PHTHALIDE STUDIES, INCLUDING THE ORIENTATION OF PHTHALIDES FORMED FROM 5-METHOXY-3-METHYLBENZOIC ACID

by

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The author is sincerely appreciative for the kind and excellent guidance afforded by Dr. E. H. Charlesworth during this research project; and also to the National Research Council for grants which made the continuance of this work possible.

ABSTRACT

It was observed in this investigation that when 5-methoxy-3-methylbenzoic acid was heated with formaldehyde and hydrochloric acid under various heating conditions, one simple and three chloromethylphthalides were produced. The orientation of all four of these products was determined. Their infra red absorption spectra are also included.

A systematic study was undertaken to determine the influence of nuclear substituent groups on the course of the reaction of aromatic acids in the Edwards, Perkin and Stoyle condensation. In this way, a plausible explanation for the occurence of the products obtained above was possible.

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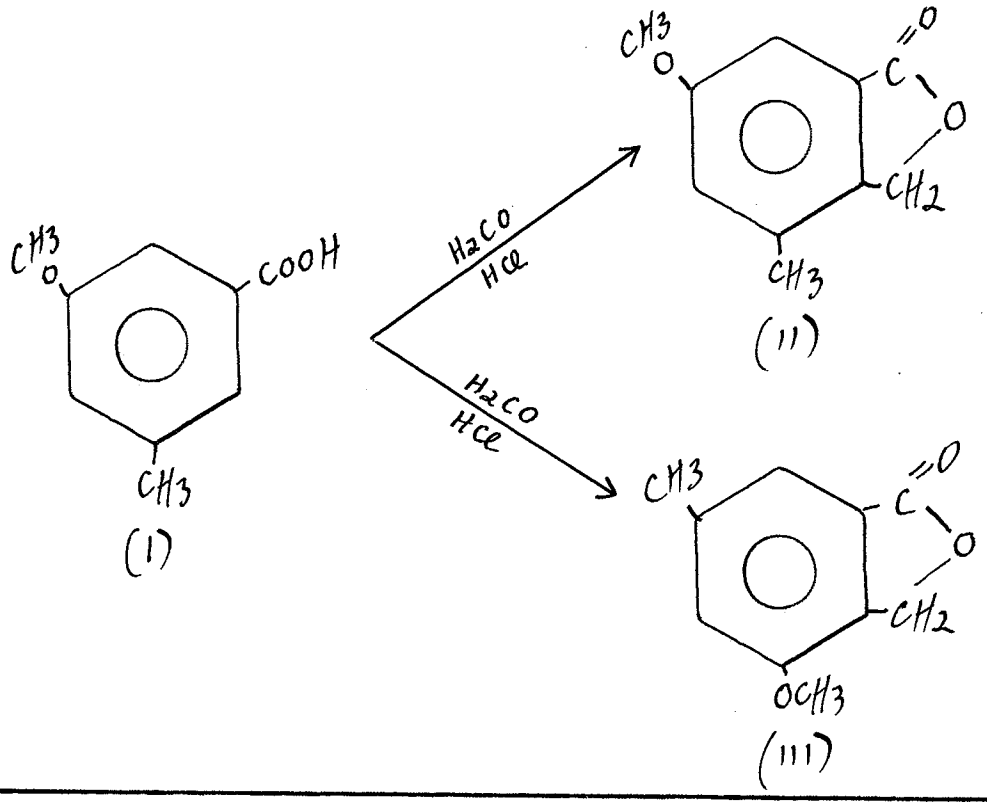
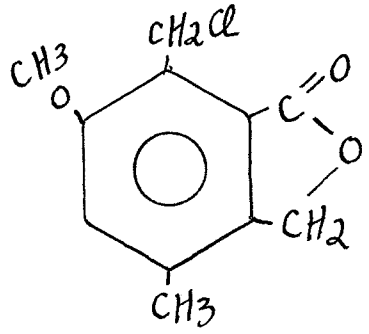
INTRODUCTION

In 1945, Charlesworth, Yan, et al. (18) isolated two products when 5-methoxy-3-methylbenzoic acid (1)* was heated with concentrated hydrochloric acid, formaldehyde (37%), and glacial acetic acid. The first was thought to be 3-methoxy-5-methylphthalide (111) and the second, a chloromethyl derivative of this simple phthalide. Ring closure may take place in one of two ways for phthalide formation, thus forming compound (11) and (111).

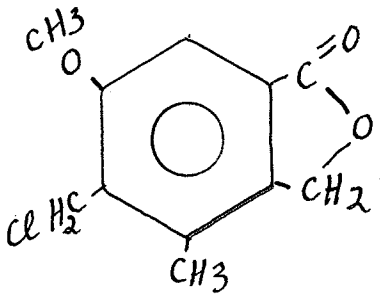


* For nomenclature and numbering of ring structures employed in this thesis, see appendix, page 138.

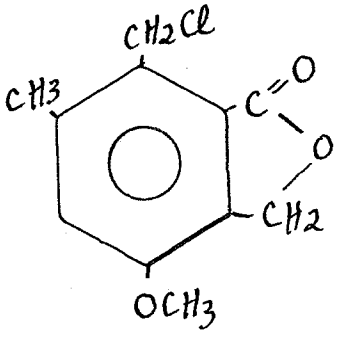
In each of these simple phthalides there are two positions that can be occupied by the second entering chloromethyl group. Thus a total of four different chloromethylphthalides, (1V), (V), (V1) and (V11) are theoretically possible.



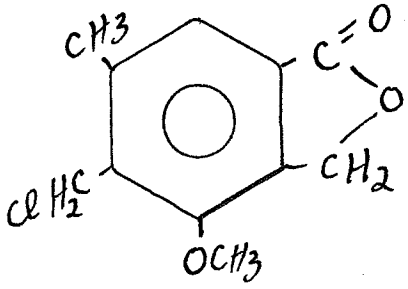
(1V)



(V)



(V1)



(V11)

On repeating this reaction, and by varying experimental conditions, we have been able to isolate not two, but four products. The first was the simple phthalide (11), and the others the three isomeric chloromethylphthalides (1V), (V1) and (V11). Apparently this is the maximum number of products which can be isolated from this reaction. To get a clearer

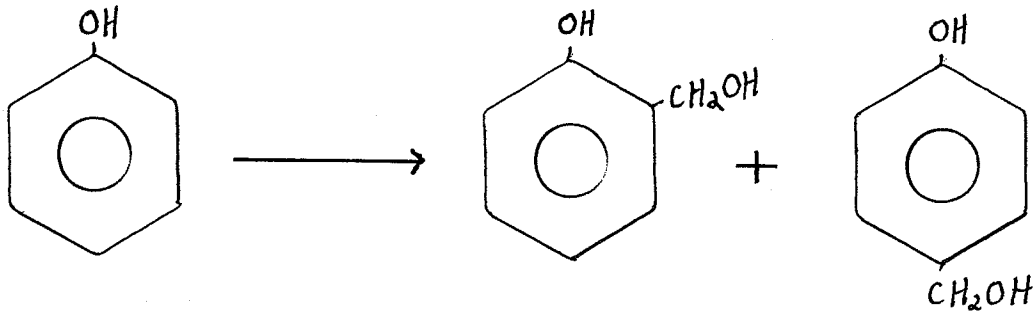
understanding as to why only four out of the possible six phthalides were produced, a careful study was made on how substituents in the benzene nucleus influence phthalide formation.

It appears that there are two fundamental conditions governing phthalide formation: first, the types of substituents already in the ring and second, their positions relative to a carboxyl group.

The present investigations were undertaken to determine the correct orientations, assumed above, for all four products isolated from the condensation of 5-methoxy-3-methylbenzoic acid with formaldehyde in acid solution.

LITERATURE SURVEY

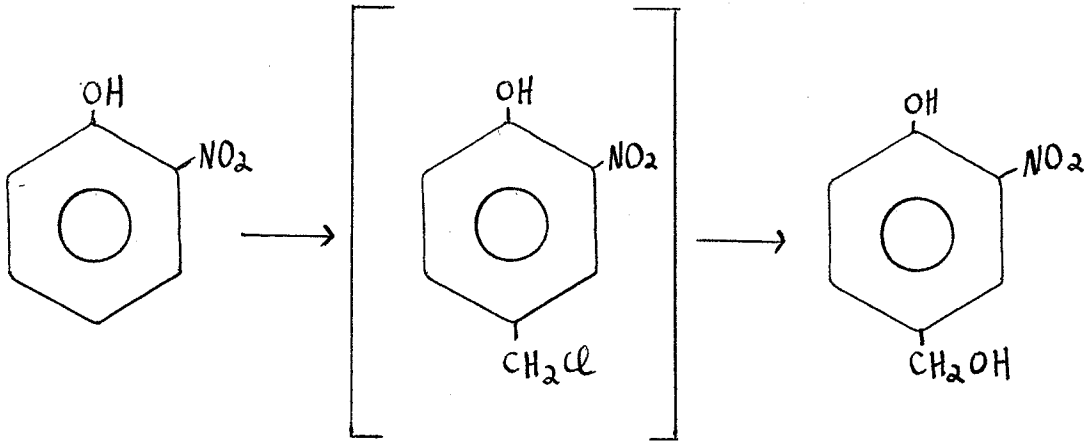
The action of formaldehyde on aromatic compounds has been studied by a number of investigators under a variety of experimental conditions and with varying results. Manasse (47) and Lederer (44) have shown that phenols and their ethers react with formaldehyde in the presence of cold aqueous alkali to yield the corresponding benzyl alcohols. For example, Manasse had prepared ortho and para hydroxybenzyl alcohols from phenol.



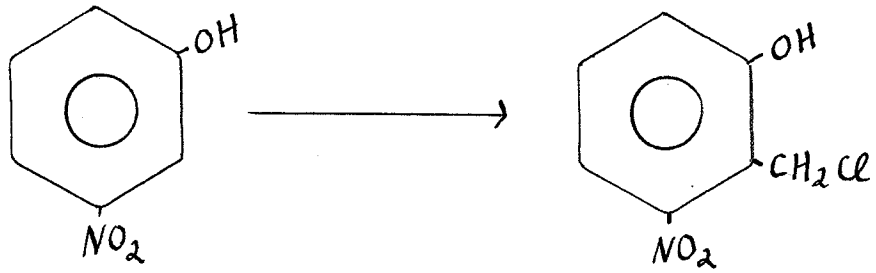
On the other hand phenols, phenolic ethers as well as the aromatic hydrocarbons and the halogen derivatives of these substances react with formaldehyde in acid solution to yield the corresponding chloromethyl derivative.

Stoermer and Behn (71) found that the action of formaldehyde solution in the presence of concentrated hydrochloric acid on certain aromatic compounds led to the synthesis of aromatic alcohols. These authors point out however, that the introduction of the chloromethyl group was probably the first stage in the reaction, with the subsequent formation

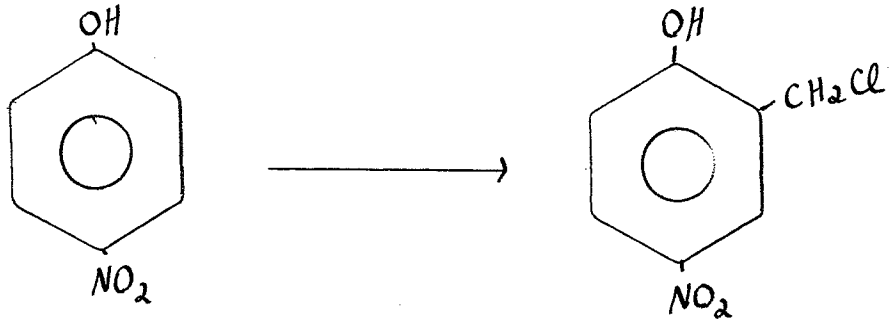
of the alcohol by hydrolysis. It was deduced from their experimental results that the presence of a negative group such as -CHO, $-NO_2$, and -Cl in the ortho position relative to the hydroxyl group of phenols, caused the latter to condense with formaldehyde in the presence of hydrochloric acid to form hydroxybenzyalcohols containing the methylol group in the para position with respect to the hydroxyl group. For example, o - nitrophenol gave 4-hydroxy-3-nitrobenzylalcohol.



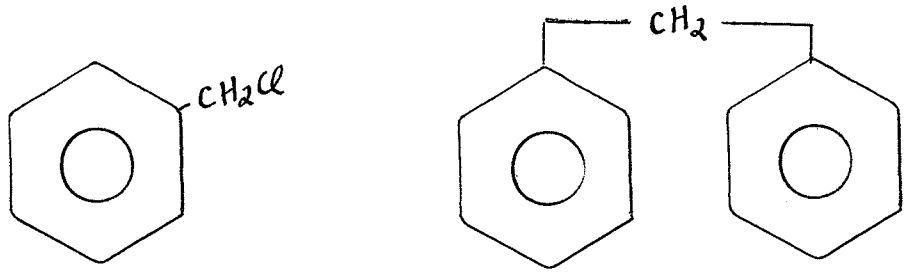
There are many references cited in the literature however, where the chloromethyl derivative is stable enough to be isolatable in good yields. Buehler, Deebel and Evans (10) produced 2-hydroxy-6-nitrobenzyl chloride by heating m-nitrophenol with formaldehyde and concentrated hydrochloric acid.



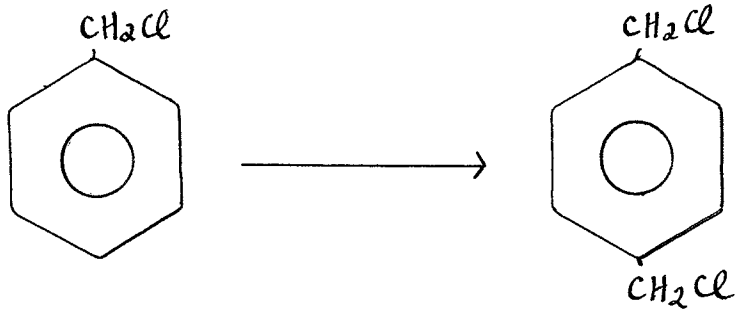
Buehler, Kirchner and Deebel, as reported in Organic Synthesis (54), isolated 2-hydroxy-5-nitrobenzyl chloride when p-nitrophenol is reacted with hydrogen chloride gas and formaldehyde.



Grassi-Cristaldi and Maselli (35) were the first to show that the product obtained by the action of hydrogen chloride on paraformaldehyde reacted with benzene in presence of aluminum chloride to yield benzyl chloride and diphenylmethane.



Under such conditions however, only traces of benzyl chloride could have been formed, since it would react very readily with unchanged benzene in the presence of aluminum chloride to form diphenylmethane. The introduction of a chloro- or bromo- methyl group into monosubstituted benzenoid compounds, such as toluene or chlorobenzene, appears to take place exclusively in the para position. No evidence was found of the corresponding ortho-derivatives in the products. Benzyl chloride similarily gave only ω, ω^1-dichloro-p-xylene.



The presence of a nitro group directs a chloromethyl group into the meta-position.

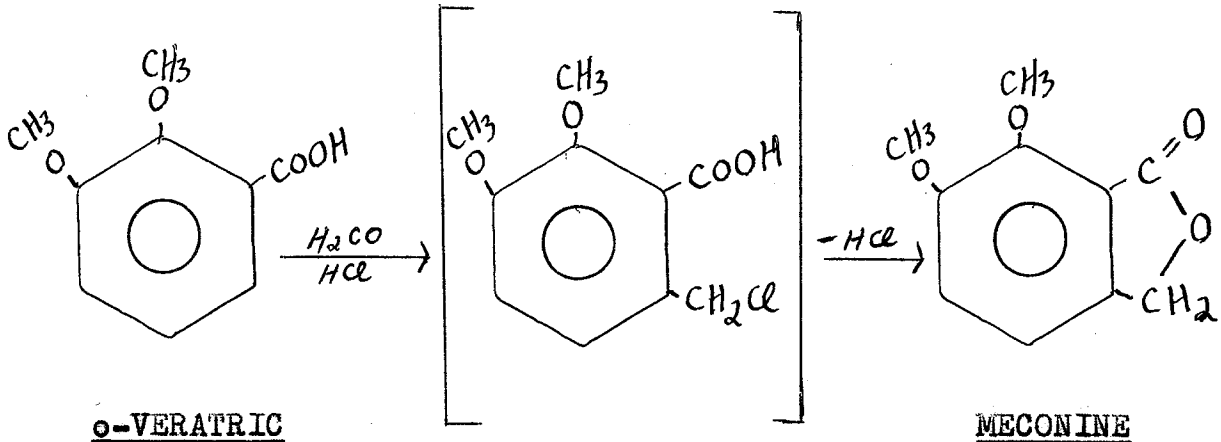
Stephen, Short and Gladding (70) did a systematic study on the preparation of chloromethyl derivatives of monosubstituted benzenoid compounds. These authors described the preparation of benzyl chloride and compounds related to it by the direct introduction of the chloromethyl group into the aromatic nucleus. This method consisted of treating an aromatic compound in the presence of a dehydrating agent such as anhydrous zinc chloride, with the product obtained by the action of hydrogen chloride on paraformaldehyde or aqueous solutions of formaldehyde. This product has been shown to consist of s-dichloromethyl ether (73), (46), (45).

From 1927 to 1940, R. Quelet (62) and his co-workers extended the work of Stephen, Short and Gladding by an extensive investigation of the introduction of the chloromethyl group into the aromatic nucleus. It is of interest to note here, however, that they failed to investigate the action of these reagents on any aromatic acids. In general these authors have found that a variety of condensing agents are available of the reaction. Such substances as anhydrous zinc chloride, zinc chloride monohydrate and petroleum ether were used. This work has been thoroughly summarized by Rennie (65).

The action of formaldehyde in acid solution on aromatic acids, however, had received little attention up to 1925. The reactions of several acids had been studied, some in connection with researches on other types of reaction and

some as the result of direct investigation. The acids thus studied were of the more complex type and the results obtained were often indefinite and, in some cases, the products isolated were not the substances normally desired from the reaction.

The first paper written on this subject in 1925, may be said to be that of Edwards, Perkin and Stoyle (24). These authors 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:



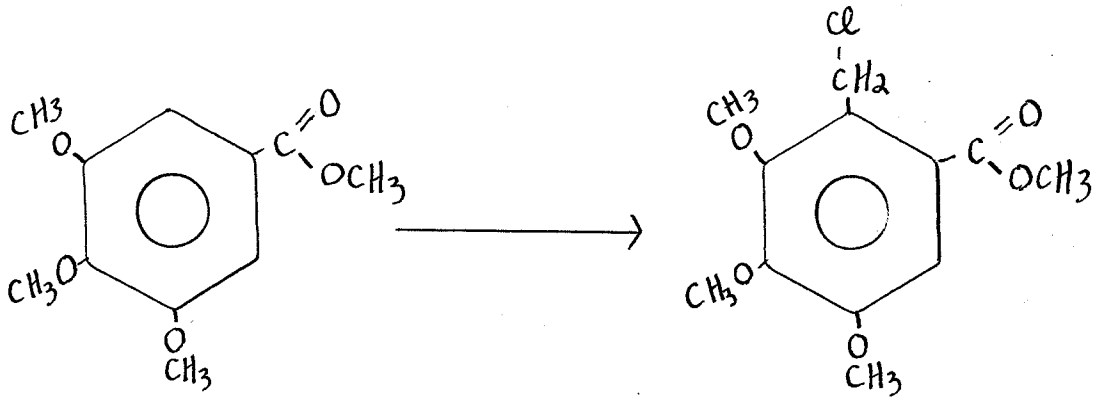
o-VERATRIC ACID

MECONINE A PHTHALIDE

Presumably, the chloromethyl group enters the benzene nucleus ortho to the carboxyl group. The intermediate, however is very unstable and apparently never isolated.

