# A DETERMINATION OF THE CONFIGURATION OF 5-METHOXY-3-METHYLPHTHALIDE AND THE CHLOROMETHYL DERIVATIVES OF THIS COMPOUND

by

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To Dr. E.H. Charlesworth, with sincerest gratitude for his expert guidance, and patient supervision during this research project.

I am also indebted to Dr. G.E. Dunn for his assistance regarding the spectroscopic work, and to the National Research Council for the grants which made this work possible.

# ABSTRACT

When 5-methoxy-3-methylbenzoic acid was heated with formaldehyde, hydrochloric acid and glacial acetic acid, one simple phthalide, among other products, was isolated. The configuration of this compound was definitely established as 5-methoxy-3-methylphthalide. By varying experimental conditions, not one, but four chloromethylphthalides were also isolated from the reaction mixture. Infra red absorption spectra were used to establish this fact. A possible explanation for the appearance of the five products mentioned is presented in this work.

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EXPERIMENTAL

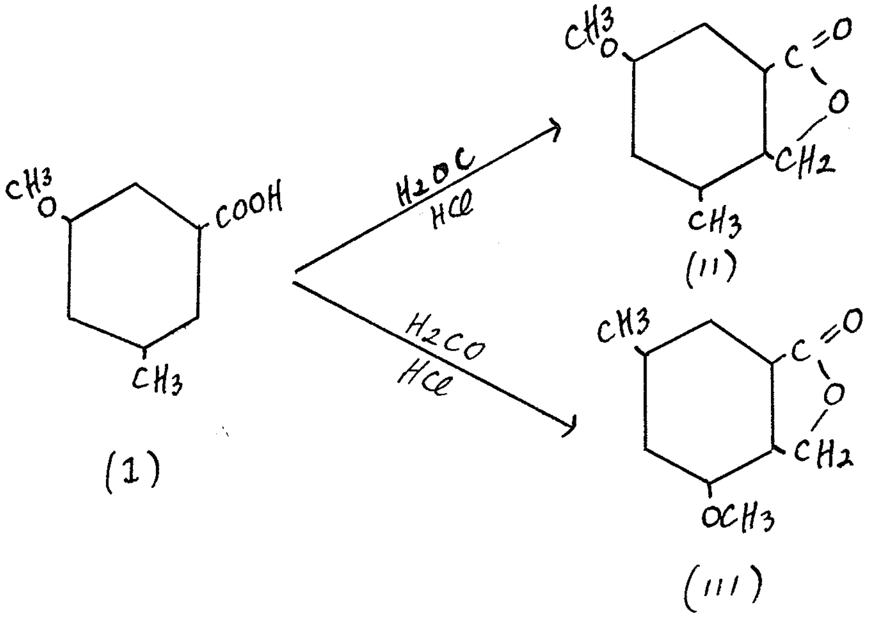
I. Preparation of 5-Methoxy-3-methylbenzoic Acid.

Method I

# INTRODUCTION

When 5-methoxy-3-methylbenzoic acid (I)[*] was heated with excess aqueous formaldehyde (40%) and concentrated hydrochloric acid, a variety of compounds were obtained. The substances produced depend greatly upon experimental conditions and include such products as a simple phthalide, along with some chloromethyl derivatives of this phthalide.

The simple condensation may be represented as follows:



However, the phthalide ring may close in two ways, thus forming the two simple phthalides (II) and (III).

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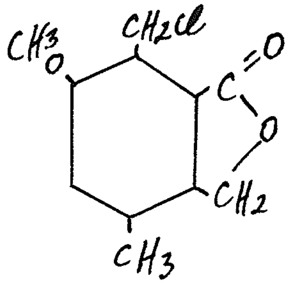
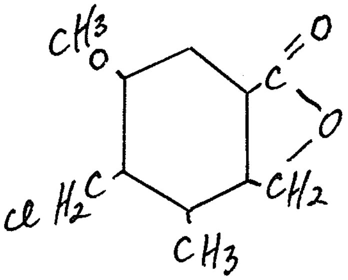
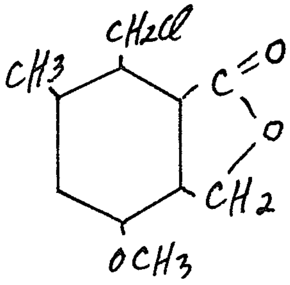
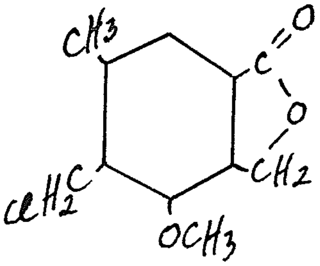
[*] For nomeclature of ring structures employed in this thesis, see appendix, page 46.

In each of these simple phthalides there are two positions that may be occupied by the entering chloromethyl group. Thus a total of four different chloromethylphthalides, (IV), (V), (VI) and (VII), are possible.


(IV)


(V)

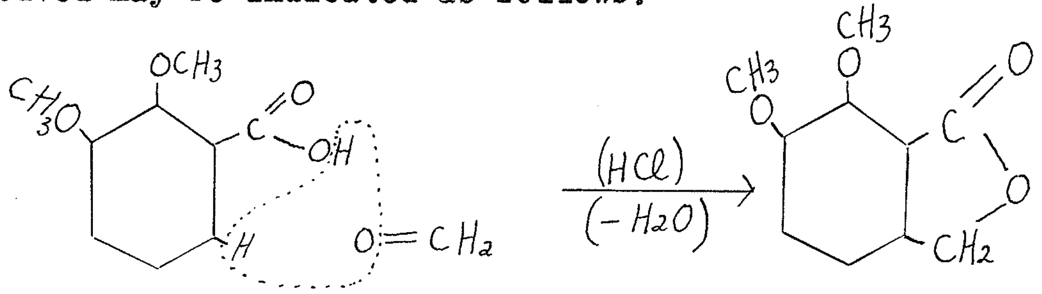

(VI)


(VII)

The present investigations were undertaken to determine, (a) whether the simple phthalide obtained from this reaction had configuration (I) or (II), and (b) to determine the orientations of the chloromethyl derivatives of this compound. These reactions had been carried out by previous graduate students in these laboratories, (19), (5), but the determination of the configuration of these products has never been undertaken.

## LITERATURE SURVEY

In 1925, Perkin, Edwards and Stoyle (13) succeeded in producing a phthalide by heating o-veratric acid with excess formaldehyde and concentrated hydrochloric acid. The reaction involved may be indicated as follows:

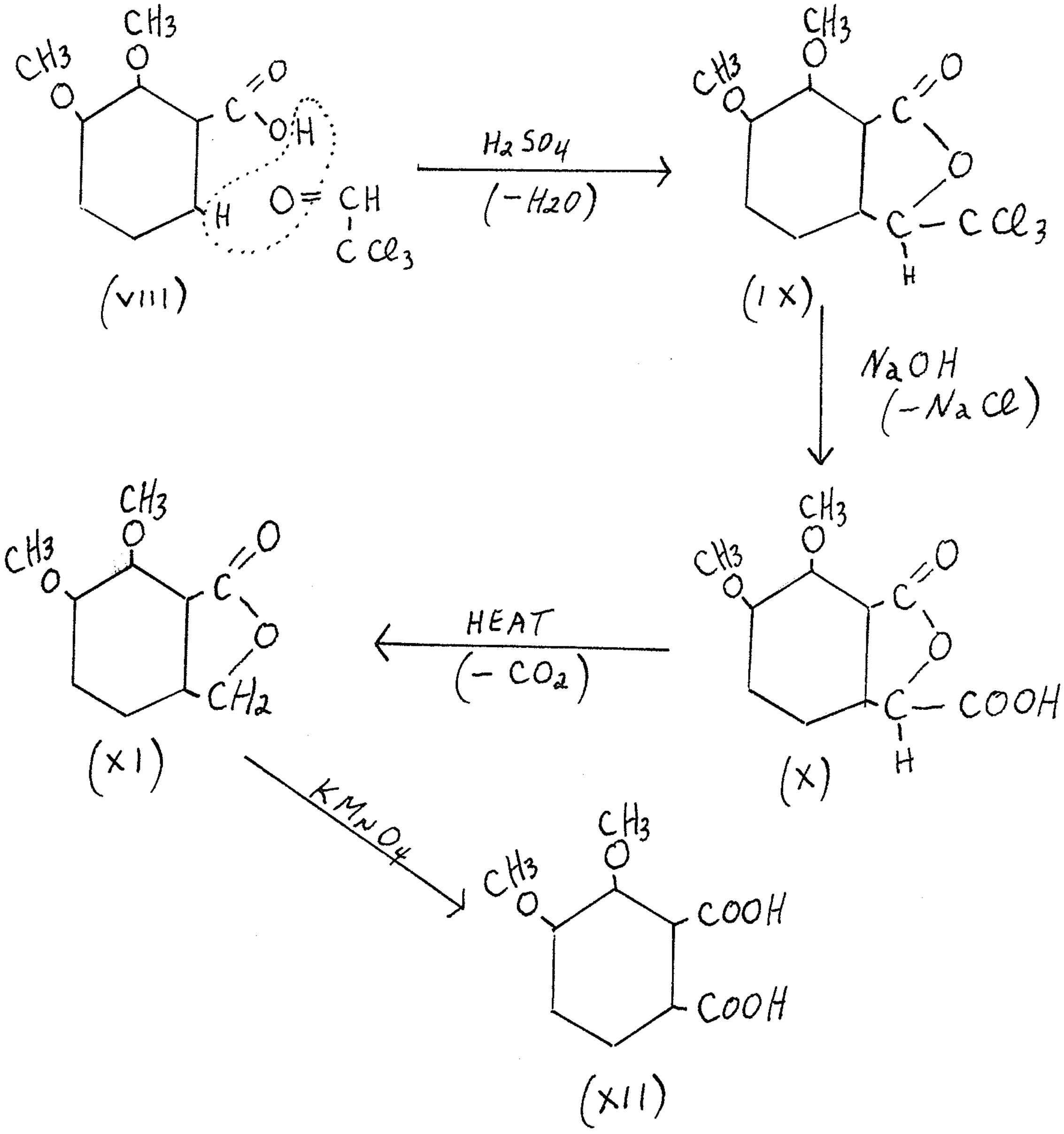


O-VERATRIC ACID

MECONINE

This was indeed a significant observation, for up to this time the classical Fritsch method (7) was the only available practical method for obtaining phthalides from their parent acids. This procedure consisted of condensing the acid with chloral hydrate in 95% sulphuric acid. Thus, applying this reaction to o-veratric acid (VIII), Fritsch obtained the corresponding trichloromethylphthalide (IX). This was then decomposed with aqueous alkali to yield the carboxylic acid (X), which on decarboxylation gave meconine (XI). Meconine, on permanganate oxidation produced the phthalic acid (XII).

One can see immediately the practical value of the formaldehyde condensation, in the fact that only one step is involved to produce the required phthalide, while for the Fritsch method, one must proceed through the much longer series as indicated below.



However, it is important to note that a phthalide is not always formed by this direct condensation method. Some typical results of aromatic acids to boiling formaldehyde and concentrated hydrochloric acid are, (1) no reaction, (2) phthalide formation, (3) chloro compound formation, (4) resin formation, and (5) dioxanyl phthalide. We shall see that although this condensation represents a short cut, it is not always applicable.

It is highly unlikely that chloromethylation results by direct reaction with the original reagents. Stephen, Gladding and Short (17), King and King (9), and others have shown that a chloromethyl group is introduced into the nucleus of the aromatic compound. Stephen, Gladding and Short suggest a mechanism involving certain intermediates which they were able to isolate and subsequently showed them to be s-dichloromethyl ether and mono-chlorodimethyl ether.

