

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BARNARD COLLEGE]

5-BROMO-2,4-DIMETHOXYBENZOYLACRYLIC ACID AND ITS ESTERS

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The work described in this paper was begun with the intention of studying a dimethoxy substituted benzoylacrylic acid and its esters but the method used in the attempt to prepare them from dimethoxybenzoylpropionic acid gave unsaturated substances with a bromine atom in the ring; the methyl ester has been shown to be methyl-5-bromo-2,4-dimethoxybenzoylacrylate.¹ The fact that the acid as well as its methyl and ethyl esters have melting points much higher than those of the various unsaturated ketonic acids and esters previously investigated in this Laboratory² suggested that they might be desirable substances for evidence of any possible relationship between the melting point of a solid which is sensitive to light and its tendency to isomerize or polymerize. No evidence on this point is obtained from the study of 5-bromo-2,4-dimethoxybenzoylacrylic acid (208°) and its methyl ester (129°), for they do not polymerize or isomerize in the sunlight. The ethyl ester, however, is extremely sensitive to light and since a low-melting substance on exposure to light usually isomerizes like a substance in solution because it melts and behaves in the molten condition as though it were in solution,³ this ethyl ester, with its melting point of 115.5°, would not be expected to isomerize but to polymerize as is usually the case with solids in the dry condition. It has been found that the ethyl ester is rapidly changed to a polymer which is probably a cyclobutane derivative; it is the only unsaturated ketonic ethyl ester of the five investigated to form a polymer and the only one with a melting point above 55°.

The tendency of a bromine atom in the ring to favor the formation of crystalline substances has made possible the investigation of reactions with this ketonic acid which could not be studied with benzoylacrylic acid and its simpler substitution products. Such a reaction is that which the methyl ester of 5-bromo-2,4-dimethoxybenzoylacrylic acid undergoes in methyl alcohol solution containing a trace of potassium hydroxide. Two structural isomers are possible which are a result of 1:4 addition to the two conjugated systems of double linkages in the ester, $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_2\text{BrOCCH}=\overset{4}{\text{C}}\overset{1}{\text{C}}\overset{2}{\text{C}}\overset{3}{\text{C}}=$

¹ Rice, *THIS JOURNAL*, **48**, 3125 (1926).

² Rice, *ibid.*, **45**, 222 (1923); **46**, 214, 2319 (1924); **48**, 269 (1926).

³ (a) Stobbe, *Ber.*, **52**, 666 (1919); (b) Stobbe and Steinberger, *Ber.*, **55**, 2225 (1922); (c) Stobbe and Lehfeldt, *Ber.*, **58**, 2415 (1925).

$$\begin{array}{c} 3 \quad 2 \quad 1 \\ \text{CHC}=\text{O}; \text{ if the } (\text{COOCH}_3) \text{ determines the addition, the product would} \\ 1 \\ 4 \quad \text{OCH}_3 \end{array}$$

be a β -methoxy ester, $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_2\text{BrCOCHOCH}_3\text{CH}_2\text{CO}_2\text{CH}_3$, but if the (CO) determines the addition, the product would be an α -methoxy ester, $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_2\text{BrCOCH}_2\text{CHOCH}_3\text{CO}_2\text{CH}_3$. The proof that the latter is the case rests on the fact that the β -methoxy ester was prepared in a way which left no doubt as to its structure and it was found to be not identical but isomeric with the methoxy ester formed in the addition reaction. The results of further study of the bromodimethoxy acid and its esters will be reported later.

Experimental Part

2,4-Dimethoxybenzoylpropionic acid⁴ was prepared from resorcinol dimethyl ether and succinic anhydride by the Friedel and Crafts reaction. After the dark red solid addition product had been decomposed with water, steam was forced through the mixture until the carbon disulfide and resorcinol dimethyl ether were removed. The colorless product which crystallized from the hot aqueous solution was a mixture of acids and a mixture was always obtained though the conditions of carrying out the reaction were varied in an attempt to find the factors favoring the formation of pure dimethoxy acid. The crude product—75 to 85%—was separated partially after several recrystallizations from 50% acetic acid to give a yield of 65–75% of pure dimethoxy acid. The residue was still a mixture which was shown to contain 2-hydroxy-4-methoxybenzoylpropionic acid by isolation of the methyl ester of this acid melting at 87°⁴ on esterification of the residue; the acid itself was not separated.

Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_5$: C, 60.50; H, 5.88. Found: C, 60.28; H, 5.95.

β -Bromo-5-bromo-2,4-dimethoxybenzoylpropionic Acid, $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_2\text{BrCOCHBrCH}_2\text{CO}_2\text{H}$.—The bromo acid is formed when the dimethoxy acid is suspended in chloroform and treated with bromine; on evaporation of the chloroform it was left as a solid which was purified by recrystallizing it first from glacial acetic acid and then from methyl alcohol. It separates from both solvents in colorless needles melting at 165° with decomposition. When the crude acid was recrystallized from methyl alcohol it was changed completely into its methyl ester, esterification apparently being brought about by the hydrogen bromide held by the solid.

Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{O}_5\text{Br}_2$: C, 36.36; H, 3.03. Found: C, 36.54; H, 3.59.

5-Bromo-2,4-dimethoxybenzoylacrylic Acid, $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_2\text{BrCOCH}=\text{CHCO}_2\text{H}$.—The unsaturated acid was prepared by heating a concentrated glacial acetic acid solution of the bromo acid with potassium acetate in a boiling water-bath for two hours. It crystallized as the solution cooled, was filtered off, washed with water and dried; it is sparingly soluble in boiling water, soluble in boiling methyl alcohol, acetone, benzene, chloroform and glacial acetic acid and almost insoluble in ether. It was purified with

⁴ Perkin and Robinson, *J. Chem. Soc.*, 93, 506 (1908).

both benzene and glacial acetic acid as solvents—yield 95–99% calculated from the saturated acid. The bright yellow needles melt at 208°.

Anal. Calcd. for $C_{12}H_{11}O_5Br$: C, 45.71; H, 3.49. Found: C, 46.10; H, 3.52.

The unsaturated acid can be prepared most readily by brominating a glacial acetic acid solution of the saturated acid and heating this solution of the bromo acid in boiling water for two hours with potassium acetate. The acid which separates on adding a few drops of concd. hydrochloric acid and cooling the solution in an ice-bath melts at 205–208° and the yield is practically quantitative.

5-Bromo-2,4-dimethoxybenzoylpropionic Acid, $(CH_3O)_2C_6H_2BrCOCH_2CH_2COOH$.—This acid was obtained in 75% yield by treating a suspension of unsaturated acid cooled in ice with an aqueous solution of sodium hydrosulfite. The solid which separated on diluting and acidifying the solution was pure and melted at 187° after two recrystallizations from methyl alcohol.

Anal. Calcd. for $C_{12}H_{13}O_5Br$: C, 45.42; H, 4.10. Found: C, 45.62; H, 4.20.

The unsaturated acid is so sparingly soluble in cold ether and benzene that it is not practical to study the action of sunlight on the acid in these solvents; a solution of it in glacial acetic acid was exposed for three months but there was no change in the substance except for a slight amount of decomposition. After exposure for the same length of time, the powdered unsaturated acid was still yellow; a change in melting point of the solid, however, may indicate a very slow formation of a polymer but such a substance was not isolated.

The methyl ester of dimethoxybenzoylpropionic acid was obtained in quantitative yield by heating a methyl alcohol solution of the pure acid for two hours with concd. sulfuric acid; the solution was poured onto cracked ice, powdered sodium carbonate was added as long as solid ester continued to separate and the ester was filtered off, washed with ice water and dried. It can be used without recrystallization for preparation of the unsaturated ester. It separates from methyl alcohol with solvent of crystallization in heavy, transparent needles melting at 49°; they become opaque after several hours and melt at 58–59°, the melting point given by Perkin and Robinson.⁴

When this ester was treated in chloroform solution with one molecular equivalent of bromine under most carefully regulated conditions for bromination, the residue, after removal of the solvent, was an oil which failed to crystallize and which gave an untractable mixture on treatment with potassium acetate. The only unsaturated substance separated from the mixture held a bromine atom, so after the reaction had been repeated several times with the same results, it was deemed useless to try to prevent a bromine atom from entering the ring. Therefore, in subsequent work with this ester, as well as with the ethyl ester and the acid, two molecular equivalents of bromine were used for bromination.

