, *Ber.*, **46**, 1489 (1913).

[9] Hoenig, *Ber.*, **18**, 3447 (1885).

[10] Teppema, *Rec. trav. chim.*, **42**, 30 (1925).

[11] Bogert and Boroschek, THIS JOURNAL, **23**, 753 (1901).

[12] Bogert and Renshaw, *ibid.*, **28**, 618 (1906).

[13] Ref. 4 b, p. 86.

[14] Ref. 4 b, p. 61.

plete removal of nitrogen, filtered, acidified with hydrochloric acid to Congo Red paper and evaporated to dryness. The last stages of the evaporation were carried out over a water-bath and finally in an oven at 150°. The yellow residue was pulverized and extracted at room temperature with 400 cc. of absolute methyl alcohol, filtered and the residue washed with methyl alcohol. The yellow filtrate and the washings were combined and distilled to remove most of the methyl alcohol. The residue in the distilling flask was poured into an evaporating dish and heated over a water-bath. The methyl ester of 3,4-dicarboxyphenylarsonic acid remained as a sticky, yellow-brown substance. On drying overnight in an oven at 140° the sticky compound changed to a yellow, crystalline material; yield, 77–80%.

Hydrolysis of the Dimethyl Ester of 3,4-Dicarboxyphenylarsonic Acid.—Fifty g. of the crude dimethyl ester of 3,4-dicarboxyphenylarsonic acid was dissolved in 300 cc. of absolute ethyl alcohol. Alcohol which was free from water was used in order to obtain the sodium salt as a solid rather than as an oil. Some of the salt and arsenic trioxide present in the crude ester did not dissolve and were removed by filtration. When a solution of 25 g. of metallic sodium in 400 cc. of ethyl alcohol was added, the cream-colored sodium salt precipitated immediately. The mixture was refluxed for one hour. Excess sodium was used to prevent the product from darkening and becoming sticky. The sodium salt was filtered, washed with ethyl alcohol and dried overnight at 140°. The yield was quantitative.

Preparation of the Silver Salt of 3,4-Dicarboxyphenylarsonic Acid.—Fifty-nine grams of the sodium salt of 3,4-dicarboxyphenylarsonic acid was dissolved in 100 cc. of water, forming a very viscous, brown solution. The solution was slightly acidified with nitric acid and upon the addition of a solution containing 108 g. of silver nitrate in 100 cc. of water, the silver salt precipitated.

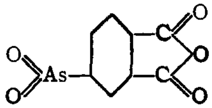
Preparation of 3,4-Dicarboxyphenylarsonic Acid.—The silver salt was filtered, washed with water and, while still wet, was suspended in 300 cc. of water. Concd. hydrochloric acid was added until the heavy, curdy precipitate of silver chloride was completely formed. On filtering off the silver chloride, a yellow filtrate was obtained which contained 3,4-dicarboxyphenylarsonic acid in solution. The filtrate was decolorized with charcoal and the silver salt reprecipitated on the addition of a solution of 100 g. of silver nitrate in 100 cc. of water. The white silver salt was filtered, suspended in water, acidified with hydrochloric acid and the silver chloride removed by filtration. On evaporation of the filtrate and drying in an oven at 80°, pure 3,4-dicarboxyphenylarsonic acid remained as a light yellow, crystalline mass; yield 40%, calculated on the basis of the sodium salt.

3,4-Dicarboxyphenylarsonic acid melts and effervesces at 180°. Clusters of light yellow crystals are obtained from a very concentrated solution of 3,4-dicarboxyphenylarsonic acid. It is highly soluble in hot or cold water and in methyl alcohol and insoluble in ether, benzene and chloroform.

Anal. Sample dried at 80°, subs., 0.1891: 24.50 cc. of 0.05312 *N* iodine solution. Calcd. for $C_8H_7O_7As$: As, 25.85. Found: 25.81.

Derivatives

The Anhydride.—The anhydride of 3,4-dicarboxyphenylarsonic acid was prepared by heating the free acid for three days at 160° under reduced pressure in the presence of phosphorus pentoxide. Water splits off from the carboxyl groups and the arsonic acid group, forming the following compound



The anhydride condensed with phenol and resorcinol, forming compounds similar to phenolphthalein and fluorescein.

Anal. Subs., 0.1016, 0.0904: 15.90, 14.30 cc. of 0.04986 *N* iodine solution. Calcd. for $C_8H_3O_6As$: As, 29.51. Found: 29.26, 29.58.

The Methyl Ester.—The methyl ester of 3,4-dicarboxyphenylarsonic acid is a light yellow, crystalline solid which is readily soluble in water, ether, benzene, chloroform, methyl alcohol and ethyl alcohol.

Anal. Subs., 0.5272, 0.2725: 68.00, 34.47 cc. of 0.04933 *N* iodine solution. Calcd. for $C_{10}H_{11}O_7As$: As, 23.57. Found: 23.86, 23.40.

The Ethyl Ester.—The ethyl ester of 3,4-dicarboxyphenylarsonic acid was prepared by refluxing the free acid with absolute ethyl alcohol for fourteen hours. On evaporation of the alcohol and drying in a vacuum oven at 80°, a yellow, sticky material remained which solidified on cooling. The ethyl ester of 3,4-dicarboxyphenylarsonic acid readily absorbs moisture and is soluble in water, methyl alcohol, ether and carbon tetrachloride.

Anal. Subs., 0.2703, 0.1739: 32.20, 20.75 cc. of 0.04845 *N* iodine solution. Calcd. for $C_{12}H_{15}O_7As$: As, 21.66. Found: 21.64, 21.68.

The Neutral Trisodium Salt.—The neutral trisodium salt of 3,4-dicarboxyphenylarsonic acid is a cream-colored solid very soluble in water, and insoluble in methyl alcohol, ether, benzene and chloroform.

Anal. Subs., 0.1346, 0.1122: 14.50, 12.30 cc. of 0.05312, 0.04986 *N* iodine solution. Calcd. for $C_8H_4O_7AsNa_3$: As, 21.05. Found: 21.45, 20.50.

The Tetrasodium Salt.—The tetrasodium salt of 3,4-dicarboxyphenylarsonic acid is a cream-colored solid very soluble in water and insoluble in methyl alcohol, ether, benzene and chloroform.

Anal. Subs., 0.0947, 0.1050: 9.8, 11.07 cc. of 0.04986 *N* iodine solution. Calcd. for $C_8H_3O_7AsNa_4$: As, 19.83. Found: 19.35, 19.72.

The Silver Salt.—The silver salt of 3,4-dicarboxyphenylarsonic acid is a white solid, insoluble in water, methyl alcohol, ether, benzene and chloroform.

Anal. Subs., 0.1272, 0.7251: 0.1001, 0.5671 g. of AgCl. Calcd. for $C_8H_3O_7AsAg_4$: Ag, 60.14. Found: 59.22, 58.86.

Summary

1. 3,4-Dicarboxyphenylarsonic acid has been prepared and its properties have been studied.

2. The anhydride, methyl ester, ethyl ester, trisodium salt, tetrasodium salt and the silver salt of 3,4-dicarboxyphenylarsonic acid have been prepared and their properties determined.

3. Derivatives of the anhydride are being studied.

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