[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF CORNELL UNIVERSITY]

PARA-HYDROXYBENZOYL-ORTHO-BENZOIC ACID AND SOME OF ITS DERIVATIVES

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Received November 21, 1921

p-Hydroxybenzoyl-*o*-benzoic acid was first made by Friedländer,[1] who prepared it by the decomposition of phenolphthalein-oxime with dil. sulfuric acid. In 1917 Orndorff and Murray[2] prepared the acid from phenolphthalein by this method and studied its condensation with various phenols. They also prepared a diacetate of the acid, melting at 137–140°.

This investigation was undertaken for the purpose of studying the properties and characteristic reactions of *p*-hydroxybenzoyl-*o*-benzoic acid and of some of its derivatives.

Experimental

The melting points given in the following pages are uncorrected and were made in an electrically heated Dennis melting-point apparatus,[3] the heat being so regulated as to give a rise in temperature of 1° in 5 seconds. The thermometer used was a standard one. An electrically heated tube[4] was used for bringing substances to constant weight by means of heat. Samples for analysis were dried in a desiccator over conc. sulfuric acid. The values used for the atomic weights are those given in the 1920 table of international atomic weights.[5] In stating the approximate solubility in various solvents of the substances obtained the classification of Mulliken[6] was used.

***p*-Hydroxybenzoyl-*o*-benzoic Acid.**—This substance was prepared from phenolphthalein by the method of Friedländer. The yield of crude acid from 100 g. of phenolphthalein is 75.0 g. (calculated 76.05 g.). The crude acid has a light greenish-yellow color, which is easily removed by one recrystallization from hot water, provided the solution is boiled with bone black. The acid crystallizes from hot water as colorless plates which are usually diamond-shaped with irregular edges. It is very soluble in hot 95% alcohol, hot methyl alcohol and hot glacial acetic acid, difficultly soluble in hot water, very difficultly soluble in hot benzene, soluble in cold aqueous 5% sodium hydroxide giving a pale yellow solution, and is soluble in cold conc. sulfuric acid, giving a bright yellow solution, from which *p*-hydroxybenzoyl-*o*-benzoic acid may be recovered unchanged. The pure acid melts at 213° with evolution of gas.

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[1] Friedländer, *Ber.*, **26**, 176 (1893).

[2] Orndorff and Murray, THIS JOURNAL, **39**, 679 (1917).

[3] Dennis, *J. Ind. Eng. Chem.*, **12**, 366 (1920).

[4] *Am. Chem. J.*, **48**, 477 (1912).

[5] THIS JOURNAL, **41**, 1886 (1919).

[6] Mulliken, "Identification of Pure Organic Compounds," **1905**, vol. I, p. 38.

Some of the pure, desiccator-dried acid was used for the following analyses.

The molecular weight of the acid was determined by titration with 0.1 *N* sodium hydroxide solution, using methyl red as indicator.

Subs., (I) 0.2016, (II) 0.1957, (III) 0.5008, cc. 0.1 *N* NaOH, (I) 8.33, (II) 8.08, (III) 20.68. Calc. for $C_{14}H_{10}O_4$: 242.15. Found: (I) 242.02, (II) 242.20, (III) 242.17.

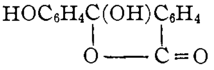
These results show that the acid titrates as a monobasic acid. The combustion analyses gave the following results.

Subs., 0.1999, 0.1989; CO_2, 0.5093, 0.5048, H_2O, 0.0762, 0.0754. Calc. for $C_{14}H_{10}O_4$: C, 69.41; H, 4.16. Found: C, 69.51, 69.24; H, 4.27, 4.24.

The solubility of the acid in distilled water, 95% ethyl alcohol, methyl alcohol and benzene at 21° was determined.

Solvent	Pts. of solvent which dissolve 1 part of acid	G. of acid soluble in 100 cc. of solvent
Water......................	1578.8	0.0632
95% alcohol................	2.28	36.00
Methyl alcohol.............	6.83	11.58
Benzene....................	7193.2	0.0121

p-Hydroxybenzoyl-*o*-benzoic acid is a γ-ketonic acid and in the free condition probably has the lactone structure I. In its salts and esters has the ketone structure II.



$$\begin{array}{l}HOC_6H_4C(OH)C_6H_4\\ \quad\;\; O \text{———} C{=}O\end{array}$$

I

$HOC_6H_4COC_6H_4COOM$

II

A similar structure has already been suggested for 2,4-dihydroxybenzoyl-*o*-benzoic acid by Graebe, Kohn and Huguenin[7] and for benzoyl-*o*-benzoic acid by Haller and Guyot,[8] while Graebe has assumed the lactone structure for the acetate of benzoylbenzoic acid.[9]

Action of Dry Ammonia Gas on *p*-Hydroxybenzoyl-*o*-benzoic Acid.—When dry ammonia gas is passed over dry *p*-hydroxybenzoyl-*o*-benzoic acid it is absorbed and the material assumes a pale yellow color.

