

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BARNARD COLLEGE]

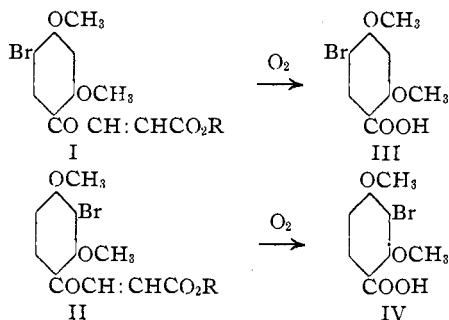
THE ORIENTATION OF THE BROMINE ATOM IN BROMO-DIMETHOXYBENZOIC ACID

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A series of unsaturated ketonic esters has been made in this Laboratory by bromination of saturated esters and subsequent elimination of hydrogen bromide from the bromo esters.¹ When this method of preparation was applied to saturated ketonic esters with two methoxyl groups in the *meta* position in the benzene ring, bromination gave products with bromine in the nucleus as well as in the side chain. Oxidation of the corresponding unsaturated esters, which must be I or II, leads to the formation of a bromo-dimethoxybenzoic acid which must be III or IV.



For orientation of the bromine atom attempts were made to eliminate carbon dioxide from the acid and thus obtain 4- or 2-bromoresorcinol dimethyl ether. The 4-bromo ether would be expected to react with activated magnesium and carbon dioxide like 4-iodoresorcinol dimethyl ether to give dimethyl- β -resorcylic acid;² but the 2-bromo ether would behave like 2-iodoresorcinol dimethyl ether, which does not react with activated magnesium.³ This method failed because it was not possible to eliminate carbon dioxide from the acid.

Synthesis of this acid from 4,6-dibromoresorcinol dimethyl ether by substitution of one bromine atom by a carboxyl group was unsuccessful because the dibromo ether does not react with activated magnesium.

The successful method for determination of the constitution of the acid was its synthesis from β -resorcylic acid. The bromo acid which is obtained by direct bromination of β -resorcylic acid and is described in the literature as 2- or 4-bromo- β -resorcylic acid⁴ has been proved to be isomeric

¹ Rice, *THIS JOURNAL*, **45**, 222 (1923); **46**, 214, 2319 (1924); **48**, 269 (1926).

² Kauffmann and Kieser, *Ber.*, **45**, 2333 (1912).

³ Kauffmann and Franck, *Ber.*, **40**, 4015 (1907).

⁴ Zehenter, (a) *Monatsh.*, **2**, 480 (1881); (b) **8**, 293 (1897). (c) Hemmelmayr, *ibid.*, **33**, 971 (1912).

with the 2-bromo acid which is obtained from β -resorcylic acid by indirect means;⁵ it is therefore 4-bromo- β -resorcylic acid. On methylation it gives the acid under investigation, which is proof for Formula III and hence Formula I for the unsaturated ester.

Experimental Part

5-Bromo-2,4-dimethoxybenzoic Acid, $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_2\text{BrCOOH}$.—The acid obtained in quantitative yield by the oxidation of 5-bromo-2,4-dimethoxybenzoylacrylic acid with potassium permanganate can be purified by recrystallization from acetone or xylene. It melts at 193° and is sparingly soluble in boiling water, acetone, xylene, chloroform and methyl alcohol.

Anal. Subs., 0.1555: CO_2 , 0.2358; H_2O , 0.0496. Calcd. for $\text{C}_8\text{H}_6\text{O}_4\text{Br}$: C, 41.38; H, 3.44. Found: C, 41.35; H, 3.54.

The methyl ester was prepared by allowing the methyl alcohol solution of the acid saturated with dry hydrogen chloride to stand overnight or by heating its methyl alcohol solution with concd. sulfuric acid. It separated from methyl alcohol in firm, colorless needles; m. p., 117° .

Anal. Subs., 0.1527: CO_2 , 0.2447; H_2O , 0.0569. Calcd. for $\text{C}_{10}\text{H}_{11}\text{O}_4\text{Br}$: C, 43.63; H, 4.00. Found: C, 43.70; H, 4.14.