A very interesting paper by Haworth et al. (37) showed however, that a chloromethyl group entering the benzene nucleus ortho to a methylated carboxylic substituent

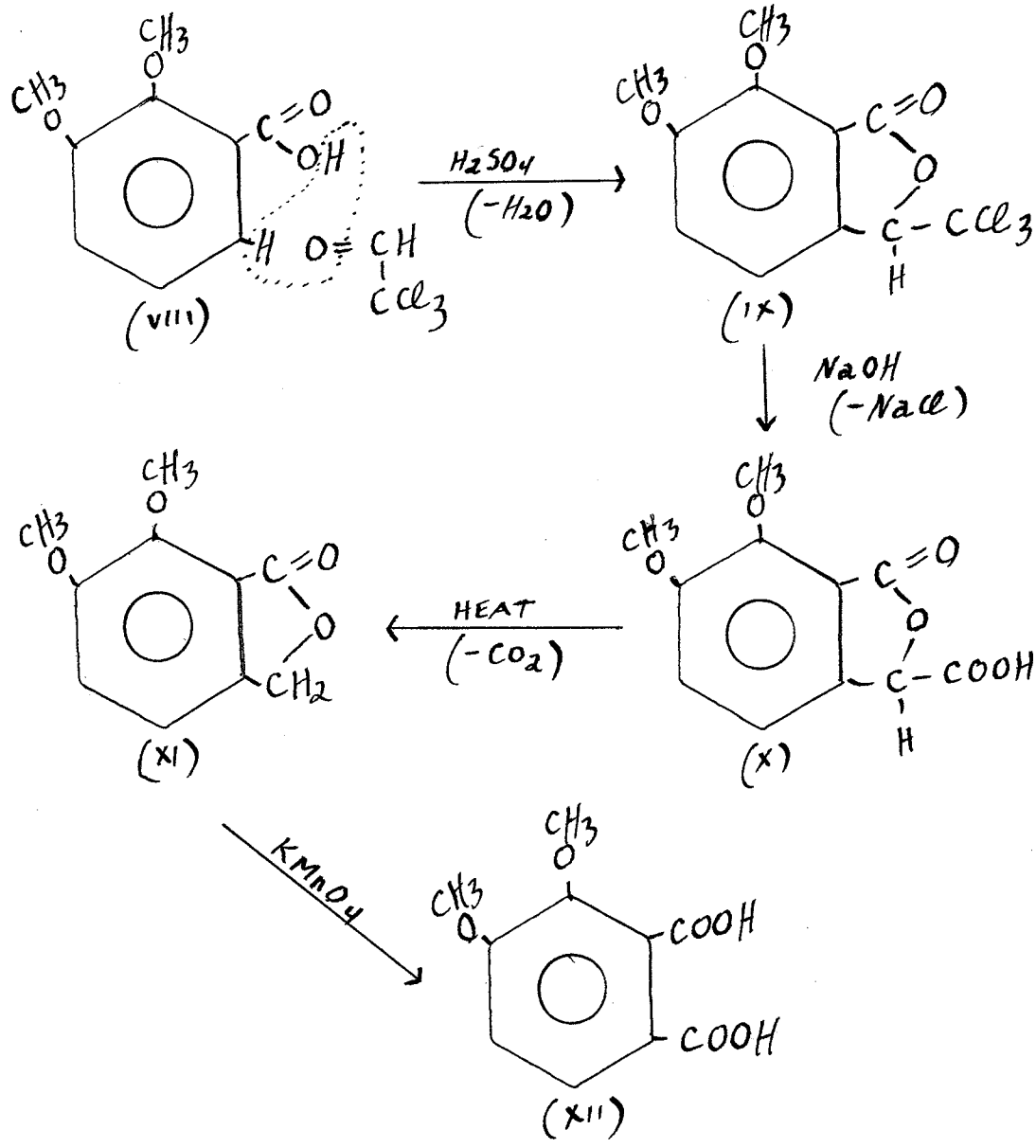
is quite stable. These authors reacted methyl-3,4,5-trimethoxybenzoate with hydrochloric acid and formaldehyde to produce the chloromethyl derivative of the above mentioned ester.



This lactone ring formation was indeed a significant observation, for up to this time the classical Fritsch method (26) was the only available practical method for obtaining phthalides from their parent acids. In this procedure the acid was condensed with chloral hydrate in 95% sulphuric acid. Thus, applying this reaction to o-veratric acid (Vlll), Fritsch obtained the corresponding trichloro-methyphthalide (lX). This was then decomposed with aqueous alkali to yield the carboxylic acid (X), which on decarboxylation gave the corresponding phthalide, meconine (Xl). Meconine, on permanganate oxidation produced the phthalic acid (Xll).

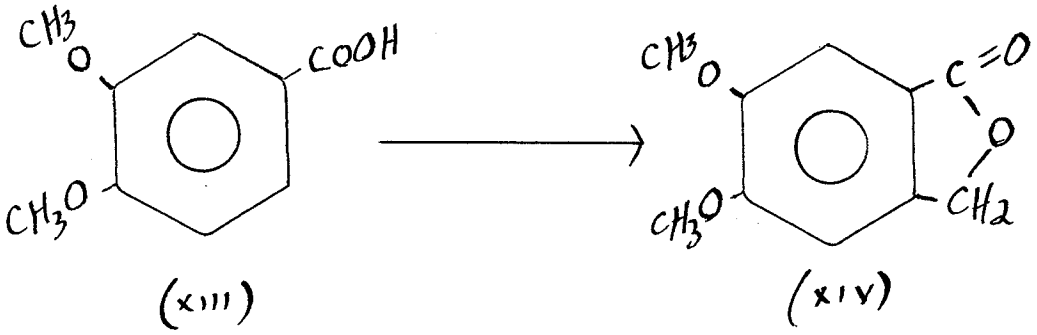
One can see immediately the practical value of the formaldehyde condensation, in the fact that only one step is involved to produce the required phthalide, while for the

Fritsch method, one must proceed through the much longer series as indicated below.



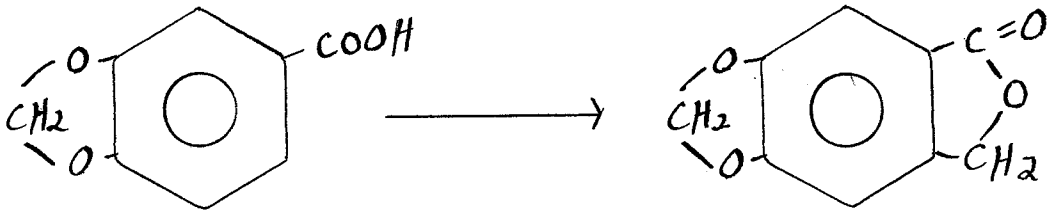
Edwards, Perkin and Stoyle extended their method to m-meconine (XIV), which had been first produced by Perkin (57) from the degradation products of cryptopine derivatives, by condensing veratric acid (XIII) with formaldehyde in

presence of concentrated hydrochloric acid.



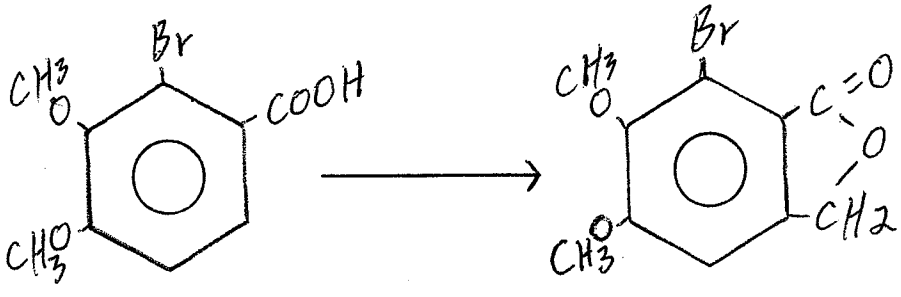
(XIII) (XIV)

These authors found that the veratric acids do not condense at all readily with either s-dichlorodimethyl ether or with cold aqueous formaldehyde in acid solution. They also mentioned that an unsuccessful attempt had been made to prepare the methylene ether of 4,5-dihydroxyphthalide by the action of formaldehyde on piperonylic acid according to the following reaction.



Even after long boiling, the reaction did not occur and only a small amount of material of high molecular weight was obtained.

Ray and Robinson (64) improved the yield of meconine from o-veratric acid (VIII) by adding glacial acetic acid to the reaction mixture. They were able to produce the phthalide of 3,4-dimethoxybenzoic acid using this modification.



However, it is important to note that not all substituted aromatic acids produce phthalides by this direct condensation method. Some typical results of heating aromatic acids with formaldehyde and concentrated hydrochloric acid are (1) no reaction, (2) simple phthalide formation, (3) chloromethylphthalide formation, (4) dimerization or resinification, (5) formation of a dioxane ring. We shall see that although this condensation represents a short cut to the phthalide in certain cases, it is not always applicable.

It is highly unlikely that chloromethylation results by direct reaction with the original reagents. Stephen, Short and Gladding (70), Quelet (62), Blanc (6) and others have shown that a chloromethyl group is introduced into the nucleus of the aromatic compound. Stephen, Short and Gladding suggested a mechanism involving certain intermediates

which they were able to isolate and subsequently showed them to be s-dichloromethyl ether and a small amount of monochloromethyl ether.

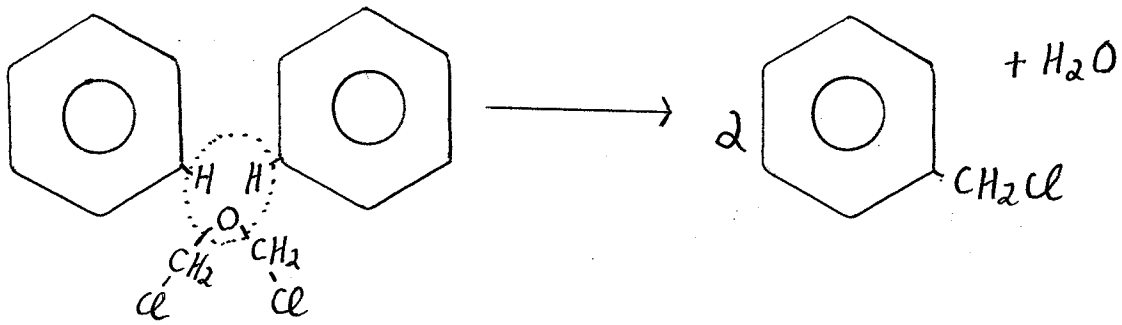
The formation of the s-dichloromethyl ether involves the reaction indicated below.

$$2HCHO + 2HCl \longrightarrow (CH_2Cl)_2O + H_2O$$

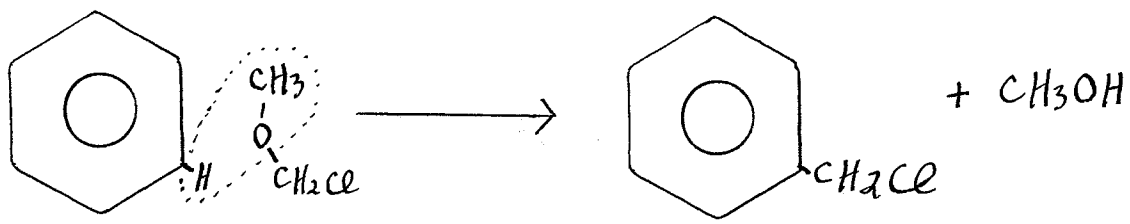
The production of the monochloromethyl ether is accounted for by the fact that commercial aqueous formaldehyde contains some methyl alcohol. The formation of this ether may, therefore, be indicated as follows.

$$CH_2O + CH_3OH + HCl \longrightarrow CH_3OCH_2Cl + H_2O$$

Stephen, Short and Gladding suggest that both these intermediates then react with the aromatic compound in the presence of a dehydrating agent to produce chloromethyl derivatives. For example, with s-dichloromethyl ether:-



The monochloromethyl ether may react directly as shown below



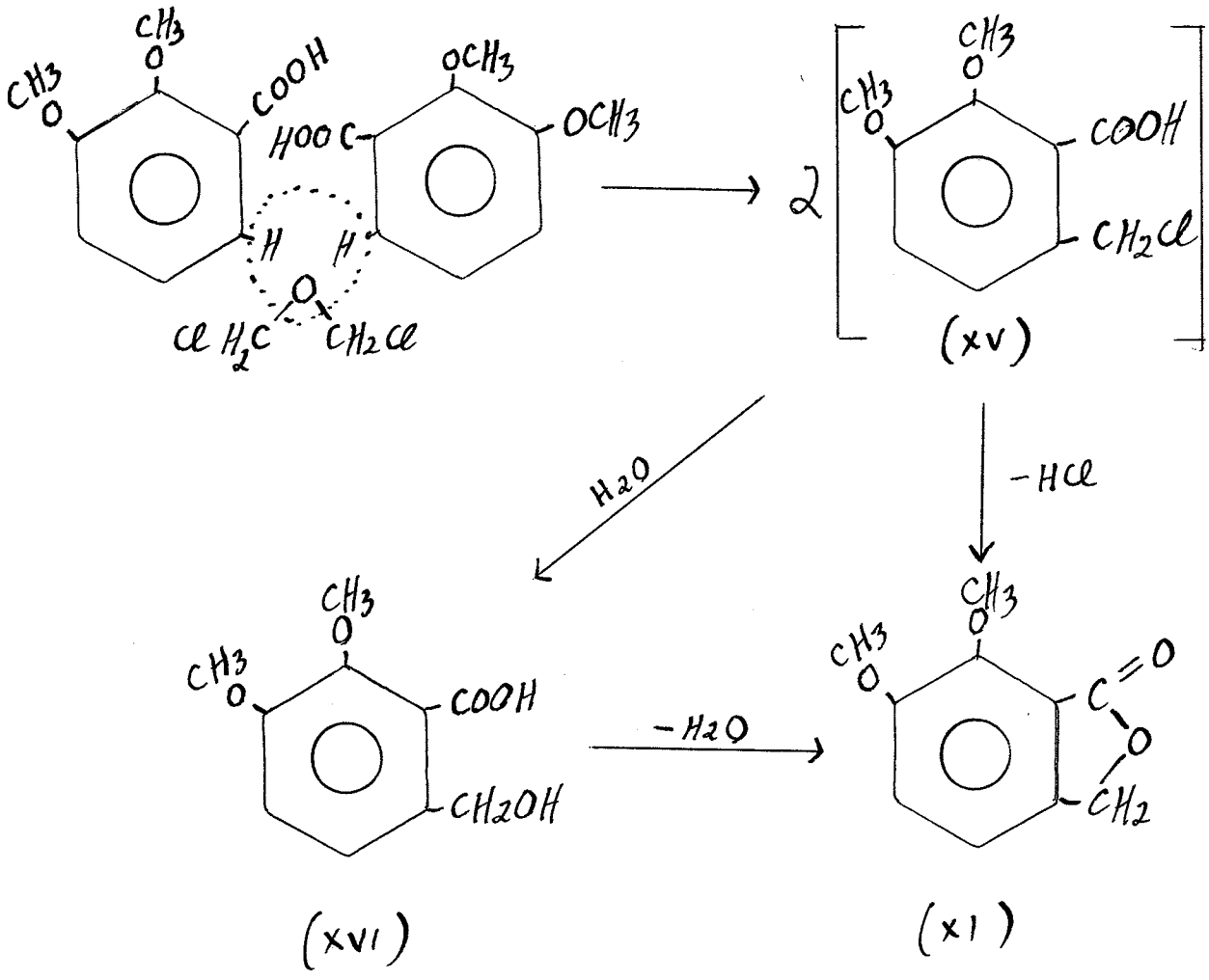
or this monochloromethyl ether is first converted to the s-dichloromethyl ether, which in turn produces benzyl chloride as before.

$$CH_3 \cdot O \cdot CH_2Cl + H_2O \longrightarrow CH_3OH + Cl \cdot CH_2OH$$

$$2Cl \cdot CH_2OH \longrightarrow (CH_2Cl)_2O + H_2O$$

Stephen, Short and Gladding produced samples of these two ethers and used them to prepare benzyl chloride, showing that the same product was formed in each case as by the usual condensation method. They have observed, however, that the reaction of s-dichloromethyl ether is much faster than that of the monochloromethyl ether and so it is unlikely the reaction involves a direct attack of $CH_3 \cdot O \cdot CH_2Cl$ on the aromatic compound as shown above, but rather proceeds as indicated in the subsequent choice.

On the basis of the above mechanism for the introduction of the chloromethyl group into the aromatic nucleus, Yan (76) Sinder (68) and Charlesworth et al.(18) showed how phthalide formation can take place in the reaction of an aromatic acid with hydrochloric acid and formaldehyde. The formaldehyde and hydrochloric acid first react to form s-dichloromethyl ether, which then introduces a chloromethyl group into the aromatic nucleus, thus producing the unstable intermediate (XV). For phthalide formation to occur, the chloromethyl group must of course be introduced ortho to the carboxyl group. For example, meconine was formed from o-veratric acid as done originally by Edwards, Perkin and Stoyle.

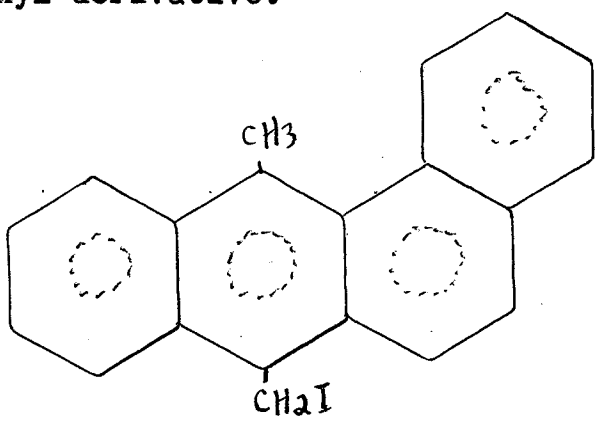


The final reaction to produce ring closure may take place in one of two ways. The chloromethyl group and the carboxyl group may lose hydrogen chloride directly to form phthalide (XI), or hydrolysis of the chloromethyl group may take place first to form the benzyl alcohol (XVI), the lactone ring then forming by a loss of water between the alcohol on the carboxyl groups.

Of the two possible routes shown above for phthalide formation, the direct loss of HCl is favoured. The reason is that the chloromethyl group, which is stable when it is not ortho to a carboxyl group, is only hydrolysed to the

alcohol (XVl) in alkaline solution, while these condensations are all done in acid solution where hydrolysis is difficult.

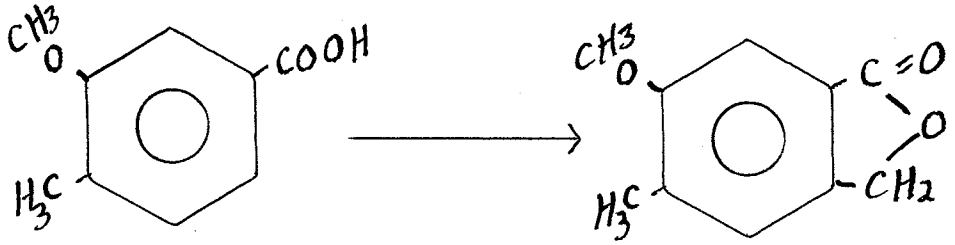
The hydrochloric acid employed in the Edwards, Perkin and Stoyle condensations may be replaced by either hydrobromic or hydriodic acids. Various workers have reported successful bromomethylations and iodomethylations of aromatic compounds by this reaction. Darzens and Levy (23) produced α-bromomethylnaphthalene; Stephen, Short and Gladding (70) reported the isolation of p-chlorobenzyl bromide; Sandin and Fieser (66) converted 9-methyl-1,2-benzanthracene to 9,10-dimethyl-1,2-benzanthracene through the iodomethyl derivative.



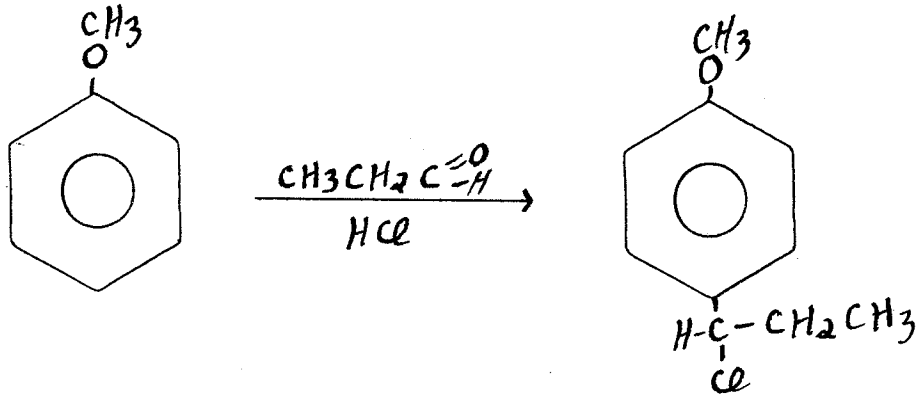
The use of hydrobromic and hydriodic acids has, however, thus far not been recorded in connection with condensations of aromatic acids.