Analyses. Subs., 0.2375, 0.1335, 0.8153: wt. of salt, 0.2788, 0.1569, 0.9588. Calc. for $C_{14}H_{10}O_4.(NH_3)_{2.5}$: NH_3, 14.95. Found: 14.81, 14.91, 14.97.

The acid exhibits toward ammonia an abnormal absorptive power, since it takes up 2.5 molecules of ammonia. On standing in an evacuated desiccator over conc. sulfuric acid the material loses ammonia slowly and comes to constant weight when only one molecule of ammonia remains.

Analyses. Subs., 0.1335, 0.8153: wt. of salt, 0.1430, 0.8735. Calc. for $C_{14}H_{10}O_4.(NH_3)$: NH_3, 6.57. Found: 6.64, 6.66.

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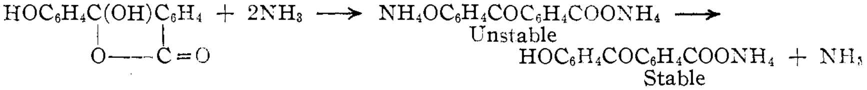
[7] Graebe, Kohn and Huguenin, *Arch. sci. phys. nat.*, **30**, 91 (1893).

[8] Haller and Guyot, *Compt. rend.*, **119**, 140; and *Ber.*, **27**, Ref., 664 (1894). *Bull. soc. chim.*, [3] **25**, 52 (1901).

[9] Graebe, *Ber.*, **33**, 2027 (1900).

This mono-ammonium salt is colored only slightly yellow. When dry air was passed over it at 80° for 5 hours it suffered no loss in weight.

p-Hydroxybenzoyl-*o*-benzoic acid at first forms with dry ammonia an unstable, slightly colored, *di*-ammonium salt, which by the loss of ammonia forms the stable *mono*-ammonium salt. It is probable that the excess of ammonia over the two molecules is attached to the carbonyl group.



$$HOC_6H_4\underset{\displaystyle |}{C}(OH)\underset{\displaystyle |}{C_6H_4} + 2NH_3 \longrightarrow \underset{\text{Unstable}}{NH_4OC_6H_4COC_6H_4COONH_4} \longrightarrow$$
$$O\text{———}C{=}O$$
$$\underset{\text{Stable}}{HOC_6H_4COC_6H_4COONH_4} + NH_3$$

Monosodium Salt.—A warm solution of 5 g. of *p*-hydroxybenzoyl-*o*-benzoic acid in 25 cc. of absolute ethyl alcohol was added to a solution of 0.5 g. of sodium (calculated for monosodium salt, 0.475 g.) in 30 cc. of absolute alcohol. The sodium salt began to separate almost immediately in the form of small, colorless needles. These were filtered from the mother liquor and washed with cold absolute alcohol. The salt is very soluble in hot water and in hot 95% alcohol, and difficultly soluble in hot absolute alcohol. It turns yellow when heated to 110–120°, and the anhydrous salt takes up water in the air soon becoming colorless again. The air-dried salt when dried in a desiccator lost only 2% in weight, this loss being due to alcohol held mechanically, and there was no change in color. The desiccator-dried sample was analyzed for sodium by fuming down with conc. sulfuric acid.

Analyses. Subs., 0.3494, 0.4001: Na_2SO_4, 0.0797, 0.0915. Calc. for $C_{14}H_9O_4Na$: Na, 8.70. Calc. for $C_{14}H_9O_4Na$, C_2H_5OH: Na, 7.41. Found: 7.38, 7.41.

The molecule of alcohol is removed by heating the salt in a current of dry air at 130°.

Analyses. Subs., 0.2360, 0.5523: loss, C_2H_5OH at 130°, 0.0350, 0.0824. Calc for $C_{14}H_9O_4Na$, C_2H_5OH: C_2H_5OH, 14.85. Found: 14.83, 14.92.

Silver Salt.—This salt was prepared by heating a solution of *p*-hydroxybenzoyl-*o*-benzoic acid in alcohol with a solution of silver nitrate in alcohol and water for 2 hours. The salt separated from the solution on cooling as small, grayish colored crystals, slightly soluble in cold, more soluble in hot water. The salt cannot be recrystallized from hot water because of the separation of metallic silver. It is slightly soluble in hot or cold 95% alcohol, and the solutions soon acquire a brownish tinge.

The desiccator-dried salt was analyzed by igniting a weighed amount in a porcelain crucible and weighing the metallic silver so obtained.

Analyses. Subs., 0.4014, 0.4008: Ag, 0.1240, 0.1239. Calc. for $C_{14}H_9O_4Ag$: Ag, 30.91. Found: 30.89, 30.91.

The molecular weight of *p*-hydroxybenzoyl-*o*-benzoic acid calculated from these results is 242.25 and thus confirms the results of the titration of the acid with 0.1 *N* sodium hydroxide solution (p. 1519).

Barium Salt.—This salt was prepared by heating an aqueous solution of the acid with barium carbonate for 3 hours. The liquid was filtered and from the filtrate there separated on standing large, 6-sided, greenish-yellow crystals. The salt is difficultly soluble in hot water and very difficultly soluble in hot 95% alcohol. The pure barium salt softens at 245° and melts with evolution of gas at 259°.

