Summary

Redetermination of the degrees of dissociation of methoxyl substituted hexaarylethanes by the magnetic susceptibility method has shown that the values in the literature determined by cryoscopic molecular weight values are too high due to the instability of these ethanes. The new values show that the o-methoxyl group is much less effective than the o-methyl group in causing dissociation. In the m- and p-positions the methoxyl groups are also somewhat less effective than methyl groups but the difference is less marked.

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[CONTRIBUTION NO. 35 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Action of Formaldehyde on m-Hydroxybenzoic Acid. I

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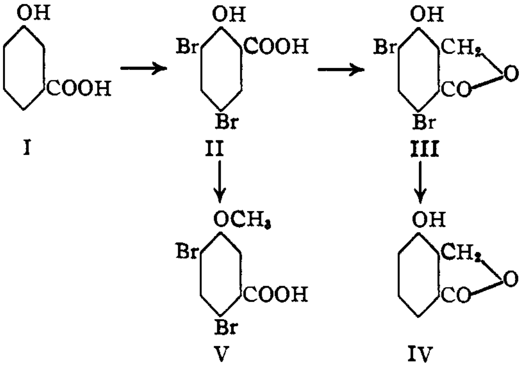
This study is one of a series[3] dealing with the action of formaldehyde on substituted phenols in hydrochloric acid solution. At room temperature m-hydroxybenzoic acid produces chiefly two compounds melting at 175 and 254°. The latter is the subject of this investigation. This compound, of formula $C_8H_6O_3$, contains a hydroxyl group since it gives unsaponifiable methoxy and ethoxy derivatives, and an acetyl derivative. In addition, the presence of a phthalide ring is indicated by the fluorescence which develops with resorcinol and sulfuric acid.

Of the possible structures, 4-hydroxy- or 6-hydroxyphthalide, for the condensation product, the latter is ruled out since the melting points of our product and of its methoxy and ethoxy derivatives do not agree with those of the known 6-hydroxyphthalide and its known methoxy and ethoxy derivatives. Indirectly, then, the structure of our compound corresponds to that of 4-hydroxyphthalide.

Direct methods for proving the structure were:

1. Oxidation of the methoxy derivative with dilute potassium permanganate produced the known 3-methoxyphthalic acid, which in turn with methyl alcohol and hydrogen chloride gave the known dimethyl 3-methoxyphthalate.

2. It was found possible to synthesize 4-hydroxyphthalide by blocking the reactive positions (those o- or p- to the hydroxyl) with the exception of 2-, then introducing the phthalide ring and finally removing the blocking groups. This synthesis was accomplished by brominating m-hydrobenzoic acid, I, in glacial acetic acid solution to give 4,6-dibromo-3-hydroxybenzoic acid, II. Although the structure of this acid was arrived at by analogy by Coppadoro,[4] we confirmed its structure by conversion into the known 4,6-dibromo-3-methoxybenzoic acid, V. On treatment of II with methylal, hydrochloric and sulfuric acids, 4-hydroxy-5,7-dibromophthalide, III, was obtained. The latter could not be debrominated with sodium and ethyl or amyl alcohols, or with zinc and alcoholic potassium hydroxide, but on hydrogenation under pressure with Raney nickel at a temperature of 150–200°, it gave 4-hydroxyphthalide, IV, identical with the original condensation product.



It is interesting to note that the orientation in this condensation is similar to that which occurred at low temperatures in the case of m-nitrophenol,[5] in that the entering group takes the position ortho to the two substituents.

Experimental

I. Preparation of 4-Hydroxyphthalide.—m-Hydroxybenzoic acid, m. p. 200–201°, 25 g., was dissolved in 500 cc. of 40% U. S. P. formaldehyde, and 500 cc. of concentrated hydrochloric acid and 25 cc. of concentrated sulfuric acid were added. The solution was stirred at 30–40° in a three-necked, round-bottomed flask, equipped with a mercury-sealed stirrer, a thermometer, and a glass tube with an opening of about 1 mm. in diameter leading to the bottom of the flask for introducing dry hydrogen chloride. Any excess of hydrogen chloride was removed through an exhaust tube, in the side arm of the flask opposite to the one containing the inlet, attached to an aspirator pump. After the introduction of hydrogen chloride gas for two hours, followed by cooling in the refrigerator, the precipitate which had formed was filtered off and crystallized once from water to give 6 to 8 g. of white crystals, m. p. 254°. Dilution of the filtrate with water to twice its volume and then standing overnight in the refrigerator gave more crystals, which when crystallized twice from water weighed 6 to 8 g. and melted at 175°.

