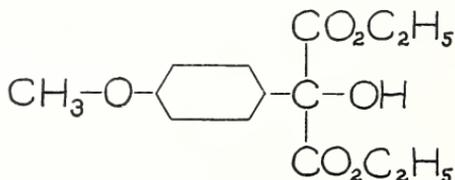


## Further Observations on the Synthesis of Mandelic Acid Derivatives

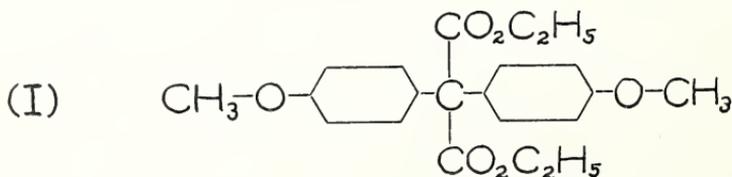
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During the past four years we have synthesized more than thirty substituted mandelic acids. The method used for the most of these syntheses has been described previously in this journal and elsewhere,<sup>1, 2</sup> and consists essentially of reacting benzene or a substituted benzene with ethyl oxomalonate in the presence of anhydrous stannic chloride. The aryl hydroxy substituted malonic esters thus produced are saponified with potassium hydroxide acidified with hydrochloric acid and decarboxylated, producing the corresponding mandelic acids.

Early in the course of these syntheses, the senior author attempted to prepare p-methoxy mandelic acid by reacting anisole with ethyl oxomalonate and stannic chloride. The intermediate expected following the usual reaction scheme was:



But the compound formed boiled much higher than predicted and was practically unaffected when saponification was attempted in twenty per cent aqueous potassium hydroxide. The aqueous alkali was extracted with ether and the unsaponifiable material purified. Analysis and the melting point indicated this compound to be (I).

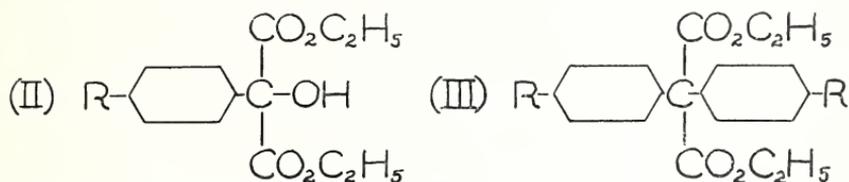


This reaction is what one might expect inasmuch as the para hydrogen of phenolic compounds is more reactive than in alkyl substituted benzenes.

<sup>1</sup> Riebsomer, Irvine and Andrews, 1938. Proc. Indiana Acad. Sci. 47:139.

<sup>2</sup> Riebsomer, Irvine and Andrews, 1938. J. Amer. Chem. Soc. 60:1015.

This same compound had been prepared previously<sup>4</sup> by treating an anisole-ethyl oxomalonate mixture with concentrated sulphuric acid instead of anhydrous stannic chloride. These same authors had also demonstrated that concentrated sulphuric acid would induce a reaction between alkyl benzenes and ethyl oxomalonate to produce a mixture of (II) and (III)

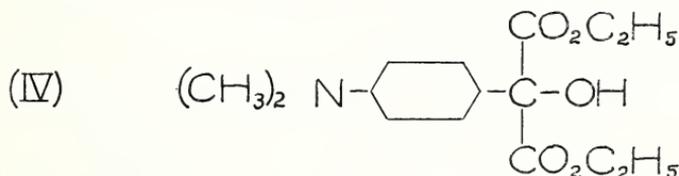


but failed to state any details about yields and experimental conditions.

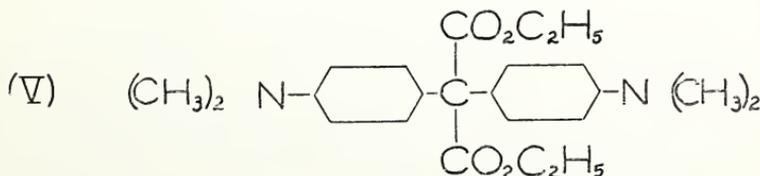
Since certain of the substituted mandelic acids prepared previously had shown marked bactericidal properties *in vitro* and had some commercial promise, and since concentrated sulphuric acid was less expensive and more convenient to handle than anhydrous stannic chloride, a study was made using a variety of concentrations of sulphuric acid in a typical synthesis to determine its efficacy as the condensing agent.

In nearly all cases when concentrated sulphuric acid was used as the condensing agent, both compounds (I) and (II) were produced but always in a relatively poor yields. Table I in the experimental part summarizes the results.

These results with concentrated sulphuric acid stimulated interest in the use of certain other condensing agents. As early as 1909, Guyot and Michel<sup>5</sup> showed that dimethyl aniline and other comparable compounds and ethyl oxomalonate in the presence of glacial acetic acid reacted readily to form compounds such as (IV)



and that by treating (IV) with excess dimethyl aniline in the presence of phosphorous oxychloride that compound (V) was produced.



<sup>4</sup> Guyot and Esteva, 1909. *Comp. Rend.* **148**:719.