Methyl 5-Bromo-2-hydroxy-4-methoxybenzoate, $\text{CH}_3\text{OC}_6\text{H}_2(\text{OH})\text{BrCOOCH}_3$.—Attempt was made to obtain the mono ester of a known isophthalic acid derivative⁶ by treatment of the ester (m. p., 117°) with magnesium and carbon dioxide. The product obtained has been shown to be 5-bromo-2-hydroxy-4-methoxybenzoate formed by demethylation of one of the hydroxyl groups of the ester.⁷

The ester (m. p., 117°) could not be made to react with magnesium when the usual means for starting a Grignard reaction were tried but it united slowly when heated with activated magnesium; carbon dioxide was passed into the solution and the mixture treated with ice and concd. hydrochloric acid. The brown residue from the evaporation of the ether extract was washed with a mixture of ether and methyl alcohol and the undissolved solid recrystallized twice from a mixture of chloroform and methyl alcohol; it separates in colorless needles melting at 143° .

Anal. Subs., 0.1635: CO_2 , 0.2493; H_2O , 0.0483. Calcd. for $\text{C}_8\text{H}_7\text{O}_4\text{Br}$: C, 41.38; H, 3.44. Found: C, 41.58; H, 3.28.

This substance in 20% sodium hydroxide solution was heated for one hour with dimethyl sulfate, the solution was acidified with sulfuric acid and extracted with ether. The solid obtained from the ether, after purification, did not depress the melting point of the ester used in the Grignard reaction; further, the acid obtained from it on hydrolysis melts at 193° and is 5-bromo-2,4-dimethoxybenzoic acid.

Though carbon dioxide can be eliminated easily from bromodihydroxybenzoic acids it was not possible to remove it from the dimethoxy acid. The acid was recovered unchanged after boiling for 30 hours with water and with xylene and it distilled in a vacuum without decomposition. The calcium salt of the acid was heated to 360° in a vacuum with soda lime without bringing about decomposition, but it decomposed completely when heated with lime or soda lime at atmospheric pressure.

The position of the bromine atoms in the product obtained by bromination of resorcinol dimethyl ether has been determined by synthesis of this substance from 4,6-

⁵ Hemmelmayr, *Monatsh.*, **33**, 981 (1912); **35**, 1 (1914).

⁶ Eijkman, Bergema and Henrard, *Chem. Centr.*, **76** [I], 814 (1905).

⁷ Späth, *Monatsh.*, **35**, 325 (1914).

dibromoresorcinol (m. p., 115°) by methylation with sodium and methyl iodide. 4,6-Dibromoresorcinol dimethyl ether (m. p., 138°) was treated in dry benzene solution with activated magnesium in the presence of absolute ether; although the reaction was carried out several times, no trace of product could be found and each time the dimethyl ether was entirely recovered.

3-Bromo-2,4-dihydroxybenzoic Acid was prepared from β -resorcylic acid by the method of Hemmelmayr.⁵ It was obtained in the form of fine, pale straw-colored needles; m. p., 200°.

2-Bromoresorcinol, $C_6H_2(OH)_2Br$.—An aqueous solution of the 3-bromo acid was boiled for three hours, cooled and extracted with ether; the ether extract was washed with ammonium carbonate solution and water and the ether allowed to evaporate. The solid which remained separated in long, colorless needles which were pure and melted at 102.5° after three recrystallizations from chloroform; yield, 80%.

Anal. Subs., 0.1525: CO_2 , 0.2129; H_2O , 0.0374. Calcd. for $C_6H_5O_2Br$: C, 38.09; H, 2.64. Found: C, 38.07; H, 2.72.