The first crystals produced a fluorescence when heated with resorcinol and sulfuric acid, but there was no color

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[3] For the previous publication, see *J. Org. Chem.*, **6**, 902 (1941).

[4] Coppadoro, *Gazz. chim. ital.*, **32**, II, 332–339 (1902).

[5] Buehler, Deebel and Evans, *J. Org. Chem.*, **6**, 216 (1941).

with ferric chloride, no precipitate with alcoholic silver nitrate, no indication of the presence of a dioxane ring with phloroglucinol and sulfuric acid, and attempts to esterify with several alcohols were unsuccessful.

Anal. Calcd. for $C_8H_6O_3$: C, 64.00; H, 4.03; neut. equiv., 150. Found: C, 63.94, 63.68; H, 4.24, 4.14; neut. equiv. (indirect), 151, 150.

(a) **4-Methoxyphthalide.**—The hydroxyphthalide, 3 g., was treated in the usual manner with an excess of 10% sodium hydroxide solution and an excess of dimethyl sulfate. After warming for thirty minutes, the solution was acidified with hydrochloric acid and cooled. The solid, which separated, was crystallized three times from water to give 1.3 g., m. p. 127°.

Anal. Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91; OCH_3, 18.91; mol. wt., 164. Found: C, 65.58, 65.75; H, 4.80, 4.67; OCH_3, 18.54, 18.55; mol. wt. (cryoscopic, benzene), 166, 166.

(b) **4-Ethoxyphthalide.**—4-Hydroxyphthalide, 2 g., in 100 cc. of 10% sodium hydroxide solution was treated with 5 cc. of diethyl sulfate in the usual manner. The product, thrice crystallized from ethanol–water, weighed 1.8 g., m. p. 170°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66; neut. equiv., 178. Found: C, 67.52, 67.40; H, 5.72, 5.60; neut. equiv. (indirect), 179, 179.

(c) **4-Acetoxyphthalide.**—The hydroxyphthalide, 2.3 g., was acetylated by the method of Pratt and Robinson[6] in which it was mixed with 2.5 g. of potassium carbonate and 6.4 cc. of acetic anhydride. When the first reaction had subsided, 1.3 g. more of potassium carbonate and 5 cc. more of acetic anhydride were added. After thirty minutes the mixture was diluted with approximately 100 cc. of water, potassium carbonate was added in slight excess and then the solution was acidified with hydrochloric acid. Cooling produced crystals, which when crystallized three times from water gave 1.4 g., m. p. 96–97°.

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.50, 62.54; H, 4.50, 4.48.

II. Oxidation of 4-Methoxyphthalide

3-Methoxyphthalic Acid.—4-Methoxyphthalide, 2 g., in 200 cc. of *N* potassium hydroxide solution was heated to 60–70° for one hour and then potassium permanganate solution (2 g. in 200 cc. of water) was added gradually during one and one-half hours. The reaction mixture was held at 75° for another hour and one-half, after which the excess permanganate was removed with sodium bisulfite. Filtration removed the manganese dioxide and the filtrate, upon being acidified with hydrochloric acid and evaporated to one-third its volume, was extracted with ether. The solid obtained on evaporation was taken up in water and the solution was made basic with sodium bicarbonate and then filtered. The filtrate was again acidified, evaporated to dryness, and the residue was leached with ether. Evaporation gave a product which was crystallized twice from benzene–ethanol solution (10:1), norite having been used the first time, to yield 0.5 g., m. p. 167–168° (Bentley, Robinson and Weizmann[7] give 173–174°).

Anal. Calcd. for $C_9H_8O_5$: C, 55.11; H, 4.10. Found: C, 55.11, 55.34; H, 4.29, 4.22.