Methyl- β -bromo-5-bromo-2,4-dimethoxybenzoylpropionate, $(CH_3O)_2C_6H_2BrCOCHBrCH_2CO_2CH_3$.—A chloroform solution of the ester of the dimethoxy acid, cooled in an ice-bath, was treated with two molecular equivalents of bromine and the solvent removed by drawing dry air through the solution. The residue was a cake of crystalline solid which melted at 103° after two recrystallizations from methyl alcohol.

Anal. Calcd. for $C_{13}H_{14}O_5Br_2$: C, 38.05; H, 3.41. Found: C, 38.10; H, 3.54.

Methyl-5-bromo-2,4-dimethoxybenzoylacrylate, $(CH_3O)_2C_6H_2BrCOCH=CHCO_2CH_3$.—The methyl alcohol solution of the bromo ester, 20 g. in 200 cc. of methyl alcohol, was boiled for two hours with 10 g. of potassium acetate. The yellow unsaturated ester which separated in long needles as the solution cooled was filtered off, washed with ice water and dried; yield, 97%. After removal of the chloroform, the bromo ester can be used without purification for the preparation of the unsaturated ester; yield,

95-98%. The ester is soluble in boiling benzene, methyl alcohol, acetone, chloroform and glacial acetic acid and all of these solvents can be used for recrystallizing it. On melting it behaves like a substance holding solvent of crystallization; the solid after recrystallization from methyl alcohol softens at 129° and melts at 138°, solidifies on cooling and melts sharply at 129°. The point where the ester softens varies somewhat with specimens recrystallized from different solvents but the melting point of the re-solidified substance is always 129°.

Anal. Calcd. for $C_{12}H_{18}O_2Br$: C, 47.41; H, 3.95. Found: C, 47.11; H, 4.03.

The unsaturated ester is hydrolyzed extremely slowly by boiling with 10% sodium carbonate solution but more readily by boiling with dilute hydrochloric acid to give the unsaturated acid.

Methyl-5-bromo-2,4-dimethoxybenzoylpropionate, $(CH_3O)_2C_6H_3BrCOCH_2CH_2CO_2CH_3$.—This substance was formed when an ice-cold methyl alcohol solution of the ester was treated with sodium hydrosulfite; the solid which was precipitated when the solution was diluted with ice water separated from methyl alcohol in fine, colorless needles melting at 117°.

Anal. Calcd. for $C_{13}H_{18}O_4Br$: C, 47.13; H, 4.53. Found: C, 47.10; H, 4.45.

Hydrolysis of this ester gave the corresponding acid melting at 187°.

The yellow, unsaturated ester was recovered unchanged from its benzene solution which had been exposed to the sunlight; when it was exposed as a powdered solid 70% was recovered unchanged and the rest was a brown, amorphous mass from which no crystalline substance could be separated.

Ethyl-2,4-dimethoxybenzoylpropionate, $(CH_3O)_2C_6H_3COCH_2CH_2CO_2C_2H_5$.—An absolute alcohol solution of dimethoxybenzoylpropionic acid containing concd. sulfuric acid was refluxed for two hours; the solid ester which separated when the solution was poured onto ice was filtered off and washed with ice water. On recrystallization from alcohol large, transparent crystals were obtained which melted at 44°, slowly became opaque, and melted at 68.5°; yield, 94%.

Anal. Calcd. for $C_{14}H_{18}O_4$: C, 63.15; H, 6.76. Found: C, 63.14; H, 6.89.

