

The replacement series of organic groups as derived from the halogenation of mixed stannanes is not generally applicable and must be restricted in use to the reaction from which it was derived.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BARNARD COLLEGE]

THE FRIEDEL AND CRAFTS REACTION WITH MALEIC ANHYDRIDE AND RESORCINOL DIMETHYL ETHER. THE ADDITION OF AROMATIC ETHERS TO UNSATURATED SUBSTANCES

BY GRACE POTTER RICE

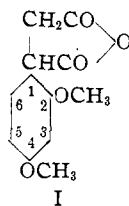
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Several examples of the reactivity of maleic anhydride in addition reactions have been recorded in the literature in recent years. Diels and Alder¹ have studied the reactions which this anhydride and other substances, having extremely reactive double linkages, undergo when treated with a large and varied list of unsaturated substances. So specific is this type of reaction that it has been used by Windaus² to prove that a conjugated system of double linkages in an ergosterol derivative is destroyed by irradiation, since the irradiated product failed to react with maleic anhydride.

Kuhn and Wagner-Jauregg³ have studied the addition of maleic anhydride to polyenes and very recently Conant and Scherp⁴ have obtained evidence that a reaction takes place between maleic anhydride and free radicals.

In this Laboratory it has now been found that maleic anhydride combines with resorcinol dimethyl ether in the presence of aluminum chloride to give a saturated anhydride, dimethoxyphenylsuccinic anhydride (I). This reaction can be explained by a mechanism involving a 1,4-addition to maleic anhydride. The anhydride I was unexpectedly obtained, along with other substances, when the Friedel and Crafts reaction with maleic anhydride and resorcinol dimethyl ether was carried out for the purpose of preparing dimethoxybenzoylacrylic acid, II. The fact that this unsaturated acid has been shown to form an addition product with resorcinol dimethyl ether in the presence of aluminum chloride may account in part for the low yield.

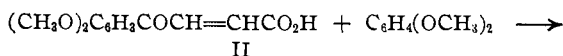


¹ Diels and Alder, *Ann.*, **460**, 98 (1928); *Ber.*, **62**, 554, 2081, 2087 (1929); *Ann.*, **486**, 191, 202, 211 (1931).

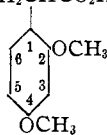
² Windaus, Gaede, Köser and Stein, *ibid.*, **483**, 27 (1930).

³ Kuhn and Wagner-Jauregg, *Ber.*, **63**, 2662 (1930).

⁴ Conant and Scherp, *THIS JOURNAL*, **53**, 1941 (1931).



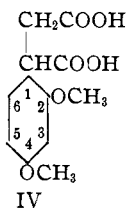
II



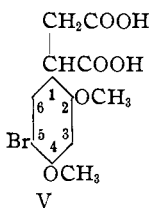
III

Certainly a diminished yield of unsaturated acid II accompanies an increased yield of the ketonic acid III in the Friedel and Crafts reaction.

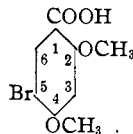
That the substituting group in III is in the α -position to the COOH group rests on the analogy with the mode of addition of various addends to benzoylacrylic ester and its substitution products.⁵ That the point of union of the substituting group is that indicated at carbon atom 1 in III is based on the proof of the point of union of this same substituting group in dimethoxyphenylsuccinic acid IV, obtained from the anhydride I by hydrolysis. It is as follows



IV

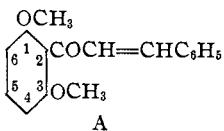


V



Dimethoxyphenylsuccinic acid IV forms one monobromo substitution product and it has not been possible to prepare a dibromo compound from this acid. If the side chain were at carbon atom 3 or at carbon atom 6, both of those substances would be expected to form dibromo substitution products since both of them have two hydrogen atoms which are alike. The bromodimethoxysuccinic acid obtained from IV gives a known product on oxidation, 5-bromo-2,4-dimethoxybenzoic acid.⁶ The position of the side chain in IV must, therefore, be that indicated.