Dimethyl 3-Methoxyphthalate.—A solution of the acid, 1 g. in 10 cc. of ethanol and 140 cc. of ether was cooled to 5° and diazomethane was added until a yellow color appeared. The ester was recovered in the usual manner, washed with sodium bicarbonate solution, then with water and finally crystallized from ethanol several times by the addition of water. The pure product, 0.8 g., melted at 73–74° (Onnertz[8] gives 71°).

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.39. Found C, 59.40, 59.52; H, 5.32, 5.40.

III. Synthesis of 4-Hydroxyphthalide

3-Hydroxy-4,6-dibromobenzoic Acid (II).—This acid was prepared by the method of Robertson.[9] Sixty-nine g. (0.5 mole) of *m*-hydroxybenzoic acid dissolved in a minimum amount of glacial acetic acid at 50° was treated with 77 cc. (1.5 moles) of bromine and the solution was allowed to stand at 50° for two hours. Cooling in the refrigerator gave crystals, which when crystallized from water amounted to 36 g. Three additional crystallizations from water gave a product melting at 198–199° (Robertson gives 201–202°).

Anal. Calcd. for $C_7H_4Br_2O_3$: Br, 54.01. Found: Br, 53.93, 53.98.

3-Methoxy-4,6-dibromobenzoic Acid (V).—The acid, 10 g., was dissolved in 10% sodium hydroxide solution of such an amount that the resulting solution was decidedly alkaline. Dimethyl sulfate in excess was added in the customary manner over a half hour period. About 10 cc. of 25% sodium hydroxide solution was then introduced and the solution was boiled for fifteen minutes. Acidification and cooling in the refrigerator gave a white, gelatinous mass. Solution in the minimum amount of boiling methanol, followed by the addition of water of an amount just short of that necessary to cause precipitation at the boiling point, and then slow cooling yielded white, fluffy crystals. Repetition of the above process twice more gave 6 g. (57%) of the acid, m. p. 205° (Hodgson and Beard[10] give 202–203°).

Anal. Calcd. for $C_8H_6Br_2O_3$: Br, 51.57; neut. equiv., 310. Found: Br, 51.34, 51.34; neut. equiv., 301, 304.

4-Hydroxy-5,7-dibromophthalide (III).—The dibromo acid, 26.8 g., dissolved in 250 cc. of methylal, was treated with 400 cc. of concentrated hydrochloric acid and 12 cc. of concentrated sulfuric acid. Hydrogen chloride was bubbled through this solution at 50–55°, with stirring, for six hours, after which the reaction mixture was diluted to two liters with water and cooled. The white crystalline product which formed was crystallized three times as described above by solution in the minimum amount of methanol followed by the addition of water. Final product, 16.9 g. (60%), m. p. 146°, gave a fluorescence with resorcinol and sulfuric acid, but it reacted negatively toward ferric chloride and alcoholic silver nitrate.

Anal. Calcd. for $C_8H_4Br_2O_3$: Br, 51.90. Found: Br, 52.18, 52.00, 51.86.

4-Hydroxyphthalide (IV).—The dibromophthalide, 1 g., in absolute ethanol with 0.5 g. of Raney nickel was shaken with hydrogen at 150–200° and 500 lb. pressure for three hours. The product recovered on evaporating the ethanol was crystallized twice from water to give 0.2 g. (41%), m. p. 254°. A mixed melting point with the original condensation product showed no depression.

Anal. Calcd. for $C_8H_6O_3$: C, 64.00; H, 4.03. Found: C, 63.78, 63.99; H, 4.35, 4.32.

Summary

At room temperature one of the products of the condensation of formaldehyde and *m*-hydroxybenzoic acid in acid medium is 4-hydroxyphthalide.

Although the structure of this phthalide may be inferred by indirect means, it has been established by oxidative and synthetic methods.

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(6) Pratt and Robinson, *J. Chem. Soc.*, **127**, 1184 (1925).

(7) Bentley, Robinson and Weizmann, *ibid.*, **91**, 110 (1907).

(8) Onnertz, *Ber.*, **34**, 3747 (1901).

(9) Robertson, *J. Chem. Soc.*, **81**, 1483 (1902).

(10) Hodgson and Beard, *ibid.*, **127**, 880 (1925).