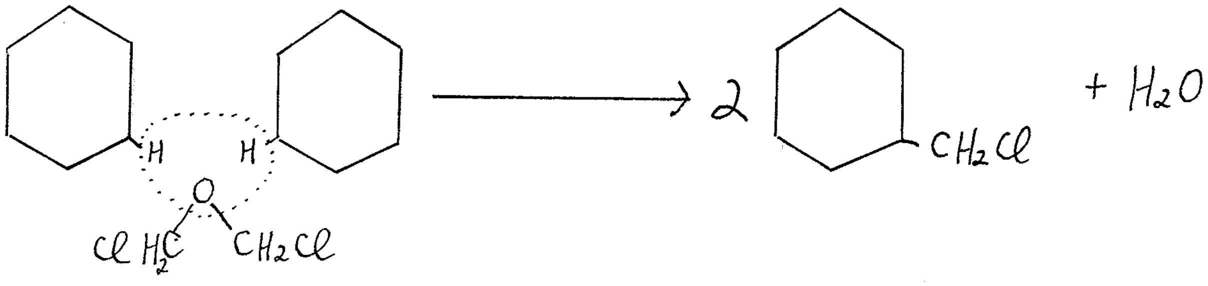
The formation of the s-dichloromethyl ether involves the reaction indicated below.

$$2HCHO + 2HCl \text{ —— } (CH_2Cl)_2O + H_2O \qquad (a)$$

The production of the mono-chlorodimethyl ether is accounted for by the fact that commercial aqueous formaldehyde contains some methyl alcohol. The formation of this compound may, therefore, be indicated as follows.

$$2\ CH_3OH + HCl \text{ —— } CH_3O.CH_2Cl \qquad (b)$$

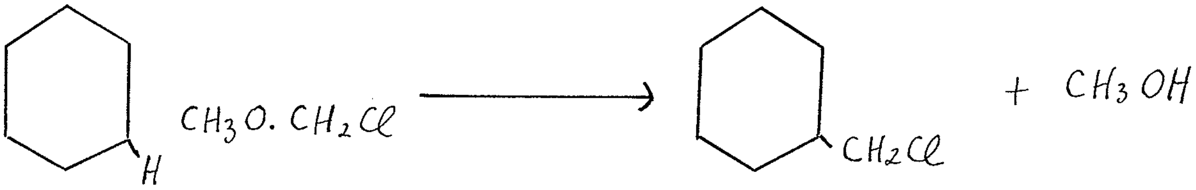
Stephen, Gladding and Short suggest that both these intermediates then react with the aromatic compound to produce chloromethyl derivatives. For example:



BENZENE

BENZYL CHLORIDE

The mono-chlorodimethyl ether may react directly as shown below

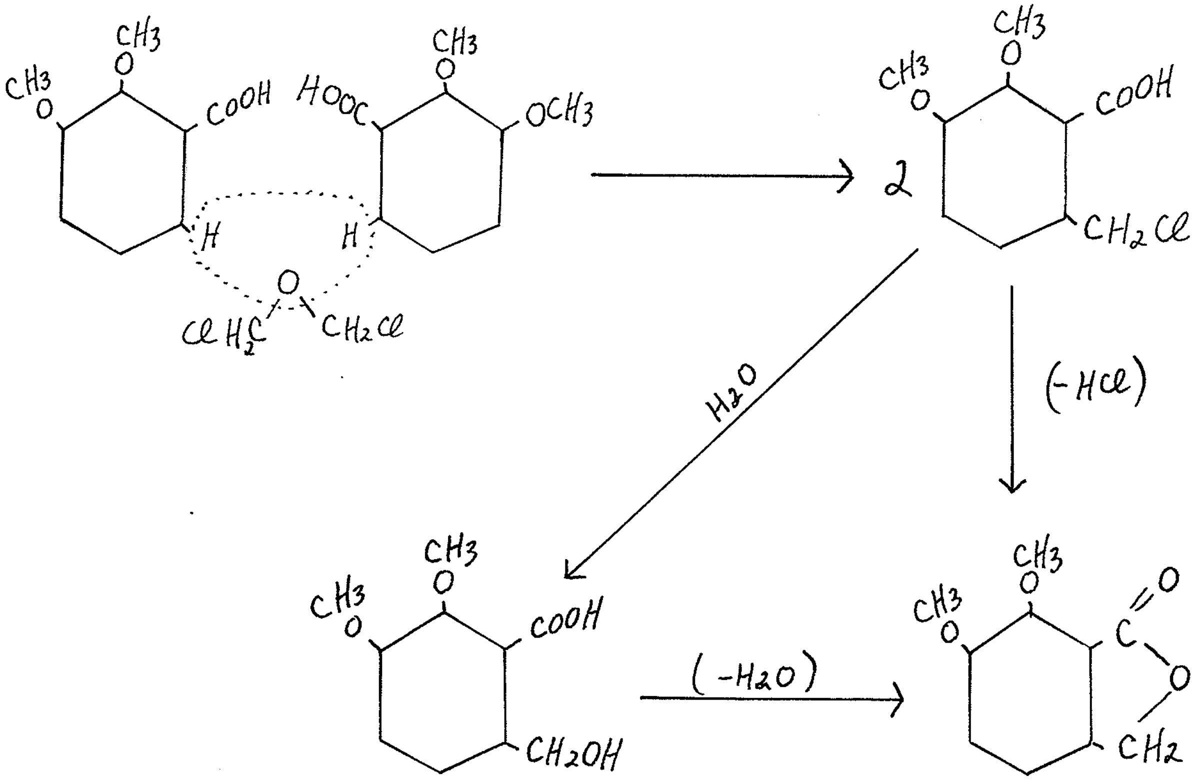


or the following reaction may take place.

$$CH_3.O.CH_2Cl + H_2O \longrightarrow CH_3OH + Cl.CH_2OH$$
$$2\ Cl.CH_2OH \longrightarrow (CH_2Cl)_2O + H_2O$$

The s-dichloromethyl ether thus produced reacts with the aromatic compound as before. However, as the reaction of s-dichloromethyl ether is much faster then that of the mono-chlorodimethyl ether, it is unlikely the reaction involves a direct attack of $CH_3O.CH_2Cl$ on the aromatic compound as shown above , but rather proceeds as indicated in the subsequent choice.

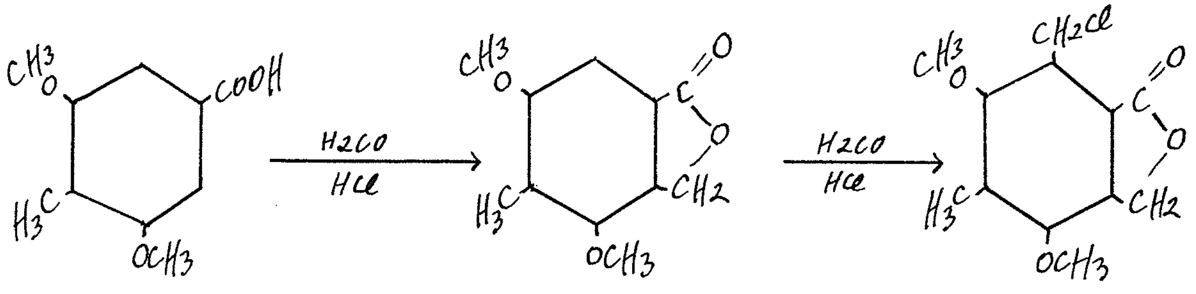
On the basis of the above mechanism suggested by Stephen, Gladding and Short for the introduction of the chloromethyl group into the aromatic nucleus, Yan (19), Sinder (16),and Charlesworth et al (5) showed how phthalide formation can take place in the reaction of an aromatic acid with hydrochloric acid and formaldehyde. The hydrochloric acid and formaldehyde react to form s-dichloromethyl ether (a), which introduces a chloromethyl group into the aromatic nucleus. For phthalide formation to occur, the chloromethyl group must be introduced ortho to the carboxyl group. The final reaction may take place in one of two ways. The chloromethyl group and the carboxyl group may lose hydrogenchloride directly to form the phthalide, or hydrolysis of the chloromethyl group may take place first to form the carboxylic benzyl alcohol, the lactone ring then forming by a loss of water between the alcohol and the carboxyl groups. For example:- the formation of meconine from o-veratric acid first done by Perkin, Edwards and Stoyle.



(XIII)

Of the two possible routes shown above for phthalide formation, the direct loss of HCl is favoured. The reason is that it has been shown that the chloromethyl group, which is stable when it is not ortho to a carboxyl group, is only hydrolysed to the alcohol (XIII) in alkaline solution, while these condensations are all done in acid solution where hydrolysis is difficult.

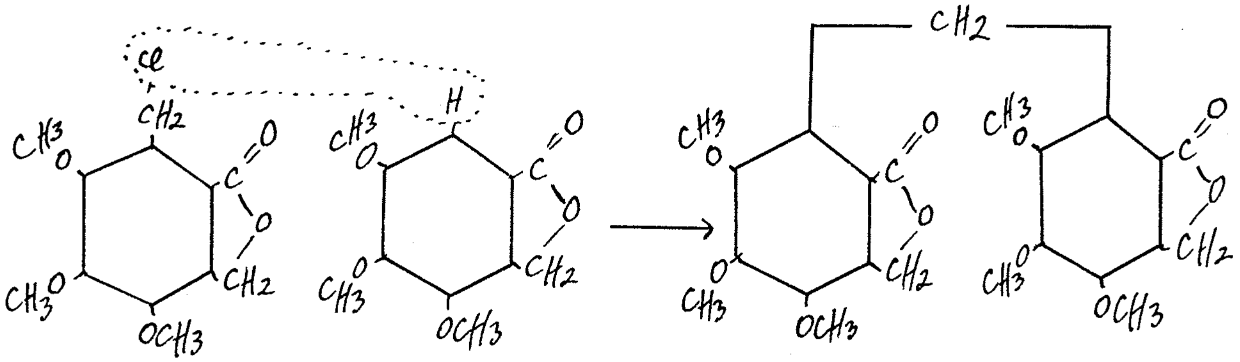
The formation of chloromethylphthalides is a possibility in these condensations. This probably takes place as follows.



(XIV) (XV)

The formation of a chloromethyl compound (XV), by the condensation of 3,5-dimethoxy-4-methylbenzoic acid (XIV), was first reported by Charlesworth and Robinson (4). Similar chloromethyl derivatives have been reported by other workers. For example, Raistrick, Robinson and Todd (14) who isolated a chloromethylphthalide from 5-methoxy-3-methylbenzoic acid.

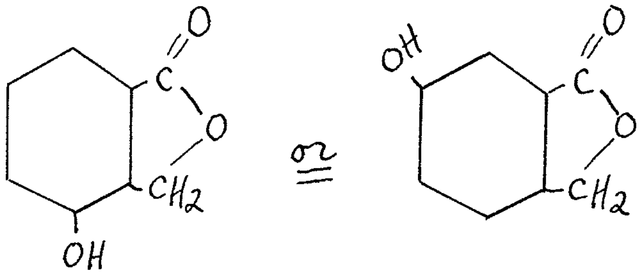
Resin formation may take place by a condensation of the chloromethyl derivatives to form diphenylmethane type compounds.



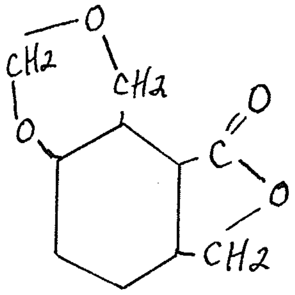
(XVII)

This work was reported by Stephen, Short and Gladding (17) and others. King and King (9) proved the structure of the diphenylmethane compound (XVII).

Buehler, Powers and Michels (2) extended the work of Perkin, Edwards and Stoyle by reacting phenolic acids with hydrochloric acid and formaldehyde. They obtained two compounds when this condensation reaction was carried out on m-hydroxybenzoic acid. One was the simple phthalide (XVIII), while a second compound of lower melting point was always present in these reactions. Buehler, Harris, Shacklett and Block (3) subsequently showed this compound to be a dioxane derivative of the simple phthalide or a dioxanyl phthalide (XIX).



(XVIII)



(XIX)

This represented the first recorded work of combined dioxane and phthalide formation from phenolic acids.

## DISCUSSION OF EXPERIMENTAL RESULTS

This discussion will elucidate the method of attack which was used in establishing the configuration of the simple phthalide isolated from the condensation reaction between 5-methoxy-3-methylbenzoic acid, formaldehyde and concentrated hydrochloric acid. Included will be a summary of the results obtained concerning the structures and the different configurations of the four chloromethyl derivatives possible from the simple phthalides (II) and (III).

As outlined briefly in the introduction, two simple phthalides are possible when 5-methoxy-3-methylbenzoic acid is heated with formaldehyde and hydrochloric acid, following the method of Perkin, Edwards and Stoyle (13). It should be noted here that all condensation reactions carried out during this work were done using a modification of this method, suggested by Rây and Robinson (15). This involved the addition of glacial acetic acid to the hydrochloric-formaldehyde mixture.