The structure of the acid IV is interesting in view of the fact that cinnamyl chloride is reported to react with resorcinol dimethyl ether to form the compound⁷ (A).



A

The ketonic acid III could be formed in the Friedel and Crafts reaction from the anhydride I as well as from the unsaturated acid II; in fact it has been shown to be formed when this anhydride is treated with resorcinol dimethyl ether and aluminum chloride, but along with the

⁵ Kohler and Engelbrecht, *THIS JOURNAL*, **41**, 764 (1919); Rice, *ibid.*, **50**, 233 (1928).

⁶ Rice, *ibid.*, **48**, 3125 (1926).

⁷ Simonis and Danischewski, *Ber.*, **59**, 2914 (1926).

acid III there is also obtained about an equal quantity of an isomeric acid,⁸ $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_3\text{COCHCH}_2(\text{COOH})\text{C}_6\text{H}_3(\text{CH}_3\text{O})_2$. Since not a trace of the isomeric acid has been detected in the reaction with maleic anhydride and resorcinol dimethyl ether, it seems probable that the ketonic acid III is formed from the unsaturated acid and not from the anhydride.

Numerous examples have been reported of the use of aluminum chloride and of sulfuric acid to bring about addition reactions between unsaturated substances and benzene, toluene, phenol, resorcinol, and hydroquinol.⁹ The reaction between resorcinol dimethyl ether and maleic anhydride, however, is not brought about by either hydrogen chloride or sulfuric acid but only by aluminum chloride. In view of the fact that anisole does not add to the unsaturated ketone, $\text{C}_6\text{H}_5\text{CH}=\text{CHCOC}_6\text{H}_4\text{OCH}_3$,¹⁰ even in the presence of aluminum chloride, it seems of interest to attempt to determine how general is the reaction between aromatic ethers and unsaturated substances with unusually reactive conjugated systems of double linkages such as maleic anhydride and substituted benzoylacrylic acids. An investigation of this subject is under way in this Laboratory.

Experimental Part

The Friedel and Crafts Reaction.—Freshly distilled maleic anhydride,¹¹ 53.6 g., which was recrystallized from chloroform immediately before using, was dissolved in 71.5 g. of resorcinol dimethyl ether. This solution, which had a characteristic dark, yellow-green color,¹² was treated with 150 g. of carbon disulfide slowly while being stirred rapidly with an electric stirrer in order that the maleic anhydride might separate in as small crystals as possible. The mixture was cooled with ice, 80 g. of finely powdered aluminum chloride was added gradually and the stirring continued until the dark red product turned to a solid mass. This was decomposed with ice and concd. hydrochloric acid and the granular solid which separated was filtered by suction and left to dry; 111 g. of product melting at 105–130° was obtained. This solid was powdered and extracted several times with small quantities of ether, which removed most of the resorcinol dimethyl ether and left 76 g. of a slightly yellow product melting at 135–160°. When this was dissolved in acetone, dimethoxyphenylsuccinic anhydride I (37.4 g.) crystallized in fine, colorless needles; the residue from the acetone filtrate was boiled with a small quantity of toluene, which left undissolved 3.7 g. of yellow dimethoxybenzoylacrylic acid, II. The toluene solution held a mixture of anhydride and yellow acid. Part of the residue from the toluene was separated by taking advantage of the fact that the yellow acid creeps from a benzene solution of the mixture and leaves the anhydride in solution; the rest of the residue from toluene was dissolved in 50% acetic acid. The yellow acid crystallized in almost pure condition and the filtrate deposited dimethoxyphenylsuccinic acid IV formed by hydrolysis of the anhydride; 49.2 g. of anhydride,

⁸ Compare Mayer and Stamm, *Ber.*, **56**, 1424 (1923).

⁹ Liebermann and Hartmann, *ibid.*, **24**, 2582 (1891); **25**, 957 (1892); Eijkman, *Chem. Centr.*, **II**, 2045 (1907); **II**, 1100 (1908); Kohler, *Am. Chem. J.*, **31**, 642 (1904); **42**, 379 (1909); Niederl and Natelson, *THIS JOURNAL*, **53**, 272 (1931).