Ethyl-β-bromo-5-bromo-2,4-dimethoxybenzoylpropionate, $(CH_3O)_2C_6H_2BrCOCH_2BrCH_2CO_2C_2H_5$.—A chloroform solution of the ester was treated with two molecular equivalents of bromine, the solvent removed and the solid recrystallized once from alcohol. It separated in thick needles melting at 114.5°; yield, 97%.

Anal. Calcd. for $C_{14}H_{16}O_4Br_2$: C, 39.62; H, 3.77. Found: C, 39.77; H, 4.07.

Ethyl-5-bromo-2,4-dimethoxybenzoylacrylate, $(CH_3O)_2C_6H_2BrCOCH=CHCO_2C_2H_5$.—The unsaturated ester is formed when the bromo ester is refluxed for two hours with potassium acetate. The ester which crystallized as the solution cooled was filtered off and washed with ice water; it is soluble in boiling organic solvents and crystallizes from benzene and alcohol in firm, yellow plates melting at 115.5°; yield of pure product 96%.

Anal. Calcd. for $C_{14}H_{16}O_4Br$: C, 48.97; H, 4.37. Found: C, 48.79; H, 4.25.

In subsequent preparations, the bromo ester was used without recrystallization for making the unsaturated ester.

Action of Sunlight on Ethyl-5-bromo-2,4-dimethoxybenzoylacrylate

The yellow ethyl ester undergoes a remarkably rapid change when powdered and exposed to the sunlight. The colorless solid formed was boiled with several portions of alcohol which left undissolved a substance melting at 265° and practically insoluble in all the common organic sol-

vents; from 6.1 g. of ester, 5.3 g. was obtained (87%). It is soluble in boiling nitrobenzene and separates completely from a saturated solution in transparent plates melting at 266°; its molecular weight was determined in nitrobenzene with the use of a Woods metal bath to insure regular boiling of the solvent.

Anal. Calcd. for $(C_{14}H_{16}O_5Br)_2$: C, 48.97; H, 4.37; mol. wt., 686. Found: C, 48.64; H, 4.27; mol. wt., 713.

The polymer is stable in the dark but it gradually turns yellow when left in diffused daylight.

From the alcohol a small quantity of substance (129–130°) was separated which did not react with bromine and was stable to light in benzene solution in the presence of iodine; a molecular weight determination by the Rast method indicated that the substance has twice the molecular weight of the unsaturated ester. Its behavior, however, was irregular, for the camphor solution was yellow after the solid mixture had been melted several times and each successive melting point of this yellow solid was lower, showing that depolymerization was taking place. Evidently this polymer is not stable at the melting point of camphor, 178°.

Anal. Calcd. for $(C_{14}H_{16}O_5Br)_2$: C, 48.97; H, 4.37. Found: C, 49.11; H, 4.59.

Reaction of Unsaturated Methyl Ester in Methyl Alcohol Solution Containing a Trace of Potassium Hydroxide

Methyl- α -methoxy-5-bromo-2,4-dimethoxybenzoylpropionate, $(CH_3O)_2C_6H_2BrCO-CH_2CHOCH_3CO_2CH_3$, and α -Methoxy-5-bromo-2,4-dimethoxybenzoylpropionic Acid, $(CH_3O)_2C_6H_2BrCOCH_2CHOCH_3CO_2H$.—A mixture of these substances is obtained when a methyl alcohol solution of methyl-5-bromo-2,4-dimethoxybenzoylacrylate, cooled in a freezing mixture, is stirred vigorously for three minutes with a few drops of potassium hydroxide solution (2:3). If sufficient solvent was used to keep the unsaturated ester in solution at the low temperature of the reaction, the methoxy acid was the chief product formed; if a suspension of the unsaturated ester was used, the methoxy ester separated at once and could be filtered off, but it was mixed with unsaturated ester which had escaped reaction, and if stirring was continued, in this case, until the yellow ester had reacted completely considerable hydrolysis of the methoxy ester took place and both the methoxy acid and ester were contaminated with sticky yellow decomposition products. The reaction can be carried out with the speed necessary for its success if the unsaturated ester (3 g.) is dissolved in hot methyl alcohol (150 cc.) and enough chloroform added to prevent the ester from crystallizing when the solution is cooled. After stirring for three minutes with a few drops of potassium hydroxide solution, the mixture was acidified with concd. hydrochloric acid, the lower chloroform layer drawn off and the upper layer extracted once with chloroform. Evaporation of the solvent left 3.3 g. of solid which gave, after four recrystallizations from methyl alcohol, 2.9 g. of methoxy ester (117°) and 0.3 g. of methoxy acid (189°), a quantitative yield. The ester is soluble in cold chloroform, hot ether, benzene and methyl alcohol; it crystallizes from benzene and methyl alcohol in fine, colorless needles. The acid is sparingly soluble in ether, benzene and hot chloroform and extremely soluble in methyl alcohol; it is purified most readily by recrystallization from a mixture of methyl alcohol and chloroform.