Charlesworth et al. (18) succeeded in producing the phthalide m-meconine by heating veratric acid with formaldehyde and hydrobromic acid. The same product was isolated when hydriodic acid was substituted for hydrobromic acid. Similarily, 5-methoxy-4-methylphthalide was produced

from 3-methoxy-4-methylbenzoic acid when either hydrobromic or hydriodic acid was used in place of hydrochloric acid.



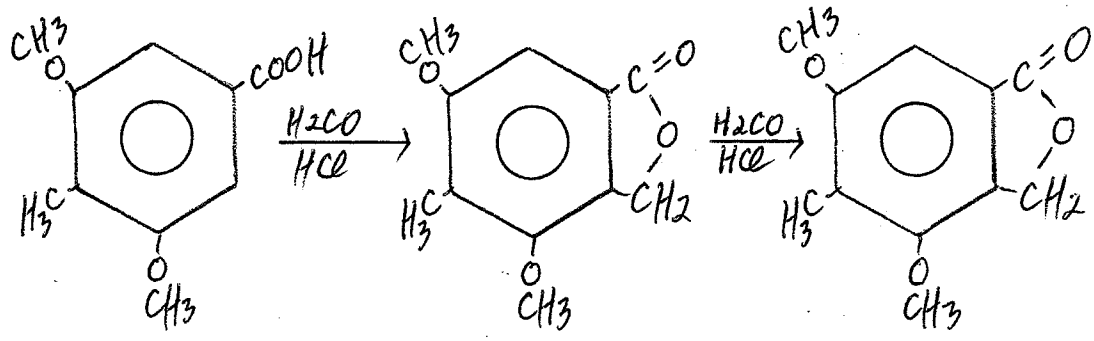
Quelet (62) has shown that other aliphatic aldehydes besides formaldehyde may be condensed with aromatic compounds in the presence of hydrogen chloride. Chloroalhylation occurs with the chlorine on the α-carbon with respect to the ring. Anisole with propionic aldehyde yields p-(α-chloropropyl) anisole.



Attempts by Charlesworth et al. (18) to extend this reaction to the formation of α-alkylated phthalides proved unsuccessful. Apparently polymerization of the aldehyde took place before condensation with the aromatic

acid could occur.

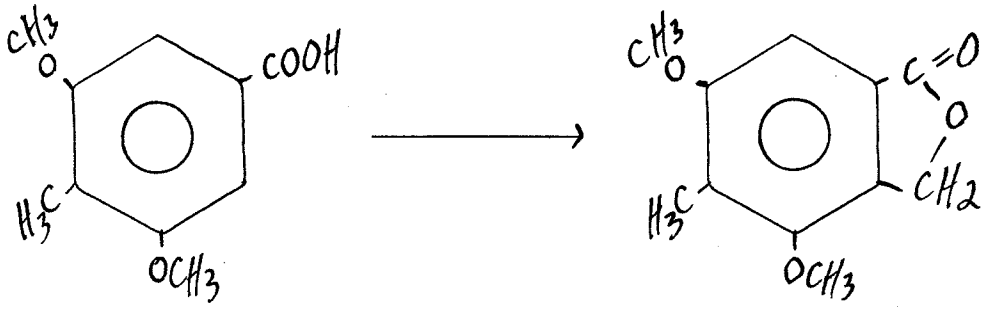
The formation of chloromethylphthalides is a possibility in these condensations.,This probably takes place as follows:-



In the course of an investigation involving the synthesis of Helminthosporin (4,5,6-trihydroxy-2-methyl-anthraquinone), Raistrich, Robinson and Todd (63) found it necessary to prepare a sample of 3-methoxy-5-methyl-phthalide from the corresponding 3-methoxy-m-toluic acid and they attempted to accomplish this by the method of Edwards, Perkin and Stoyle (24). This method did not yield the expected phthalide and the authors isolated an unidentified chloroproduct which was not referred to in their paper and did not appear to be the trichlorophthalide. (Private communication). The attempt was therefore abandoned and the required phthalide was obtained by the Fritsch (26) reaction with chloral hydrate.

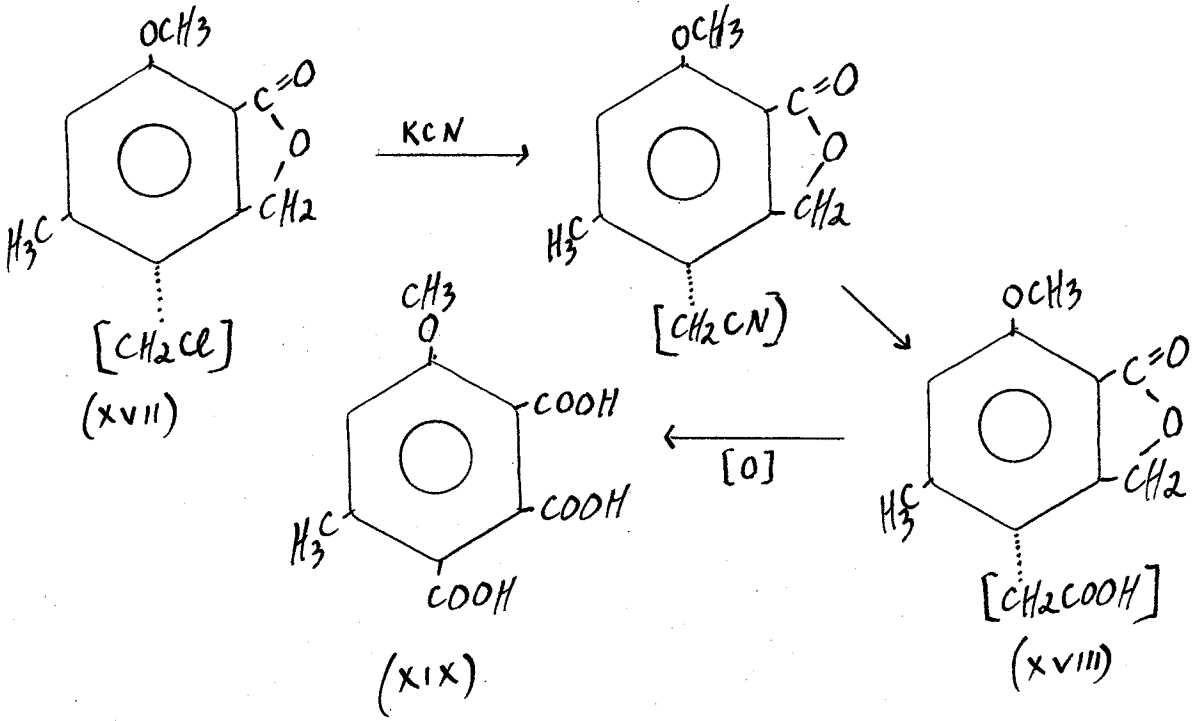
Charlesworth and Robinson (19) while working on the preparation of a dimethoxyphthalic acid, attempted to

use the method of Edwards, Perkin and Stoyle in the preparation of 4-methyl-3,5-dimethoxyphthalidecid according to the following reaction.



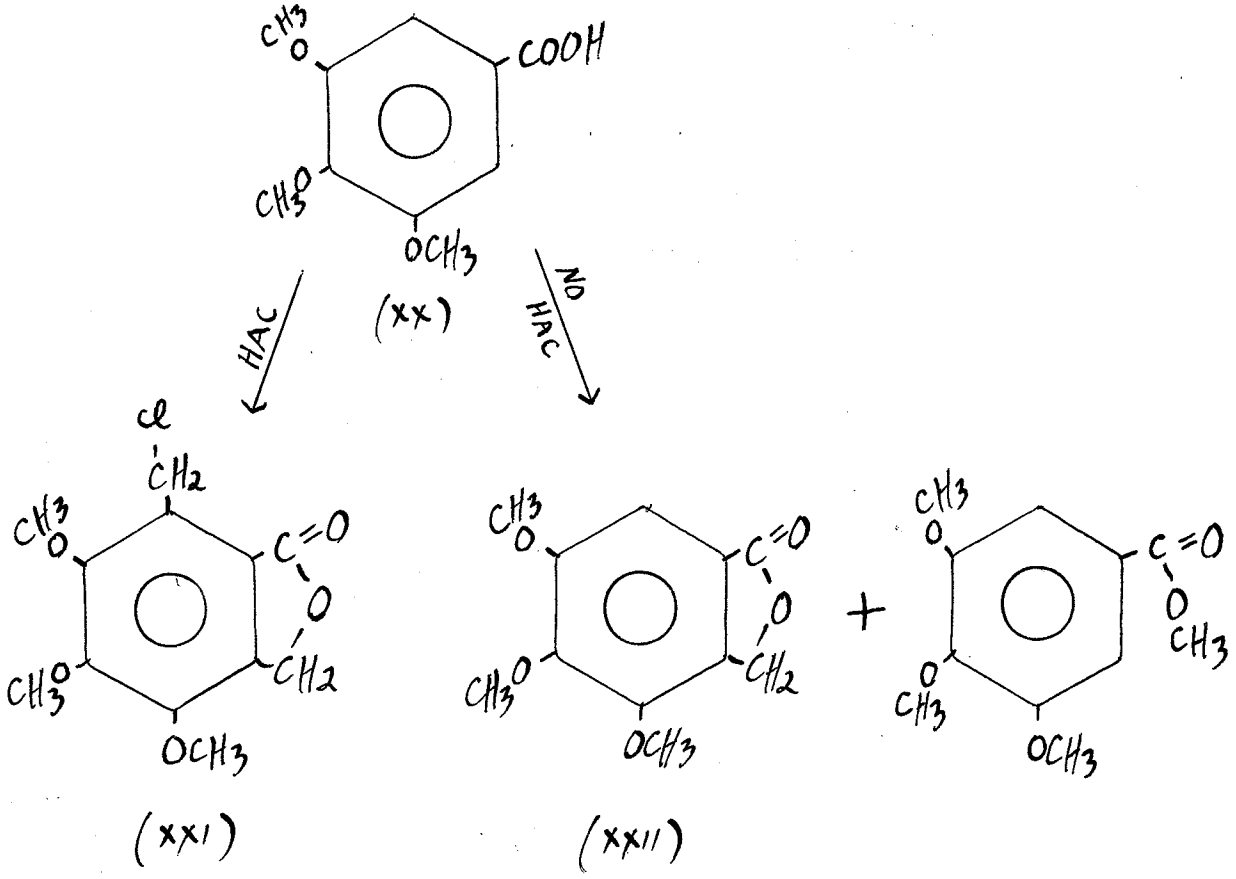
Here, as in the case of Raistrich et al. (63), the phthalide was not produced, but similarily an unidentified chloroproduct was obtained.

That the chloromethyl group is attached to the ring has been established by Charlesworth et al. (18) by the following series of reactions; formula (XVll) and the 6-position of the chloromethyl group being used for convenience only.



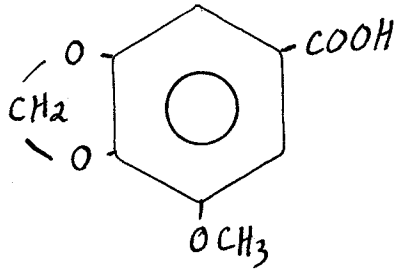
Oxidation of the phenylacetic acid (XVlll) opened the phthalide ring to give the tricarboxylic acid (XlX).

Paul (56) obtained the chloromethylphthalide (XXl) on condensing trimethylgallic acid (XX) with hydrochloric acid and formaldehyde, if, in addition, acetic acid was added to the reaction mixture. Without acetic acid this author claims the ordinary phthalide (XXll) was formed, together with the methyl ester of trimethyl gallic acid.



Similar results were obtained with myristicinic acid (XXlll). Condensing this aromatic acid with hydrochloric acid and

formaldehyde, in the presence of acetic acid, produced a chloromethylphthalide, and an ordinary phthalide when the acetic was omitted.



(XXIII)

When Yan (76) and Rennie (65) attempted to repeat Paul's work, they were unable to reproduce the same results.

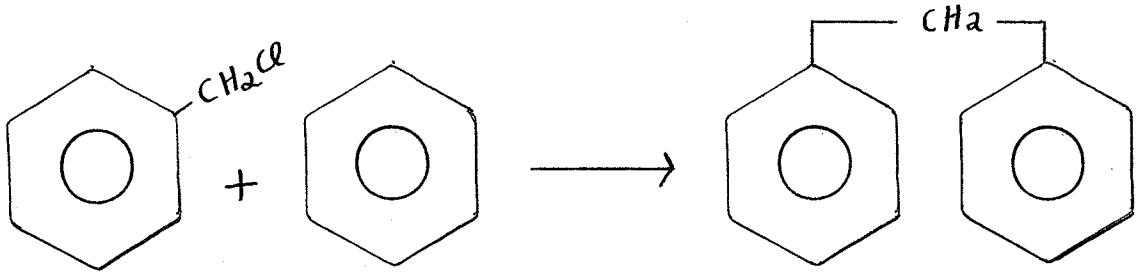
King and King (42) have reinvestigated the problem of trimethyl gallic acid. Unlike Paul, they did not require the use of acetic acid in the condensations. By altering the quantity of hydrochloric acid however, these authors could produce either the simple phthalide or the chloromethyl product. Using only a small quantity of the mineral acid they obtained the non-chlorinated phthalide (XXII), whose structure was proven by the Fritsch synthesis; by increasing the amount of the hydrochloric acid, they isolated the chloromethylphthalide (XXI).

Evidently, the normal phthalide must be formed first in the reaction. To prove this point, King and King condensed this simple phthalide with a further quantity

of formaldehyde and hydrochloric acid, obtaining thereby, the chlorinated phthalide.

Apparently, it is possible in some cases to produce a variety of products by varying experimental conditions. Wilson et al. (74) were able to isolate the simple phthalide meconine by reacting o-veratric acid with formaldehyde and hydrochloric acid in the cold. No evidence of the chloromethylphthalide was present by this method. The normal method of heating these reagents together gave only the chloromethyl derivative of meconine.

The formation of a chloromethyl aromatic compound is usually accompanied by the production of a diphenylmethane derivative, which is formed by the condensation of the chloromethyl compound with the original aromatic compound. For example



The latter reaction depends on the kind of dehydrating agent employed, since those reactions in which zinc chloride were used only furnished small amounts of the diphenylmethane derivatives, whereas the use of sulphuric acid under similar conditions invariably caused the formation

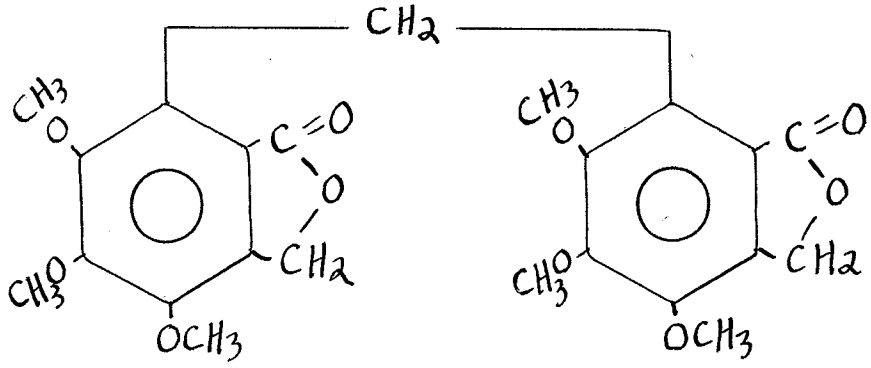
of large quantities of these substances. In both instances, however, the temperature is an important factor, because, as a rule, diphenylmethane derivatives are formed to some extent by heating a mixture of a chloromethyl compound with another aromatic compound. The conditions for this reaction are more favourable when substances such as sulphuric acid, metallic oxides or even traces of metals like iron, zinc and mercury are present.

Stephen, Short and Gladding (70) showed that diphenylmethane was formed by treating benzyl chloride with benzene and concentrated sulphuric acid, and in the absence of benzene a substance of complex nature was formed by the reaction of benzyl chloride itself. They found the above statements hold true for other chloromethyl compounds; also if these reactions are carried out at temperatures above 35^{o}, it was found in most cases, that larger yields of the diphenylmethane derivative were produced. In some of the many publications of Quelet (59),(60),(61), the formation of different diphenylmethane compounds is mentioned.

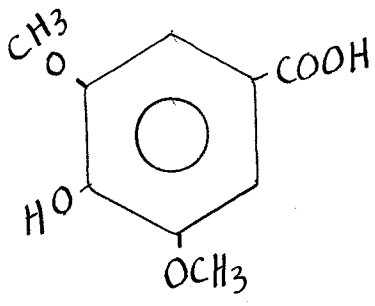
The condensation reactions on aromatic acids however, are normally carried out without the use of a dehydrating agent. Still many examples of these diphenylmethane products are cited in the literature. A possible explanation for this behaviour has been presented in the section "Discussion of Experimental Result".

King and King (42) found that the treatment of the

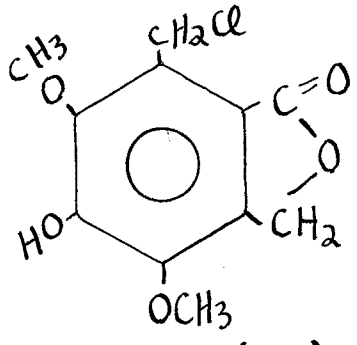
once recrystallized specimens of the 3,4,5-trimethoxyphthalide or of its chloromethyl derivative with boiling alcohol gave a sparingly soluble residue which they identified as the dimer, the methylenebisphthalide.



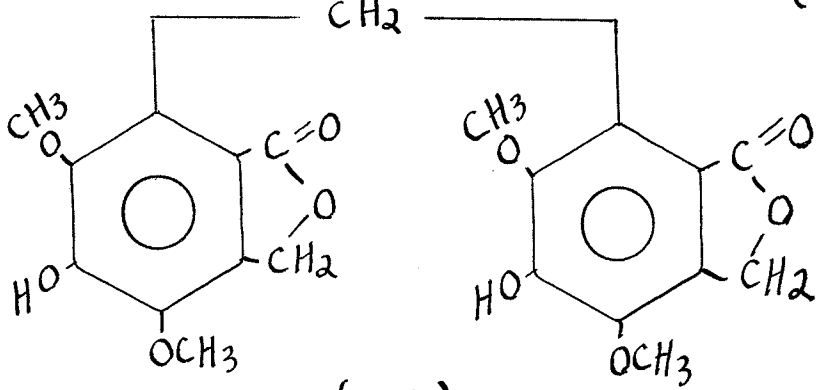
Syringic acid (XXlV) was reported by King and King to give the 6-chloromethyl-4-hydroxy-3,5-dimethoxyphthalide (XXV) together with 6,6[1]-methylenebis-4-hydroxy-3,5-dimethoxyphthalide (XXVl)



(xxIV)

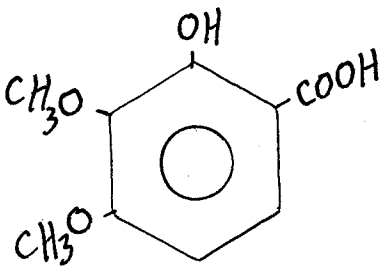


(xxv)

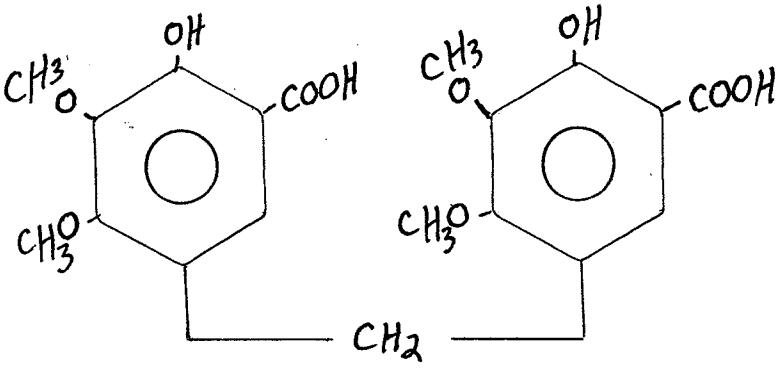


(xxvI)

This latter compound was methylated to give the same dimer as obtained previously from trimethylgallic acid. However, pyrogallolcarboxylic acid -3,4-dimethyl ether (XXVll) did not condense normally but gave according to King and King the 5,5[1]-methylenebis-2-hydroxy-3,4-dimethoxybenzoic acid (XXVlll).



