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## PARA-CHLOROMERCURI-BENZOIC ACID AND RELATED COMPOUNDS<sup>1</sup>

### Preliminary Paper

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Of the three possible mercurated benzoic acids the only one known at the present time is the *ortho* compound, which is the only product isolated from the direct mercuration of benzoic acid.<sup>3</sup> The method finally selected for the preparation of the *para* acid was the alkaline permanganate oxidation of *p*-tolylmercuric chloride, the preparation of which has been developed in this Laboratory.<sup>4</sup> Acid oxidizing media could not be used because of the splitting of the C-Hg linkage by acid.

*p*-Chloromercuri-benzoic acid is an amorphous white powder, insoluble in water and in organic solvents except the alcohols, in which it dissolves to a very limited extent. It is soluble in alkalis and alkali carbonates giving the sodium salts of hydroxymercuri- and chloromercuri-benzoic acids, respectively. The position of the mercury in relation to the carboxyl groups was established by replacement by bromine and by iodine to form *p*-bromo- and *p*-iodobenzoic acids, melting at 250° and 266°, respectively.<sup>5</sup>

Sodium salts of the hydroxymercuri, chloromercuri, bromomercuri and iodomercuri acids were prepared. They are all soluble in water, the solubility decreasing in the order, OH, Cl, Br, I. The salts of the alkaline earth metals and the heavy metals are insoluble in water.

The *p*-mercuri-bis-benzoic acid has been prepared. Several of the reagents usually employed to make mercuri-bis compounds<sup>6</sup> failed to produce the desired change. Sodium iodide produced only the iodomercuri compound. On the other hand, sodium sulfide and ferrous hydroxide even in the calculated amounts resulted in the splitting of the C-Hg

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<sup>2</sup> Research Fellow under a grant from the Public Health Institute of Chicago. Some of these compounds are being investigated pharmacologically under the direction of Dr. A. S. Loevenhart of the University of Wisconsin under a similar grant.

<sup>3</sup> Dimroth, *Ber.*, **32**, 764 (1899); "Habilitationsschrift," Tübingen, 1900. *Chem. Zentr.*, **1901**, I, 454. Pesci, *Atti. accad. Lincei*, [5] **9**, I, 255 (1900); *Chem. Zentr.*, **1900**, I, 1097; *Atti. accad. Lincei*, [5] **10**, I, 362 (1901); *Chem. Zentr.*, **1901**, II, 108.

<sup>4</sup> Whitmore, Hamilton and Thurman, *THIS JOURNAL*, **45**, 1066 (1923).

<sup>5</sup> Probably the best method for preparing these acids in a high state of purity is from the *p*-chloromercuri-benzoic acid. Further study is being made on these and related preparations.

<sup>6</sup> Whitmore, "Organic Compounds of Mercury," Chemical Catalog Co., New York, **1921**, p. 36.

linkage with the production of benzoic acid. This result is surprising since these reagents have been used successfully in preparing mercuri-bis compounds from other mercurated benzoic acids.<sup>7</sup> The only reagents which were found to give the mercuri-bis compound were sodium stannite and sodium thiosulfate. The sodium salt of the mercuri-bis compound was also prepared.

The acid chloride of *p*-chloromercuri-benzoic acid was prepared by means of phosphorus pentachloride and thionyl chloride. This acid chloride is rather unreactive. The only definite compound prepared from it was the *n*-butyl ester.

### Experimental Part

***p*-Chloromercuri-benzoic Acid**,  $\text{ClHgC}_6\text{H}_4\text{CO}_2\text{H}$ .—One hundred g. of crude *p*-tolylmercuric chloride<sup>4</sup> and 144 g. of potassium permanganate were added to 1 liter of 6 *N* sodium hydroxide solution and 2.5 liters of water and the mixture was heated to 95° for 15 minutes during stirring. The solution was cooled and treated with a slight excess of alcohol. The manganese dioxide was removed by filtration and the filtrate was acidified with hydrochloric acid. The precipitated *p*-chloromercuri-benzoic acid was filtered, washed, and dried at 100°; yield, 90%. It is a white, amorphous powder which is insoluble in all solvents except the alcohols, in which it dissolves to a very slight extent. No satisfactory method of purifying the compound was found. Its structure was proved by treatment with iodine in ethyl alcohol, which gave a 95% yield of *p*-iodobenzoic acid; m. p., 266–267°.

**Sodium *p*-Hydroxymercuri-benzoate**,  $\text{HOHgC}_6\text{H}_4\text{CO}_2\text{Na}$ .—Twenty-five g. of *p*-chloromercuri-benzoic acid was treated with 50 cc. of ethyl alcohol and then with 50 cc. of water and 100 cc. of 6 *N* sodium hydroxide solution and the mixture refluxed until solution was practically complete. The slight residue was removed by filtration and the filtrate cooled. The sodium salt crystallized in white, lustrous plates; yield, 73%. The product was finally purified by recrystallization from 50% alcohol.