Dried in a desiccator the salt lost only 0.17% in weight. The water of crystallization in the desiccator-dried salt was determined by heating portions of it in a current of dry air at 125°.

Analyses. Subs., 0.5345, 0.5759: loss at 125°, 0.0294, 0.0322. Calc. for $C_{28}H_{18}O_8Ba.2H_2O$: H_2O, 5.50. Found: 5.50, 5.59.

The anhydrous salt was then analyzed for barium.

Analyses. Subs., 0.5051, 0.5437: $BaSO_4$, 0.1885, 0.2031. Calc. for $C_{28}H_{18}O_8Ba$: Ba, 22.17. Found: 21.96, 21.98.

The barium salt was examined by Professor A. C. Gill of the Mineralogical Department of Cornell University, who reported: "This salt is probably triclinic. Measurements gave a double refraction of 0.071."

The formula of the barium salt is $HOC_6H_4COC_6H_4COOBaOOCC_6H_4COC_6H_4OH$.

Calcium Salt.—The calcium salt prepared from *p*-hydroxybenzoyl-*o*-benzoic acid and calcium carbonate, crystallizes in clusters of small, pale yellow, glistening needles. It is easily soluble in hot water and hot 95% alcohol. When heated, it softens at 252° and melts with evolution of gas at 262–263°.

Heated in a current of dry air at 125° for a few hours, the air-dried salt loses weight corresponding to 2 molecules of water of crystallization. Water was seen to condense on the sides of the drying tube.

Analyses. Subs., 0.2793, 0.3051; loss at 125°, 0.0182, 0.0200. Calc. for $C_{28}H_{18}O_8Ca.2H_2O$: H_2O, 6.45. Found: 6.52, 6.56.

The colorless anhydrous salt was analyzed for calcium.

Analyses. Subs., 0.2611, 0.2851: cc. 0.1 *N* $KMnO_4$, 9.96, 10.82. Calc. for $C_{28}H_{18}O_8Ca$: Ca, 7.67. Found: 7.64, 7.60.

The air-dried salt was analyzed in the same manner.

Analyses. Subs., 0.3040, 0.2017, 0.3813: cc. 0.1 *N* $KMnO_4$, 10.79, 7.09, 13.60. Calc. for $C_{28}H_{18}O_8Ca.2H_2O$: Ca, 7.18. Found: 7.11, 7.04, 7.15.

Zinc Salt.—(a) This salt was first obtained in an attempt to reduce *p*-hydroxybenzoyl-*o*-benzoic acid in aqueous solution with zinc dust. A solution of 10 g. of the acid in 750 cc. of water was boiled with 1 g. of zinc dust for 15 hours, and then filtered to remove the excess zinc. On standing, clusters of colorless crystals separated. The salt, purified by recrystallization from hot water, melts at 80–81°. It is very soluble in hot 95% alcohol and difficultly soluble in hot water. It melts under boiling water. When hydrolyzed by acids it gives *p*-hydroxybenzoyl-*o*-benzoic acid. Some of the air-dried material was analyzed.

Analyses. Subs., 0.2008, 0.2019, 0.3017: $ZnNH_4PO_4$, 0.0531, 0.0532, 0.0799; $Zn_2P_2O_7$, 0.0447, 0.0449, 0.0672. Calc. for $C_{28}H_{18}O_8Zn.7H_2O$: Zn, 9.70; calc. for $C_{28}H_{18}O_8Zn.7.5\ H_2O$: Zn, 9.58; calc. for $C_{28}H_{18}O_8Zn.8H_2O$: Zn, 9.45. Found: Zn calc. from $ZnNH_4PO_4$: 9.69, 9.66, 9.71; Zn calc. from $Zn_2P_2O_7$: 9.55, 9.54, 9.55.

In order to determine whether the salt crystallizes with 7, 7.5, or 8 molecules of water, samples were heated to constant weight in a drying tube at 81°. Water was seen to condense on the sides of the tube and the salt turned yellow.

Analyses. Subs., 0.2538, 0.2430: loss at 81°, 0.0503, 0.0486. Calc. for $C_{28}H_{18}O_8Zn.7H_2O$: H_2O, 18.72; calc. for $C_{28}H_{18}O_8Zn.7.5H_2O$: H_2O, 19.78; calc. for $C_{28}H_{18}O_8Zn.8H_2O$: H_2O, 20.83. Found: 19.81, 20.00.

These results indicate that the zinc salt crystallizes with 7.5 molecules of water. The anhydrous salt was also analyzed.

Analyses. Subs., 0.2035, 0.1944: $ZnNH_4PO_4$, 0.0660, 0.0641; $Zn_2P_2O_7$, 0.0556, 0.0534. Calc. for $C_{28}H_{18}O_8Zn$: Zn, 11.94. Found: Zn calc. from $ZnNH_4PO_4$, 11.88, 12.14; Zn calc. from $Zn_2P_2O_7$, 11.72, 11.78.

(b). The same salt was prepared by heating an aqueous solution of *p*-hydroxybenzoyl-*o*-benzoic acid with zinc carbonate. It crystallizes in clusters of colorless plates melting at 80–81°. Analyses of the air-dried material gave results which agreed with those obtained for the preceding zinc salt.