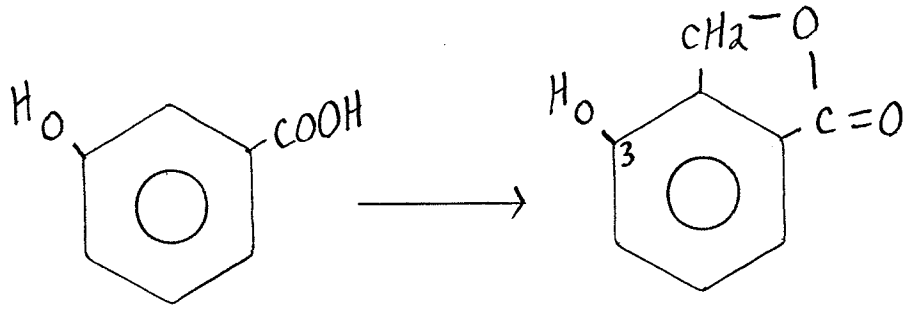
(XXVII)



(XXVIII)

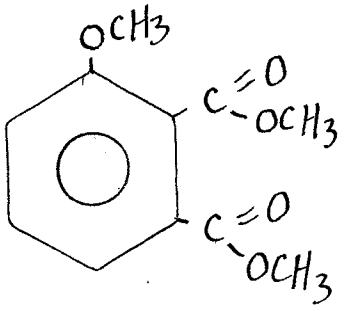
This would then illustrate a new case of dimerization without phthalide formation.

In 1944, Buehler, Powers and Michels (12) found that the condensation of m-hydroxybenzoic acid with formaldehyde and hydrochloric acid in the presence of sulphuric acid gave two products; one of which, melting at 254°, was isolated and identified as the simple 3-hydroxyphthalide (XXlX), the phthalide ring closing in the position ortho to the hydroxyl substituent.

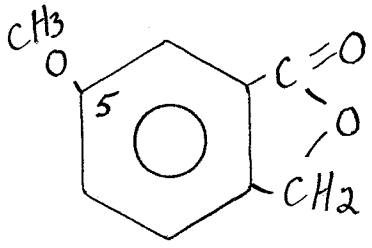


(XXIX)

Oxidation of the methyl ether of phthalide (XXIX) produced the known 3-methoxyphthalic acid, which in turn gave the known dimethyl 3-methoxyphthalate (XXX).



(XXX)

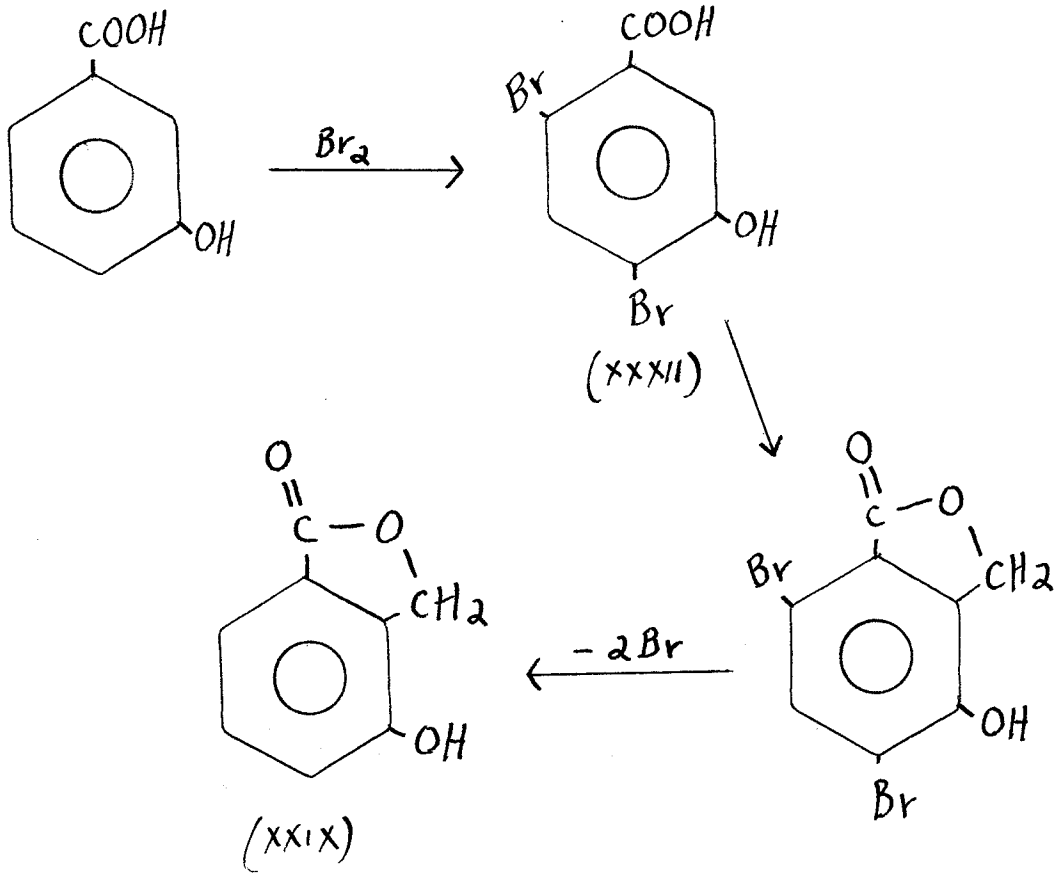


(XXXI)

These oxidation products were not identical to those of 5-methoxyphthalide (XXXI) reported by Chakravarti and Perkin (15).

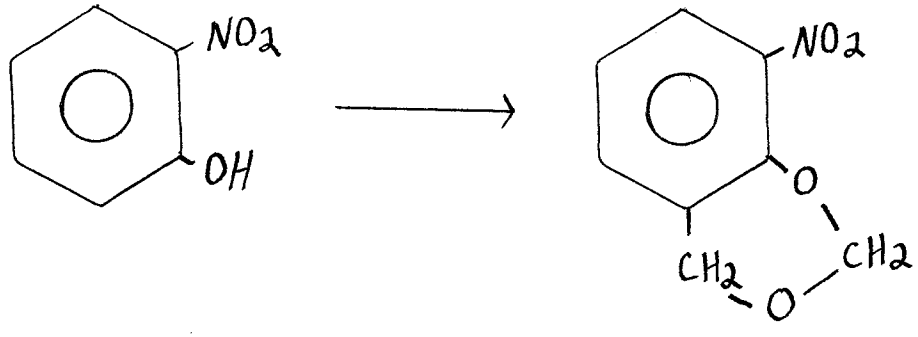
Further proof was presented by Buehler et al. (12) by the synthesis of the 3-hydroxyphthalide (XXIX). m-Hydroxybenzoic acid was brominated to give the known dibromo

acid (XXXll) which was then condensed with formaldehyde and hydrochloric acid. Due to the orientation of the dibromo acid (XXXll), only one possible phthalide could result from the condensation. The dibromophthalide was dehalogenated with Raney nickel under pressure to yield 3-hydroxyphthalide (XXlX).

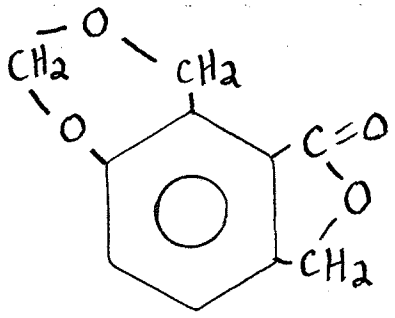


In 1946, Buehler, Harris, Schaklett and Block (11) discovered the nature of the second condensation product as 6-hydroxymethyl-1,3-benzodioxan-5-carboxylic acid lactone (XXXlll). This substance reacted favorably to indication tests for dioxane and phthalide rings,i.e., it

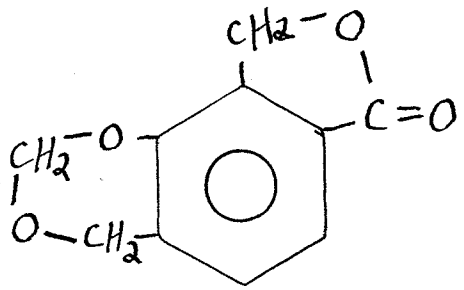
gave a red to orange precipitate when heated with phloroglucinol in strong sulphuric acid solution to indicate the dioxanyl ring, and develops fluorescence with resorcinol and sulphuric acid to show a phthalide ring. The structure of the benzodioxan compound made through the action of formaldehyde on o-nitrophenol, has been proven by Borsche and Berkhout (8).



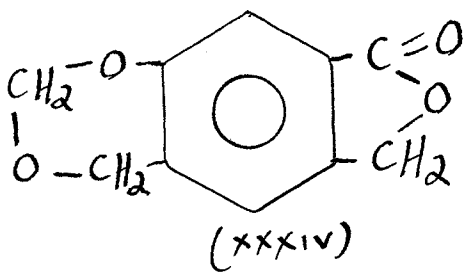
In Buehler's case, there were three possible formulae for the dioxanylphthalide compound. They are (XXXIII), (XXXIV) and (XXXV).



(XXXIII)

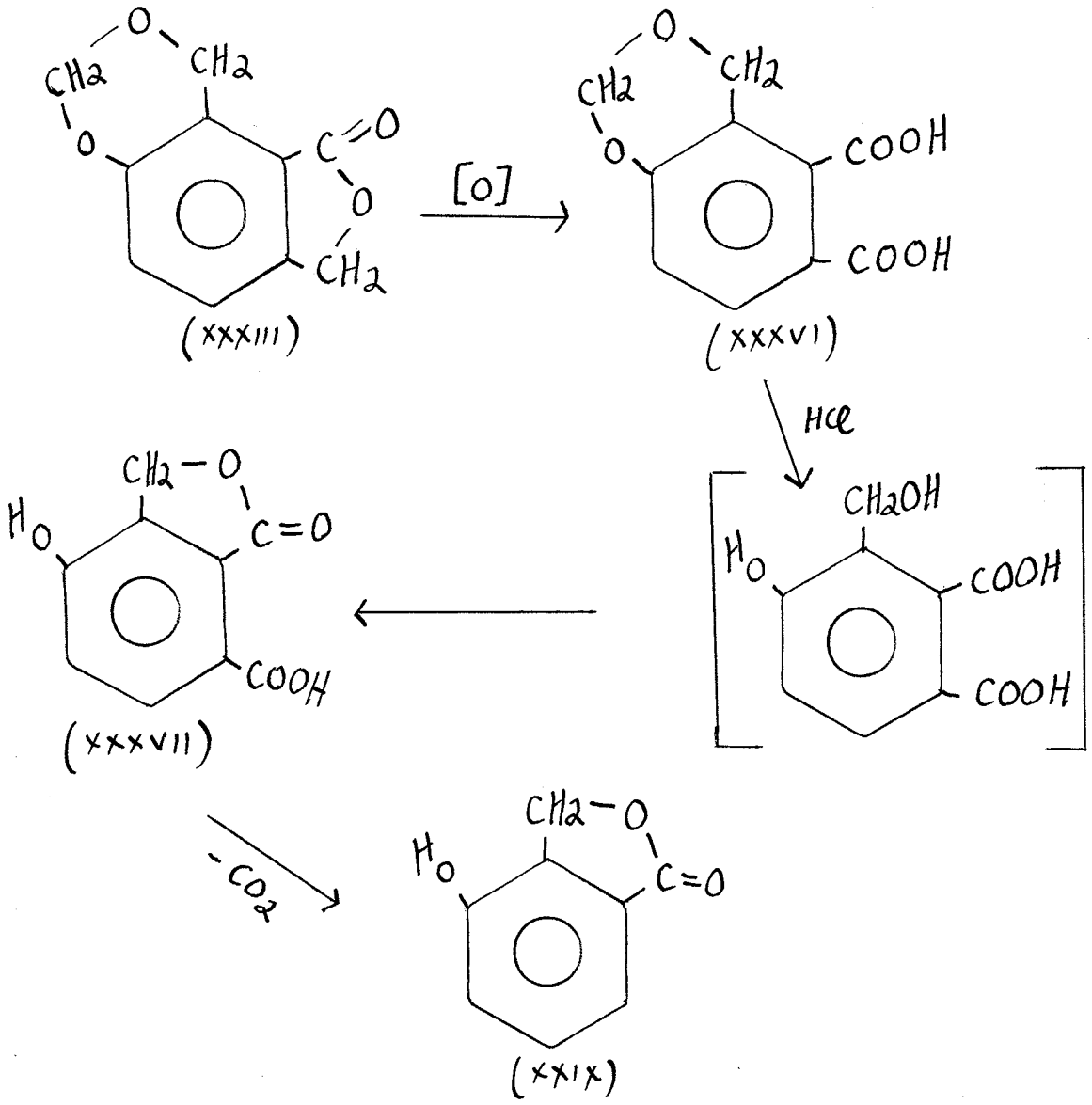


(XXXV)

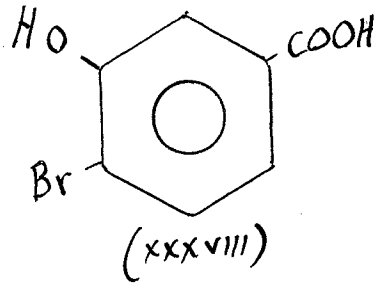


(XXXIV)

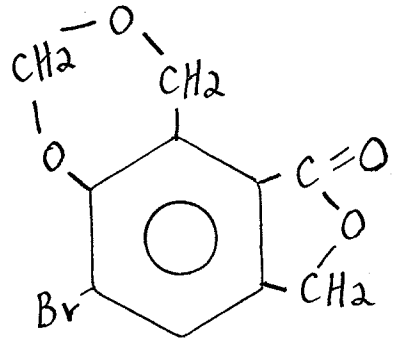
However, structures (XXXIV) and (XXXV) were ruled out on the basis of oxidation and synthetic work. Alkaline permanganate oxidation of the benzodioxan lactone (XXXIII) produced a dicarboxylic acid (XXXVI) which on heating with hydrochloric acid rearranged to form a hydroxy-carboxyphthalide (XXXVII) which, in turn, on decarboxylation in quinoline gave a hydroxyphthalide (XXIX) identical to the simple phthalide obtained in the original condensation of m-hydroxybenzoic acid.

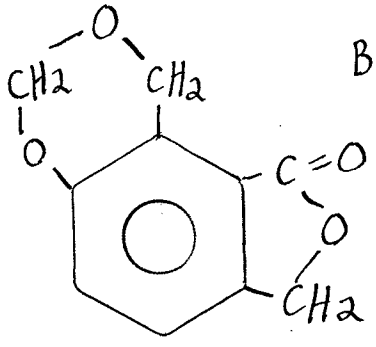


Although the evidence thus far supports structure (XXXlll), these authors found other results which pointed to formula (XXXlV) as being the correct one. To solve this problem, structure (XXXlll) and (XXXlV), but not (XXXV) were synthesized. The direct bromination of m-hydroxybenzoic acid gave 4-bromo-3-hydroxybenzoic acid (XXXVlll), which condensed with formaldehyde and hydrochloric acid to give the bromo-dioxanylphthalide. Debromination of this lactone produced the compound of structure (XXXlll).



(XXXVIII)

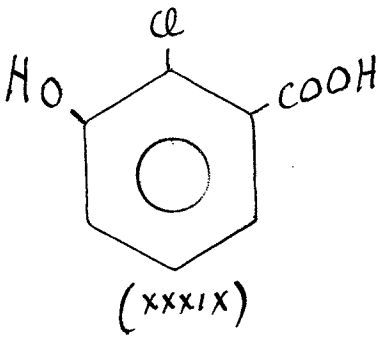




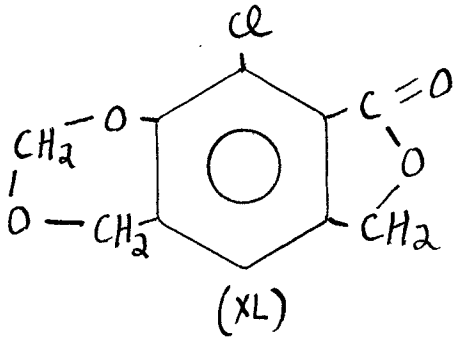
(XXXIII)

Similarily, the chlorination of m-hydroxybenzoic acid resulted in the formation of the 2-chloro-3-hydroxybenzoic acid (XXXlX), which condensed to give the chlorodioxanyl-phthalide (XL). Structure (XXXlV) was obtained on dechlorination, and was not identical with the original

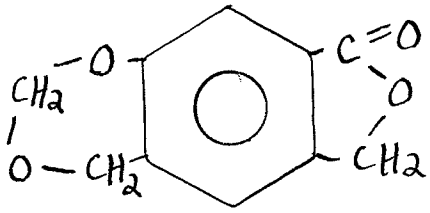
condensation product from m-hydroxybenzoic acid.



(XXXIX)



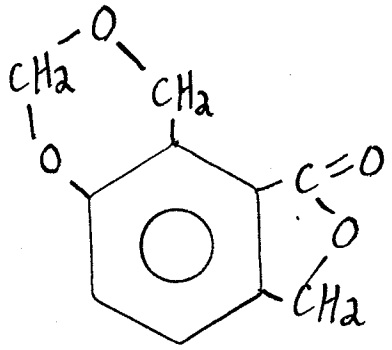
(XL)



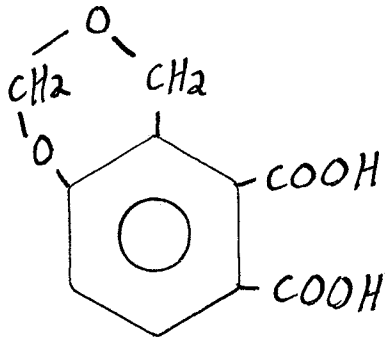
(XXXIV)

In 1950, Buehler and Block (9) reported the degradation products of the lactone of 6-hydroxymethyl-1,3-benzodioxan-7-carboxylic acid (XXXIV), which had been previously prepared as directed by Buehler, Harris, Schaklett and Block (11) in 1946. However, no mention was made with regard to whether the lactone was the direct condensation product of m-hydroxybenzoic acid or the synthetic compound obtained from the dechlorination of the chlorodioxylphthalide (XL).