Anal. (117°). Calcd. for $C_{14}H_{17}O_6Br$: C, 46.53; H, 4.70; mol. wt., 361. Found: C, 46.57; H, 4.83; mol. wt., 357.

Anal. (189°). Calcd. for $C_{13}H_{15}O_6Br$: C, 44.95; H, 4.32. Found: C, 44.92; H, 4.30.

The methoxy acid was also obtained when β -bromo-5-bromo-2,4-dimethoxybenzoylpropionic acid was treated cautiously in ice-cold methyl alcohol solution with sodium methylate. The methoxy acid can be changed into its methyl ester by the usual esterification methods and the ester can be hydrolyzed by very cautious treatment with alkali to give the methoxy acid. When the methoxy ester was heated for two hours on a water bath with dil. hydrochloric acid (1:2) about equal parts of unsaturated acid and unsaturated methyl ester were obtained.

Synthesis of α - and β -Hydroxy Acids

α -Hydroxy-5-bromo-2,4-dimethoxybenzoylpropionic Acid, $(CH_3O)_2C_6H_2BrCOCH_2CHOHCO_2H$.—This acid was formed when the unsaturated acid and its methyl ester were boiled with dilute hydrochloric acid for many hours, but even after repeated attempts an amount of it sufficient for preparation of the ester or its ether was not accumulated. It is readily soluble in water, alcohol and hot chloroform; from chloroform it separates in fine needles melting at 172°.

Anal. Calcd. for $C_{12}H_{13}O_6Br$: C, 43.24; H, 3.90. Found: C, 43.84; H, 3.86.

β -Hydroxy-5-bromo-2,4-dimethoxybenzoylpropionic Acid, $(CH_3O)_2C_6H_2BrCOCHOHCH_2COOH$.—Since the α -hydroxy acid could not be obtained in quantity, the β -hydroxy acid was prepared in order to compare the ester of its ether with the methoxy ester (117°). A mixture of 14 g. of β -bromo-5-bromo-2,4-dimethoxybenzoylpropionic acid and 1000 cc. of 10% sodium carbonate solution was shaken in a machine for three hours; on acidification a solid was precipitated which crystallized from methyl alcohol and from water in colorless needles melting at 179° with decomposition; yield of pure acid 80%.

Anal. Calcd. for $C_{12}H_{13}O_6Br$: C, 43.24; H, 3.90. Found: C, 43.32; H, 3.76.

Methyl- β -methoxy-5-bromo-2,4-dimethoxybenzoylpropionate, $(CH_3O)_2C_6H_2BrCOCHOCH_3CH_2CO_2CH_3$.—This substance was formed when a methyl alcohol solution of the β -hydroxy acid was heated for eleven hours on a water-bath with methyl iodide and silver oxide; it crystallizes from methyl alcohol in needles melting at 134.5°.

Anal. Calcd. for $C_{14}H_{17}O_6Br$: C, 46.53; H, 4.70. Found: C, 46.71; H, 4.77.