¹⁰ Kohler, *Am. Chem. J.*, **44**, 63 (1910).

¹¹ Terry and Eichelberger, *THIS JOURNAL*, **47**, 1076 (1925).

¹² Pfeiffer and Böttler, *Ber.*, **51**, 1819 (1919).

5.6 g. of unsaturated acid and 5.2 g. of dimethoxyphenylsuccinic acid were separated in pure condition. The residue left after evaporation of the ether used for washing the crude solid was distilled with steam; this removed resorcinol dimethyl ether and left a dark red oil from which no solid could be separated.

Dimethoxyphenylsuccinic Anhydride I, $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_3\text{CH}-\text{CH}_2\text{CO}-\text{O}-\text{CO}$.—The anhydride crystallizes from acetone, benzene, toluene, chloroform and a mixture of chloroform and ether in colorless needles melting at 147° . It is readily obtained by warming dimethoxyphenylsuccinic acid with acetyl chloride and by distilling the acid in a vacuum. On boiling with water or 50% acetic acid it gives the corresponding acid.

Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{O}_5$: C, 61.01; H, 5.08. Found: C, 61.07; H, 5.01.

Dimethoxyphenylsuccinic Acid IV, $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_3\text{CH}(\text{COOH})\text{CH}_2\text{COOH}$.—The acid crystallizes from water, methyl alcohol, acetone and 50% acetic acid in large, transparent crystals which melt at 160° , leaving a purple coloration in the top of the melting point tube.

Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_6$: C, 56.69; H, 5.51; CH_3O , 24.40. Found: C, 56.87; H, 5.79; CH_3O (Pregl), 24.86.

Dimethoxybenzoylacrylic Acid II, $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_3\text{COCH}=\text{CHCO}_2\text{H}$.—The acid is sparingly soluble in toluene and boiling water, readily soluble in chloroform, acetone and boiling methyl alcohol; it separates in fine yellow needles which lose their color at 180° and then darken and melt at 189° with decomposition.

Anal. Calcd. for $\text{C}_{12}\text{H}_{12}\text{O}_5$: C, 61.01; H, 5.08. Found: C, 60.63; H, 5.01.

Methyl Dimethoxybenzoylacrylate, $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_3\text{COCH}=\text{CHCO}_2\text{CH}_3$.—A poor yield of the ester was obtained by refluxing a methyl alcohol solution of the acid with concn. sulfuric acid. It forms yellow needles which melt at 85° after two recrystallizations from methyl alcohol.

Anal. Calcd. for $\text{C}_{13}\text{H}_{14}\text{O}_6$: C, 62.40; H, 5.60. Found: C, 62.80; H, 5.77.

The unsaturated acid gives a product containing nitrogen when treated with diazomethane; this reaction as well as a method for the preparation of the ester in good yield is still under investigation.

α -Dimethoxyphenyl- β -dimethoxybenzoylpropionic Acid III, $(\text{CHO})_2\text{C}_6\text{H}_3\text{COCH}_2-\text{CH}(\text{COOH})\text{C}_6\text{H}_3(\text{CH}_3\text{O})_2$.—When the Friedel and Crafts reaction was repeated under as nearly the same conditions as was possible, only 0.4 g. of unsaturated acid was separated. In this case the crystalline solid, left after removal of the anhydride and unsaturated acid, was treated with cold methyl alcohol; 9.7 g. of substance melting at $125-147^\circ$ was obtained. By fractional recrystallization from 50% acetic acid this mixture was separated into two acids; the more soluble one was dimethoxyphenylsuccinic acid IV and the less soluble one an acid which melted at 160° on recrystallization from methyl alcohol; it is α -dimethoxyphenyl- β -dimethoxybenzoylpropionic acid, III. From 9.7 g. of solid, 4.7 g. of IV and 3.7 g. of III were obtained in pure condition. The residue from the ether used for washing the crude product deposited 2 g. of III when it was treated with methyl alcohol.