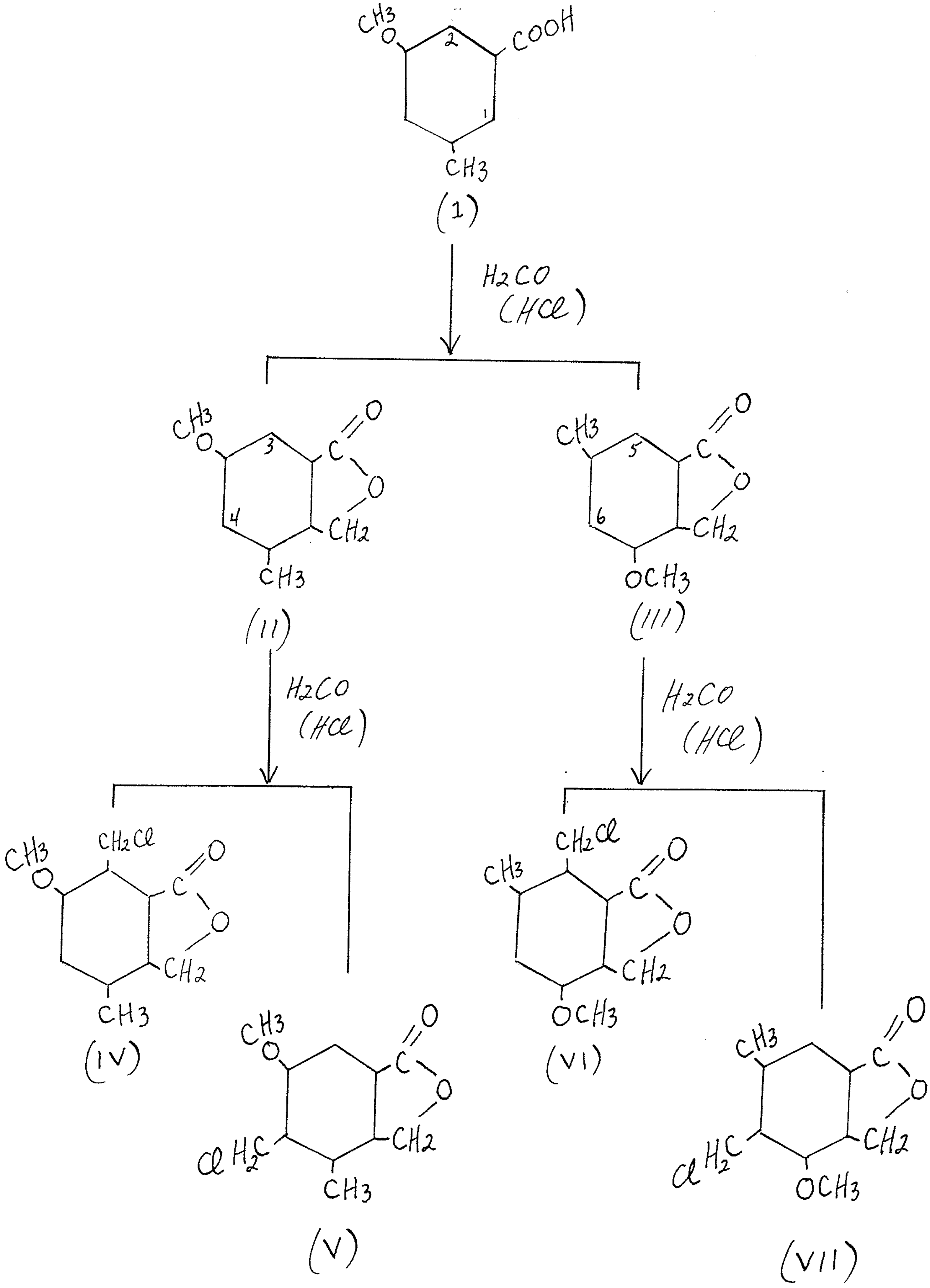
Yan (19) carried out condensation reactions on this acid with and without glacial acetic acid. When glacial acetic acid was used, he was able to isolate two products. The first was a compound supposedly free of chlorine and melting at 131.5 - 133.0°. This compound was not analysed or examined further, but he suggested that it might be the simple phthalide of melting point 135.5° isolated by Meldrum (11). This material, however, proved to be the chloromethylphthalide of melting point 133.5 - 135.5°. The second product obtained contained chlorine and had a melting point of 176 - 178°. This, Yan stated, would be the chloromethyl derivative obtained from the simple phthalide (II) or (III). When glacial acetic acid was omitted from this reaction, Yan was unable to isolate this lower melting material. The crude reaction product was much gummier and it was much more difficult to obtain a pure sample of the chloromethylphthalide. In this case there was some high melting product (275 - 280°) insoluble in alcohol. Analysis tended to indicate that it was an impure specimen of a diphenylmethane type.

The present work consisted partly in isolating all the compounds possible from this reaction. Hence glacial acetic acid was always used. By this method, not one, but four chloromethyl derivatives were isolated, along with one simple phthalide. Separations were carried out without any evidence of gumminess.

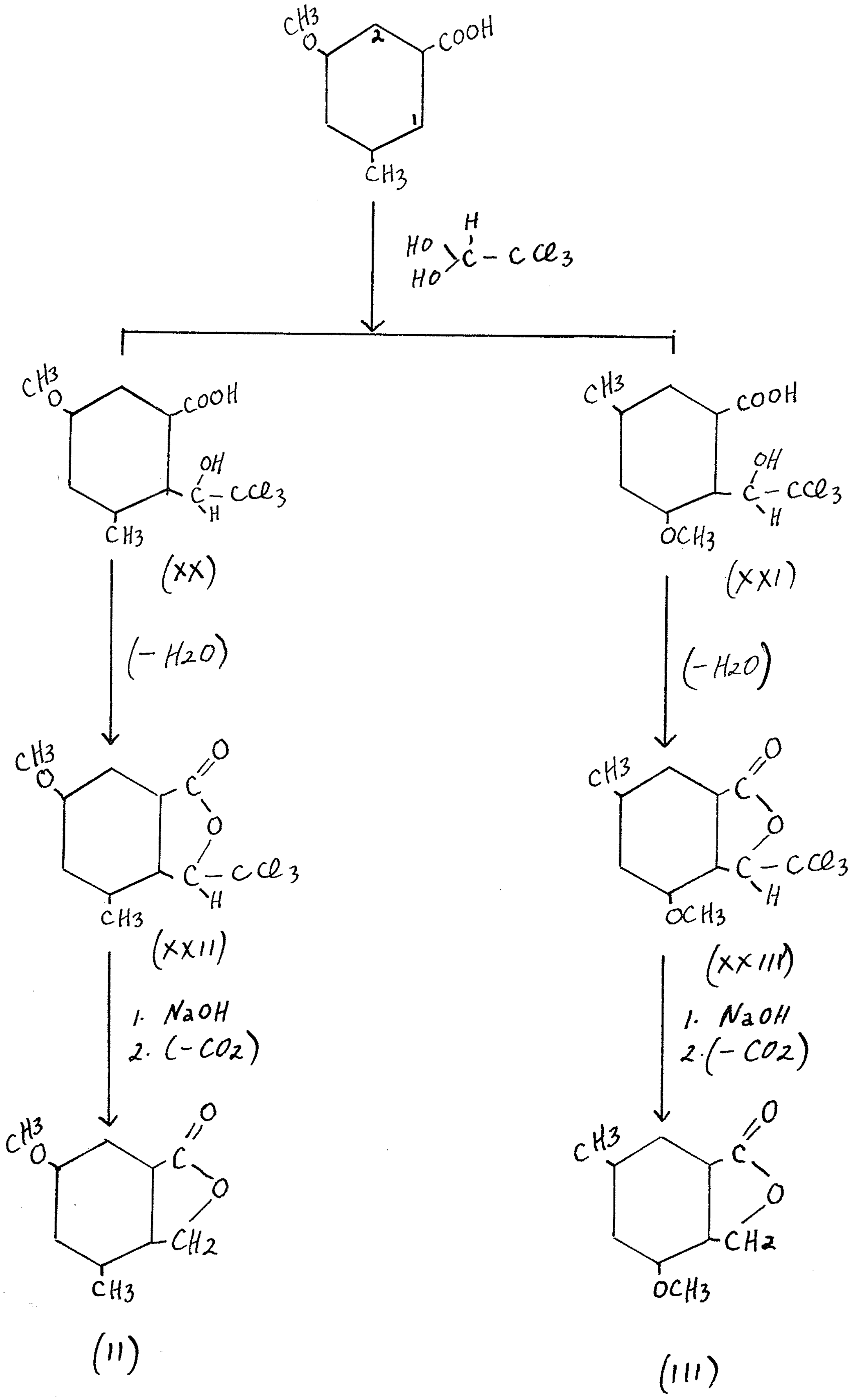
The schematic diagram, page 12, should help in visualizing the steps involved for the production of all products.

When 5-methoxy-3-methylbenzoic acid (I) is heated with formaldehyde and concentrated hydrochloric acid, the chloromethyl group will enter the benzene nucleus at positions 1 and 2, giving rise to the two simple phthalides (II) and (III). On further reaction, the second chloromethyl group will enter position 5 and 6 of compound (III) giving rise to the two chloromethylphthalides (VI) and (VII). Similarly, we obtain (IV) and (V). Therefore, the maximum number of compounds which are possible from this reaction are six, two simple phthalides and four chloromethylphthalides. But, as mentioned previously, only one simple phthalide was ever isolated.

To determine the configuration of the simple phthalide produced, a Fritsch synthesis was carried out on 5-methoxy-3-methylbenzoic acid, according to directions given by Meldrum (II).

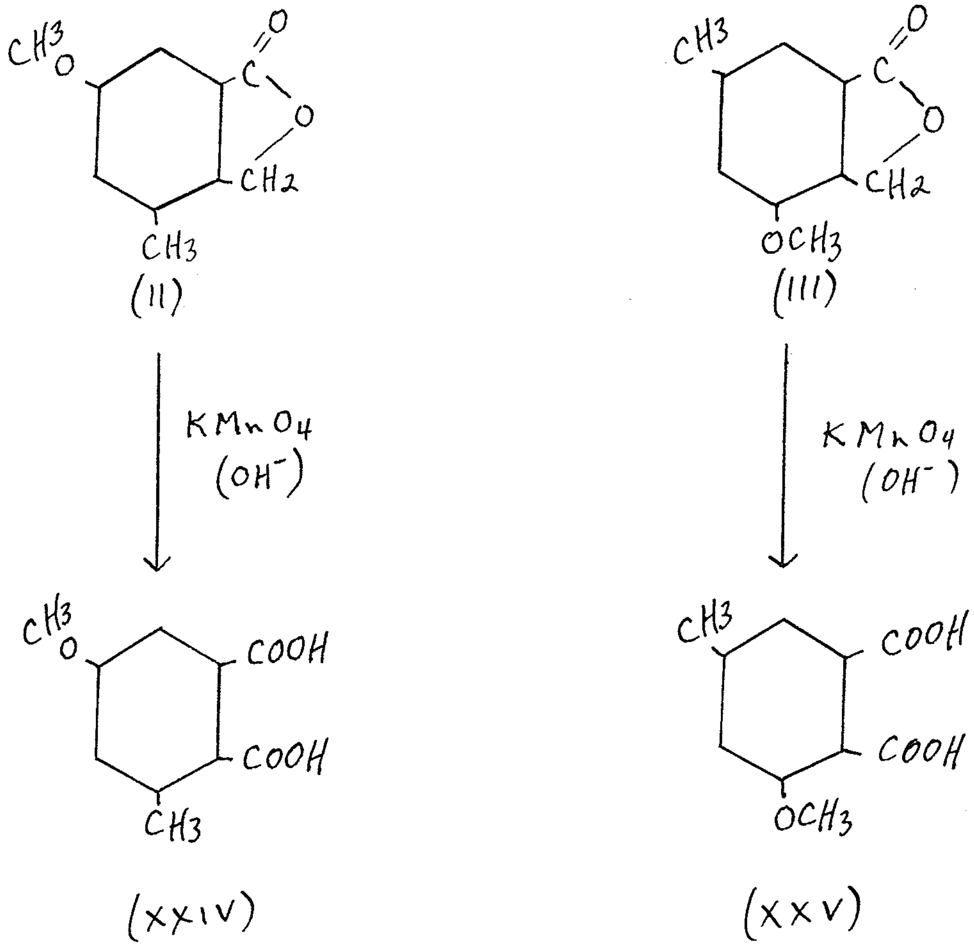

(1)
$H_2CO$
(HCl)
(II)
$H_2CO$
(HCl)
(III)
$H_2CO$
(HCl)
(IV)
(V)
(VI)
(VII)

By this method, two simple phthalides, (II) and (III) were eventually produced. The steps involved were as follows.

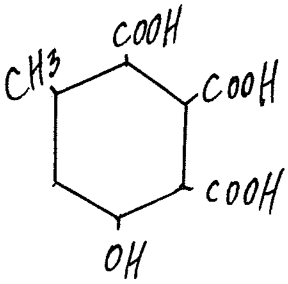


The chlorohydrate can enter position 1 and 2 and give rise to the two compounds (XX) and (XXI). With loss of water, the two trichloromethylphthalides (XXII) and (XXIII) are formed. These in turn, are converted to the carboxylic acids with aqueous alkali, and on decarboxylation the final phthalides are produced. The melting points associated with these two phthalides were 133.5 - 134.5° and 104 - 105°.

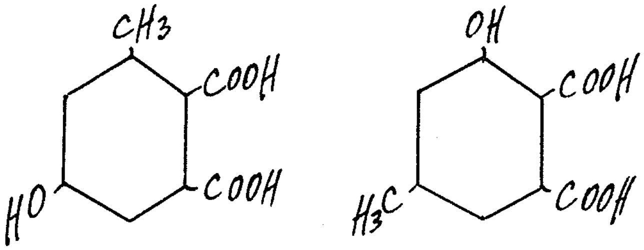
The configurations of these two isomers had previously been established by Meldrum in the following manner:- On oxidation of (II) and (III) with alkaline potassium permanganate he obtained the two different dicarboxylic acids (XXIV) and (XXV)



It was found, however, that demethylation of these dicarboxylic acids was impracticable when treated with hydriodic acid, as in the usual way. However, when cochenillic acid (XXVI) is heated under various conditions, β-coccinic acid (XXVII), among other products, is produced.

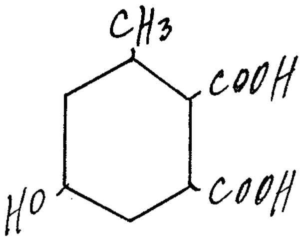


(XXVI)



(XXVII)

Because this is a hydroxyphthalic acid derived from (XXVI), there are two possible structures for this compound. There was no distinct colour reaction when compound (XXVII) was treated with ferric chloride, as an ortho phenolic acid would normally give. Therefore β-coccinic acid must have the following structure.



This compound, when methylated, proved identical with (XXIV) by the 'mixed melting point' method. This material had been derived from the phthalide (II) of melting point 104 - 105°. The second phthalide obviously would be the 133.5 - 134.5° isomer.