Analyses. Subs., 0.3021, 0.3042, 0.2511: $ZnNH_4PO_4$, 0.0799, 0.0798, 0.0661; $Zn_2P_2O_7$, 0.0669, 0.0668, 0.0556. Calc. for $C_{28}H_{18}O_8Zn.7.5H_2O$: Zn, 9.58. Found: Zn calc. from $ZnNH_4PO_4$, 9.69, 9.61, 9.64; Zn calc. from $Zn_2P_2O_7$, 9.49, 9.42, 9.49.

Diacetate.—(a) One part of *p*-hydroxybenzoyl-*o*-benzoic acid was boiled with 6 parts of acetic anhydride for 2 hours and the solution was then poured into cold water. A colorless oil separated, which solidified after a time giving white crystals which were removed from the liquor by filtration and dried. This material melted at 137–140°. Miss Murray[10] states that a sharper melting point could not be obtained, but it was found that recrystallization from acetic acid and then from 95% alcohol gave a very pure product melting at 162–163°. The diacetate is converted by treatment with warm alcoholic sodium hydroxide or conc. sulfuric acid into *p*-hydroxybenzoyl-*o*-benzoic acid.

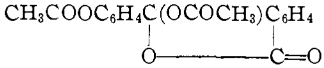
The desiccator-dried material was analyzed by determining the number of acetyl groups, using a modification of the Wenzel method.[11]

Analyses. Subs., 0.2009, 0.2011: cc. 0.1 *N* iodine, 0.00, 0.00; cc. net 0.1 *N* NaOH, 12.34, 12.36. Calc. for $C_{14}H_8O_4(C_2H_3O)_2$: C_2H_3O, 26.38. Found: 26.43, 26.45.

(b). One part of *p*-hydroxybenzoyl-*o*-benzoic acid was boiled with one part of fused sodium acetate and 8 parts of acetic anhydride for 2 hours. The diacetate so obtained melted after recrystallization from hot 95% alcohol at 162–163°. Analysis of the pure, dried material gave the following results.

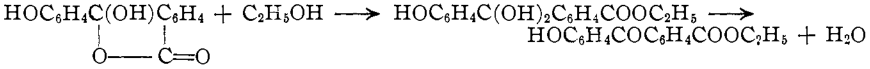
Analyses. Subs., 0.2004, 0.2001: cc. 0.1 *N* iodine, 0.10, 0.00; cc. net 0.1 *N* NaOH, 12.28, 12.24. Calc. for $C_{14}H_8O_4(C_2H_3O)_2$: C_2H_3O, 26.38. Found: 26.37, 26.32.

The structure of the diacetate of *p*-hydroxybenzoyl-*o*-benzoic acid is as follows.



$$\begin{array}{l} CH_3COOC_6H_4C(OCOCH_3)C_6H_4 \\ \qquad\qquad\quad |\qquad\qquad\quad | \\ \qquad\qquad\quad O\text{————}C{=}O \end{array}$$

Ethyl Ester.—Fifteen g. of *p*-hydroxy-benzoyl-*o*-benzoic acid was dissolved in 75 cc. of 95% alcohol and to the solution was added 15 cc. of conc. sulfuric acid. The solution was boiled for 3 hours and was then poured into dil. sodium carbonate solution containing enough sodium carbonate to neutralize the sulfuric acid present. A colorless oil separated which solidified on standing for several hours. The reaction is as follows:



$$\begin{array}{l} HOC_6H_4C(OH)C_6H_4 + C_2H_5OH \longrightarrow HOC_6H_4C(OH)_2C_6H_4COOC_2H_5 \longrightarrow \\ \qquad\quad |\qquad\quad | \qquad\qquad\qquad\qquad\qquad\qquad\qquad HOC_6H_4COC_6H_4COOC_2H_5 + H_2O \\ \qquad\quad O\text{——}C{=}O \end{array}$$

The ester was recrystallized several times from large amounts of hot water in which it is not very soluble. On cooling, the solutions become milky in appearance and then deposit colorless, needle-like crystals, which melt at 114–115°. The ester is very soluble in hot 95% alcohol, cold methyl alcohol and hot acetic acid. When dissolved in 5% sodium hydroxide it is converted into *p*-hydroxybenzoyl-*o*-benzoic acid. A desiccator-dried sample was analyzed.

Analyses. Subs., 0.1802, 0.1822: CO_2, 0.4700, 0.4753; H_2O, 0.0864, 0.0857. Calc. for $C_{16}H_{14}O_4$: C, 71.09; H, 5.22. Found: C, 71.15, 71.17; H, 5.37, 5.26.

ACTION OF DRY AMMONIA GAS ON THE ETHYL ESTER.—When dry ammonia gas was passed over the dry ethyl ester, the ester absorbed ammonia and turned a lemon-yellow very rapidly. It finally formed a gummy, greenish-yellow mass. At this point it had absorbed ammonia to constant weight and the values obtained corresponded with those calculated for one molecule of ammonia.

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[10] Murray, THIS JOURNAL, **39**, 680 (1917).