<sup>5</sup> Guyot and Michel, 1909. *Comp. Rend.*, **148**:229.

Accordingly acetic anhydride was substituted for anhydrous stannic chloride in the general synthesis using toluene as the hydrocarbon, also with anisole and with phenol. None of the expected product was formed in any of these cases.

Similar experiments were tried using individually dry hydrogen chloride, phosphorous oxychloride and phosphorous pentachloride as the condensing agent, but none of these reagents were capable of bringing about the desired reaction.

### Experimental

**Di-p-Methoxy Malonic ester.** Seventeen grams of ethyl oxomalonate and 43.2 grams of anisole were mixed in a three-necked flask equipped with a stirrer, condenser and dropping funnel. Anhydrous stannic chloride (50 g.) was added slowly with stirring keeping the temperature at 0°, and the stirring continued for 5 hours. The reaction product was added to ice and hydrochloric acid, extracted with ether, dried and distilled. The main product distilled at 225° to 230° at a pressure of 2 mm. Yield 22 g. This product was heated on a steam bath with 20% aqueous potassium hydroxide for 6 hours. Most of the product failed to go into solution. It was extracted with ether, washed, dried and recrystallized from ethyl alcohol. M.p. 74-75°. Combustion analysis: calcd. for



C, 67.4; H, 6.4: found, C, 67.1, H, 6.4.

**Series of reactions using concentrated sulphuric acid in place of anhydrous stannic chloride.** The procedure was the same in each case except the quantities of sulphuric acid were varied. In each case 0.1 mole of ethyl oxomalonate, 0.24 moles of toluene were mixed with a three-necked flask, and the sulphuric acid added with stirring at 0° and the stirring continued for three hours. The product was poured into ice-water and worked up in the usual manner. The intermediate was saponified with 20% potassium hydroxide for 4 to 5 hours and the unsaponifiable portion extracted with ether, dried and weighed. The saponified portion was acidified with hydrochloric acid, decarboxylated, extracted with ether, crystallized from benzene and weighed. This portion was p-methyl mandelic acid, m.p. 143°. The unsaponifiable portion was diethyl di-p-tolyl malonate which after one crystallization from ethyl alcohol melted at 92-93°. The data are summarized in table I.

TABLE I

Moles of Sulphuric Acid	Percentage Yield of p-Methyl Mandelic Acid	Percentage Yield of Diethyl di-p-Tolyl Malonate
.01	3.3	negligible
.05	3.5	less than 1
0.1	16.7	2.3
0.15	14.7	13.0
0.22	12.0	16.0

**Acetic anhydride as condensing agent.** Twenty-eight grams of anisole, 8.7 grams of ethyl oxomalonate and 15.3 grams of acetic anhydride were stirred together at 25° for two hours. The mixture was subjected to distillation. All the material distilled up to 90° at 25 mm. which meant no reaction had taken place. This same reaction at the temperature of a steam bath also failed.

A similar reaction was tried using 23 grams of toluene, 8.7 grams of ethyl oxomalonate and 10.2 grams of acetic anhydride and heating on a steam bath for four hours. Upon distillation only the starting materials were recovered.

When 23 grams phenol, 8.7 grams of ethyl oxomalonate and 10.2 grams of acetic anhydride were stirred four hours at 100° about 1.5 grams of a liquid, b.p. 130-140° at 3 mm. was isolated. This product was saponified in the usual manner and acidified after saponification with hydrochloric acid. The product was black and nothing could be crystallized from it.

**Hydrogen Chloride as the condensing agent.** Fifty-two grams of ethyl oxomalonate and 5.5 grams of toluene were mixed in a flask kept at 0°, and dry hydrogen chloride gas was introduced until it began to pass through. The product was washed with water, and distilled. None of the expected intermediate was formed. A similar experiment using phenol instead of toluene also failed.

**Phosphorous pentachloride and phosphorous oxychloride as the condensing agents.** Twenty-three grams of toluene, 8.7 grams of ethyl oxomalonate and 15.6 grams of phosphorous pentachloride were mixed in a three-necked flask at 20° and stirred for three hours. The mixture was poured into ice-water, washed and distilled in the usual manner. The entire product distilled before the temperature had reached 115° at 3 mm. Therefore there was none of the desired reaction. An exactly similar experiment with phosphorous oxychloride also failed.

The authors wish to express their gratefulness to Dean William M. Blanchard, who was instrumental in securing a research grant from the Indiana Academy of Science to promote our research program.

### Summary

1. When anisole is used in the Ando synthesis instead of benzene hydrocarbons, the reaction takes an unusual course and di-p-methoxyphenyl malonic ester is formed.

2. Concentrated sulphuric acid used instead of anhydrous stannic chloride in this synthesis produces diaryl malonic esters as well as the expected aryl hydroxy malonic esters, but always in relatively poor yields.

3. Acetic anhydride, dry hydrogen chloride gas, phosphorous pentachloride and phosphorous oxychloride when used instead of stannic chloride in the Ando synthesis fail to promote the reactions.