5-Bromo-2,4-dihydroxybenzoic Acid, $C_6H_2(OH)_2BrCOOH$.—The monobromo- β -resorcylic acid, which is a product of direct bromination of β -resorcylic acid, was first prepared in 1881 by Zehenter^{4a} with the use of ether as solvent; the melting point of his acid after recrystallization from water was 184° and the recorded analysis indicated a pure substance. Later, this acid was prepared by Hemmelmayr in glacial acetic acid solution^{4b} and described as a substance melting at 212° after recrystallization from water, but no analyses of the product were given. β -Resorcylic acid has been brominated in this Laboratory with ether, with glacial acetic acid and with chloroform as solvents, and a mixture of monobromo and dibromo acids was invariably obtained even on most careful bromination at a low temperature. β -Resorcylic acid is so sparingly soluble in carbon disulfide that bromination could not be carried out readily in this solvent; the only good solvent for bromination is glacial acetic acid. The monobromo and dibromo acids in the mixture (m. p., 195–201°), which were precipitated when the glacial acetic acid solution was diluted with ice water, cannot be separated by recrystallization from water, from alcohol and water or from glacial acetic acid and water. The only solvent which proved satisfactory for separation was a mixture of acetone and chloroform; with this, 50–60% of the crude product could be isolated as pure 5-bromo-2,4-dihydroxybenzoic acid. Ten recrystallizations from this mixture of solvents gave an acid with a constant melting point of 204°; the transparent crystals still held a molecule of water which they lost at 95°, becoming opaque.

Anal. Subs., 0.1565: CO_2 , 0.1922; H_2O , 0.0403. Calcd. for $C_7H_5O_4Br.H_2O$: C, 33.46; H, 2.78. Found: C, 33.49; H, 2.86.

Subs., 0.1816: loss at 95°, 0.0130. Calcd. for $C_7H_5O_4Br.H_2O$: H_2O , 7.17. Found: 7.15.

Subs., 0.1686 (dry): CO_2 , 0.2229; H_2O , 0.0353. Calcd. for $C_7H_5O_4Br$: C, 36.05; H, 2.14. Found: C, 36.05; H, 2.32.

The two substances in the 40–50% of residue could not be separated by fractional crystallization from any solvent or mixture of solvents tried; it was possible, however, to isolate most of the monobromo acid present in it by taking advantage of the fact that very little of the monobromo acid is decomposed when its aqueous solution is boiled for two hours, while the dibromo acid is decomposed completely to give a dibromoresorcinol which is extremely soluble in water. The aqueous solution of the residue, after being boiled for two hours, therefore, deposits a monobromo acid which is pure and after two recrystallizations from acetone and chloroform melts at 204°. No trace of 2-bromoresorcinol was found in the aqueous solution, which indicates that 3-bromo-2,4-dihydroxybenzoic acid is not a product of direct bromination of β -resorcylic acid.

The mixture of 5-bromo-2,4-dihydroxybenzoic acid (204°) and 3-bromo-2,4-dihydroxybenzoic acid (200°) melts at 175°.

The dimethoxy acid under investigation could not be demethylated to give one of these dihydroxy acids.

4-Bromoresorcinol, $C_6H_3(OH)_2Br$.—Zehenter^{4a} described a bromoresorcinol melting at 91° which he obtained by boiling his bromo acid (m. p., 184°) with water; this substance is now proved to be 4-bromoresorcinol; it melts at 103° when it is made from pure bromo- β -resorcylic acid (m. p., 204°).

Anal. Subs., 0.1550: CO_2 , 0.2175; H_2O , 0.0383. Calcd. for $C_6H_3O_2Br$: C, 38.09; H, 2.64. Found: C, 38.26; H, 2.74.

The mixture of this substance and 2-bromoresorcinol (m. p., 102.5°) melts at 65–82°.

4-Bromoresorcinol Dimethyl Ether, $C_6H_3(OCH_3)_2Br$.—The 4-bromoresorcinol (15 g.) was methylated with dimethyl sulfate. The ether extract of the product was dried, the ether removed and the residue distilled in a vacuum; 5 g. of a colorless liquid with a pronounced odor distilled at 135° (18 mm.).

Anal. Subs., 0.1815: CO_2 , 0.2928; H_2O , 0.0683. Calcd. for $C_8H_9O_2Br$: C, 44.24; H, 4.14. Found: C, 44.00; H, 4.18.

4-Bromoresorcinol-1-methyl Ether, $C_6H_3(OCH_3)(OH)Br$.—After removal of the dimethyl ether the alkaline solution was acidified with sulfuric acid and again extracted with ether. The residue from the ether distilled at 152° (25 mm.); yield, 7.5 g.

Anal. Subs., 0.1632: CO_2 , 0.2490; H_2O , 0.0491. Calcd. for $C_7H_7O_2Br$: C, 41.38; H, 3.44. Found: C, 41.61; H, 3.34.