[11] Wenzel, *Monatsh.*, **18**, 659 (1897). Compare Orndorff and Brewer, *Am. Chem. J.*, **26**, 121 (1901) and Orndorff and Delbridge, *ibid.*, **42**, **227** (1909).

Analyses. Subs., 0.3279, 0.1764: wt. of salt, 0.3486, 0.1875. Calc. for $C_{16}H_{14}O_4.(NH_3)$: NH_3, 5.93. Found: 5.94, 5.92.

One of the samples was placed in an evacuated desiccator over conc. sulfuric acid for several days. It lost slightly less than $^1/_2$ of the ammonia which it had absorbed.

Analysis. Subs., 0.3279: wt. of salt, 0.3389; NH_3 remaining, 0.0110. Calc. for $C_{16}H_{14}O_4.(NH_3)_{0.5}$: NH_3, 3.05. Found: 3.25.

After standing in the desiccator for several more days there was no further decrease in weight, so the amount of ammonia present was determined by titration. After removal of the ammonia, the ethyl ester crystallized.

Analysis. Subs., 0.3389: cc. 0.1 *N* HCl, 6.46; NH_3 remaining, 0.0110 g., 3.25%. Found by titration: 0.0110 g., 3.25%.

In order to make sure that the increase in weight was due to the absorption of ammonia and that no other action had occurred, the ammonia in the second sample was determined by titration.

Analysis. Subs., 0.1875: cc. 0.1 *N* HCl, 6.53; wt. of ammonia absorbed, 0.0111; found by titration, 0.0111. Calc. for $C_{16}H_{14}O_4.(NH_3)$: NH_3, 5.93. Found by titration: 5.93.

The reaction of the ethyl ester with ammonia is as follows: $HOC_6H_4COC_6H_4COOC_2H_5 + NH_3 \longrightarrow NH_4OC_6H_4COC_6H_4COOC_2H_5$.

The compound is not stable, as it loses a portion of the ammonia when left in an evacuated desiccator over conc. sulfuric acid.

Methyl Ester.—This ester was prepared from the acid and methyl alcohol. It is very soluble in hot 95% alcohol and hot glacial acetic acid. It is recrystallized from hot water in which it is readily soluble. It crystallizes in needles melting at 149–150°. A sample of the desiccator-dried ester was analyzed.

Analyses. Subs., 0.1802, 0.1883: CO_2, 0.4623, 0.4841; H_2O, 0.0770, 0.0816. Calc. for $C_{15}H_{12}O_4$: C, 70.29; H, 4.72. Found: C, 69.99, 70.14; H, 4.78, 4.85.

Professor Gill states concerning this ester: "The crystals are certainly triclinic and the occurrence of frequent truncation of one sharp end without a corresponding face at the other end seems to indicate the rather rare pedial symmetry. The double refraction is very strong,—not less than 0.200."

ACTION OF DRY AMMONIA GAS ON THE METHYL ESTER.—When dry ammonia gas was passed over the methyl ester of *p*-hydroxybenzoyl-*o*-benzoic acid, the ester turned greenish-yellow and seemed to become semi-liquid. When the material had come to constant weight, the increase in weight showed that the substance had absorbed more than 1, but less than 1.5, molecules of ammonia to 1 molecule of the ester.

Analyses. Subs., 0.1463, 0.1258: wt. of salt, 0.0588, 0.1364. Calc. for $C_{15}H_{12}O_4.(NH_3)$: NH_3, 6.23; calc. for $C_{15}H_{12}O_4.(NH_3)_{1.5}$: NH_3, 9.06. Found: 7.87, 7.77.

The ammonia absorbed by Sample II was determined by titration.

Analysis. Subs., 0.1364: cc. 0.1 *N* HCl, 6.35. NH_3 absorbed: 0.0106 g. Found by titration: 0.0108 g., 7.92%.

3,5-Dibromo-4-hydroxybenzoyl-*o*-benzoic Acid.—Tetrabromo-phenolphthalein-oxime was prepared by Friedländer and Stange[12] by the action of hydroxylamine hydrochloride on an alkaline solution of tetrabromo-phenolphthalein. This oxime is decomposed by boiling with dil. sulfuric acid into dibromo-*p*-hydroxybenzoyl-*o*-benzoic acid and dibromo-amidophenol. The acid, recrystallized from glacial acetic acid, melts at 246–248°.

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[12] Friedländer and Stange, *Ber.*, **26**, 2260 (1893).

This acid was made in the following way. One part, by weight, of *p*-hydroxybenzoyl-*o*-benzoic acid was dissolved in 6 parts of hot glacial acetic acid, and to the cooled solution 5% in excess of 2 molecules of bromine to 1 of the hydroxy acid was added, and the mixture allowed to stand overnight. The colorless crystals obtained were filtered off, washed with glacial acetic acid and dried in the air. The compound is easily soluble in hot 95% alcohol, hot methyl alcohol and hot glacial acetic acid. Recrystallized from glacial acetic acid, it melts sharply at 250°.