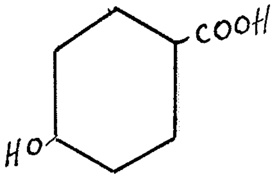
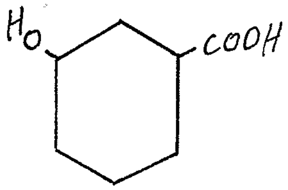
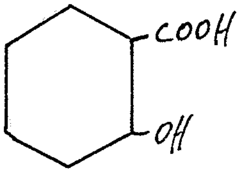
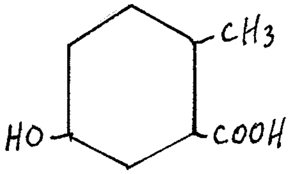
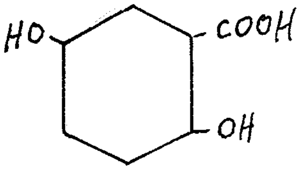
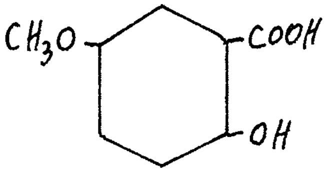
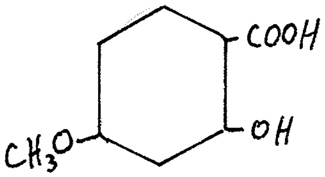
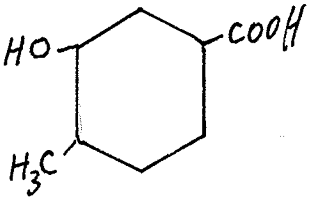
The simple phthalide isolated from our condensation reactions had a melting point of 105 - 106°. An analysis showed good agreement with the values calculated for this simple phthalide structure. Finally, mixed melting points between this material and the isomer isolated by Meldrum showed no depression. Hence the configuration of the simple phthalide (II) is definitely established.

As stated above there is a vivid color change when ferric chloride is added to a phenolic acid which has the hydroxyl and carboxylic groups ortho to one another. This test was carried out on a variety of compounds of this type and the results are shown in table 1, on page 17.

We next turned our attention to determine the configuration for the chloromethyl derivative obtained from 5-methoxy-3-methylphthalide (II). As shown in the diagram on page 12, this derivative could have structure (IV) or (V). It was found, however, that by varying the experimental conditions in this condensation reaction, four chloromethylphthalides were isolated. These had associated with them melting points of 133.5 - 135.5°, 152.5 - 154.0°, 176.5 - 178.0°, and 178.0 - 179.5°. The significant difference between the latter two compounds was their dif-

## Table 1

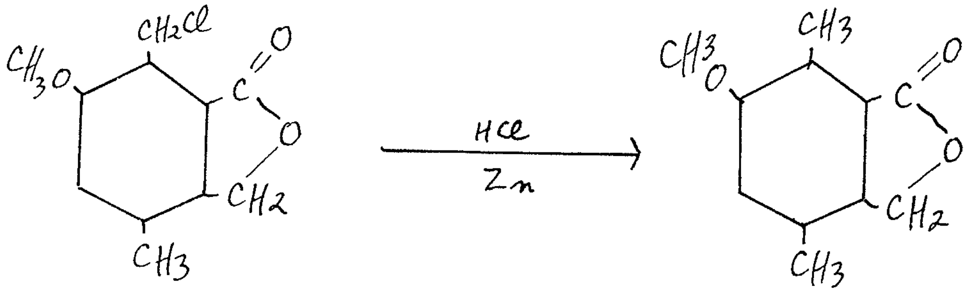
### Effects of Aqueous $FeCl_3$ Reagent on Some Phenolic Acids

| Compounds | Color Change |
|---|---|
|  | no change |
|  | no change |
|  | deep purple |
|  | no change |
|  | deep blue |
|  | deep blue |
|  | deep violet |
|  | no change |

ferent solubilities in hot ethyl alcohol, one being very soluble, while the other, with the melting point of 178.0 - 179.5°, was much less soluble. On analysis, it was shown that, within experimental error, all four compounds were identical in composition, and had values in good agreement for those calculated for the chloromethylphthalide structure.

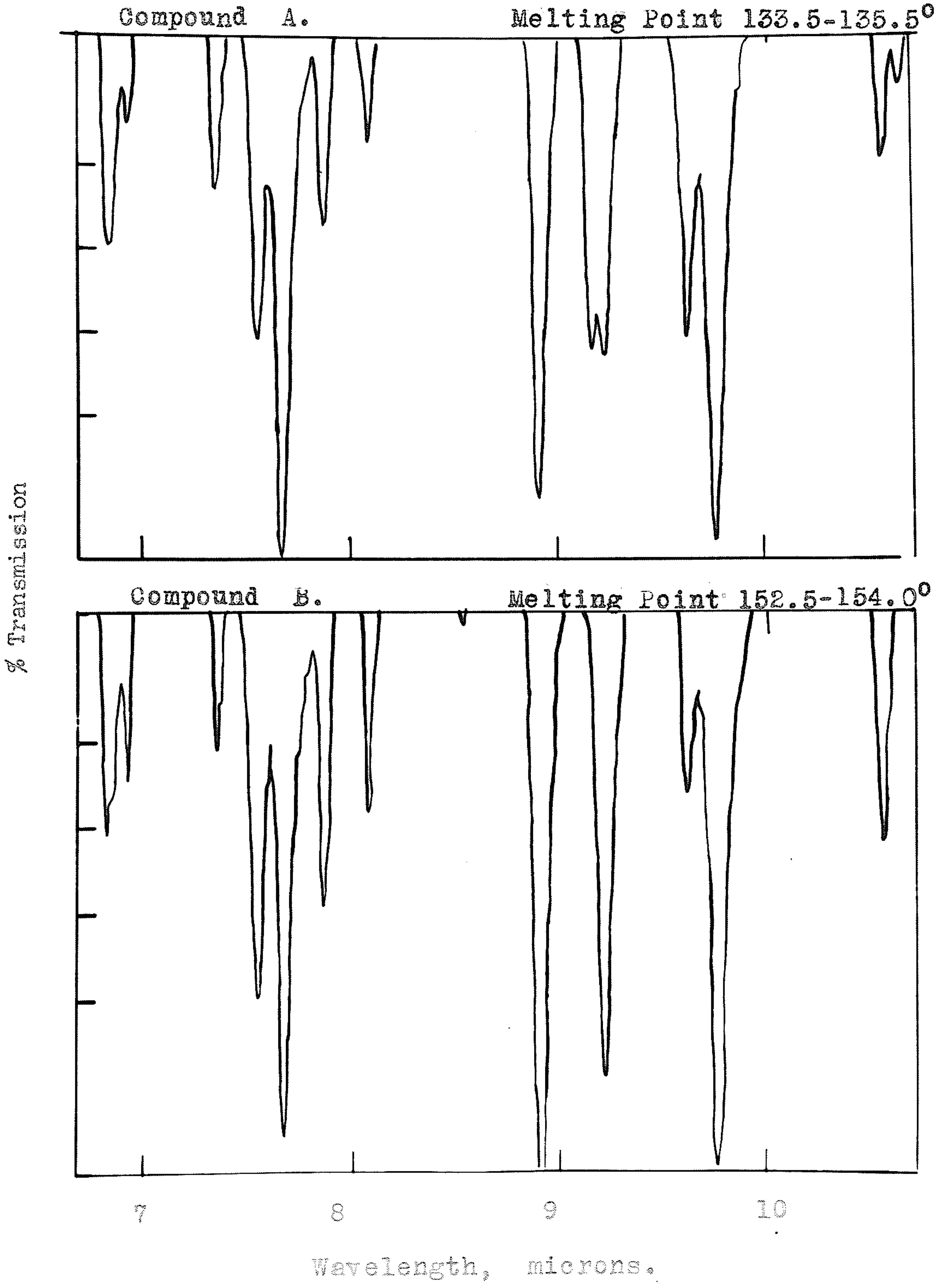
These results did in fact, indicate four distinct isomers or else dimorphic forms of the same compound. Infra red spectra were obtained for each compound. These curves showed small but distinct differences, and so would indicate that four isomers were actually produced. These spectra are reproduced on page 19 and page 20.

A further attack on this problem was to treat each of the chloromethylphthalides with concentrated hydrochloric acid and zinc dust in order to remove the chlorine atom.



In so doing we should again obtain four different melting points associated with the four new compounds formed. This indeed, was found to be the case for three of the four isomers. Insufficient

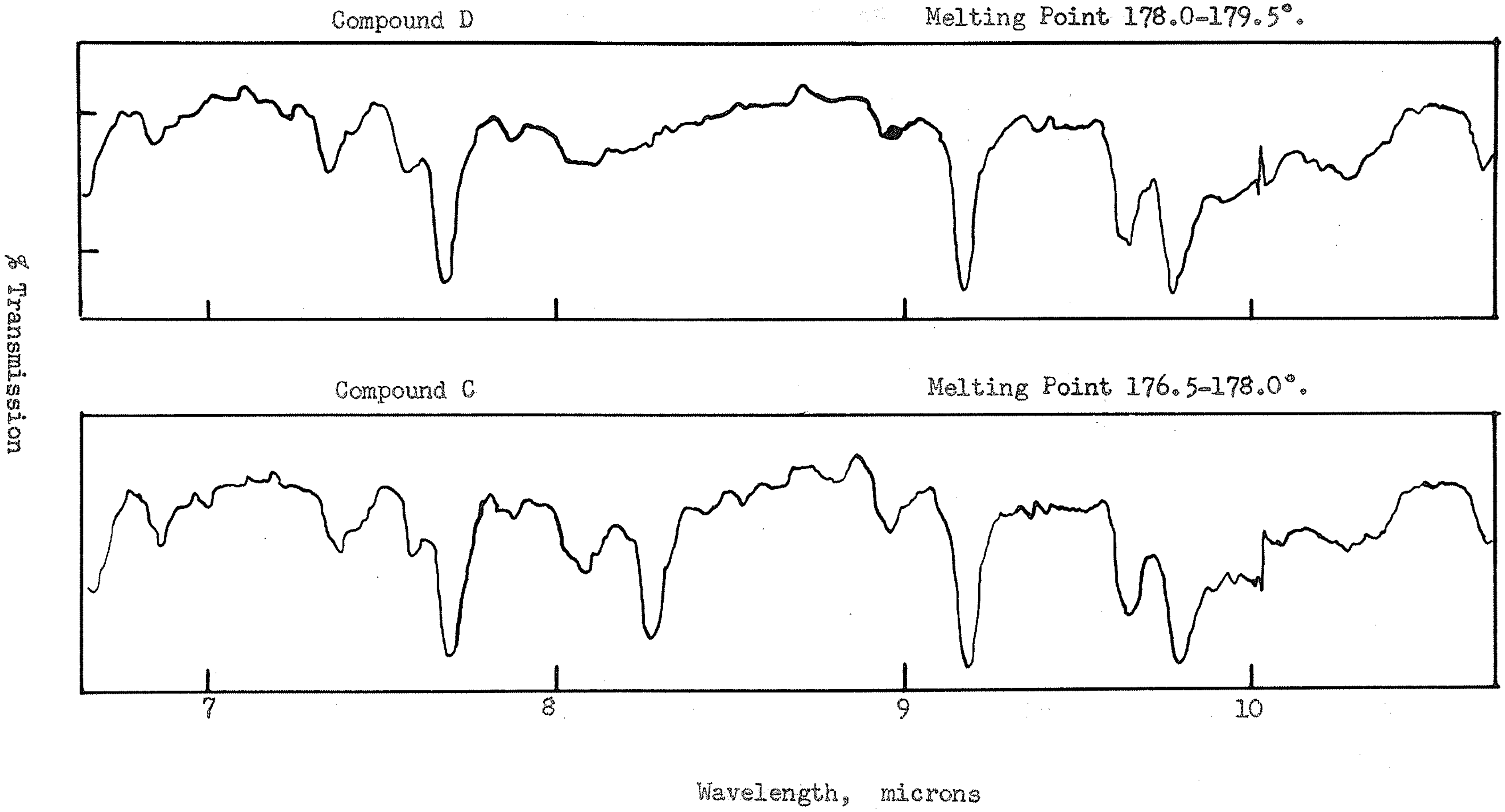
Infra Red Spectra of Chloromethylphthalides A and B in Carbon Tetrachloride.



Compound A. Melting Point 133.5-135.5°

Compound B. Melting Point 152.5-154.0°

# Infra Red Spectra Of Chloromethylphthalides C and D in Carbon Tetrachloride



material of the chloromethylphthalide of melting point 152.5 - 154.0° prevented this test from being carried out.

The significant factor determining the products obtained from this condensation reaction, was the length of time 5-methoxy-3-methylbenzoic acid was allowed to react with the formaldehyde and hydrochloric acid. Table 2 summarizes this work.