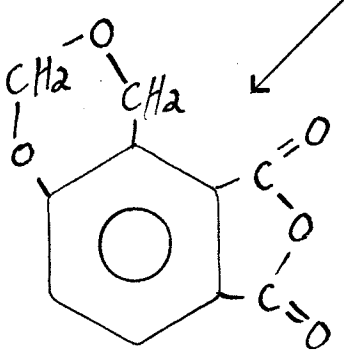
In 1951, Buehler, Slack, Shirley, Sanguinetti and Frey (13) confirmed the structure of the 5-carboxylic acid lactone (XXXIII) by oxidative work to the known trimethyl-4-methoxybenzene-1,2,3-tricarboxylate (XLV). Two different oxidative steps were performed in which each attached ring



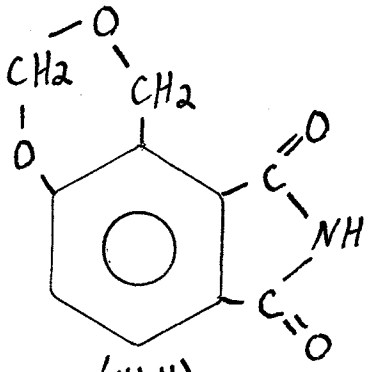
(XXXIII)



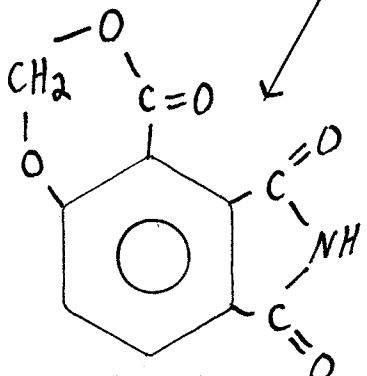
(XXXVI)



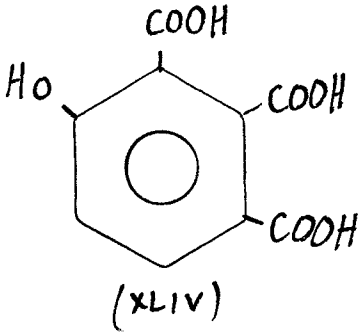
(XLI)



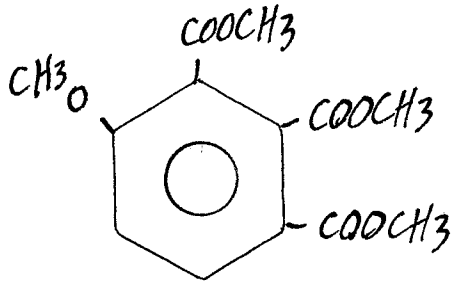
(XLII)



(XLIII)



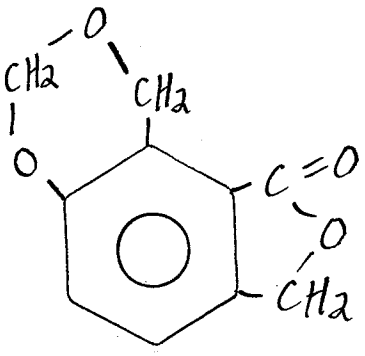
(XLIV)



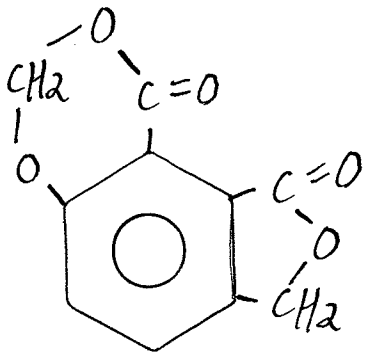
(XLV)

in turn was opened by two different ways. The first method was an extension of the 1946 work whereby the dioxanyl-phthalide compound (XXXlll) was oxidized to the dicarboxylic acid (XXXVl) with alkaline permanganate. The two ortho carboxyl groups were stabilized by conversion to the anhydride (XLl) and then to the imide (XLll). Mild oxidation of the dioxane ring with chromium trioxide in acetic acid resulted in the formation of the dioxanone imide (XLlll) which on alkaline hydrolysis gave the known 4-hydroxybenzene-1,2,3-tricarboxylic acid (XLlV). Complete methylation produced the known trimethyl-4-methoxybenzene-1,2,3-tricarboxylate (XLV).

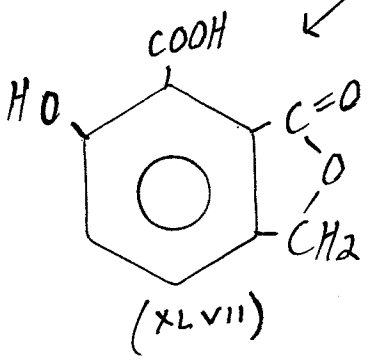
The second method consisted of opening the dioxane ring by mild oxidation, then the phthalide ring by stronger oxidation. First step was performed by mild oxidation of the lactone compound (XXXlll) with chromium trioxide in acetic acid to give the dioxanone (XLVl), followed by alkaline hydrolysis of this ester to the hydroxy-carboxy-phthalide (XLVll). Methylation of the latter compound produced the methoxy-carboxyphthalide (XLVlll) which on oxidation with alkaline permanganate gave the known 4-methoxybenzene-1,2,3-tricarboxylic acid (XLlX). Methylation with diazomethane gave the known trimethyl-4-methoxybenzene-1,2,3-tricarboxylate (XLV).



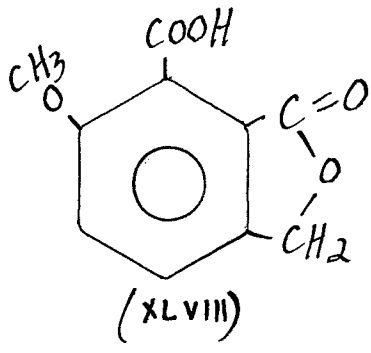
(XXXIII)



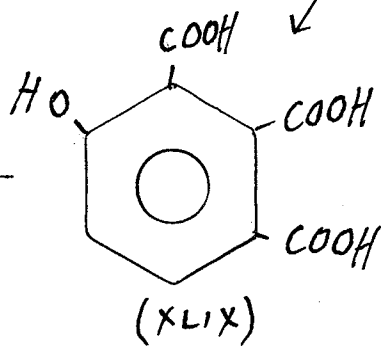
(XLVI)



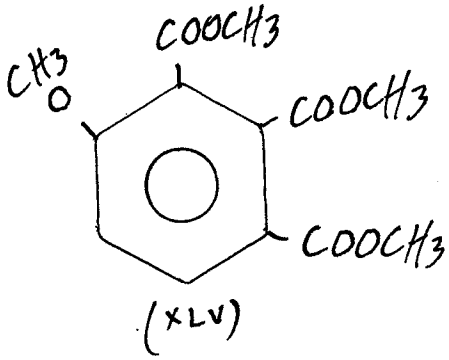
(XLVII)



(XLVIII)



(XLIX)



(XLV)

DISCUSSION OF EXPERIMENTAL RESULTS

This discussion will elucidate the method of attack which was used to establish the orientations of the simple phthalide and the three chloromethylphthalides which were isolated from the condensation reaction between 5-methoxy-3-methylbenzoic acid, concentrated hydrochloric acid, formaldehyde and glacial acetic acid.

As outlined briefly in the introduction, two simple phthalides are theoretically possible in the condensation reaction with 5-methoxy-3-methylbenzoic acid, following the method of Edwards, Perkin and Stoyle (24). It should be noted here that all condensation reactions carried out during this research project, unless otherwise stated, were done using a modification of this method, suggested by Ray and Robinson (64). This involved the addition of glacial acetic acid to the hydrochloric-formaldehyde mixture.

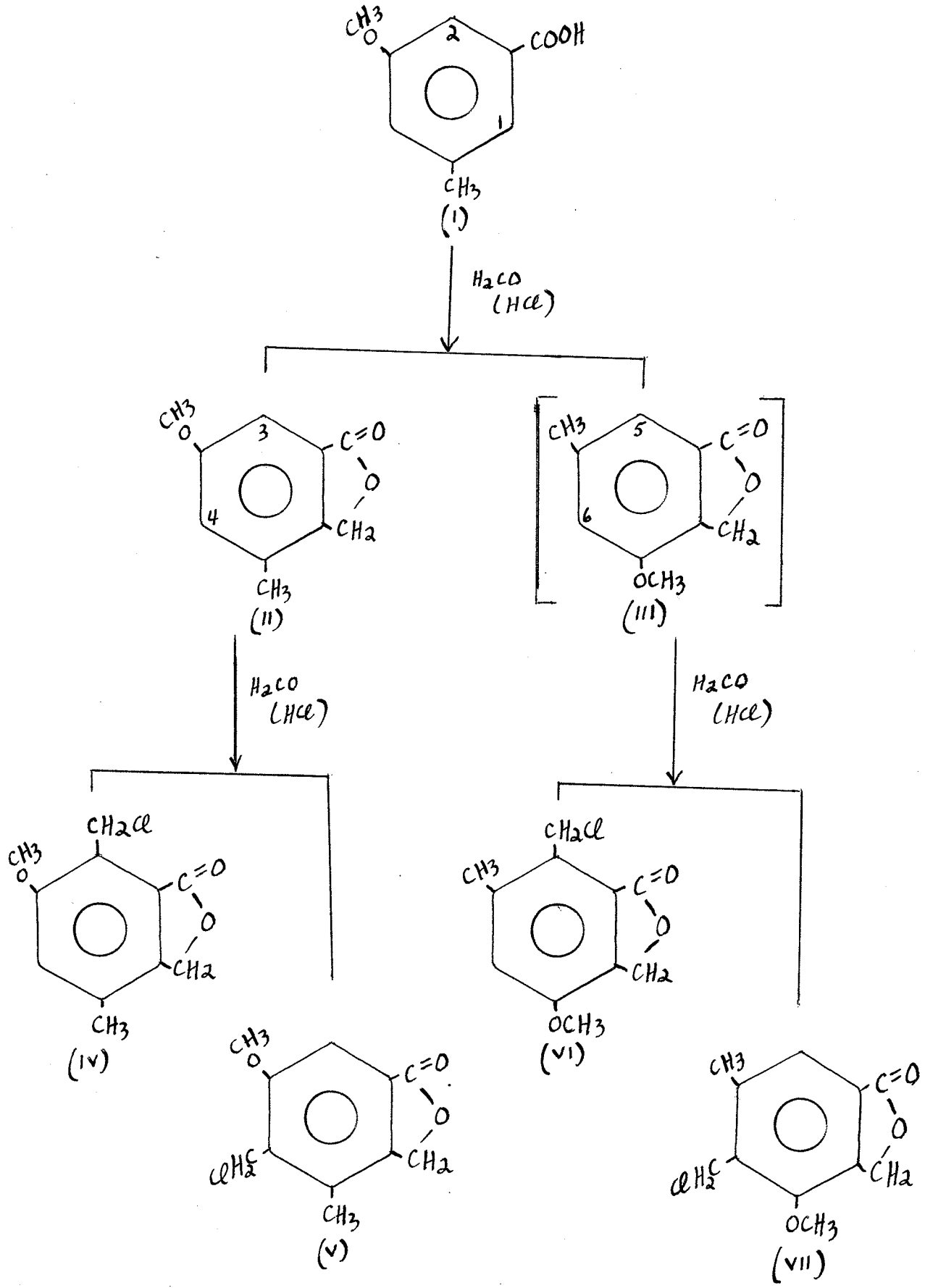
Yan (76) carried out condensation reactions on this acid with and without glacial acetic acid. When glacial acetic acid was used, he was able to isolate two products. The first was a compound supposedly free of chlorine and melting at 131.5 - 133.0°. This compound was not analysed or examined further, but he suggested that it might be the simple phthalide of melting point 135.5° isolated by Meldrum (49). This material, however, has been shown in this investigation to be the chloromethylphthalide of melting point 133.5 - 135.5°. The second product obtained

by Yan contained chlorine and had a melting point of 176 - 178°. This, he stated, would be the chloromethyl derivative obtained from the simple phthalide (11) or (111). When glacial acetic acid was omitted from this reaction, Yan was unable to isolate the 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 three chloromethylphthalides were isolated, along with one simple phthalide. Separations were carried out without any evidence of gumminess.

The schematic diagram, page 38, should help in visualizing the steps involved for the production of all products.

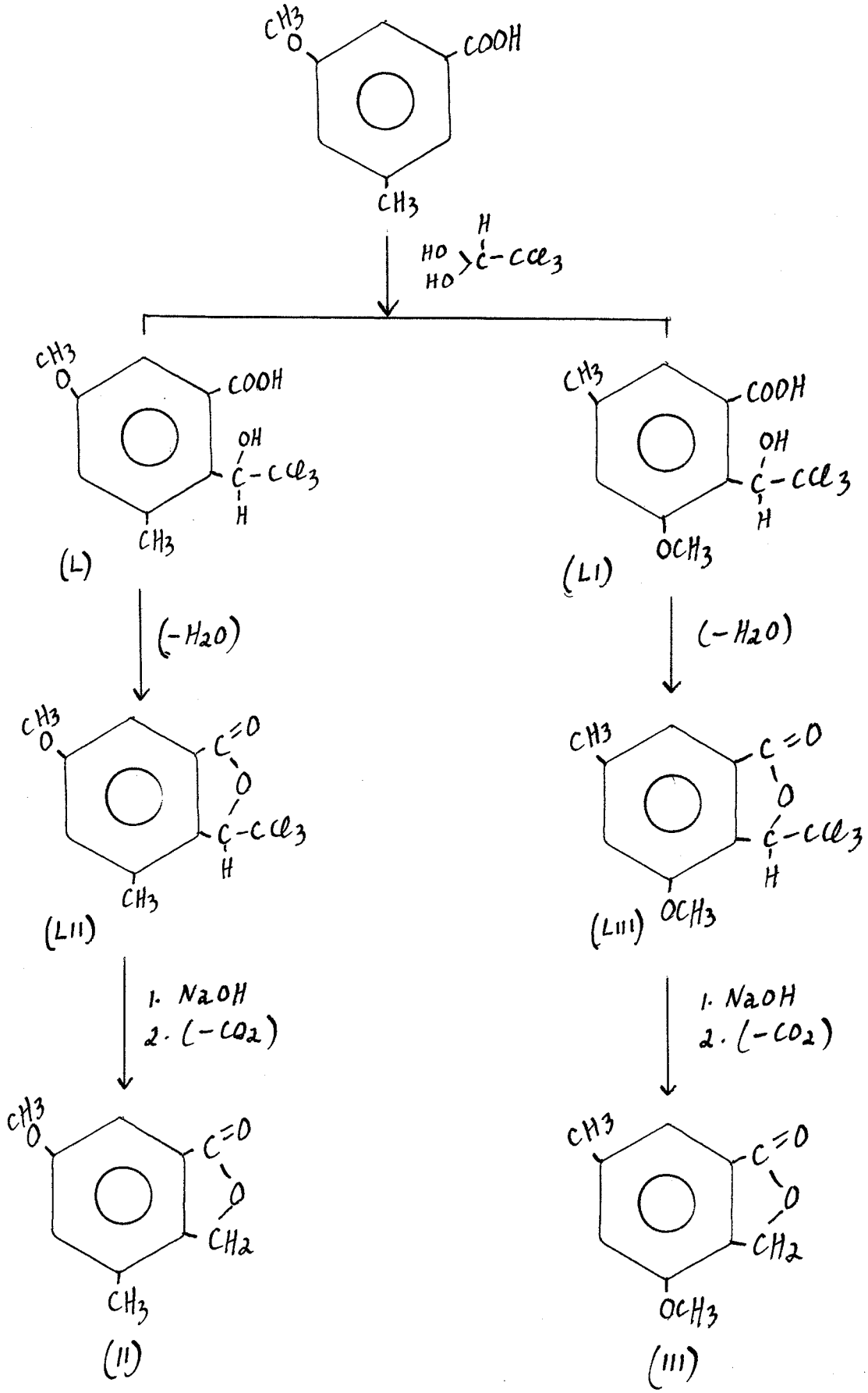
When 5-methoxy-3-methylbenzoic acid (1) is heated with formaldehyde in acid solution, the chloromethyl group will enter the benzene nucleus at positions 1 and 2, giving rise to the two simple phthalides (11) and (111). On further reaction, a second chloromethyl group can enter position 5 and 6 of compound (111) giving rise to the two chloromethylphthalides (V1) and (V11). Similarily, one may obtain (1V) and (V). Therefore, the maximum number of

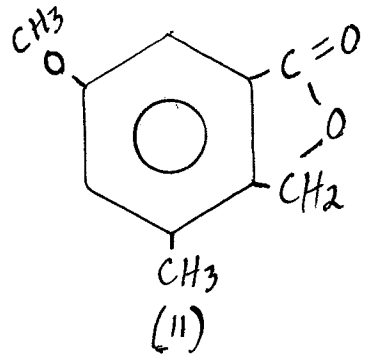

CH3
2
COOH
1
CH3
(I)
H2CO
(HCl)
CH3
3
C=O
O
4
CH2
CH3
(II)
CH3
5
C=O
O
6
CH2
OCH3
(III)
H2CO
(HCl)
H2CO
(HCl)
CH2Cl
CH3
C=O
O
CH2
CH3
(IV)
CH3
C=O
O
ClH2C
CH2
CH3
(V)
CH2Cl
CH3
C=O
O
CH2
OCH3
(VI)
CH3
C=O
O
ClH2C
CH2
OCH3
(VII)

compounds which are theoretically possible from this reaction are six, two simple phthalides and four chloromethylphthalides. But, as mentioned previously, only one simple and three chloromethylphthalides were ever isolated.

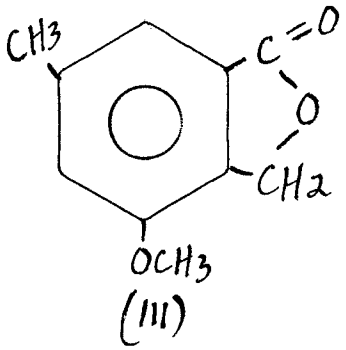
To determine the orientation of the simple phthalide produced, a Fritsch synthesis was carried out on 5-methoxy-3-methylbenzoic acid, according to directions given by Meldrum (49). By this method, the two simple phthalides, (11) and (111) were eventually produced. The steps involved are shown on page 40. The chloral can attack either positions 1 or 2 and give rise to the two compounds (L) and (L1). On lactonization, the two trichloromethylphthalides (L11) and (L111) 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 orientations of these two isomers had previously been established by Meldrum in the following manner:- On oxidation of (11) and (111) with alkaline potassium permanganate he obtained the two different dicarboxylic acids (L1V) and (LV). It was found, however, that demethylation of these dicarboxylic acids was impracticable when treated with hydriodic acid in the usual way.

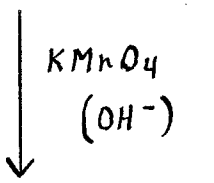

CH3
O
COOH
CH3
HO
HO
H
C-CCl3
OH
C-CCl3
H
(L)
(LI)
OCH3
(-H2O)
C=O
O
(LII)
(LIII)
1. NaOH
2. (-CO2)
CH2
(II)
(III)

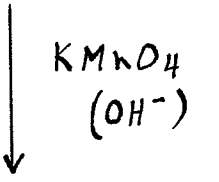


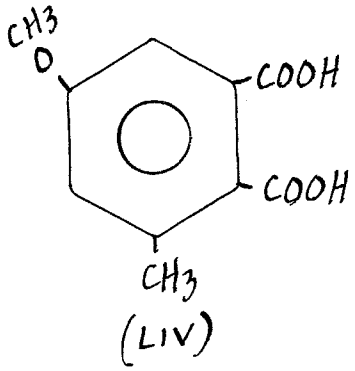
(II)



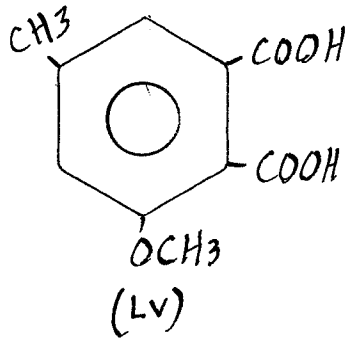
(III)







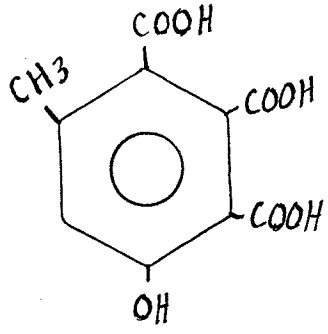
(LIV)



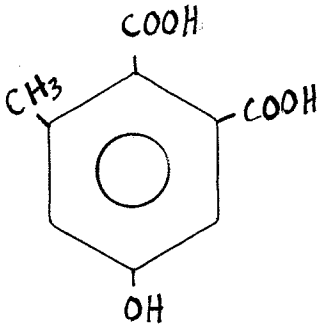
(LV)

However, when cochenillic acid (LVI) is heated under various conditions, ∝-coccinic acid, among other products, is produced. Because this is a hydroxyphthalic acid derived from (LVI), there are two possible structures for ∝-coccinic acid namely (LVII) and (LVIII). There was no distinct colour reaction when ∝-coccinic acid was treated with ferric chloride, as an ortho phenolic acid would normally give. Therefore ∝-coccinic acid must have the

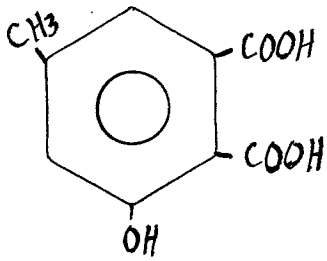
hydroxyl meta to the carboxyl substituent or be structure (LV11).



(LVI)



(LVII)



(LVIII)

This compound (LV11), when methylated, proved identical with (L1V) by the 'mixed melting point' method. This material had been derived from the phthalide (11) 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 the Meldrum method showed no depression. Hence the orientation of the simple phthalide (11) is definitely established as 5-methoxy-3-methylphthalide.

As stated above there is a vivid color change when ferric chloride is added to a phenolic acid which has the

hydroxyl and carboxyl 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 44.