Anal. Calcd. for $\text{C}_{20}\text{H}_{22}\text{O}_7$: C, 64.17; H, 5.88; CH_3O , 33.15. Found: C, 64.38; H, 5.92; CH_3O (Pregl), 33.67.

The Friedel and Crafts reaction has been carried out fourteen times under a variety of conditions, using carbon disulfide as solvent, petroleum ether as solvent and using no solvent and the temperature has been varied over a wide range. One reason that the best yield in these many reactions was only 60% of all products together is the lack of solubility of maleic anhydride at the temperature at which the reaction gives the smallest quantity of unmanageable oil. The solid anhydride becomes coated with the vis-

cous aluminum chloride addition product and is not attacked. When the reaction was carried out without a solvent it was extremely vigorous and a large amount of oil was obtained from which only a few grams of the products described could be separated. From this reaction a fifth substance melting at 185–187° was isolated which may be a result of demethylation, in the presence of aluminum chloride, of one methoxyl group in each aromatic nucleus of the acid III. It has not been possible, however, to change it into III by methylation with dimethyl sulfate.

Anal. Calcd. for $C_{18}H_{18}O_7$: C, 62.42; H, 5.20. Found: C, 61.83; H, 5.87.

Perkin and Robinson¹³ have found that an analogous reaction takes place when resorcinol dimethyl ether and succinic anhydride are treated in the molten condition with aluminum chloride. It is probable that a large part of the untractable material is formed as a result of the demethylating action of aluminum chloride. No reaction, however, could be made to take place between maleic anhydride and resorcinol dimethyl ether by using gaseous hydrogen chloride or sulfuric acid in place of aluminum chloride.

5-Bromo-2,4-dimethoxyphenylsuccinic Acid, V, $(CH_3O)_2C_6H_2BrCH(COOH)CH_2COOH$.—Dimethoxyphenylsuccinic acid was brominated in carbon disulfide, chloroform, glacial acetic acid and ether. The same product was always obtained and this could not be induced to react with a second molecule of bromine in boiling glacial acetic acid or in the sunlight. The crude product, after washing with ether, was a chalk-white powder melting at 219°; yield, 88%.

Anal. Calcd. for $C_{12}H_{10}O_6Br$: C, 43.24; H, 3.90. Found: C, 43.54; H, 3.99.

One gram of this acid was refluxed for fifteen hours in acetone solution with potassium permanganate. On acidifying the aqueous solution obtained by boiling the oxides of manganese with water, 0.3 g. of solid melting at 186–193° was precipitated. After recrystallization from acetone the solid showed no depression of melting point when mixed with a specimen of 5-bromo-2,4-dimethoxybenzoic acid.

Dimethyl Dimethoxyphenylsuccinate, $(CH_3O)_2C_6H_3CH(COOCH_3)CH_2COOCH_3$.—This ester, prepared by refluxing a methyl alcohol solution of the acid IV with concd. sulfuric acid, could not be induced to crystallize before it was distilled in a vacuum (b. p. 231° at 31 mm.). The solid separates from methyl alcohol in heavy transparent plates which melt at 60°; yield of pure product, 92%.

Anal. Calcd. for $C_{14}H_{16}O_6$: C, 59.57; H, 6.38. Found: C, 59.66; H, 6.34.

Methyl 5-Bromo-2,4-dimethoxyphenylsuccinate, $(CH_3O)_2C_6H_2BrCH(COOCH_3)CH_2COOCH_3$.—This ester was brominated in order to determine whether it is possible to obtain isomeric monobromo derivations or a dibromo derivative in spite of the fact that only one bromine compound is formed from the corresponding acid. Bromination in chloroform solution gave a quantitative yield of bromo ester which melted at 90° after two recrystallizations from methyl alcohol.

Anal. Calcd. for $C_{14}H_{17}O_6Br$: C, 46.53; H, 4.70. Found: C, 46.22; H, 4.70.