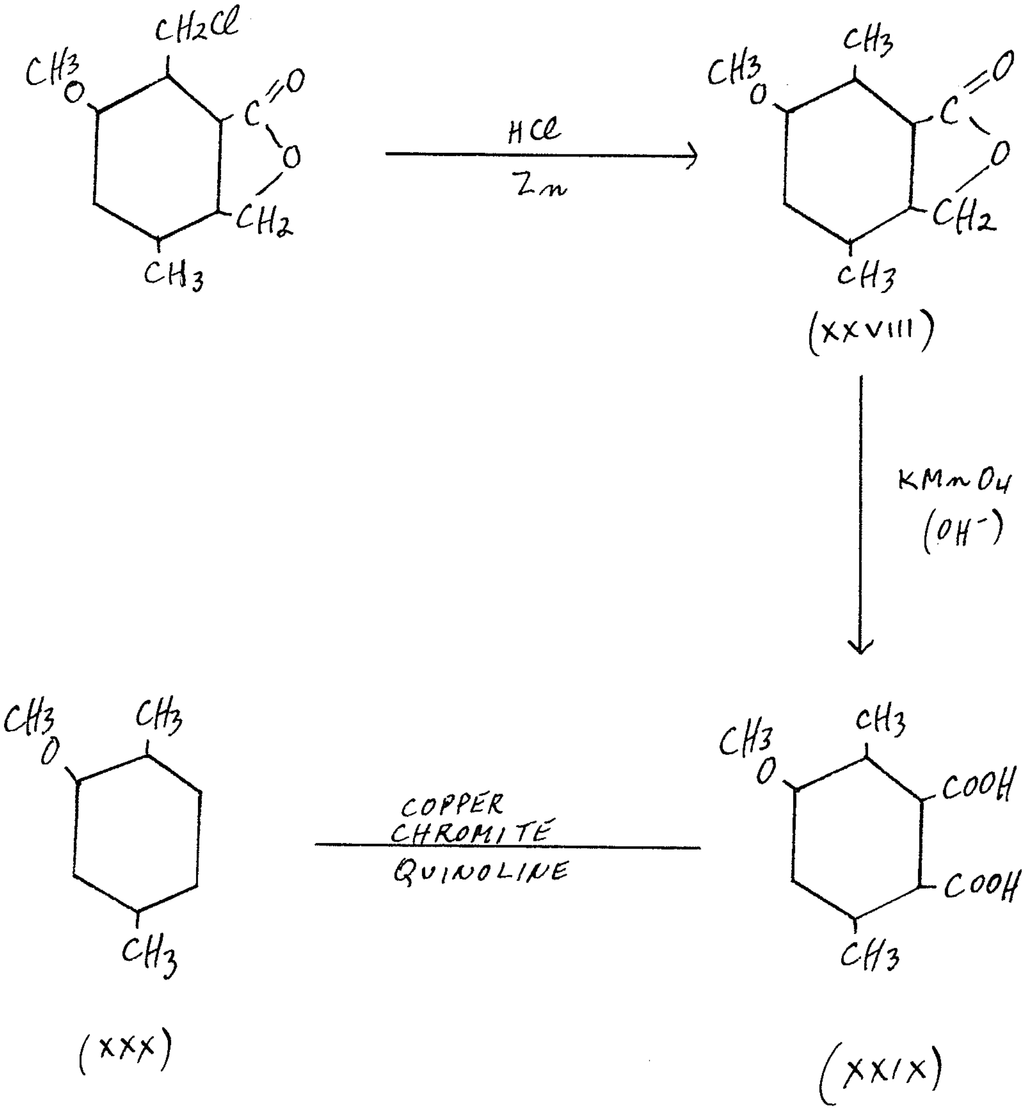
Table 2

| Condensation Time | Melting Points of Isomers Isolated |
|---|---|
| 2 minutes or less | 105 - 106°, 133.5 - 135.5°, 152.5 - 154.0°. |
| 4 minutes to 90 minutes | 105 - 106°, 133.5 - 135.5°, 176.5 - 178.0°. |
| 90 minutes to 270 minutes | 105 - 106°, 133.5 - 135.5°, 176.5 - 178.0°, 178.0 - 179.5°. |
| up to 6 hours | almost exclusively 178.0-179.5°. |

It should be noted that the 152.5 - 154.0° isomer was isolated only when the condensation was held to a very short time. When the reaction time was extended to approximately 90 minutes or longer, the 178.0 - 179.5° isomer began to settle out of the solution, and could be separated very easily.

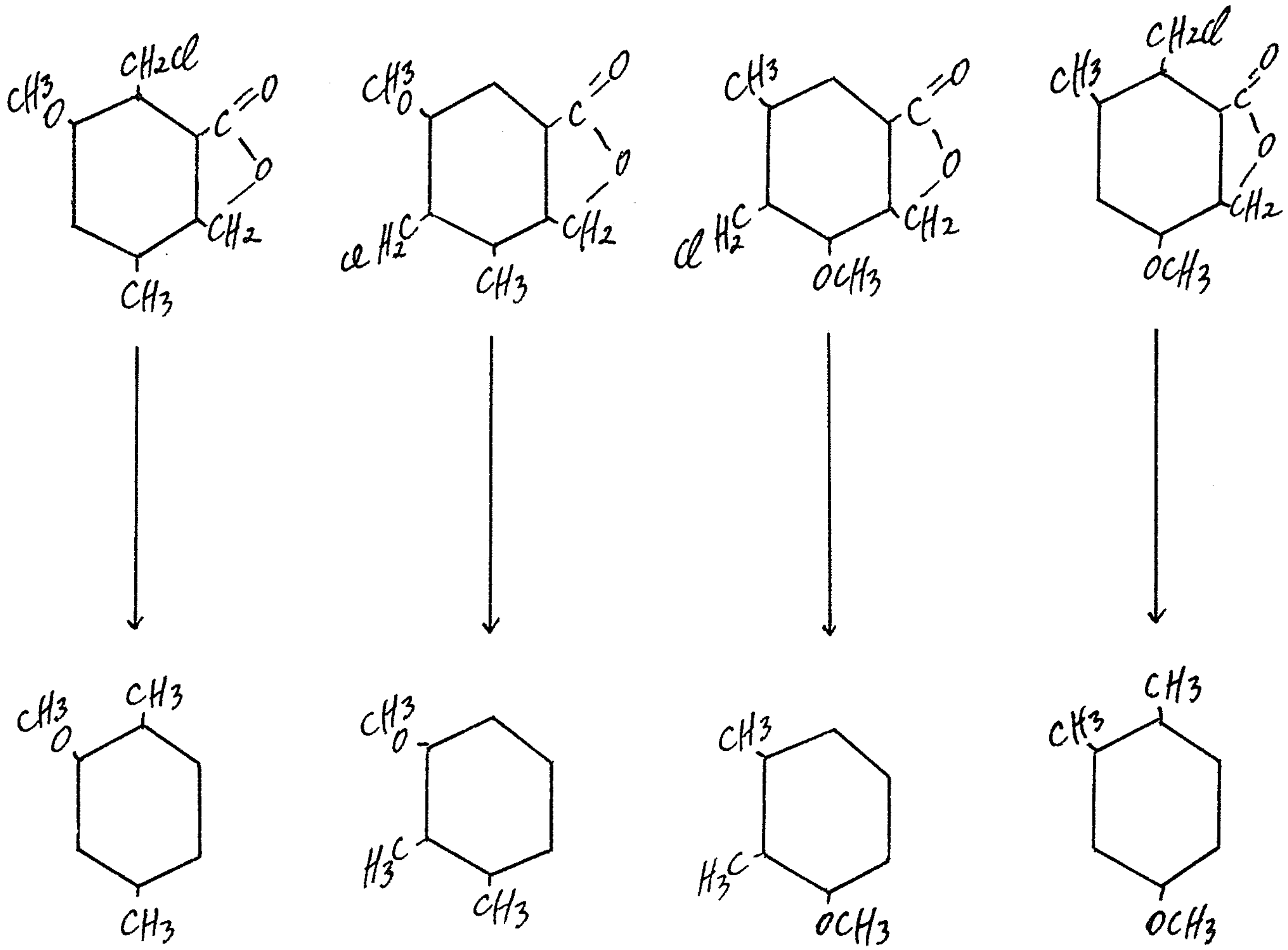
With the existence of four isomeric chloromethylphthalides clearly indicated, it was next necessary to affix a definite configuration, either (IV), (V), (VI) or (VII) (see page 12), to each of the different melting points which had previously been obtained.

One means of attack is indicated below. Lack of time prevented a completion of this portion of the work, and although only one isomer was done experimentally, there is no reason why all cannot be carried through the same steps to final conclusions.



The chloromethylphthalide on reduction with concentrated hydrochlorine acid and zinc dust gave the chlorine-free phthalide (XXVIII). This material in turn was oxidized to the dicarboxylic acid (XXIX), and on dicarboxylation, would yield the 2-methoxy-p-xylene (XXX).

If this series of reactions is carried out on all four isomers, the following methoxyxylenes would be produced.



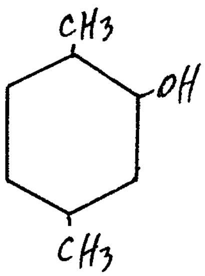
(XXXI) (XXXII)

same substance

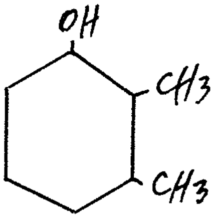
(XXX)

(XXXIII)

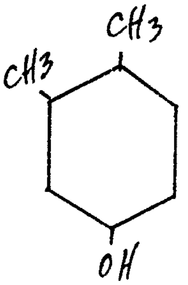
The three phenols, all solids, and corresponding to the above methyl ethers are commercially available.



2,5-dimethyl phenol



2,3-dimethyl phenol



3,4-dimethyl phenol

On methylation, these would yield the products (XXX), (XXXIII), (XXXII) (or (XXXI)). Infra red spectra of these known materials could then be compared to the spectra of the methoxyxylene compounds obtained from the reaction outlined above. In this way, a definited configuration could be established for at least two of the possible four isomers. The two remaining chloromethylphthalide isomers, which gave the identical xylenes (XXXI) and (XXXII), might be differentiated by a closer examination of all four spectra.

It is also possible, by demethylation, to convert compounds (XXX), (XXXI), (XXXII) and (XXXIII) to their corresponding phenols. If this were done, mixed melting points would again definitely establish the configuration for two of the four isomers.

On examination of the schematic outline on page 12, one might wonder why the simple phthalide (III) was not isolated from this reaction, when all other products were eventually obtained.

A possible answer to this problem might be found from examining a set of rules dealing with the influence of nuclear substituent groups on the course of the reaction of an aromatic acid with formaldehyde and hydrochloric acid. These generalizations were first put forward by Anderson (1) and actually summarize the results of various condensation reactions carried out up to that time. These rules, on the whole, have been substantiated by further experimental work carried out by later investigators.

1. Ortho orientation forces are not nearly as important as para directing ones.

2. In nearly every case found so far, where a simple phthalide is formed, there was a methoxyl group in the 5 (or 3) position, that is, para to the position where the chloromethyl group must be introduced to form a phthalide ring with the carboxyl group.

This second rule must be modified slightly in light of our present investigations. The only way that the four chloromethylphthalide isomers could form, would be through the simple phthalide (II) and (III). The formation of phthalide (III) would necessitate a chloromethyl group entering the benzene nucleus para to a methyl group, rather than a methoxyl group. But this is an ortho and para directing substituent, and so does not constitute an exception. The fact that a methoxyl group will stimulate the para position to a much greater extent than a methyl group must be taken into consideration.

3. In every case where a chloromethylphthalide is formed, the starting material had a methoxyl group in the 3 (or 5) position. After simple phthalide formation, the second chloromethyl group can enter only if there is a second ortho and para directing substituent in a position para to that of the entering chloromethyl group. Again a slight modification is necessary, for similar reasons to those stated above. That is, the second directing group could be a methyl group as well as a methoxyl group. Indeed, it would appear that any electron donating group should do.

Finally, it might be said, that when 5-methoxy-3-methylbenzoic acid (I) is heated with formaldehyde, concentrated hydrochloric acid, and glacial acetic acid, both simple phthalides (II) and (III) are in fact produced. From each of these phthalides, two chloromethyl derivatives were produced and eventually isolated, giving the four isomers, (IV), (V), (VI) and (VII). However, as soon as the simple phthalide (III) was formed, it would immediately be converted to a chloromethylphthalide because of the strong electron releasing methoxyl group in the para position. For this reason, then, we were never able to isolate this particular phthalide. In compound (II), on the other hand, we have a much weaker ortho and para directing methyl group, and so this material would not form the chloromethyl derivatives as quickly, thus making an isolation possible.

A point which bears more consideration deals with the fact that when the condensation time is continued for six hours, only the one chloromethylphthalide was isolated. If the assumption is correct, that these four chloromethylphthalides are produced through the two simple phthalides, it would indicate that isomerization took place between compounds (II) and (III). This then would be a plausible explanation for the isolation of only one chloromethyl isomer.

## EXPERIMENTAL

### Preparation of 5-methoxy-3-methylbenzoic acid

Two methods were used in the synthesis of this acid.