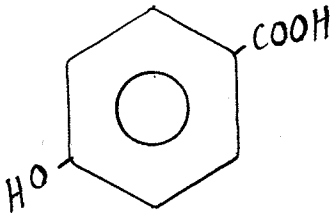
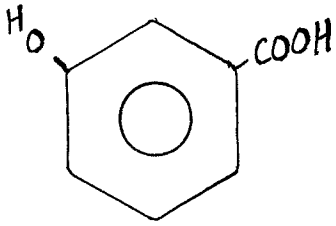
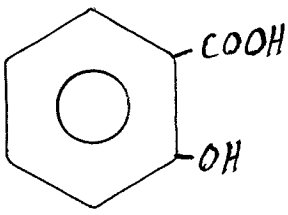
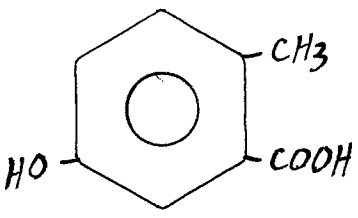
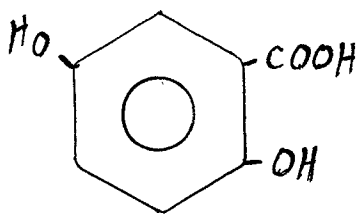
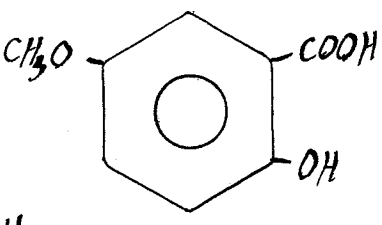
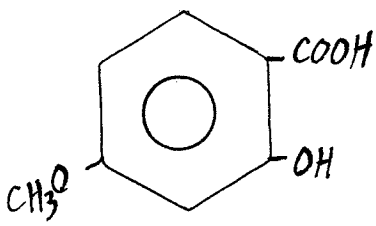
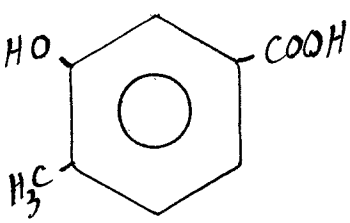
The next problem to receive attention was the determination of the orientation of the chloromethylphthalide derived from 5-methoxy-3-methylphthalide. As shown in the diagram on page 38, this derivative could have structure (IV) or (V). It was found however, that by varying the experimental conditions in this condensation reaction, not one, but three chloromethylphthalides were eventually isolated. These had associated with them melting points of 134.0 - 135.0°, 152.5 - 154.0° and 178.0 - 179.5°. On analysis, it was shown that within experimental error, all three compounds were identical in composition and had values in good agreement for those calculated for the chloromethylphthalide structure.

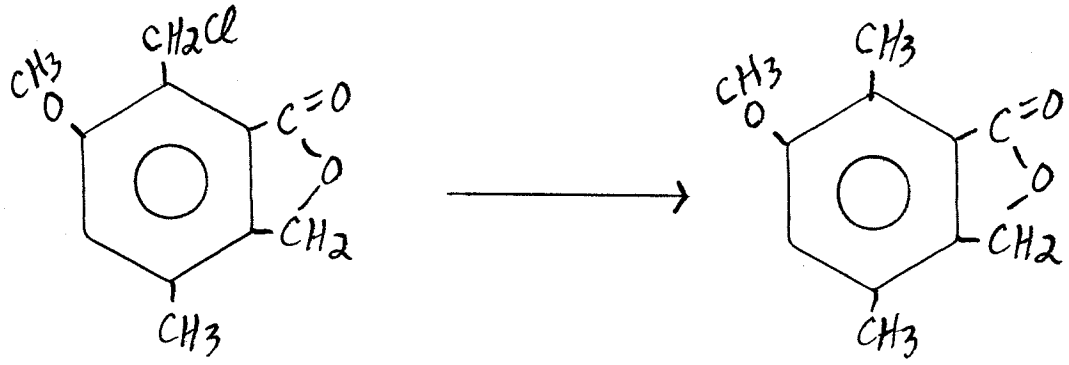
At this stage of the work, one was faced with the problem of deciding whether these three chloromethylphthalides were actually distinct isomers, or simply dimorphic forms of the same compound. Infra red spectra were therefore obtained for each isomer. These curves showed small but distinct differences, and are reproduced on pages 95,96.

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.

Table 1

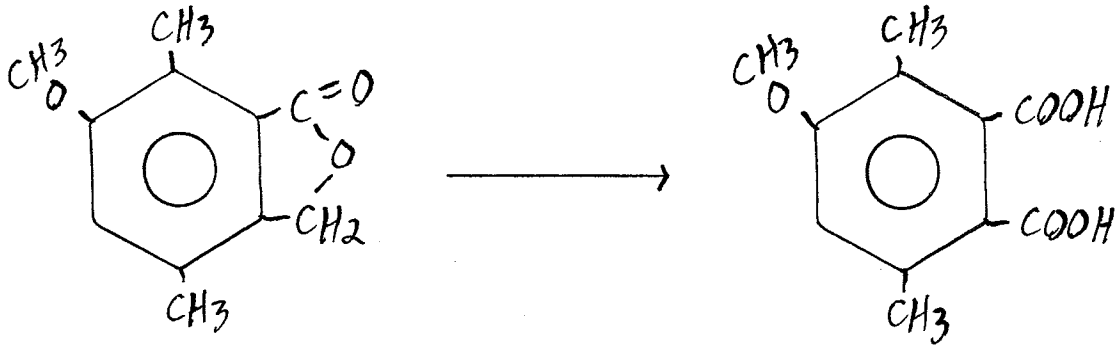
Effects of Aqueous $FeCl_3$ Reagent on Some Phenolic Acids

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



In so doing, one would obtain three chlorine free phthalides with a different melting point associated with each if three isomers had actually been produced. This indeed was found to be the case.

Similarily, if each of the chlorine free phthalides were oxidized thus opening the lactone ring, as for example:



there would be produced three substituted phthalic acids, each with a different melting point. This again was found to be the case. However, the free phthalic acids were very difficult to obtain in a pure state. They would immediately revert to their anhydride forms when purification was attempted. The melting points associated with the

phthalic acids are in reality those melting points corresponding to their respective anhydrides.

From this preliminary experimental work, it was concluded that there are indeed three distinct chloromethylphthalides and not merely a dimorphic compound. Table 2 summarizes the melting points of these nine different products.

Table 2

Melting Points °C

Chloromethylphthalide Isomers	Chlorine Free Phthalides	Phthalic Anhydrides
(VI) 134.0 - 135.0	179.5 - 180.5	229.5 - 231.5
(VII) 152.5 - 154.0	174.0 - 175.5	208.0 - 209.5
(IV) 178.0 - 179.5	169.5 - 170.0	185.0 - 186.5

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

When the mixture was heated for two minutes or less, that is heated just for the length of time necessary to put everything into solution, three products were isolated. There was a chlorine free simple phthalide melting at 105.0 - 106.0°, and two phthalides containing chlorine of melting points 134.0 - 135.0° and 152.5 - 154.0°. It should be noted here that the 152.5 - 154.0° isomer was only isolated

when the condensation was held to this very short heating period. There was no evidence of the third chloromethylphthalide of melting point 178.0 - 179.5°. The only time this latter isomer could be found was when the reaction proceeded for twenty minutes or longer. One could then obtain this particular phthalide along with the 134.0 - 135.0° isomer. The simple phthalide melting at 133.5 - 134.5° was never isolated under any conditions.

Why then, should these products [redacted] be so dependent upon the length of reaction time? Why are only four out of a possible six products produced?

Before we are able to obtain possible answers to these and other questions, it is necessary at this time to digress and consider a more theoretical approach to the whole study of phthalide formation. Why are phthalides formed from certain substituted aromatic acids and not from others? Why are chloromethylphthalides formed in some cases and not in others?

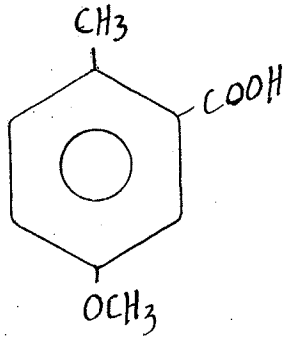
In 1949, Anderson (16) formulated a set of rules for predicting the products from the Edwards, Perkin and Stoyle condensation. These rules were strictly empirical and represented a careful study and evaluation of most condensation reactions known to that date. An up to date listing of all condensation reactions are given in the appendix, page 140, table 3. These rules deal with the influence of nuclear substituent groups on the course of the reaction of

an aromatic acid with formaldehyde and hydrochloric acid and are as follows:-

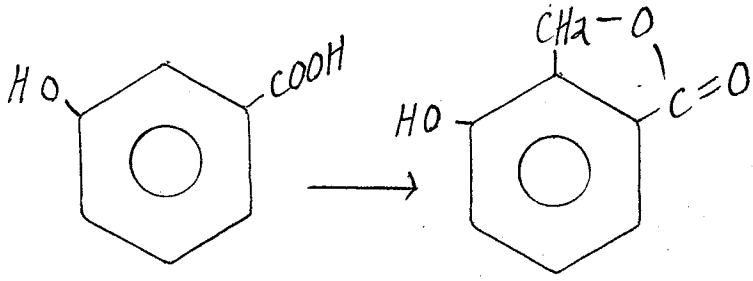
1) Apparently, ortho orientating forces are not nearly so important as para directing ones. In nearly every case found so far where a simple phthalide has been formed, there was a strong ortho-para directing group (in most cases a methoxyl group) in the 3- position of the free acid. That is para to the position where the chloromethyl group must be introduced to form a phthalide ring with the carboxyl group. There are two exceptions to this rule:-

a) 5-methoxy-2-methylbenzoic acid (LIX)

b) m-hydroxybenzoic acid (LX)



(LIX)

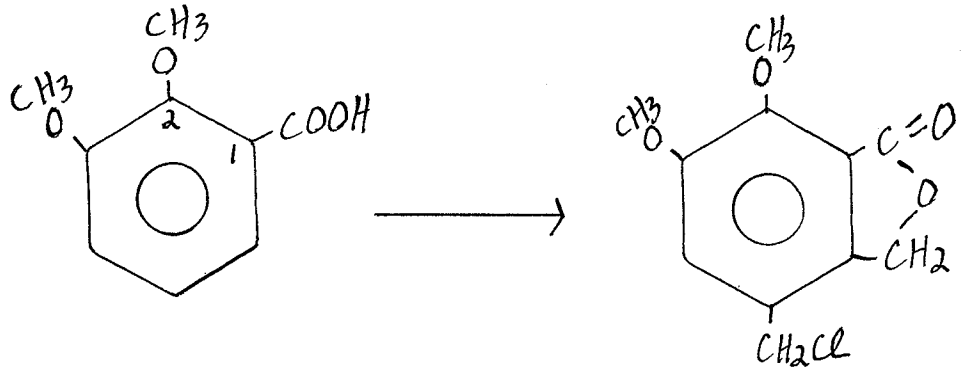


(LX)

In the case of 5-methoxy-2-methylbenzoic acid, lactone formation was due to ortho directing forces of the methoxyl group in the 5- position, since the 3- position was vacant and the para directing forces could not activate the 6- position.

m-Hydroxybenzoic acid is a direct exception to the suggested rules. The lactone ring closure also was due to the ortho directing forces of the hydroxyl group, even though the position para to the hydroxyl group is vacant.

2) Those compounds which form products other than, or besides simple phthalides, seem to follow the same general plan. In every case where a chloromethyl phthalide is formed, the starting material had an ortho-para directing group (in most cases a methoxyl group) in the 2- or 5- position.



After simple phthalide formation, the second chloromethyl group enters para to this secondary directing group.

3) Dimerization or resinification takes place whenever one or more of the following conditions are fulfilled:

a) a hydroxyl group is in the 5- position of the original acid,

b) there is no ortho-para directing group in the 3-position of the original acid

c) a chloromethylphthalide is formed during the condensation of the original acid.

When dimerization takes place due to condition (b) a phthalide ring may or may not be formed. Even if a phthalide ring does form in these reaction, it must be secondary to the dimerization step. Possibly if the dephenylmethane derivative is formed through the 3- position, this group might direct a second chloromethyl to the 6- position where phthalide formation could take place.

4) Dioxane ring formation, like chloromethylphthalide formation is secondary to the introduction of the phthalide ring. In each case there is a hydroxyl group in the 3-position of the original acid.

Rules (3) and (4) play only a minor role in the overall study of phthalide formation, and will therefore not be dealt with further. Very little investigation has been done to date on dimers and resins. Also, too few examples of dioxane ring formations are available for a comprehensive study at this time.

This research project dealt primarily with the first two rules. Possible explanation for the products obtained from the condensation reaction with 5-methoxy-3-methylbenzoic acid might be obtained from an application of them. It was therefore deemed necessary to test these rules

further by carrying out a systematic study of condensation reactions on certain selected substituted aromatic acids. This work, it is hoped, will give a clearer understanding to the first two rules outlined above.

There are apparently two important factors to be considered when phthalides or chloromethylphthalides are formed in condensation reactions. Firstly, the type of substituents already in the ring determines whether or not the benzene nucleus can be activated sufficiently for lactone formation to take place. Such ortho-para directing substituents as -OH, -OMe and to a smaller extent the $-CH_3$ group seem to be essential for ring closure. On the other hand negative groups such as -COOH,$-NO_2$, etc. greatly retard the tendency for this reaction to take place. Secondly, even if the benzene nucleus is activated by the above mentioned groups, no phthalide or chloromethyl-phthalide formation takes place unless these groups are located at very specific positions relative to the carboxyl substituent. It appears then, that the substituents already in the aromatic nucleus and their position relative to the carboxyl group are all important.

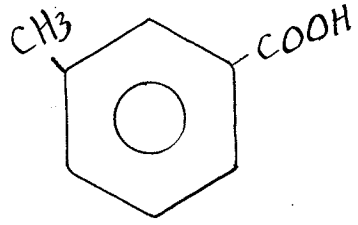
This condensation reaction apparently proceeds by an electrophilic attack of the entering chloromethyl group at a position ortho to the carboxyl substituent. From a consideration of resonance effects, this ortho position is electron deficient, and to overcome this deficiency, a strong electron donating substituent must be positioned

ortho or para to this particular site in order for lactone formation to take place. Weak ortho-para directing substituents, for example the $-CH_3$ group, cannot overcome this electron deficiency caused by the original carboxyl substituent, and so no phthalide formation is possible.

Generally then, with one methoxy group attached to the aromatic acid, phthalide formation will take place if this group is properly situated with respect to the carboxyl group. With two strong negative groups (eg. -COOH) and only one positive group (eg. $-OCH_3$), the benzene ring is so electron deficient that normally no reaction takes place. With two strong positive groups and one negative group, the benzene ring is so activated that the reaction in many cases cannot be stopped at the required simple phthalide stage but proceeds directly to their chloromethyl derivative or even to a biphenylmethane type compound. The following discussion will help clarify most of these points.

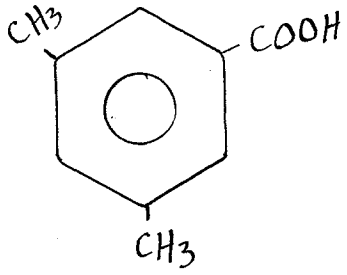
The first series of compounds examined were the isomeric toluic acids. Other experimenters have already attempted condensation reactions with them, and with negative results. Yan (18) worked with 2-methylbenzoic acid and Rennie (18) (65) with both the m- and p- isomers. However these condensations were attempted without the use of glacial acetic acid. The reaction was therefore repeated on 3-methylbenzoic acid using acetic acid. This particular acid was chosen because the two substituents on

the ring are so situated that phthalide formation, if possible, would take place.



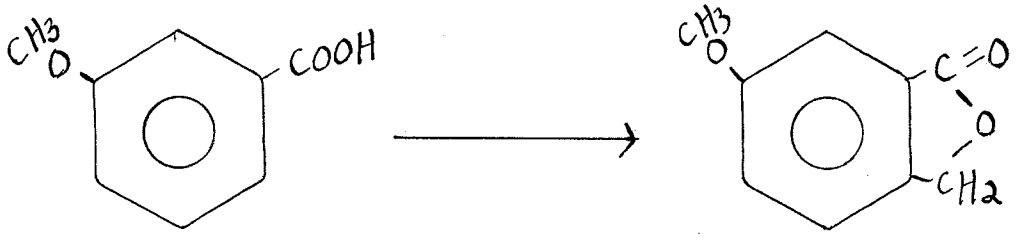
The ortho-para directing methyl group (but quite weak), is in a para position to where the chloromethyl group must enter in order to form a phthalide. But even after five hours of heating, only starting material was recovered. Apparently then, as stated above, the methyl group alone cannot overcome the electron deficiency caused by the strong electron withdrawing carboxyl group, and no lactone ring closure therefore takes place.

When a second methyl group is introduced into the benzene nucleus, thus forming for example, 3,5-dimethylbenzoic acid,



still no ring closure took place when this acid was heated with formaldehyde in acid solution, even though these methyl substituents are again situated in good positions to stimulate phthalide formation. It would appear then that the methyl group alone, as an ortho-para directing substituent, influences phthalide formation reactions only slightly.

The next series of acids studied were the O-, m- and p-methoxybenzoic acids. Consider the meta isomer. This condensation reaction was done by Chakravart et al. (15).



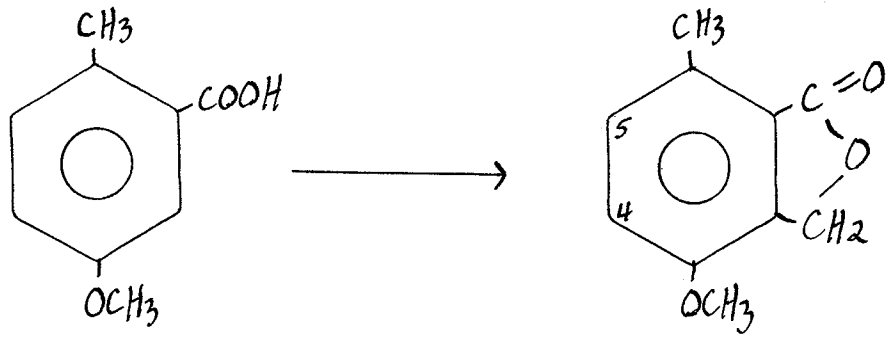
(XXXI)

In this case there is a strong ortho-para directing methoxyl group situated in a good position for phthalide formation; i.e. in a para position to where the chloromethyl group must enter in order for a lactone ring to form. In this case however, unlike that for the corresponding methyl substituent, the methoxyl group is a strong enough electron donator to overcome this electron deficiency caused by the

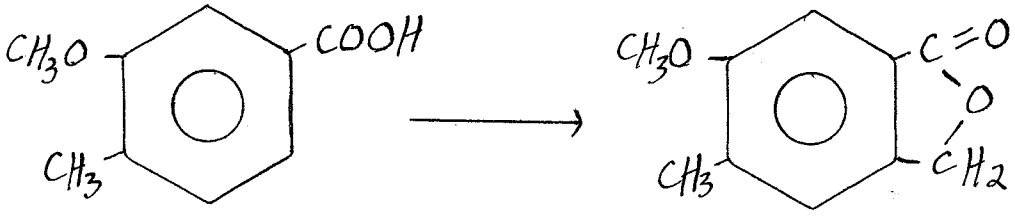
carboxyl group and so the expected 5-methoxyphthalide (XXXl) is indeed formed.

When either 2-methoxybenzoic (22) or 4-methoxybenzoic acid (22),(15) was heated with formaldehyde in acid solution however, no phthalide was produced. For lactone ring closure to take place, the entering chloromethyl group must of course enter the benzene nucleus ortho to the carboxyl substituent. For this to happen, an electron donating group must be in a para position to this site. In these two compounds, this is not the case with the result that no ring closure is possible.

A number of products are possible depending upon the position of the groups, when a methyl along with a methoxyl substituent is present in the aromatic nucleus. For example with 5-methoxy-3-methylbenzoic acid, one simple phthalide and three chloromethylphthalides were isolated. But more will be said later about this particular compound. With 5-methoxy-2-methylbenzoic acid the only product isolated was 3-methoxy-6-methylphthalide. No chloromethylphthalide was produced.