The dibromo compound was analyzed by Mr. H. A. Bedient in this laboratory. Analysis I was made by the lime method,[13] while Analysis II was carried out by fusion of the sample with 2 g. of powdered potassium nitrate and 8 g. of ground potassium hydroxide (halogen-free) in a nickel crucible and analysis of the product as in the lime method.

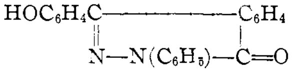
Analyses. Subs., (I), 0.2000, (II) 0.1688: cc. 0.1 *N* $AgNO_3$, (I) 9.93, (II) 8.50. Calc. for $C_{14}H_8O_4Br_2$: Br, 39.96. Found: (I) 39.68, (II) 40.24.

***p*-Hydroxybenzoyl-*o*-benzoic Acid Phenylhydrazone.**—Kaiser[14] has prepared the phenylhydrazone of diphenyl-phthaloylic acid, and *o*-benzoylbenzoic acid phenylhydrazone has been made by Roser[15] and also by H. Meyer and Turnau.[16]

Ten g. of finely powdered *p*-hydroxybenzoyl-*o*-benzoic acid was heated with 9 g. of phenylhydrazine (calculated 4.2 g.) at 160°. Water vapor was evolved and the material turned yellow. After 3 hours the heating was discontinued and the material in the flask was treated with water containing some hydrochloric acid. The crystalline product was filtered off, dried and recrystallized from hot 95% alcohol. The phenylhydrazone crystallizes as small, colorless needles melting at 267–268°. It is soluble in hot glacial acetic acid.

Analyses. Subs., 0.1795, 0.1819: CO_2, 0.5037, 0.5100; H_2O, 0.0726, 0.0784. Calc. for $C_{20}H_{14}O_2N_2$: C, 76.41; H, 4.49. Found: C, 76.55, 76.49; H, 4.53, 4.82. Subs., 0.1566: cc. 0.1 *N* H_2SO_4, 9.62. Calc. for $C_{20}H_{14}O_2N_2$: N, 8.91. Found: 8.60.

The formula of the phenylhydrazone may be written:



$$\begin{array}{lcr} HOC_6H_4C & \text{———————} & C_6H_4 \\ \| & & | \\ N & —N(C_6H_5)— & C{=}O \end{array}$$

Hydroxy-phenylphthalide.—Hydroxy-phenylphthalide was prepared by Bistrzycki and Oehlert[17] by condensing phthalaldehydic acid with phenol. Their product melted after previous softening at 148–151°, and its acetate melted at 125–126.5°. Hans Meyer[18] obtained hydroxy-phenylphthalide by reducing *p*-hydroxybenzoyl-*o*-benzoic acid in alcoholic solution with zinc and hydrochloric acid. His product melted at 157–160°, and the acetate melted at 125–126°.

Ten g. of *p*-hydroxybenzoyl-*o*-benzoic acid was dissolved in 75 cc. of 95% alcohol and to this solution was added 3 g. of zinc and 8 cc. of conc. hydrochloric acid. The solution was boiled for 2$^1/_2$ hours and then filtered while hot into 4 liters of hot water. A yellow oil separated and later solidified. It was recrystallized by dissolving it in as small an amount of hot 95% alcohol as possible and pouring the hot solution into hot water. Hydroxy-phenylphthalide crystallizes as small, colorless needles melting at 164–165°. It is very soluble in hot 95% alcohol and in hot glacial acetic acid. A desiccator-dried sample was analyzed.

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[13] *Am. Chem. J.*, **41**, 397 (1909).

[14] Kaiser, *Ann.*, **257**, 98 (1890).

[15] Roser, *Ber.*, **18**, 805 (1885).

[16] Meyer and Turnau, *Monatsh.*, **30**, 483 (1909).

[17] Bistrzycki and Oehlert, *Ber.*, **27**, 2632 (1894).

[18] Meyer, *Monatsh.*, **20**, 363 (1899).

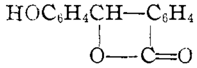
Analyses. Subs., 0.1814, 0.1800: CO_2, 0.4952, 0.4898; H_2O, 0.0767, 0.0745. Calc. for $C_{14}H_{10}O_3$: C, 74.32; H, 4.46. Found: C, 74.47, 74.23; H, 4.73, 4.63.

ACETATE.—The acetate, prepared by heating one part of hydroxy-phenylphthalide with one part of fused sodium acetate and 20 parts of acetic anhydride, was recrystallized from hot 95% alcohol, in which it is very soluble. It crystallizes as small, colorless needles, melting with previous softening at 125–126°. A desiccator-dried sample was analyzed.

Analyses. Subs., 0.1831, 0.1850: CO_2, 0.4813, 0.4845; H_2O, 0.0748, 0.0748. Calc. for $C_{16}H_{12}O_4$: C, 71.62; H, 4.51. Found: C, 71.71, 71.45; H, 4.57, 4.52.

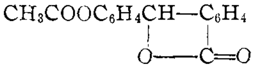
Professor Gill states concerning this acetate: "The double refraction in the plates is about 0.050, making the maximum for the substance about 0.100. The crystals are without much doubt triclinic, simulating rhombic shape."