### Method 1

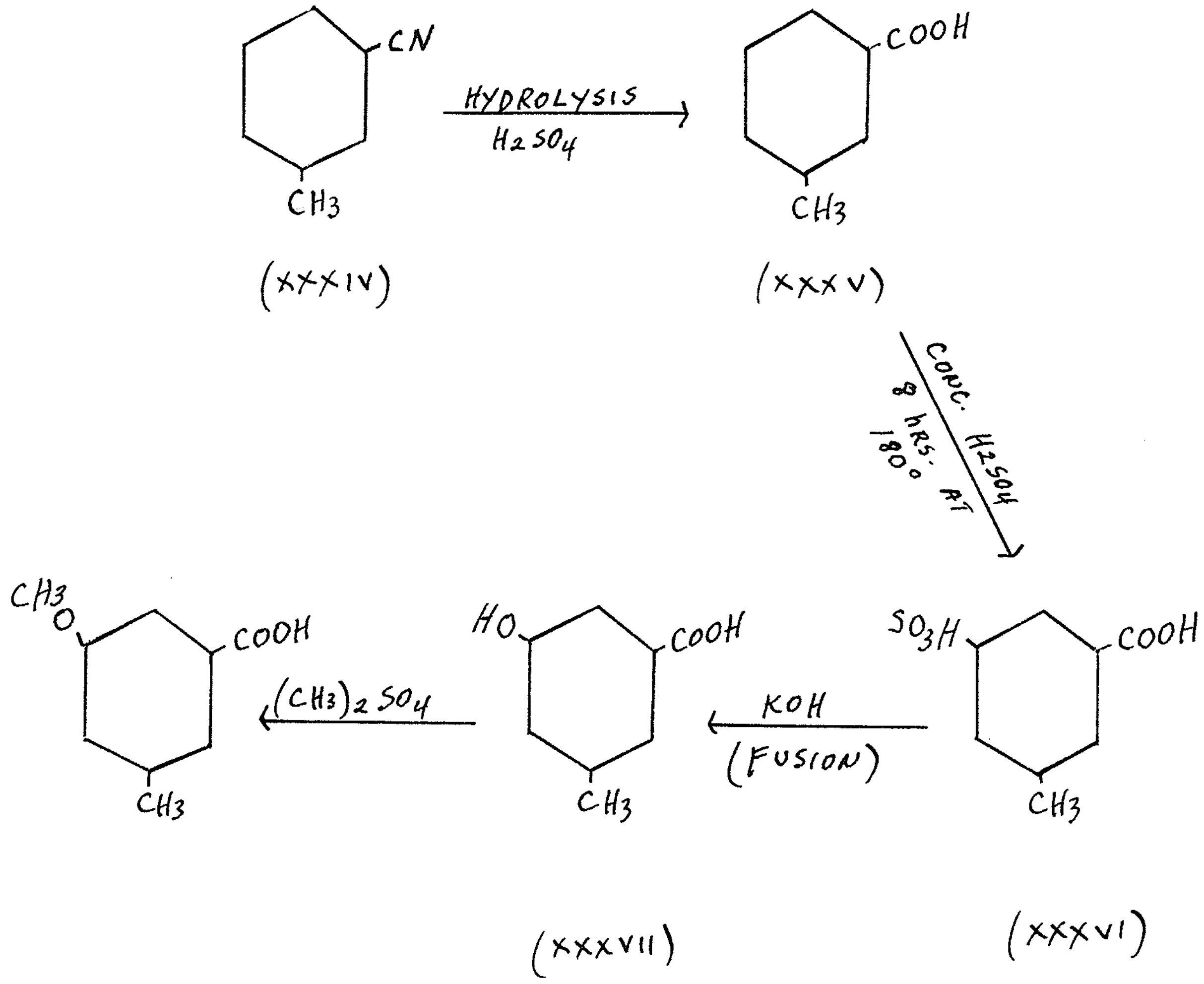
Most of the acid required for this investigation was synthesized from 3-cyanotoluene (XXXIV), which on hydrolysis gave the 3-methylbenzoic acid (XXXV), and subsequently through the 5-sulfo- (XXXVI) and 5-hydroxy-3-methylbenzoic acids (XXXVII) to 5-methoxy-3-methylbenzoic acid.

### Hydrolysis of 3-cyanotoluene

The 3-cyanotoluene was hydrolysed by refluxing with concentrated sulfuric acid (95%) in accordance with Cohen's direction (6). There was always a violent reaction at the onset of the hydrolysis, but this was eventually controlled by having a good stirrer in operation throughout the reaction. Good yields of our required material was then obtained.

### Sulphonation of m-toluic acid

The m-toluic acid obtained above was sulphonated by the method of Meldrum and Perkin (10). It should be noted that a standing period in the cold for at least two days and usually three, was required before complete separation of the 5-sulfo-3-methylbenzoic acid took place. This crude product was then filtered on a sintered glass funnel (medium). At this stage, it was very necessary to get the material as dry as possible to prevent bad splattering in the alkali fusion step to follow. Two methods were tried. The first was to take the damp product and let it stand over night in a vacuum desiccator containing potassium hydroxide pellets. The second method was to extend the filtration period for twenty four hours or longer. This latter method proved much more successful at producing nicely dried material, and was eventually adopted.



Alkali fusion of the sulphonic acid

This stage proved to be the most difficult in the synthesis, and until this was mastered, not only poor yields were obtained, but in some cases our 5-hydroxy-3-methylbenzoic was very badly contaminated with an oily substance which could not be removed. This oily material was probably due to some oxidation of our phenol.

The crude 5-sulfo-3-methylbenzoic acid obtained from 60 grams of the 3-methylbenzoic acid was thoroughly dried as outlined above. Approximately 285 grams of potassium hydroxide pellets, with 8 - 10 ml. of water were heated in a nickel crucible to a temperature of 180 - 200° C. All the crude sulfo compound, if dried properly, can then be added within a period of 10 - 15 minutes. The melt was quickly taken to 260°, and held there for about 10 minutes with occasional stirring. The sample was allowed to cool, and leached with about 700 ml. of water. The solution was neutralized with dilute sulphuric acid, and made slightly alkaline with a few pellets of potassium hydroxide. On cooling, large quantities of potassium sulphate came down and were filtered off. A small amount of charcoal was added to the filtrate, which was then concentrated to about 500 ml. Again on cooling more potassium sulphate came down and was removed. The filtrate was then acidified with concentrated hydrochloric acid, where a thick, light brown precipitate settled. Normally, only one crystalization from water and charcoal was necessary to get a relatively pure product of melting point 207.0 - 208.5°.

## Methylation of 5-hydroxy-3-methylbenzoic acid

The method used was essentially that of Tambor (18) and utilized by Anderson (1). 5-hydroxy-3-methylbenzoic acid

(20 gm.) was dissolved in sodium hydroxide solution (100 gm., 20%) in a three neck flask. While the solution was cooled and stirred in an atmosphere of nitrogen, dimethyl sulphate (35 gm.) was added in three portions over 15 minutes. The reaction mixture was stirred $\frac{1}{2}$ hour longer, then sodium hydroxide (5 gm.) was added and the mixture refluxed for 45 minutes to destroy any excess dimethyl sulphate. A stirrer was kept in operation at this stage to avoid bad bumping. The solution was cooled and the crude acid which was precipitated by acidification with dilute hydrochloric acid was filtered, washed with water, and dried. On crystallization from 50% acetic acid and a little charcoal, 5-methoxy-3-methylbenzoic acid (13-15 gm.) was obtained as fine white needles with melting point at 135 - 136°.

A good supply of m-toluic acid was made available soon after this project was begun, thus eliminating the hydrolysis step.

### Method 2

A smaller amount of 5-hydroxy-3-methylbenzoic acid was prepared from ethyl acetopyruvate (12), much according to details given by Meldrum and Perkin (10) and outlined by Yan (19). Although this method would produce a purer acid, the yields were so low, that it was decided to prepare all our starting acid by method 1.

### Condensation of 5-methoxy-3-methylbenzoic acid with formaldehyde, hydrochloric acid and glacial acetic acid

The general method followed was that used by Perkin, Edwards and Stoyle (13) as modified by Rây and Robinson (15).

This procedure was employed in all condensations carried out, with modifications in the period of heating, the proportions of formaldehyde, and the method of separation of the reaction products.

As shown in table 2, the length of time the condensation reaction was allowed to proceed proved to be a very important factor in determining the products formed by this condensation.

## I Condensation time 2 minutes or less.

5-methoxy-3-methylbenzoic acid (4 gm), concentrated hydrochloric acid (25 ml.), aqueous formaldehyde (10 ml., 40% solution) and glacial acetic acid (25 ml.) were mixed in a 100 ml. one neck round bottom flask fitted with a water condenser. The flask was then placed in a hot water bath and held there only long enough to permit the 5-methoxy-3-methylbenzoic acid to go into solution. This usually took about two minutes. The flask was removed from the hot water and quickly placed into an ice bath to insure no further reaction. On standing over night in the refrigerator a yellowish precipitate formed, was filtered off, and well washed with water.

### a) Isolation of 5-methoxy-3-methylphthalide (II)

Cold water was added to the filtrate obtained above, where a white precipitate came down. This solution was allowed to stand over night at which time the precipitate was filtered and washed with water. Repeated crystallization from 95% ethyl alcohol finally produced the 5-methoxy-3-methylbenzoic acid (II) of melting point 105 - 106°*.

Analysis

Calculated for $C_{10}H_{10}O_3$: C, 67.41%; H, 5.62%.
Found: C, 66.90%; H, 5.64%.

A small quantity of material insoluble in ethyl alcohol and with a melting point above 275° was found and would indicate the diphenylmethone resin type compound. (see page 8) This material was not examined further.

b) Isolation of the two chloromethylphthalides of melting point 133.5 - 135.5° (A) and 152.5 - 154.0° (B)

The yellowish precipitate mentioned above, which separated directly from the reaction mixture, was crystallized from ethyl alcohol. A little charcoal was used in order to obtain white crystals. These, in turn, were subjected to small fractions of boiling ethyl alcohol, approximately 5 ml., while the crude product was still on the filter funnel. This was continued until it appeared that no more of the more soluble material (A) was left, usually 4 to 6 portions of ethyl alcohol were necessary. The more soluble material (A) was collected, leaving the less soluble product (B) still on the filter paper. This latter material (B) was recrystallized from glacial acetic acid and then ethyl alcohol until the white chloromethylphthalide of melting point 152.5 - 154.0° was obtained.

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* For yields produced in all these reactions, see General Notes, page 36.

Analysis

Calculated for $C_{11}H_{11}O_3Cl$:

C, 58.28%; H, 4.86%; Cl, 15.66%

Found: C, 58.24%; H, 5.06%; Cl, 15.36%

The more soluble material (A) mentioned above, was recrystallized from glacial acetic acid and then ethyl alcohol to produce the chloromethylphthalide of melting point 133.5° - 135.5°.

Analysis

Calculated for $C_{11}H_{11}O_3Cl$:

C, 58.28%; H, 4.86%; Cl, 15.66%

Found: C, 58.26%; H, 5.21%; Cl, 15.35%

## II Condensation time of 4 minutes to 90 minutes

### Isolation of the chloromethylphthalide of melting point 176.5°-178.0°. (C)

The procedure followed here was identical to that in part I, except, of course, for the length of time the condensation was continued. The 5-methoxy-3-methylphthalide (II) was recovered as before. In this case, however, the two chloromethylphthalides isolated from the yellowish precipitate were the 133.5 - 135.5° (A) and the 176.5 - 178.0° (C) isomers, with no evidence of the 152.5 - 154.0° (B) compound. The two isomers (A) and (C) were separated with boiling ethyl alcohol as outlined previously (I b ).

Analysis on (C)

Calculated for $C_{11}H_{11}O_3Cl$:

C, 58.28%; H, 4.86%; Cl, 15.66%

Found: C, 58.39%; H, 5.07%; Cl, 15.64%

## III Condensation Time of 90 minutes to 270 minutes

### a) Isolation of the chloromethylphthalide of melting point 178.0° - 179.5° (D)

When the condensation time was continued for approximately one and a half hours or longer, a light brown precipitate began to settle out. The solution was filtered immediately after the flask was removed from the hot water bath, and the filtrate placed in the refrigerator. The collected precipitate was washed with water, then crystallized from glacial acetic acid. A little charcoal was added in order to remove color impurities from this product. The resulting white crystals were then extracted with boiling ethyl alcohol (95%). The residue, or insoluble material was crystallized from glacial acetic acid to produce the chloromethylphthalide (D).

Analysis

Calculated for $C_{11}H_{11}O_3Cl$:

C, 58.28%; H, 4.86%; Cl, 15.66%

Found: C, 58.45%; H, 4.92%; Cl, 15.34%

### b) Insolation of the chloromethylphthalide (C)

The soluble material from the hot alcoholic extraction mentioned above was allowed to cool in an ice bath. The resulting precipitate was removed by filtration and washed with water. Crystallization from glacial acetic acid produced the chloromethylphthalide (C).

The filtrate from III (a), which had previously been put into the refrigerator for cooling, contained a thick light brown precipitate. This material was collected, washed with water and allowed to dry. When this precipitate was extracted with boiling ethyl alcohol, a small residue remained on the filter paper. This proved to be more of the chloromethylphthalide (D).

### c) Isolation of the chloromethylphthalide of melting point 133.5° - 135.5°

A little charcoal was added to the hot ethyl alcohol filtrate from the above extraction to remove color impurities. On cooling, the resulting white crystals were collected. By the fractional crystallization method outlined in I (b), one obtains the two chloromethylphthalides (A) and (C).

## IV Condensation time of 6 hours

Only one run was carried out for this length of time, and only the chloromethylphthalide (D) could be isolated.

During the 6 hour heating period, excess formaldehyde (0.8 ml.) and hydrochloric acid (1.5 ml.) was twice added to replace any of these materials which were boiled away.

After refluxing for approximately 1½ hours, some solid material began to settle out. After 5½ hours a large quantity had collected. A thick brown precipitate formed when the flask was cooled. The solution was filtered, and the material so obtained was washed with water, then crystallized from glacial acetic acid with a little charcoal. The final product melting at 178.0 - 179.5° was obtained.