α -Dimethoxyphenylethane- α,β -dicarbonic Acid- β -methyl Ester, $(CH_3O)_2C_6H_3CH(COOH)CH_2COOCH_3$.—A solution of 17.2 g. of dimethoxyphenylsuccinic anhydride in 200 cc. of methyl alcohol was refluxed for three hours and the solution evaporated to 150 cc.; 2 g. of anhydride separated and on further evaporation the filtrate deposited 12.4 g. of ester melting at 139–141.5°; yield, 72%. After recrystallization from methyl alcohol the colorless needles melted at 142.5°. This ester was first obtained in the course of purifying a Friedel and Crafts product, as the acid IV is readily esterified by boiling it with methyl alcohol.

Anal. Calcd. for $C_{13}H_{16}O_6$: C, 58.20; H, 5.97. Found: C, 58.20; H, 6.13.

¹³ Perkin and Robinson, *J. Chem. Soc.*, 93, 509 (1908).

α -Dimethoxyphenylethane- α,β -dicarbonic Acid- α -methyl Ester, $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_3\text{CH}(\text{COOCH}_3)\text{CH}_2\text{COOH}$.—This ester is obtained from the dimethyl ester of IV by allowing it to stand for two hours at room temperature with a methyl alcohol solution of potassium hydroxide. The product from hydrolysis of 5.5 g. of dimethyl ester was poured onto ice, the dimethyl ester (2.1 g.) was filtered off and the filtrate extracted with ether; evaporation of the ether left a solid (2.3 g.) melting at $100\text{--}115^\circ$. By repeated recrystallizations from methyl alcohol, 0.3 g. of pure ester melting at 117° was separated. Analysis indicated that the rest was a mixture of the two isomeric mono esters. On hydrolysis with aqueous potassium hydroxide it gave a quantitative yield of the acid IV.

Anal. Calcd. for $\text{C}_{13}\text{H}_{16}\text{O}_6$: C, 58.20; H, 5.97. Found: subs. (117°), C, 58.06; H, 5.90; mixture: C, 58.03; H, 6.12.

The structures of these two isomers are inferred from analogy with the corresponding esters of phenylsuccinic acid.

The ketonic acid III is formed as the only product of reaction when resorcinol dimethyl ether is treated with dimethoxybenzoylacrylic acid and aluminum chloride.

Methyl α -Dimethoxyphenyl- β -dimethoxybenzoylpropionate, $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_3\text{COCH}_2\text{CH}(\text{COOCH}_3)\text{C}_6\text{H}_3(\text{CH}_3\text{O})_2$.—This ester was prepared by saturating a methyl alcohol solution of the acid with hydrogen chloride. The solid, obtained in quantitative yield, crystallizes in clusters of silky needles melting at 140° .

Anal. Calcd. for $\text{C}_{21}\text{H}_{24}\text{O}_7$: C, 64.94; H, 6.18. Found: C, 65.07; H, 6.37.

Semicarbazone of α -Dimethoxyphenyl- β -dimethoxybenzoylpropionic Acid, $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_3\text{C}(=\text{NNHCONH}_2)\text{CH}_2\text{CH}(\text{COOH})\text{C}_6\text{H}_3(\text{CH}_3\text{O})_2$.—The ketonic acid gives a 90% yield of semicarbazone on standing for twelve hours with semicarbazide; after washing with boiling methyl alcohol, the powder melted at 204° .

Anal. Calcd. for $\text{C}_{21}\text{H}_{25}\text{O}_7\text{N}_3$: C, 58.46; H, 5.80. Found: C, 58.52; H, 6.13.

α -5-Bromo-2,4-dimethoxyphenyl- β -bromo- β -(5-bromo-2,4-dimethoxybenzoyl)-propionic Acid, $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_2\text{BrCOCHBrCH}(\text{COOH})\text{C}_6\text{H}_2(\text{CH}_3\text{O})_2\text{Br}$.—The ketonic acid, suspended in carbon disulfide and cooled with ice, was treated with three molecular equivalents of bromine. On removal of the solvent the crude, colorless solid forms a cerise-colored coating which was removed by washing with cold methyl alcohol. The acid then melts (dip) with decomposition at 213° to a cherry-red melt.