An absolute ether solution of 4-bromoresorcinol dimethyl ether reacts vigorously with activated magnesium. A very rapid stream of carbon dioxide was passed into the flask, the white addition product was decomposed in the usual way and the ether extract washed with dil. sodium carbonate solution. The residue from the ether was chiefly resorcinol dimethyl ether; the sodium carbonate solution gave on acidification the dimethyl ether of β -resorcylic acid (m. p., 108°) which was identified by comparison with a specimen made from 4-iodoresorcinol dimethyl ether.

The acid (m. p., 204°) was dissolved in a 10% sodium hydroxide solution and treated gradually with a large excess of dimethyl sulfate; the mixture was kept in a water-bath (60–70°) for one hour. The solid obtained on acidifying the solution was filtered off by suction, washed, dried and extracted with benzene. The benzene deposited a solid which after three recrystallizations from methyl alcohol melted at 143°; analysis and a mixed-melting-point determination showed that it is the same substance that was obtained in the Grignard reaction with the ester of 4-bromodimethoxybenzoic acid.

That the hydroxyl group is in the *ortho* position and not in the *para* position is probable because the carboxyl group in the *ortho* position to the hydroxyl group in the bromo- β -resorcylic acid would be expected to interfere with methylation more than a bromine atom in the *ortho* position to a hydroxyl group. Evidence for this is the fact that 4,6-dibromoresorcinol forms a dimethyl ether readily with methyl iodide and sodium, while the hydroxyl group *ortho* to a carboxyl group in β -resorcylic acid is not methylated by methyl iodide and sodium.⁸ Further evidence for the structure of the Grignard product is the fact that the acid obtained from it loses carbon dioxide as do the bromodihydroxybenzoic acids, although much

⁸ Perkin, *J. Chem. Soc.*, 67, 990 (1895).

more slowly, while carbon dioxide could not be eliminated from the acid with a methoxyl group in the *ortho* position to the carboxyl group.

The product of methylation, not soluble in benzene, melted at 232° with decomposition; this was separated with a mixture of acetone and chloroform into two acids, one melting at 193° and the other at 247° with decomposition. The former substance gave no depression of the melting point when mixed with the bromodimethoxy acid under investigation and is that substance. The acid melting at 247° gave with methyl alcohol and dry halogen chloride the ester melting at 143° and is, therefore, the acid of the ester. It is soluble in alcohol, ether and acetone and insoluble in benzene and chloroform.

Anal. Subs., 0.1553: CO_2 , 0.2217; H_2O , 0.0407. Calcd. for $\text{C}_8\text{H}_7\text{O}_4\text{Br}$: C, 38.86; H, 2.83. Found: C, 38.93; H, 2.91.

Except when methylation of 5-bromo-2,4-dihydroxybenzoic acid was carried out with a small quantity of acid, some of it invariably escaped reaction with dimethyl sulfate.

4-Bromoresorcinol-3-methyl Ether, $\text{C}_6\text{H}_3(\text{OCH}_3)(\text{OH})\text{Br}$.—Carbon dioxide was slowly eliminated from the acid melting at 247° by boiling its aqueous solution for 30 hours. The acidified solution was extracted with ether, the ether extract washed with ammonium carbonate solution and water and the ether removed; the solid residue was extremely soluble in the usual organic solvents except ligroin and petroleum ether. It can be purified by dissolving in a very small quantity of benzene and cooling the solution in ice. It separates in small needles melting at 84° . It can also be purified by distillation in a vacuum.

Anal. Subs., 0.1775, 0.1500: CO_2 , 0.2717, 0.2282; H_2O , 0.0576, 0.0533. Calcd. for $\text{C}_7\text{H}_7\text{O}_2\text{Br}$: C, 41.38; H, 3.44. Found: C, 41.74, 41.49; H, 3.60, 3.94.

The solid melting at 84° is the isomer of the monomethyl ether made from 4-bromoresorcinol with dimethyl sulfate; this substance could not be made to solidify in contact with the solid melting at 84° . The isomerism of these ethers is proof for the structure of the substance obtained in the Grignard reaction with the ester of 4-bromodimethoxybenzoic acid.