## General Notes on the Yields and Properties of These Five Products Obtained During These Condensation Reactions.

### The simple phthalide (II) of melting point 105 - 106°

The yields of this material seemed to decrease the longer the condensation was carried on, until finally, there was no evidence of it in the 6 hour run. A typical yield from 4 grams of starting material after 2 minutes heating period was 0.9 grams

### A) The chloromethylphthalide of melting point 133.5 - 135.5°

This material seemed to be formed in approximately the same yields up to about the 2 hour heating period. Once the phthalide of melting point 178.0 - 179.5° began to form, less of the isomer could be isolated. A typical yield from a 4 gram starting sample would be 1.1 grams for a 90 minute run.

### B) The chloromethylphthalide of melting point 152.5 - 154.0°

As indicated previously, this material was only isolated when the condensation period was continued for 2 minutes or less. The average yield from 4 grams of starting material was approximately 0.6 grams.

### C) The chloromethylphthalide of melting point 176.5 - 178.0°

The yields of this product were quite good when condensation was stopped just before the appearance of the 178.0 - 179.5° isomer. Average yields would be 1.5 grams from a 4 gram sample of starting material. The yield would decrease slightly with the appearance of this above mentioned isomer.

### D) The chloromethylphthalide of melting point 178.0 - 179.5°

Obviously the yields here are proportional to the length of condensation time. For example, a 5 hour heating period would produce approximately 2.1 grams from 4 grams of starting material.

Infra red spectra were obtained for the four chloromethylphthalides A,B,C and D. These were taken on a Perkin - Elmer model 21 spectrophotometer and are reproduced on pages 19 and 20.

sample cell size - 0.5 mm.
reference cell size ($CCl_4$)- 0.5 mm.

Saturated solutions of the 4 phthalides were prepared by dissolving these compounds in hot carbon tetrachloride, and then allowing the solutions to cool to room temperature. Excess material was filtered off and a small amount of carbon tetrachloride was then added to each of the clear filtrates.

The chloromethylphthalides C and D proved to be only slightly soluble in carbon tetrachloride so that very concentrated solutions could not be obtained. For this reason, these two spectra were not as clear as those for A and B. However, the four curves do show distinct differences.

Some differences to be noted between the spectra of compounds A and B are:

1. double peak in A (9.16 $\mu$ and 9.23 $\mu$), single peak in B (9.23 $\mu$)
2. double peak in A (10.56 $\mu$ and 10.66 $\mu$), single peak in B (10.56 $\mu$)

3. small peak at B (8.55 $\mu$), not present in A.

Prominent difference between the spectra of compounds C and D is the peak in C (8.26 $\mu$), not present in D.

### Preparation of 5-methoxy-3-methylphthalide by the Fritsch method (7)

The method followed here was essentially that of Meldrum (11).

### 1. 5-methoxy-3-methyl-α-trichloromethylphthalide (XXII)

5-methoxy-3-methylbenzoic acid (5 gm.), chloral hydrate (5 gm.), and sulphuric acid (25 ml.,95.5%) were mixed together forming a very dark solution. This was allowed to stand for 48 hours. Much heat was evolved when water (50 ml.) was added. On cooling in the refrigerator a further 36 hours, a gummy substance formed in the solution. This crude material was collected and washed with 50% alcohol. Crystallization from methyl alcohol with a little charcoal produced white crystals (4.4 gm.) melting at 114.5 - 116.0°. Concentration of the filtrate gave a second yield (0.5 gm.).

### 2. 5-methoxy-3-methyl-α-carboxyphthalide

5-methoxy-3-methyl-α-trichloromethylphthalide (4.8 gm.) and ethyl alcohol (5 gm.,95%) was heated until the alcohol began to boil. Much heat was evolved when aqueous sodium hydroxide (25 ml.,15%) was added, giving a dark violet coloration. The solution was kept at 50 - 60° where a red precipitate began to form. After one hour, the precipitate began to form, was collected and crystallized from water with a little charcoal to remove color impurities. The aqueous solution was acidified with dilute hydrochloric acid, giving a yellow oil, and put in the refrigerator over night. Fluffy white crystals then formed. These were collected and crystallized from acetic acid yielding white crystals (0.3 gm.) melting at 168 - 170°.

### 3. 5-methoxy-3-methylphthalide (II)

5-methoxy-3-methyl-α-carboxyphthalide (0.21 gm.) and naphthalene (0.7 gm.) were heated in an oil bath at 180 - 190° until the evolution of carbon dioxide closed. The residue was distilled in a current of steam for 10 minutes in order to remove naphthalene. The solution was cooled in an ice bath forming a heavy white precipitate. This precipitate was collected and crystallized from water and a little charcoal to yield crystals melting at 104.5 - 105.5°.

A mixed melting point determination between this material and the 5-methoxy-3-methylphthalide obtained from I (a), showed no depression in melting point.

### Methylation of 2,5-dimethylphenol; 2,3-dimethylphenol and 3,4-dimethylphenol

The method of methylation outlined here was applicable to the three phenols listed above.

The dimethylphenol (20 gm.) was dissolved in hot sodium hydroxide solution (200 ml, 5%) in a three neck flask fitted with a stirrer. After the solution was allowed to cool slightly, dimethyl sulphate was added over a period of 15 minutes in an atmosphere of nitrogen. The reaction mixture was stirred ½ hour longer. Two layers formed, a light brown oil on top, with a milky aqueous solution on the bottom. The oil was separated, dried over anhydrous $CaSO_4$, and distilled. Yields approximately 75 - 85% based on starting material.

| | Boiling points | Beilstein values |
|---|---|---|
| Methyl ether of 2,5-dimethylphenol (XXX) | 191° | 194° |
| Methyl ether of 2,3-dimethylphenol (XXXII) or (XXXI) | 198° | 199° |
| Methyl ether of 3,4-dimethylphenol (XXXIII) | 203° | 204° |

Infra red spectra were obtained for the three methyl ethers of the phenols prepared above. These curves are reproduced on pages 41, 42 and 43.

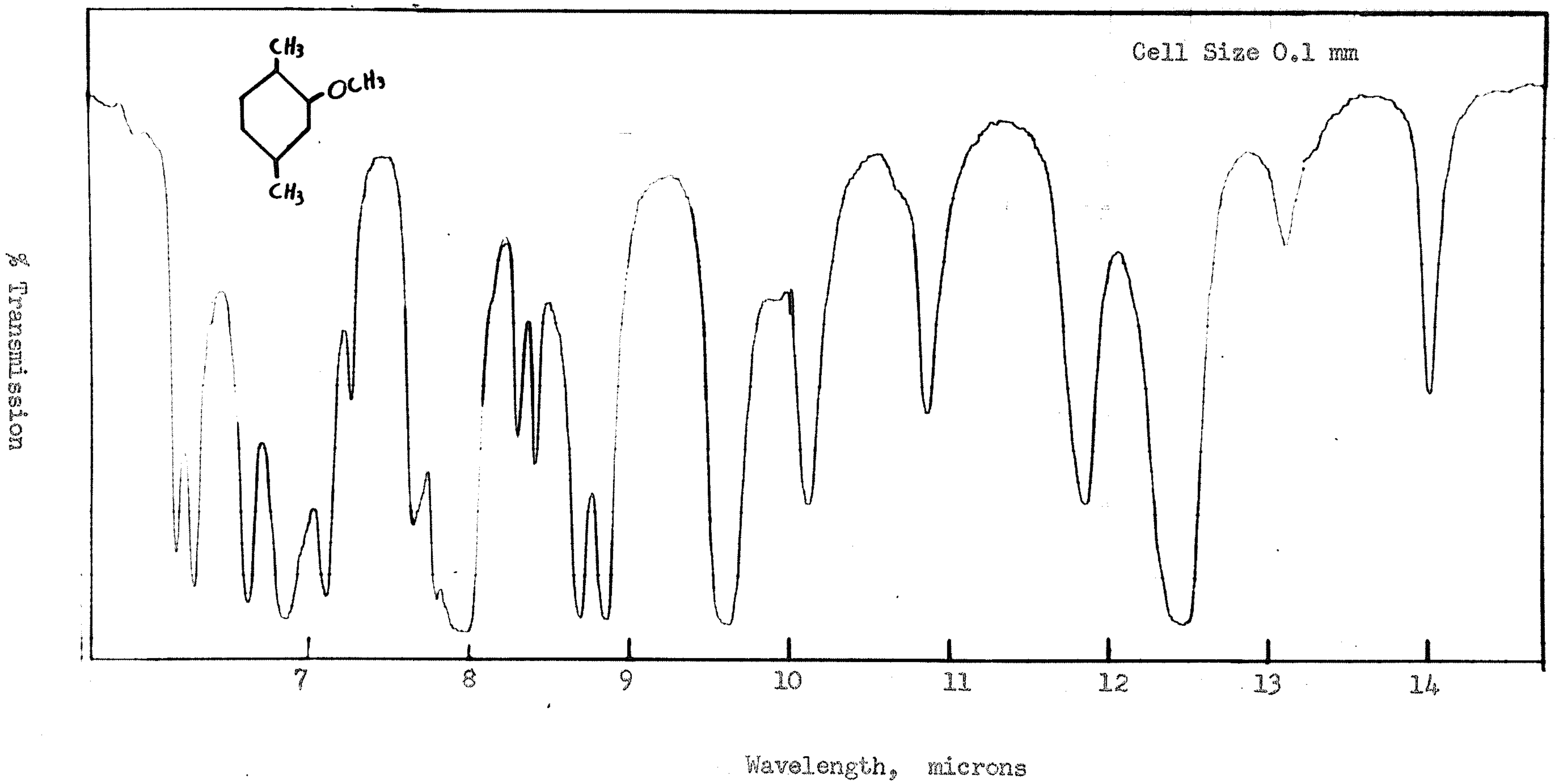
## Preparation of the Methoxyxylene from the chloromethylphthalide of melting point 178.0 - 179.5°

### 1. Preparation of dimethylmethoxyphthalide

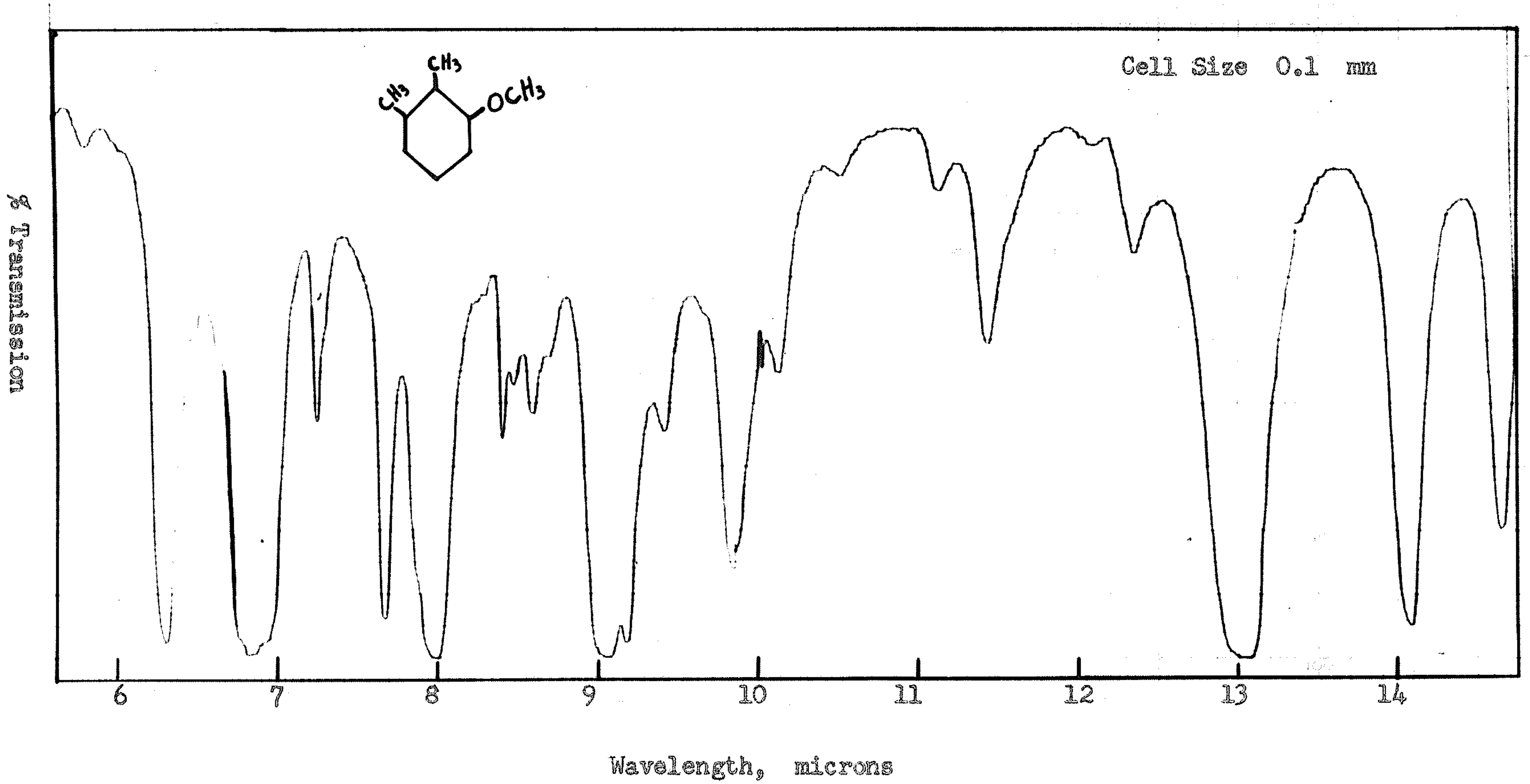
Chloromethylphthalide (3.5 gm.) of melting point 178.0 - 179.5°, zinc dust (3.7 gm.), concentrated hydrochloric acid (10 m.) and absolute alcohol (75 ml.) were refluxed over night. Excess hydrochloric acid was added until virtually all the zinc had dissolved. The solution was allowed to cool, and a thick white precipitate formed on the addition of cold water (75 ml.). This mixture was set in the refrigerator for a few hours, after which time the white crystals (3.0 gm.) were separated, washed well with water and allowed to dry. Melting point of this product was 166.0 - 167.5°.