*Anal.*<sup>8</sup> Subs., 0.2207, 0.2077: Hg, 0.1219, 0.1142. Calcd. for  $\text{C}_7\text{H}_5\text{O}_3\text{HgNa}$ : Hg, 55.6. Found: 55.2, 55.0.

**Sodium *p*-Chloromercuri-benzoate**,  $\text{ClHgC}_6\text{H}_4\text{CO}_2\text{Na}$ .—Twenty-five g. of *p*-chloromercuri-benzoic acid was boiled with a solution of 30 g. of sodium carbonate in 250 cc. of water and filtered hot. The sodium salt separated at once in ill defined crystals which were hard and granular. It is practically insoluble in cold water.

*Anal.* Subs., 0.2009, 0.2016: Hg, 0.1060, 0.1061. Calcd. for  $\text{C}_7\text{H}_4\text{O}_2\text{ClHgNa}$ : Hg, 52.9. Found: 52.8, 52.6.

**Sodium *p*-Iodomercuri-benzoate**,  $\text{IHgC}_6\text{H}_4\text{CO}_2\text{Na}$ .—Twenty-five g. of sodium *p*-hydroxymercuri-benzoate was dissolved in 200 cc. of water, the solution filtered and treated with 25 g. of sodium iodide in 25 cc. of water. A thick, curdy precipitate formed. The mixture was diluted with water to 500 cc., heated to boiling and filtered hot. Extremely fine crystals of the sodium salt separated at once. If allowed to crystallize from water slowly it forms large plates.

*Anal.*<sup>9</sup> Subs., 0.2230, 0.2441: Hg, 0.0950, 0.1043. Calcd. for  $\text{C}_7\text{H}_4\text{O}_2\text{IHgNa}$ : Hg, 42.6. Found: 42.6, 42.7.

<sup>7</sup> Ref. 6, pp. 296, 294.

<sup>8</sup> The analyses were by the gold crucible method. Ref. 6, p. 365.

<sup>9</sup> Barium oxide or dry powdered sodium hydroxide was mixed with the sodium carbonate for decomposing the mercury compound.

The iodomercuri linkage in this compound is very stable. Treatment with sodium hydroxide does not change it to hydroxymercuri as is the case with the chloromercuri and bromomercuri compounds. Long boiling with sodium iodide solution has no effect, no mercuri-bis compound or benzoic acid being formed.

Sodium *p*-Bromomercuri-benzoate,  $\text{BrHgC}_6\text{H}_4\text{CO}_2\text{Na}$ , was prepared analogously to the iodo compound.

*p*-Mercuri-bis-benzoic Acid,  $\text{Hg}(\text{C}_6\text{H}_4\text{CO}_2\text{H})_2$ .—A suspension of 50 g. of *p*-chloromercuri-benzoic acid was treated with a solution of 16 g. of stannous chloride crystals in an excess of 6 *N* sodium hydroxide solution. The acid dissolved at once and a gray precipitate of mercury appeared. The mixture was diluted to 500 cc. and boiled with a little bone black. The mixture was filtered, cooled and acidified with a slight excess of hydrochloric acid. The precipitate was filtered, washed, and dried at 100°. It was free from chlorine but contained traces of tin which were removed by solution in sodium bicarbonate, filtration and re-precipitation with hydrochloric acid; yield, 60%.

*Anal.* Subs., 0.2109, 0.2002: Hg, 0.0947, 0.0896. Calcd. for  $\text{C}_{14}\text{H}_{10}\text{O}_4\text{Hg}$ : Hg, 45.1. Found: 44.9, 44.8.

The ready solubility of the mercuri-bis acid in bicarbonate is interesting in view of the insolubility of the chloromercuri acid in this reagent.

Several other methods for preparing the acid were studied, *p*-chloromercuri-benzoic acid being the starting material in each case. Sodium iodide gave only the iodomercuri compound. Sodium thiosulfate gave mercuric sulfide and the desired compound, but in such an impure condition that the method was not further developed. Sodium sulfide gave mercuric sulfide and a solution from which benzoic acid was the only organic material recovered. This result was obtained even when no excess of the reagent was used. Ferrous hydroxide also failed to give any mercuri-bis compound. An excess of the reagent removed all of the mercury leaving benzoic acid as the only organic product. When less than the calculated amount of reagent was used, the organic products were benzoic acid and unchanged *p*-chloromercuri-benzoic acid.