2,6-Dibromoresorcinol Dimethyl Ether, $\text{C}_6\text{H}_2(\text{OCH}_3)_2\text{Br}_2$ and **2,6-Dibromoresorcinol-3-methyl Ether**, $\text{C}_6\text{H}_2(\text{OCH}_3)(\text{OH})\text{Br}_2$.—3,5-Dibromo- β -resorcylic acid, m. p., 213° , was obtained in 94% yield by brominating β -resorcylic acid at room temperature in glacial acetic acid solution. From it 2,6-dibromoresorcinol was prepared in order to determine whether it is possible to methylate the hydroxyl group which is protected by two bromine atoms. After treatment of this substance (5.4 g.) with dimethyl sulfate, the alkaline solution was extracted with ether and the residue, after removal of ether, distilled in a vacuum; 2.5 g. of a colorless liquid boiling at 155° (15 mm.) was obtained; it is the dimethyl ether.

Anal. Subs., 0.2575: CO_2 , 0.3076; H_2O , 0.0653. Calcd. for $\text{C}_8\text{H}_8\text{O}_2\text{Br}_2$: C, 32.43; H, 2.70. Found: C, 32.57; H, 2.81.

The alkaline solution was acidified with sulfuric acid and again extracted with ether. The residue from the ether distilled at 160° (24 mm.); yield, 2.1 g.

Anal. Subs., 0.2009: CO_2 , 0.2203; H_2O , 0.0400. Calcd. for $\text{C}_7\text{H}_8\text{O}_2\text{Br}_2$: C, 29.78; H, 2.12. Found: C, 29.90; H, 2.21.

The methoxyl group in this substance is undoubtedly in the 3 position.

Before the synthesis of 2-bromo- β -resorcylic acid was accomplished, indication that the position of its bromine atom was different from the position of the bromine atom in the substance described as 2- or 4-bromo- β -resorcylic acid was given by treating 3-bromo-5-nitro-2,4-dihydroxybenzoic acid, which is an intermediate product in the preparation of the 2-bromo- β -resorcylic acid, and the 2- or 4-bromo- β -resorcylic acid with nitric acid. A bromine atom protected by two *o*-hydroxyl groups is not replaced by a nitro group, while a bromine atom not so protected is replaced.

One g. of 3-bromo-5-nitro-2,4-dihydroxybenzoic acid was warmed on a water-bath for a few minutes with 15 g. of concd. nitric acid; the product was poured into ice water and the precipitated yellow solid recrystallized from alcohol; it separated in yellow needles, m. p. 189–191°, which gave no depression of the melting point of 2-bromo-4,6-dinitroresorcinol which was prepared from 2,4,6-tribromoresorcinol and nitric acid.⁹ One g. of 4-bromo- β -resorcylic acid was warmed on a water-bath with an excess of concd. nitric acid until evolution of oxides of nitrogen ceased. The solid which separated when the product was poured into water was washed with water and recrystallized from methyl alcohol. It melts at 175° and was recovered unchanged after boiling for six hours with water and therefore cannot be 3,5-dinitro- β -resorcylic acid; it was shown to be 2,4,6-trinitroresorcinol by comparison with a specimen of this substance.

Summary

The position of the bromine atom in a bromo-dimethoxybenzoic acid obtained by oxidation of bromo-dimethoxybenzoylacrylic acid has been determined.

NEW YORK, N. Y.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MARYLAND]

THE DECOMPOSITION OF UNSYMMETRICAL MERCURI-ORGANIC COMPOUNDS: A METHOD OF ESTABLISHING THE RELATIVE DEGREE OF ELECTRONEGATIVITY OF ORGANIC RADICALS

BY M. S. KHARASCH AND R. MARKER

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Purpose of Work

A study of the electronegativity of organic radicals is of much importance from the standpoint of the electronic conception of valence. The information can also be used advantageously in the interpretation of a number of baffling organic reactions.

At the present time the words "positive" and "negative" with reference to organic radicals are used very loosely and there is no adequate method of determining directly which one of two radicals is more strongly electronegative. The classification of radicals as "positive" and "negative" is hardly necessary, for according to the modern conception of valence

⁹ Dahmer, *Ann.*, **333**, 362 (1904).