Since this is the methyl ether of the β -hydroxy ester, the methoxy ester melting at 117° must have its methoxy group in the α position.

Reaction of Unsaturated Ethyl Ester in Alcohol Solution Containing a Trace of Potassium Hydroxide

Ethyl- α -ethoxy-5-bromo-2,4-dimethoxybenzoylpropionate, $(CH_3O)_2C_6H_2BrCOCH_2CHOC_2H_5CO_2C_2H_5$ and α -Ethoxy-5-bromo-2,4-dimethoxybenzoylpropionic Acid, $(CH_3O)_2C_6H_2BrCOCH_2CHOC_2H_5CO_2H$.—These substances are formed when an absolute alcohol solution of the unsaturated ethyl ester is treated with alkali in the manner described in the reaction with the unsaturated methyl ester. The ethoxy ester is readily soluble in ether, chloroform and hot methyl and ethyl alcohols; it crystallizes from alcohol in needles melting at 97°.

Anal. Calcd. for $C_{16}H_{21}O_6Br$: C, 49.35; H, 5.39. Found: C, 49.52; H, 5.52.

The ethoxy acid (139–140°) is soluble in alcohol, chloroform and boiling benzene, sparingly soluble in ether and petroleum ether; it can be recrystallized from benzene, from alcohol and from a mixture of chloroform and petroleum ether.

Anal. Calcd. for $C_{14}H_{17}O_6Br$: C, 46.53; H, 4.70. Found: C, 46.47; H, 4.65.

The ethoxy acid was obtained in 50% yield by cautious hydrolysis of the ethoxy ester with alcoholic potassium hydroxide and was separated from the unsaturated acid which is also formed by taking advantage of the lack of solubility of the latter in cold chloroform.

When the unsaturated ethyl ester was treated with potassium hydroxide in the presence of methyl alcohol in the way described for the unsaturated methyl ester, a 69% yield of the methyl ester of the methoxy acid was formed; likewise the unsaturated methyl ester in the presence of ethyl alcohol gave an 80% yield of the ethyl ester of the ethoxy acid. In neither reaction was a second substance found; the poorer yields than were obtained when the reaction was carried out with an ester in the presence of the corresponding alcohol are accounted for by the formation, in both cases, of a considerable amount of yellow decomposition product.

Summary

5-Bromo-2,4-dimethoxybenzoylacrylic acid and its methyl ester are not isomerized or polymerized in the sunlight; the ethyl ester is stable to light in benzene solution but it is rapidly polymerized when exposed as a solid. Hydrolysis of the esters with sodium carbonate solution is extremely slow and incomplete; the methyl ester gives the unsaturated acid and a trace of α -hydroxy-5-bromo-2,4-dimethoxybenzoylpropionic acid on boiling for many hours with dilute hydrochloric acid. These esters react in methyl and ethyl alcohol solution in the presence of a few drops of potassium hydroxide solution to give α -alkoxyl addition products which are a result of 1:4 addition to one of the two conjugated systems of double linkages present in the esters.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

THE RELATION OF THE STRUCTURE OF KETONES TO THEIR REACTIVITY AND AFFINITY IN ACETAL FORMATION

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The reaction of ketones with alcohols to form acetals analogous to the reaction of aldehydes with alcohols proceeds to so slight an extent, if at all, that the reaction is of no importance. In order to form the acetal of the ketones it is necessary to react the ketones with an ortho ester according to the equation $R_2C=O + HC(OR')_3 \rightleftharpoons R_2C(OR')_2 + HCO_2R'$. The reaction like that of aldehydes with alcohols is a reversible one and hence may be used for the evaluation of the relation of the structure of a ketone to the strength of the linkage between oxygen and carbon in the acetal.^{1,2,3} To this end the extent of the reaction of eight ketones

¹ Adkins and Adams, *THIS JOURNAL*, **47**, 1377 (1925).

² Hartung and Adkins, *ibid.*, **49**, 2517 (1927).

³ Street and Adkins, *ibid.*, **50**, 162 (1928).