Sodium *p*-Mercuri-bis-benzoate,  $\text{Hg}(\text{C}_6\text{H}_4\text{CO}_2\text{Na})_2$ .—Thirty-five g. of *p*-mercuri-bis-benzoic acid dissolved almost completely in 13 g. of sodium bicarbonate in 100 cc. of water. After filtration, the solution was evaporated until solid began to separate. On cooling, the precipitate redissolved. The solution was then treated with three volumes of 95% alcohol to precipitate the sodium salt. The filtrate from the sodium salt was evaporated and treated again with alcohol to obtain another crop. The precipitated salt was washed with alcohol and dried at 100°.

*Anal.* Subs., 0.1020, 0.1042: Hg, 0.0422, 0.0430. Calcd. for  $\text{C}_{14}\text{H}_8\text{O}_4\text{Na}_2\text{Hg}$ : Hg, 41.2. Found: 41.4, 41.3.

The sodium salt is very soluble in cold water. When a concentrated solution is heated, a precipitate forms which redissolves on cooling. This action is probably due to hydrolysis at the higher temperature.

*p*-Chloromercuri-benzoyl Chloride,  $\text{ClHgC}_6\text{H}_4\text{COCl}$ .—Twenty-five g. of *p*-chloromercuri-benzoic acid suspended in 150 cc. of chloroform was treated with 20 g. of phosphorus pentachloride<sup>10</sup> and boiled for ten minutes. The insoluble crude acid chloride was filtered and washed with chloroform. No method has been found for purifying the acid chloride. The content of mercury is always several per cent. high. The crude material was used in a number of reactions of acid chlorides. While it appeared to react normally, the only product obtained pure so far is the *n*-butyl ester. The acid chloride was also prepared by means of thionyl chloride.<sup>11</sup> The crude acid chloride is very slightly soluble in hot benzene and nitrobenzene and readily in cold pyridine.

<sup>10</sup> Whitmore and Middleton, *THIS JOURNAL*, **44**, 1546 (1922).

<sup>11</sup> Sachs, *Ber.*, **53**, 1741 (1920).

*n*-Butyl *p*-Chloromercuri-benzoate,  $\text{ClHgC}_6\text{H}_4\text{CO}_2\text{C}_4\text{H}_9$ .—Eight g. of the crude acid chloride, prepared from phosphorus pentachloride, was refluxed for one hour with 75 cc. of *n*-butyl alcohol and the mixture filtered hot. The insoluble residue was 1.5 g. As the filtrate cooled, a cream-colored, flocculent precipitate separated. This was filtered off, washed with cold ethyl alcohol and dried at  $100^\circ$ ; yield, 56% (calculated on the basis of 6.5 g. of chloride). After successive crystallizations from *n*-butyl alcohol, ethyl alcohol and acetone, the melting point was constant at  $170^\circ$ .

*Anal.* Subs., 0.1071, 0.1001, 0.1179: Hg, 0.0527, 0.0491, 0.0580. Calcd. for  $\text{C}_{11}\text{H}_{13}\text{O}_2\text{ClHg}$ : Hg, 48.6. Found: 49.2, 49.1, 49.2.

The present work is being continued in the form of an extended study of the relations between the chemical and physiological properties of the *ortho*-, *meta*- and *para*-mercurated benzoic acids.

### Summary

1. *p*-Mercurated benzoic acid and a number of its derivatives have been prepared.
2. A study is being made of the properties of the three isomeric mercurated benzoic acids.

EVANSTON, ILLINOIS

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### NOTE

**The Identification of Creatine.**—Mistakes and contradictions in statements concerning the properties of creatine caused the writers delay in the identification of a sample obtained from salmon flesh and submitted by Mr. Thomas D. Wyatt of the University of Oregon Medical School. Creatine is described in the following ways by different authors; bitter, biting substance, rhombic prisms;<sup>1</sup> rhombic prisms, tasteless;<sup>2</sup> rhombic prisms;<sup>3</sup> monoclinic, bitter, decomposes with effervescence at  $295^\circ \pm 5^\circ$  (uncorr.);<sup>4</sup> monoclinic prisms.<sup>5</sup>

We proved that the sample which was submitted was creatine, by analysis, quantitative loss of water of crystallization on heating and by conversion into creatinine, which was identified by the melting point of its picrate and by the Jaffe reaction. Samples of creatine were also purchased from two other sources for comparison and the properties studied.

**Taste.**—Four out of five persons, to whom samples were submitted, pronounced the substance tasteless, but the fifth described it as bitter. In the case of the individuals who declared it to be tasteless, a dry burning sensation was produced in the back of the mouth which was not noticeable for a minute or two but persisted for some time afterward.

<sup>1</sup> Mathews, "Physiological Chemistry," Wm. Wood and Co.

<sup>2</sup> Witthaus and Scott, "Textbook of Chemistry," Wm. Wood and Co.

<sup>3</sup> Hawk, "Physiological Chemistry," P. Blakiston and Sons.

<sup>4</sup> Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons.

<sup>5</sup> Beilstein, "Organische Chemie."