Hydroxy-phenylphthalide may be represented by Formula I and the acetate by Formula II.



$$\begin{array}{l} HOC_6H_4CH—C_6H_4 \\ \qquad\quad | \qquad | \\ \qquad\quad O—C{=}O \end{array}$$

I



$$\begin{array}{l} CH_3COOC_6H_4CH—C_6H_4 \\ \qquad\qquad\qquad | \qquad | \\ \qquad\qquad\qquad O—C{=}O \end{array}$$

II

***p*-Methoxybenzoyl-*o*-benzoic Acid.**—*p*-Methoxybenzoyl-*o*-benzoic acid was first prepared in 1886 by Nourrisson[19] by condensing phthalic anhydride with anisol in the presence of aluminum chloride. The acid melted at 142–143°. Nourrisson gave it the ketone structure. In 1909 Hans Meyer and Turnau[20] prepared this acid by shaking a solution of *p*-hydroxybenzoyl-*o*-benzoic acid in sodium carbonate or sodium hydroxide solution with a slight excess of dimethyl sulfate. The acid, recrystallized from alcohol, melted at 148°.

p-Methoxybenzoyl-*o*-benzoic acid was prepared in this laboratory by Mr. Frederick Nill. He made it from phthalic anhydride and anisol, using a modification of the earlier methods. The materials were kept in a closed flask surrounded by an ice-bath, the temperature of which was —5° to —10°, and the aluminum chloride was added in small portions. The flask was evacuated after each addition of aluminum chloride. Finally, the temperature was slowly raised to 55°, hydrochloric acid was added, and the excess of anisol present removed by distillation with steam. The acid, which crystallized from the solution remaining in the flask, melted at 141.5–142°.

Ten g. of *p*-hydroxybenzoyl-*o*-benzoic acid was dissolved in 100 cc. of 5% sodium hydroxide and to the solution was added 5 g. of dimethyl sulfate. The mixture was boiled for $2^1/_2$ hours and then diluted to 2 liters. Addition of acetic acid[21] to the alkaline solution resulted in the formation of an oil which later solidified. The acid is easily recrystallized from water from which it separates on cooling, first as an oil and then as thin, colorless plates. After several recrystallizations it melts at 144–145°. The acid crystallizes well from hot alcohol and hot glacial acetic acid. Hydrochloric acid converts it into the hydroxy acid. A desiccator-dried sample was analyzed.

Analyses. Subs., 0.1921, 0.2007: CO_2, 0.4960, 0.5166; H_2O, 0.0858, 0.0850. Calc. for $C_{15}H_{12}O_4$: C, 70.29; H, 4.72. Found: C, 70.44, 70.22; H, 4.99, 4.74.

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[19] Nourrisson, *Ber.*, **19**, 2103 (1886).

[20] Ref. 17, p. 485.

[21] Nill, in precipitating *p*-methoxybenzoyl-*o*-benzoic acid from alkaline solution by means of hydrochloric acid, found that when an excess of the mineral acid was used, a substance melting at 186–187° was obtained. This substance was doubtless a mixture of the methoxy and hydroxy acids.

p-Methoxybenzoyl-*o*-benzoic acid titrates as a monobasic acid. Methyl red was used as indicator.

Analyses. Subs., 0.3001, 0.2997, 0.5000: cc. 0.1 *N* NaOH, 11.72, 11.69, 19.51. Calc. for $C_{15}H_{12}O_4$: 256.17. Found: 256.06, 256.37, 256.27.

p-Methoxybenzoyl-*o*-benzoic acid probably has the lactone structure in the free state and the ketone structure in its salts.

ACTION OF DRY AMMONIA GAS.—Dry ammonia gas was passed over some of the dried acid for 6 hours, when the latter came to constant weight. The material acquired a faint yellow tinge. The gain in weight corresponded to the addition of 1.5 molecules of ammonia to one of the acid.

Analyses. Subs., 0.4133, 0.5574: wt. of salt, 0.4544, 0.6125. Calc. for $C_{15}H_{12}O_4.(NH_3)_{1.5}$: NH_3, 9.06. Found: 9.04, 9.00.

After standing in an evacuated desiccator over conc. sulfuric acid for a few days the material came to constant weight when 1 molecule of ammonia remained.

Analyses. Subs., 0.4133, 0.5574: wt. of salt, 0.4406, 0.5944. Calc. for $C_{15}H_{12}O_4.(NH_3)$: NH_3, 6.23. Found: 6.19, 6.22.

Unlike the ammonium salt of the hydroxy acid, this salt loses weight when heated at 65° in a tube in a current of dry air for 3 hours. The mono-ammonium salt is colorless. It is very soluble in hot water, and easily soluble in cold water and in hot 95% alcohol.

MONOSODIUM SALT.—This salt, obtained by the action of sodium upon *p*-methoxybenzoyl-*o*-benzoic acid in alcoholic solution, crystallizes in small, colorless needles, soluble in hot 95% alcohol and very soluble in hot water. The desiccator-dried salt was analyzed.

Analyses. Subs., 0.4062, 0.3606: Na_2SO_4, 0.1039, 0.0916. Calc. for $C_{15}H_{11}O_4Na$: Na, 8.27. Found: 8.28, 8.21.