Sodium fusion on this material gave a negative test for chlorine.

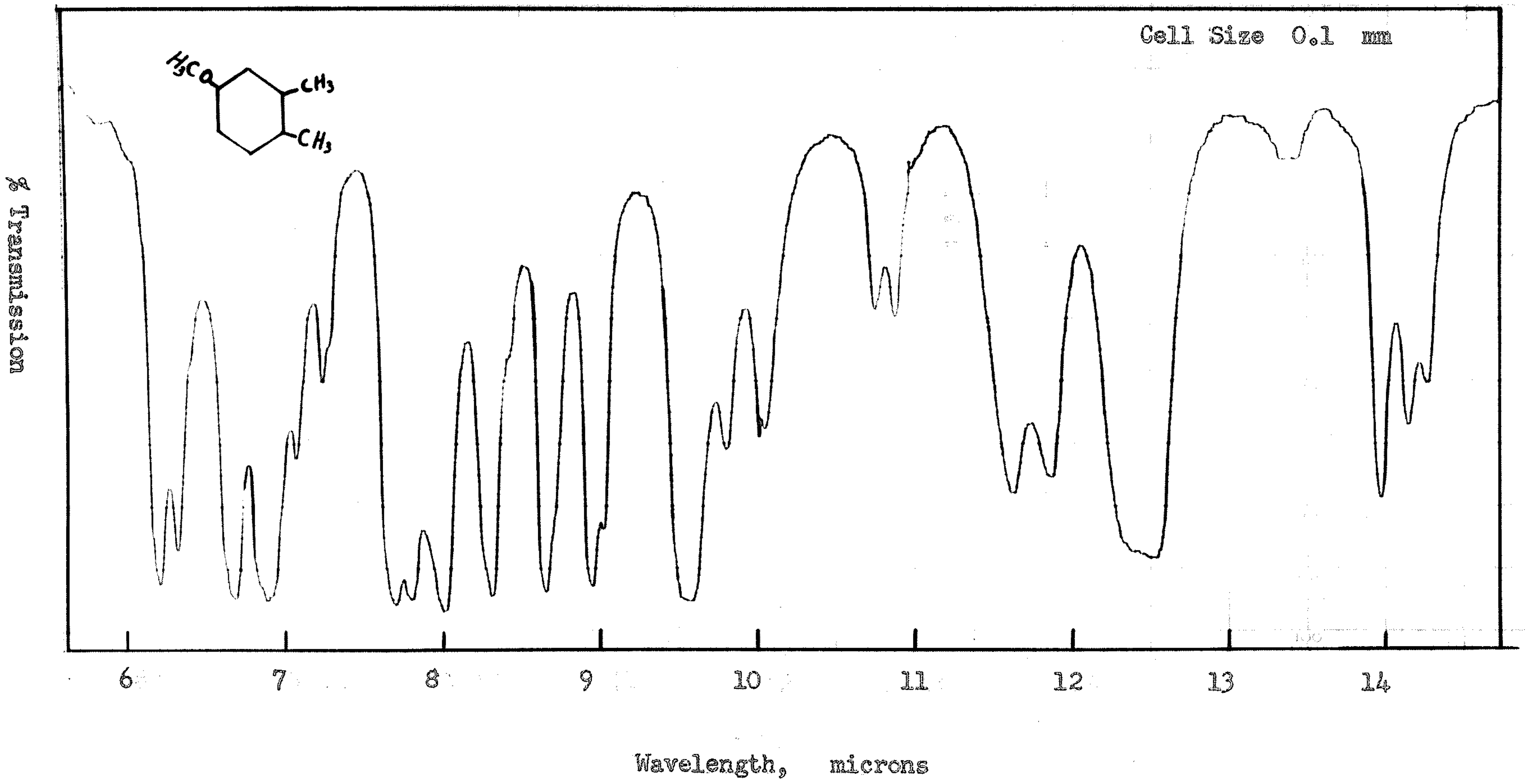
## Infra Red Spectrum Of The Methyl Ether Of 2,5-Dimethyl Phenol



## Infra Red Spectrum Of The Methyl Ether Of 2,3- Dimethyl Phenol



Infra Red Spectrum Of The Methyl Ether Of
3,4- Dimethyl Phenol



### 2. Formation of the dimethylmethoxydicarboxylic acid

Dimethylmethoxyphthalide (3.0 gm.) from above, was dissolved in potassium hydroxide solution (100 ml., 6N) by heating with frequent stirring. After cooling, finely powdered potassium permanganate (3.8 gm.) was slowly added over a ten minute period. The dark solution was allowed to stand for 36 hours at room temperature. Brown manganese dioxide was filtered off leaving a green filtrate. On acidification with dilute sulphuric acid, a white precipitate was formed. This product (2.1 gm.) was collected, washed with water, and allowed to dry.

Analysis

Calculated for $C_{11}H_{12}O_5$: C, 58.7%; H, 5.36%
Found: C, 58.4% H, 5.41%

Crystallization on this material could not be carried out, as all the acid converts to the anhydride with even a small amount of warming. There was much effervescence when some material above was added to sodium bicarbonate solution.

### 3. Decarboxylation of dimethylmethoxydicarboxylic acid

All attempts to decarboxylate this dicarboxylic acid with copper chromite in quinoline failed, the final product formed always being the anhydride.

Dimethylmethoxydicarboxylic acid (1.9 gm.), quinoline (30 ml.) and copper chromite (0.02 gm.) were mixed together and put in an oil bath at 185 - 200° for ½ hour with occasional stirring. The solution was filtered hot to remove some copper chromite and allowed to cool over night. When dilute hydrochloric acid was added however, a thick white precipitate formed. This was collected, crystallized from 50% acetic acid with a little charcoal giving white crystals melting at 183°-184°. This material did not effervesce in sodium bicarbonate solution and was the anhydride.

Analysis

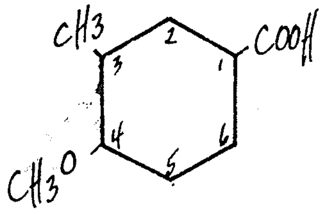
Calculated for $C_{11}H_{10}O_4$: C, 64.08%; H, 4.85%
Found: C, 63.89%; H, 5.10%

When more drastic heating conditions were attempted, the only material isolated was still the anhydride. This was done by fitting the flask with a condenser and taking the oil bath to 280 - 290° for 3 hours.

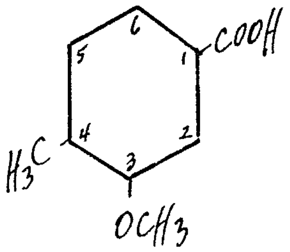
# APPENDIX

## Numbering of rings and nomenclature

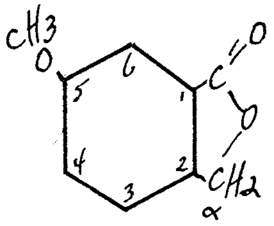
In order to avoid confusion in the systematic naming of the compounds referred to in this paper, the following system has been adopted.



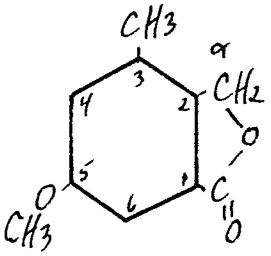
(a)



(b)



(c)



(d)

In designating the aromatic acid derivatives, the carbon atoms are numbered in such a way as to give the lowest numbers to the different substituents on the benzene nucleus, starting from the carbon to which the carboxyl group is attached, as in 3-methyl-4-methoxybenzoic acid (a) and 3-methoxy-4-methylbenzoic acid (b).

In naming phthalides, the system indicated by (c) and (d) is followed. ie. 5-methoxyphthalide as shown for (c) and 3-methyl-5-methoxyphthalide for (d).

## Summary

1. The configuration of the simple phthalide isolated from the formaldehyde condensation reaction was definitely established as 5-methoxy-3-methylphthalide.

2. The formation of all four chloromethylphthalides produced from the formaldehyde condensation reaction, was realized by varying experimental conditions.

3. Three previously unreported chloromethylphthalides have been presented. Their melting points were 133.5 - 135.5$^{0}$, 152.5 - 154.0$^{0}$ and 178.0 - 179.5$^{0}$ (or 176.5 - 178.0$^{0}$).

4. Infra red absorption spectra have definitely shown that four chloromethylphthalides were produced from the formaldehyde condensation reaction.

5. The infra red absorption spectra for the methyl ethers of the three phenols, 2,5-dimethylphenol; 2,3-dimethylphenol and 3,4-dimethylphenol were determined.

6. Tests made with ferric chloride solution on many different phenolic acids would indicate that only when a carboxyl and a hydroxyl group are ortho to one another, a vivid color change is produced.

7. The appearance of the four chloromethylphthalides and only one simple phthalide can be explained by a study of the effects the substituents on the benzene nucleus have on the re-

action products. A summary of these effects were first presented by Anderson (1) and substantiated in most cases, by later workers.

## Recommendations for Future Work

1. A substantial amount of the simple phthalide (II) and (III) should be prepared by the Fritsch (7) synthesis. These simple phthalides could in turn, be treated with formaldehyde and hydrochloride acid to yield the four chloromethyl derivatives. That is, two chloromethyl derivatives should be produced from each simple phthalide. As the configuration of the two simple phthalides are known, one could then associate the melting points of two chloromethyl isomers with each phthalide.

2. Examination of the four chloromethylphthalides (IV), (V), (VI) and (VII)(see page 2) by the method of Nuclear Magnetic Resonance should distinguish the chloromethylphthalide (V) from the others. This is possible because it is the only chloromethyl isomer of the four which does not have a nuclear proton ortho to a methyl group. It might also be possible to distinguish compound (VII) from (IV) and (VI), because in this case, the nuclear proton is between a methyl group and the carboxyl group of the lactone ring. In the isomers (IV) and (VI), we have this proton between a methyl and a methoxyl group.

3. An attempt should be made to produce $\beta$ -coccinic acid (XXVII) by demethylation of the methyl ether (XXIV) with anhydrous aluminum chloride in benzene, as outlined by Radych (M.Sc. thesis, Manitoba, 1951, page 52). Treatment by Meldrum (11) by the usual way with hydriodic acid proved unsatisfactory.

4. A good method must be found for the decarboxylation of the dimethylmethoxydicarboxylic acids.

5. Infra red spectra of the simple phthalides (II) and (III) would be desirable and should prove informative.

# BIBLIOGRAPHY

1. Anderson, H.J., *M.Sc. Thesis*, Manitoba, 1949.
2. Buehler, C.A., Powers, T.A., and Michels, J.G., *J. Am. Chem. Soc.*, 66: 417-418, 1944.
3. Buehler, C.A., Harris, J.O., Shacklett, C., and Block, B.P., *J. Am. Chem. Soc.* 68: 574-577, 1946.
4. Charlesworth, E.H., and Robinson, R., *J. Chem. Soc.*, 1531-1533, 1934.
5. Charlesworth, E.H., Rennie, R.P., Sinder, J.E., and Yan, M.M., *Can. J. Research* B,23: 17, 1945.
6. Cohen, *Practical Organic Chemistry*, MacMillan and Co., London, 1930. p.191-193.
7. Fritsch, P., *Ann* 301: 352-361, 1898.
8. Holmes, H.L., and Trevoy, L.W., *Can. J. Research* B,22: 118, 1944.
9. King, F.E., and King, T.J., *J. Chem. Soc.* 726-727, 1942.
10. Meldrum, A.N., and Perkin, W.H., *J. Chem. Soc.* 95: 1891, 1909.
11. Meldrum, A.N., *J. Chem. Soc.* 1712, 1911.
12. *Organic Syntheses*, Vol. VI, John Wiley and Sons, Inc., New York, 1926. p.40.
13. Perkin, W.H., Edwards, G.H., and Stoyle, F.W., *J. Chem. Soc.* 127: 195-199, 1925.
14. Raistrick, H., Robinson, R., and Todd, A.R., *J. Chem. Soc.* 488-489, 1933.
15. Rây, J.N., and Robinson, R., *J.Chem. Soc.* 127: 1618-1623, 1925.
16. Sinder, J.E., *M.Sc. Thesis*, Manitoba, 1943.
17. Stephen, H., Short, W.F., and Gladding, G., *J. Chem. Soc.* 117: 510-527, 1920.
18. Tambor, *Ber.* 43: 1882-1889, 1910.
19. Yan, M.M., *M.Sc. Thesis*, Manitoba, 1942