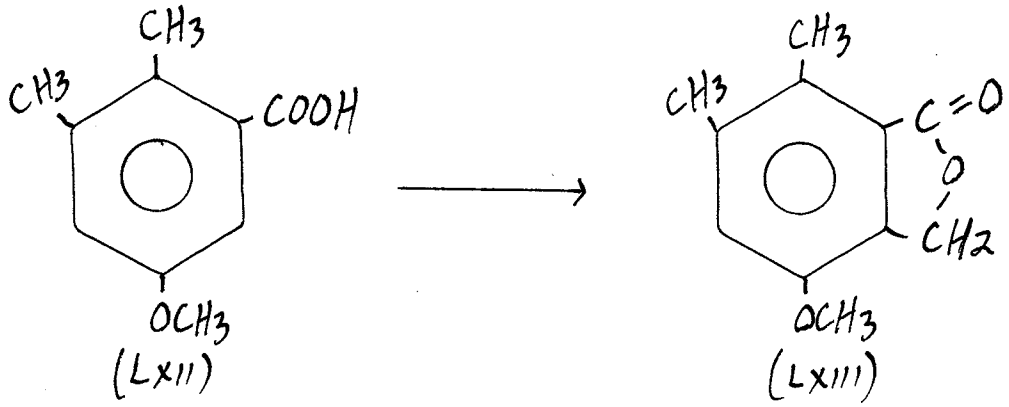


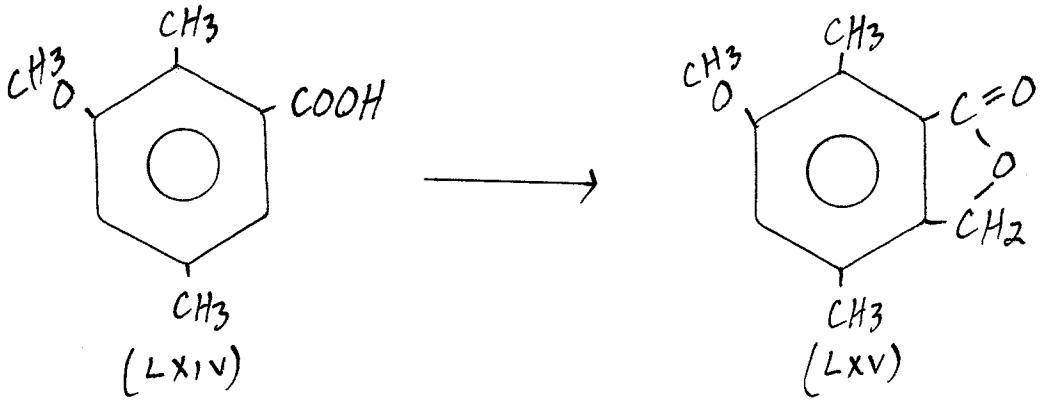
After phthalide formation, due apparently to the secondary ortho effect of the methoxyl substituent, the second chloromethyl group would have to enter position 4 or 5 in compound (LXl) in order to produce a chloromethyl derivative of the above phthalide. However, there is no ortho-para directing group in a para position to either of these sites, and so no derivative is formed. Similarily, 3-methoxy-4-methylbenzoic acid produced only the simple 4-methyl-5-mothoxyphthalide, with no evidence of a chloromethyl derivative being produced. Charlesworth et al. (18).



In this case however, there is a vacancy para to the strong electron releasing methoxyl group, so that the phthalide thus formed is due to the para effect of this substituent.

Similar results are obtained as outlined immediately above when a second methyl group is introduced into the ring to give acids of structures (LXll) and (LXlV)

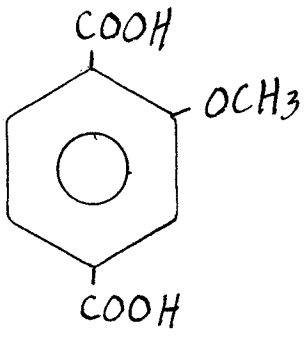




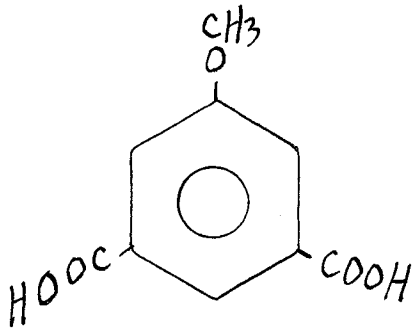
Again this secondary ortho effect of the methoxyl group initiates phthalide formation in compound (LXII). However, it should be noted that in this case there is a methyl substituent (a weak electron donating group) para to the position where the chloromethyl group must enter for lactone formation. In the case of the aromatic acid (LXIV), there is an ideal arrangement of substituents for phthalide formation, and indeed, phthalide (LXV) is produced very easily as expected.

When two strong electron withdrawing carboxyl groups

and only one electron donating group are present in the benzene nucleus, there is no ring closure in the condensation reactions. For example, 2-methoxy-p-phthalic acid (LXVl) and 3-methoxy-m-phthalic acid (LXVll) do not form phthalides when subjected to formaldehyde and hydrochloric acid, even though the methoxyl group in each case is well positioned for phthalide formation.

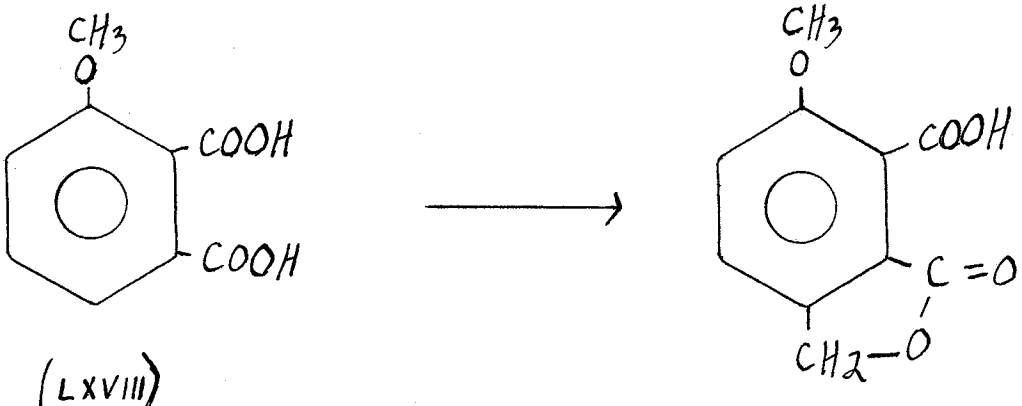


(LXVI)



(LXVII)

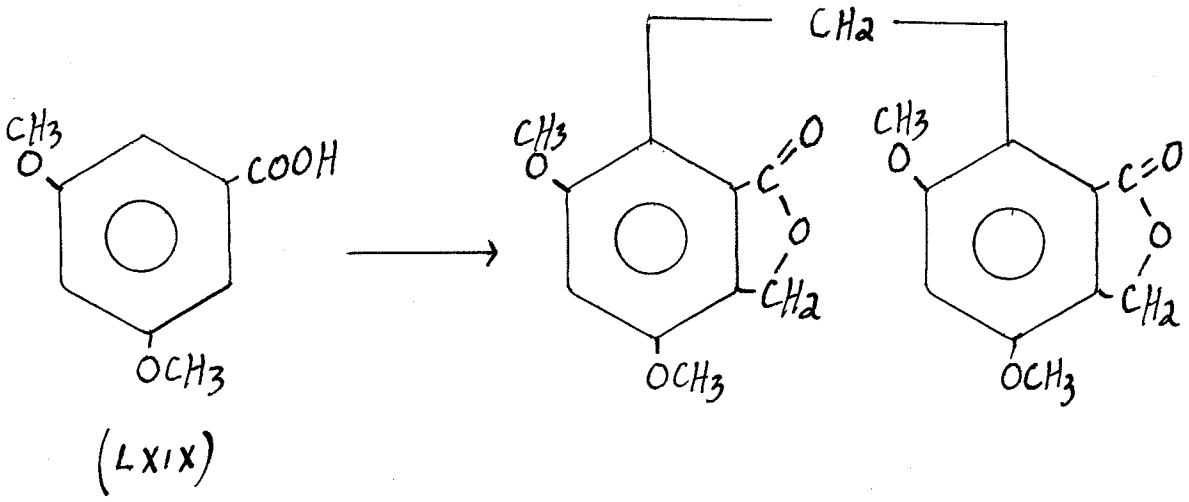
Apparently these two carboxyl substituents deactivate the ring to such an extent, that phthalide formation is not possible. However, when 3-methoxy-O-phthalic acid (LXVlll) was heated with formaldehyde in acid solution, the simple phthalide 5-methoxy-6-carboxyphthalide was produced.



(LXVIII)

This reaction would seem to constitute an exception to the rules. However, a plausible explanation for this behaviour can be found in the fact that the two carboxyl groups ortho to one another, would be forced from the plane of the ring and so reduce the deactivation process to such an extent that phthalide formation could take place.

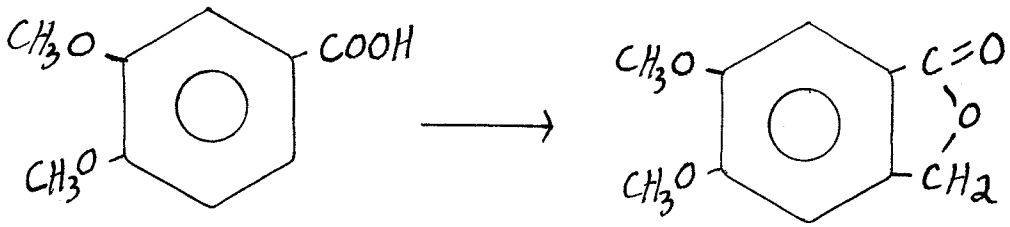
With two strong electron donating methoxyl groups present in the benzene nucleus along with only one carboxyl substituent, the ring is greatly activated. If these methoxyl groups are so situated that they each have a vacancy in the para position, it is impossible in some cases to stop the reaction at the simple phthalide stage. Instead the only products isolated are the chloromethyl-phthalides and diphenyl methane type compounds. For example, it was found that when 3,5-dimethoxybenzoic acid (LXlX) was heated with formaldehyde in acid solution, the only product isolated was an amorphous substance of high melting point which did not effervesce in bicarbonate solution. This material contained no chlorine and was quite insoluble in most organic solvents, and a combustion analysis on this crude material indicated a diphenylmethane type compound. In other words, as soon as any chloromethylphthalide was formed it immediately reacted with the simple phthalide about to produce this amorphous material ,



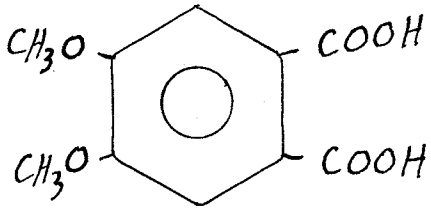
(LXIX)

It was felt that if a simple phthalide or a chloromethyl derivative could not be isolated under normal conditions, perhaps by carrying out this reaction at room temperature these latter compounds could be produced. But here again, two solids were formed, the bulk being the same diphenylmethane type compound mentioned above, while the second solid proved to be unreacted starting material.

Again, it is the position of these electron releasing groups relative to the carboxyl substituent which determine the products formed. For example, when 3,4-dimethoxybenzoic acid is subjected to the condensation reaction, only one product is isolated. This is the simple phthalide 4,5-dimethoxyphthalide. In this case only one para position is vacant and this is ortho to the carboxyl group, thus the simple phthalide below is formed. The second methoxyl group however, has its para position blocked by the carboxyl substituent, thus no further reaction can take place.



It is of interest now to carry this investigation one stage further, so as to consider the case when two carboxyl along with two methoxyl groups are present on the aromatic ring. It would be interesting to postulate results when such a compound as 4,5-dimethoxy-O-phthalic acid (LXX) is heated with formaldehyde, hydrochloric and glacial acetic acid.

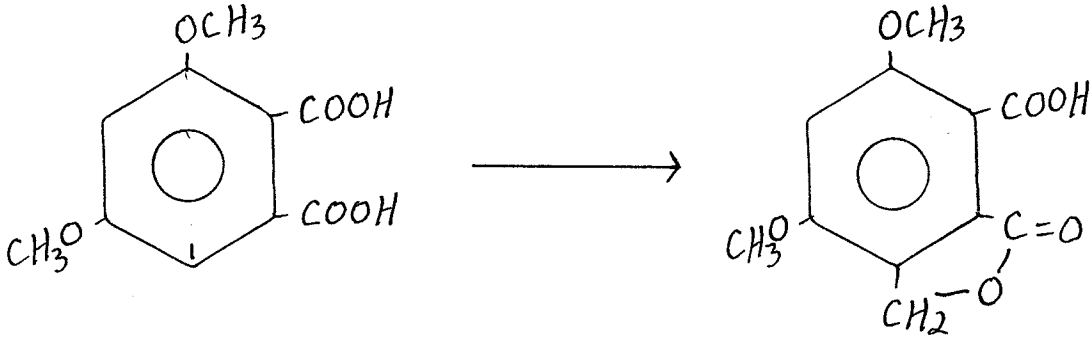


(LXX)

With the two strong electron withdrawing carboxyl and the two strong electron donating methoxyl substituents in the

same ring, a "balance of electron forces" presumably exists. In this case then, with the para positions of the two methoxyl groups blocked, one should expect no reaction to take place. This was actually found to be the case.

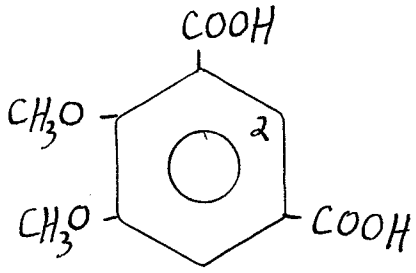
Unfortunately, because of the difficulty involved in the preparation of such acids, the above mentioned 4,5-dimethoxy-O-phthalic acid was the only one of this type which was subjected to condensation conditions. However, it is possible to theorize results one might expect from a consideration of some isomers of this phthalic acid. Consider for example, 3,5-dimethoxy-O-phthalic acid;



This acid should behave very similarily to 3-methoxy-O-phthalic acid as discussed previously. In this case, however, there is a strong ortho-para directing methoxyl substituent ortho to where the chloromethyl group must enter for phthalide formation, i.e. position 1. The simple phthalide 3,5-dimethoxy-6-carboxyphthalide should therefore

be produced very readily in this reaction.

A very interesting compound to react with formaldehyde in acid solution would be 4,5-dimethoxyisophthalic acid.

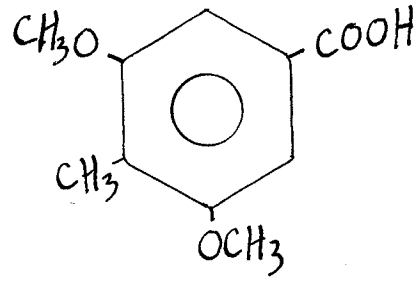


Because the carboxyl groups are not ortho to one another, their entire electron withdrawing effects might "neutralize" the electron donating effects of the two methoxyl substituents so that phthalide formation would be impossible. We suggest however, because of the arrangement of the substituents, that a phthalide would be formed with the chloromethyl group entering at position 2. It would be of great interest of course to know which carboxyl substituent is used if this ring closure did take place.

In conclusion, it could be said that in the two rules just dealt with, a sound method is available for predicting in most cases the products formed when a particular substituted aromatic acid is treated with formaldehyde in acid solution. There are surprisingly few exceptions.

An application of these rules may in some cases shed some light as to why simple phthalides cannot be

isolated from certain condensation reactions. For example, the work of Charlesworth and Robinson (19) who tried to produce the simple phthalide from 4-methyl-3,5-dimethoxy-benzoic acid.



As previously indicated they were only able to isolate a phthalide which contained chlorine. Presumably, the simple phthalide is formed normally because of the vacant positions para to each of the methoxyl groups. But as soon as this phthalide is formed, the last free site, which is para to the second methoxyl substituent is attached so quickly that the simple phthalide cannot be isolated under normal conditions.

Returning to the products obtained in the condensation reaction with 5-methoxy-3-methylbenzoic acid, one can now get some insight as to why only one simple and three chloromethylphthalides were isolated.

Presumably, both simple phthalides (11) and (111) are in fact produced. See chart on page 38. To form phthalide (11), the chloromethyl group enters a position

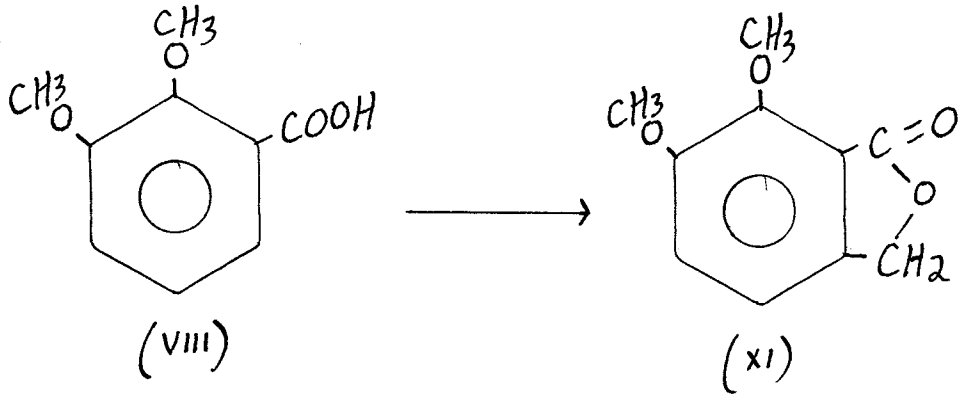
in the benzene nucleus which is para to a strong ortho-para directing group. To produce phthalide (111), the chloromethyl group enters para to a weak electron donating group, but ortho to the strong methoxyl group. Each of these simple phthalides can now give rise to two chloromethylphthalides, so that theoretically one could obtain four chloromethyl derivatives. On examining the simple phthalide (111), there is a vacant position para to the strong electron donating methoxyl substituent. It would seem reasonable then, to say that as soon as this particular simple phthalide is produced, it is immediately converted to the chloromethyl derivatives (V1) and (V11). It is for this reason that the simple phthalide (111) is never isolated from the reaction mixture. On examining phthalide (11), position 3 is opposite a weak ortho-para directing group, and so will not be nearly as reactive as its counterpart in phthalide (111). Because of this the chloromethylphthalide derived from compound (11) is never produced unless the reaction is continued for at least fifteen minutes.

To test these ideas still further, a good supply of both simple phthalides (11) and (111) were produced by the Fritsch method (26). Infra red spectra of these two compounds are reproduced on page 101. When 3-methoxy-5-methylphthalide (111) was heated with hydrochloric acid, formaldehyde and glacial acetic acid for only a length of time necessary to put the phthalide into solution (usually about two minutes), both chloromethylphthalides (V1) and

(Vll) were produced. If the heating period is extended to one hour, again only these latter two compounds are produced, with no evidence of phthalides (lV) and (V). This is a good indication that the phthalide ring is not opened during these reactions. When these reactions are repeated using 3-methyl-5-methoxyphthalide (ll) and heated for this very short period, only starting material was isolated. This would indicate that the simple phthalide (ll) is indeed much less reactive that phthalide (lll). If the heating period is extended to twenty minutes or longer, only one chloromethylphthalide was ever formed. From a careful consideration of the rules outline previously, it is possible to predict which of the two derivatives (lV) or (V) is more likely to be produced. In compound (lV) the chloromethyl group has entered a position para to an ortho-para directing group. In compound (V), the chloromethyl group has entered ortho to this substituent. If then the chloromethylphthalide derived from the simple phthalide (ll) is produced more slowly than those from phthalide (lll), it would seem reasonable to assume that it is compound (lV) which is produced and not (V). This was actually found to be the case.

It is of interest at this point to re-examine the work done by Edwards, Perkin and Stoyle (24) on condensation reactions with veratric and o-veratric acids. As already outlined, veratric acid on heating with formaldehyde in

acid solution for up to twelve hours gave only the expected 4,5-dimethoxyphthalide. No other product is theoretically possible. However, on a closer examination of o-veratric acid (VIII) one might wonder how it is that these authors were able to produce the simple phthalide (XI) and in such relatively high yields.