Anal. Calcd. for $\text{C}_{20}\text{H}_{19}\text{O}_7\text{Br}_3$: C, 39.28; H, 3.10. Found: C, 39.26; H, 2.97.

The methyl ester of this bromo acid was prepared by bromination of the ester of the ketonic acid (140°) in carbon disulfide solution. After washing with cold methyl alcohol, the crude product melted at $161\text{--}181^\circ$ and decomposed at 191° .

Anal. Calcd. for $\text{C}_{21}\text{H}_{21}\text{O}_7\text{Br}_3$: C, 40.32; H, 3.36. Found: C, 39.91; H, 3.37.

The crude bromo ester is a mixture of two substances, one melting at 210° and the other at $165\text{--}173^\circ$ and not pure. From the analysis of the crude product it may be concluded that these are probably racemic compounds as the ester has two unequal asymmetric carbon atoms.

Anal. Subs. (210°). Calcd. for $\text{C}_{21}\text{H}_{21}\text{O}_7\text{Br}_3$: C, 40.32; H, 3.36. Found: C, 40.34; H, 3.41.

The Friedel and Crafts Reaction with Resorcinol Dimethyl Ether and Dimethoxyphenylsuccinic Anhydride

β -Dimethoxyphenyl- β -dimethoxybenzoylpropionic Acid and Methyl β -Dimethoxyphenyl- β -dimethoxybenzoylpropionate, $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_3\text{COCH}(\text{CH}_2\text{COOH})\text{C}_6\text{H}_3(\text{CH}_3\text{O})_2$ and $(\text{CH}_3\text{O})_2\text{C}_6\text{H}_3\text{COCH}(\text{CH}_2\text{COOCH}_3)\text{C}_6\text{H}_3(\text{CH}_3\text{O})_2$.—A solution of 29 g. of resorcinol dimethyl ether in 70 cc. of carbon disulfide was treated with an intimate mixture of 10

g. of the anhydride I and 20 g. of aluminum chloride, both finely powdered. The mixture was warmed in a water-bath and stirred vigorously as long as there was evidence of reaction; the orange-colored viscous mass was decomposed with ice and concd. hydrochloric acid and the product filtered off and washed with cold benzene when dry; yield, 12.7 g. of substance melting at 90–135°. The crude solid can be partially separated with 50% acetic acid as a solvent. The first crop of crystals is the ketonic acid III (160°) and the second crop a new acid melting at 157° after a second recrystallization; the mixture of III and this substance melts at 140–145°.

Anal. Calcd. for $C_{20}H_{22}O_7$: C, 64.17; H, 5.88. Found: C, 64.22; H, 6.17.

The residue after these two crops had been removed persistently separated as a mixture, so it was turned into a mixture of esters which could be separated.

The aqueous solution left after filtering off the solid formed in the reaction was mixed with the residue left after removal of the benzene used to wash this solid and the mixture distilled with steam. The insoluble residue which failed to crystallize was esterified and the solid product dissolved in methyl alcohol. The ester of the acid III separated first; from the filtrate the ester of the isomeric acid was obtained as a solid melting at 104° after washing with ether.

Anal. Calcd. for $C_{21}H_{24}O_7$: C, 64.94; H, 6.18. Found: C, 65.26; H, 6.46.

The yield of pure products (65%) was as follows: 4.9 g. of acid III, 1.2 g. of the ester of acid III, 0.3 g. of isomeric acid and 3.9 g. of the ester of the isomeric acid. After this isomeric acid and its ester had become familiar substances, the residues from two Friedel and Crafts reactions with maleic anhydride were examined most carefully but the acid (157°) could not be found nor could its ester be identified when a residue was esterified. If this acid is formed in the Friedel and Crafts reaction with maleic anhydride, it has defied isolation.

Summary

In the presence of aluminum chloride resorcinol dimethyl ether combines with maleic anhydride to form dimethoxyphenylsuccinic anhydride, which may be interpreted as the result of a 1,4-addition reaction. Along with this anhydride four other substances are formed in the Friedel and Crafts reaction. These have been identified, their formation explained and derivatives of them have been prepared.

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