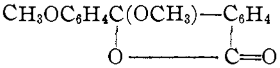
POTASSIUM SALT.—This salt was made by the action of potassium on *p*-methoxybenzoyl-*o*-benzoic acid in alcoholic solution. It crystallizes in clusters of long, colorless needles, very soluble in cold water and in hot 95% alcohol. It melts at 257° to a reddish oil. Dried in a desiccator, the air-dried salt lost only about 2% in weight. The desiccator-dried salt was analyzed for potassium.

Analyses. Subs., 0.3018: K_2SO_4, 0.0837. Calc. for $C_{15}H_{11}O_4K.H_2O$: K, 12.52; calc. for $C_{15}H_{11}O_4K.0.5C_2H_5OH$: K, 12.32. Found: 12.45.

Since this analysis did not indicate whether the salt crystallizes with 1 molecule of water or with $^1/_2$ a molecule of alcohol, and since when dried in a tube at 125° the salt did not lose any solvent of crystallization, two combustions of the desiccator-dried salt were made.

Analyses. Subs., 0.1809, 0.1747: total C, 0.1095, 0.1055; H_2O, 0.0640, 0.0623. Calc. for $C_{15}H_{11}O_4K.H_2O$: C, 57.66; H, 4.20; calc. for $C_{15}H_{11}O_4K.0.5C_2H_5OH$: C, 60.54; H, 4.45. Found: C, 60.53, 60.38; H, 3.96, 3.99.

METHYL ESTER.—Hans Meyer and Turnau[21] found that *p*-methoxybenzoyl-*o*-benzoic acid gave 2 isomeric methyl esters. One ester, melting at 63°, was prepared by treating *p*-hydroxybenzoyl-*o*-benzoic acid in alkaline solution with dimethyl sulfate; the other ester, melting at 84°, was obtained by treating the hydroxy acid with thionyl chloride and then with methyl alcohol. They gave to the latter ester the following structure.



$$\begin{array}{lcl} CH_3OC_6H_4C(OCH_3) & — & C_6H_4 \\ \qquad\qquad\; | & & \;| \\ \qquad\qquad\; O & \text{————} & C{=}O \end{array}$$

Ten g. of *p*-hydroxybenzoyl-*o*-benzoic acid was dissolved in 100 cc. of 10% sodium hydroxide solution and to this solution contained in a glass-stoppered bottle was added an excess over the calculated amount of dimethyl sulfate. The solution was shaken well. More alkali and dimethyl sulfate were added alternately from time to time and the contents of the bottle were shaken well after each addition. A colorless oil separated and later solidified. The ester is easily recrystallized from hot methyl alcohol, in which it is very soluble. It separates in colorless crystals melting at 80–81.5°. This indicates that it is identical with the second ester mentioned by Meyer and Turnau. Some of the desiccator-dried ester was analyzed.

Analyses. Subs., 0.1795, 0.1778: CO_2, 0.4678, 0.4636; H_2O, 0.0844, 0.0827. Calc. for $C_{16}H_{14}O_4$: C, 71.09; H, 5.22. Found: C, 71.09, 71.13; H, 5.26, 5.25.

Summary

1. The sodium, silver, barium, calcium and zinc salts of *p*-hydroxybenzoyl-*o*-benzoic acid have been prepared.
2. The ethyl and methyl esters of *p*-hydroxybenzoyl-*o*-benzoic acid have been prepared and the action of ammonia on them has been observed.
3. The dibromo derivative of *p*-hydroxybenzoyl-*o*-benzoic acid has been prepared by direct bromination of the acid.
4. The phenylhydrazone of *p*-hydroxybenzoyl-*o*-benzoic acid has been prepared.
5. Hydroxy-phenylphthalide and its acetate have been prepared.
6. *p*-Methoxybenzoyl-*o*-benzoic acid and its sodium and potassium salts and methyl ester have been prepared.

ITHACA, NEW YORK

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THE INFLUENCE OF VARIOUS ANTISEPTICS ON THE ACTIVITY OF LIPASE[1]

BY LEROY S. PALMER

Received December 9, 1921

One of the prerequisites of a suitable technique for measuring lipase activity is an antiseptic which does not interfere with the fat hydrolysis but which will effectively prevent the growth of bacteria and the activity of other acid producing enzymes. Very few data on this subject are found in the literature.

Kastle and Loevenhart[2] made the most comprehensive study. Their experiments were with the esterase of the pancreas and liver, using ethyl butyrate as substrate. The period of incubation in their experiments was only 15 minutes. The antiseptics examined were hydrocyanic acid, potassium cyanide, mercuric chloride, silver nitrate,

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[1] Published with the approval of the Director as Paper No. 280, Journal Series, Minnesota Agricultural Experiment Station. The studies here presented were begun at the Missouri Agricultural Experiment Station and carried to completion at the Minnesota Agricultural Experiment Station. Reported at the Philadelphia Meeting of the American Chemical Society, September, 1919.

[2] Kastle and Loevenhart, *Am. Chem. J.*, **24**, 491 (1900).