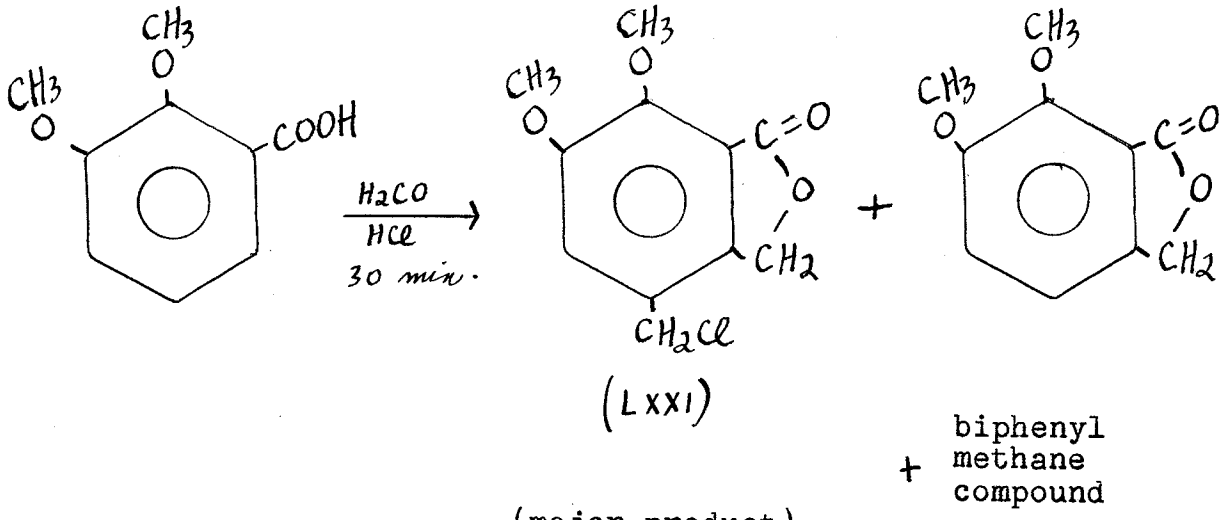


There are two strong electron donating methoxyl substituents along with only one electron withdrawing carboxyl group attached to the benzene nucleus. As discussed above this situation produces a very reactive intermediate and when these substituents are so situated that the para position to both methoxyl groups are vacant, no simple phthalide should be isolatable.

Wilson et al. (74) as already mentioned did form the simple phthalide meconine (XI) from o-veratric acid, but only by carrying out the condensation reaction in the cold. When the procedure of Edwards et al. was followed, these authors were only able to isolate the chloromethyl

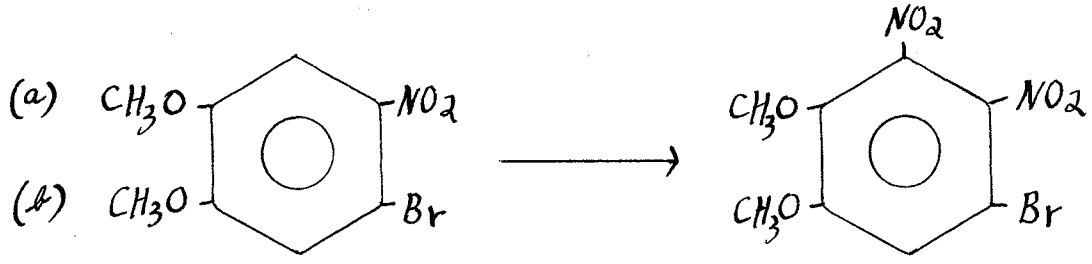
derivative of meconine. Condensation time was not mentioned however.

Similarily, Manske and Ledingham (48) repeated this reaction and isolated three compounds after a heating period of thirty minutes. The major product was 3-chloromethyl-5,6-dimethoxyphthalide (LXXI) with small quantities of the simple phthalide and some biphenylmethane derivative.

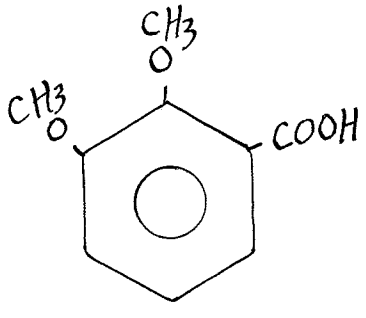


A possible explanation for this discrepancy might lie in the work done by Jones and Robinson (41). These authors directed attention to a number of benzene substituents which appeared to show that when two identical groups such as alkyloxy coexist in a molecule and direct substituents to different positions, the influence of the one which is in the o- or p- position to a negative group (eg. $-NO_2$, -COOH, etc.) is weakened so that the other alkyloxy or

similar group controls the direction taken by the reaction. For example, in the nitration of 4-bromo-5-nitroveratrole, the nitro group diminishes the directive power of the methoxy (b) in the para position to a greater extent than that of (a) in the meta position and therefore the latter induces substitution apparently abnormally, ortho to a nitro group.



Applying this idea to o-veratric acid (VIII), the carboxyl substituent will deactivate the methoxyl group which is ortho to itself.



(VIII)

This particular electron donating substituent is the one responsible for the introduction of the second chloromethyl

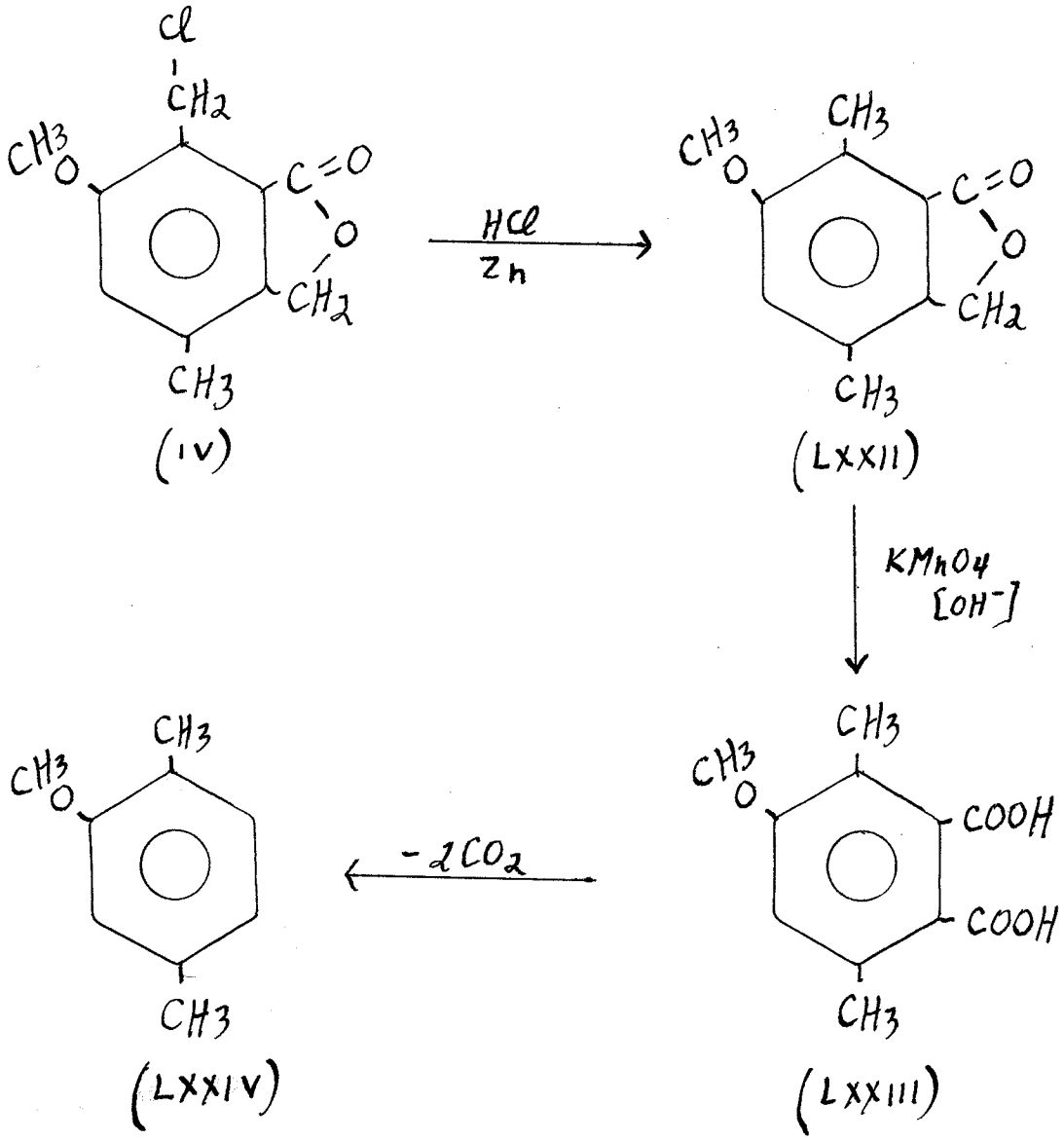
group into the benzene nucleus, thus producing the chloromethylphthalide. Hence, because of the arrangement of the substituents in the aromatic nucleus, this molecule is not so reactive as one would expect, with the result that the simple phthalide is isolatable if the condensation time is kept short.

With the existence of three isomeric chloromethylphthalides postulated, it was now necessary to affix a definite orientation to each and to associate the appropriate phthalide with its corresponding melting point. It is of course necessary only to prove the structure of compound (1V) (or (V)) as derived from the simple phthalide (11) and only one of the two chloromethylphthalides (V1) or (V11) as formed from the simple phthalide (111). Once a definite orientation can be affixed to either (V1) or (V11), the other is immediately known.

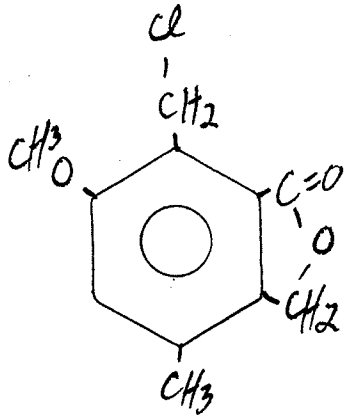
Several means of attack presented themselves. The method indicated below, which would seem to be the simplest and most direct, proved unsuccessful.

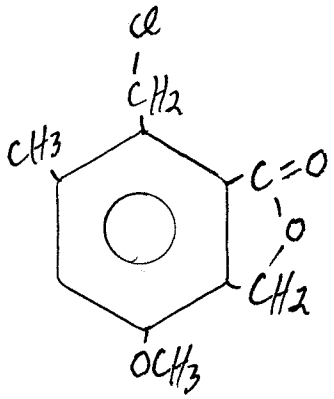
The chloromethylphthalide (1V) on reduction with concentrated hydrochloric acid and zinc dust gave the chlorine free phthalide (LXX11). This material in turn was oxidized to the dicarboxylic acid (LXX111), and on decarboxylation, would presumably yield the 2-methoxy-p-xylene (LXX1V). It was found however that the decarboxylation of the phthalic acid (LXX111) was not possible even when heated with soda line. This decarboxylation

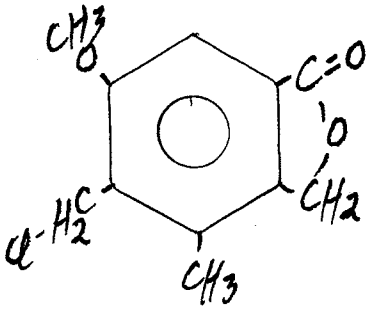
attempt failed also for 3,4-dimethyl-6-methoxyphthalic acid.

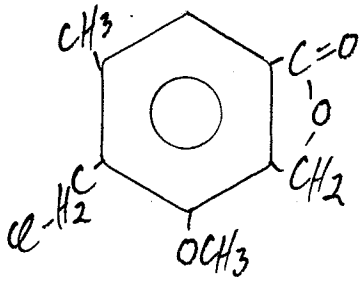


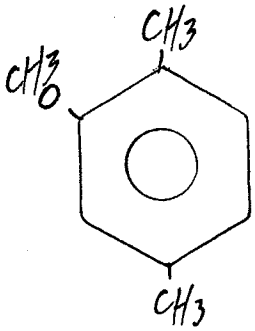
If this series of reactions could have been carried out on all four possible isomers, the following methoxyxylenes would be produced.



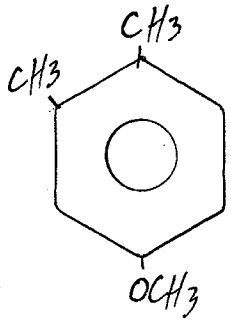




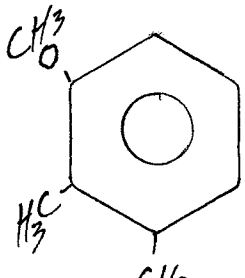




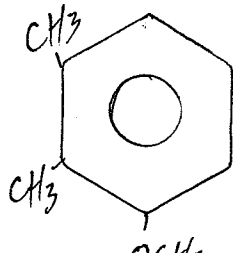
(LXXIV)



(LXXVI)



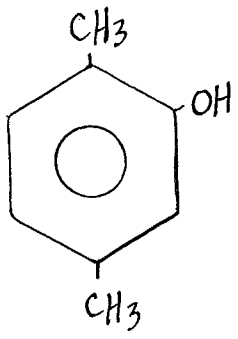
(LXXV)



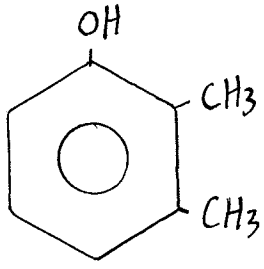
(LXXVII)

same compound

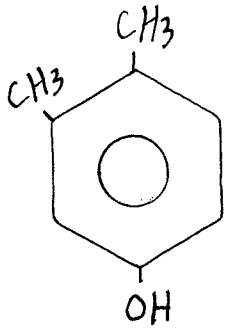
The three phenols shown below, all solids and corresponding to the above methyl ethers are commercially available.



2,5-dimethyl phenol



2,3-dimethyl phenol



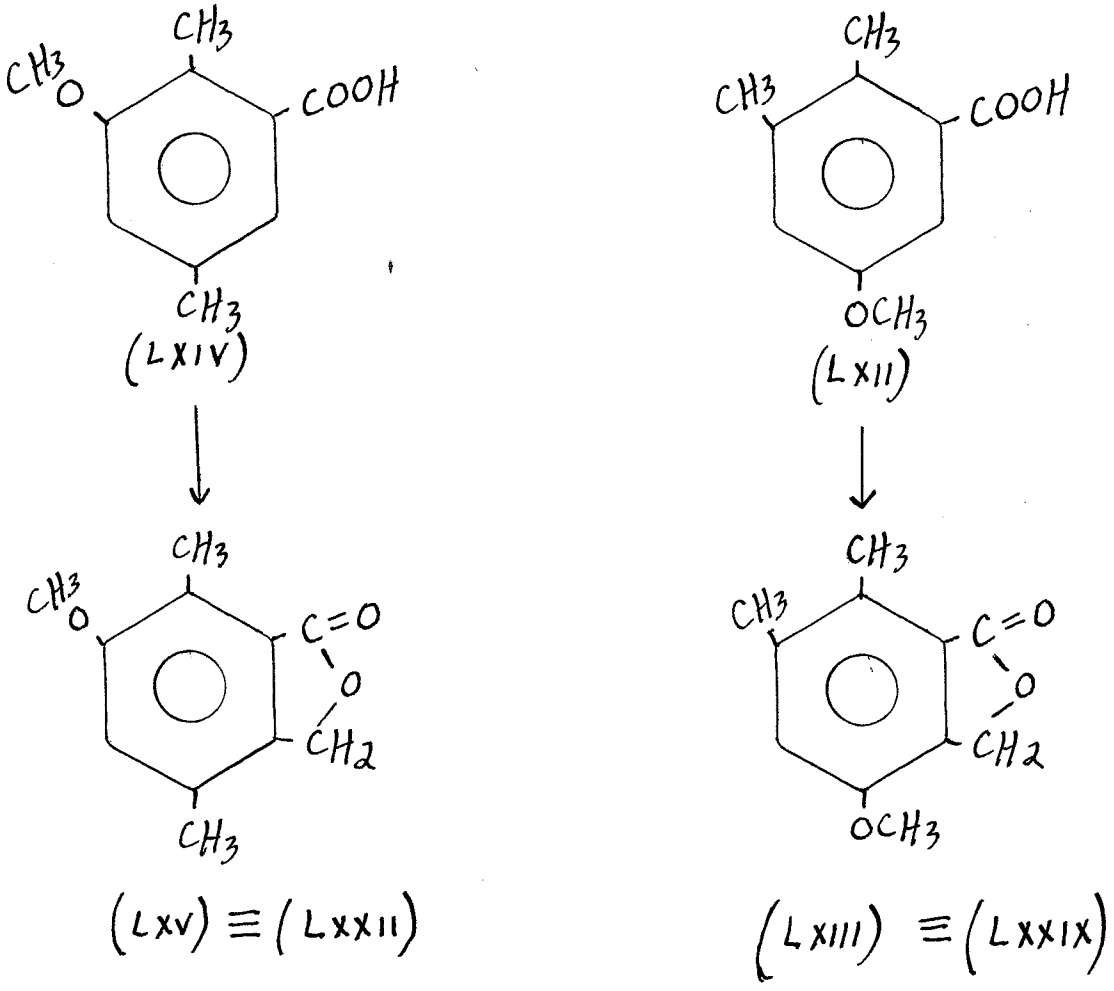
3,4-dimethyl phenol

On methylation, these would yield the products (LXX1V), (LXXV11), (LXXV) (or LXXV1). 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 definite orientation could be established for at least two of the possible three isomers.

It is also possible, by demethylation, to convert compounds (LXX1V), (LXXV), (LXXV1) and LXXV11) to their corresponding phenols. If this were done, mixed melting points would again definitely establish the orientation for two of the three isomers.

A second attack on this problem, and one which eventually proved successful, involved a synthesis of the two substituted aromatic acids (LX1V) and (LX11). Once

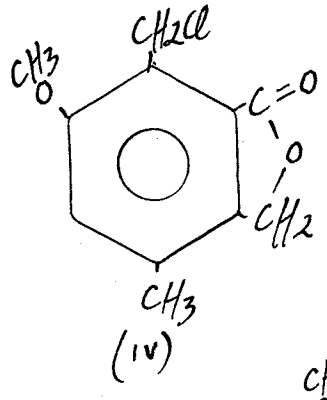
these acids were available, they were heated with hydrochloric acid, formaldehyde and glacial acetic acid to produce the corresponding phthalides (LXV) and (LXlll).



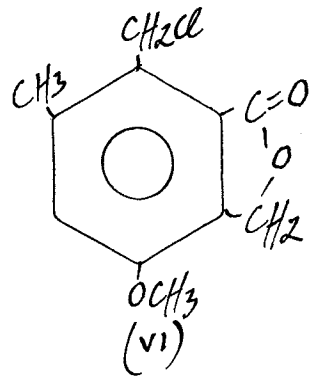
In compound (LXlV) there is a vacancy which is ortho to the carboxyl substituent and also para to a strong electron donating methoxyl group. Hence, one would expect phthalide formation to take place and in fact, this was actually found to be the case. In compound (LXll) there is a weaker methoxyl group in this para position, but a strong methoxyl substituent ortho to where the chloromethyl group must enter for phthalide

formation. Again this ring closure proceeds very smoothly.

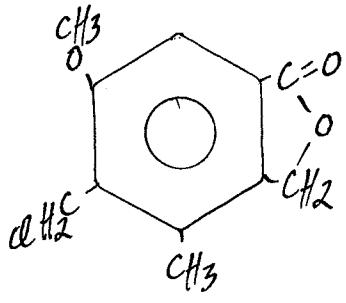
Now, reduction of the four theoretically possible chloromethylphthalides (1V), (V), (V1) and (V11) derived from 5-methoxy-3-methylbenzoic acid, would yield the corresponding chlorine free phthalides (LXX11),(LXXV11),(LXX1X) and (LXXX).



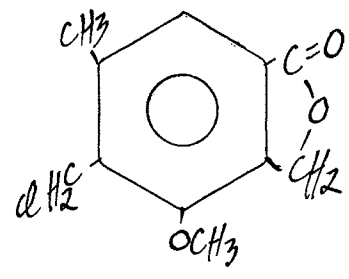
(1V)



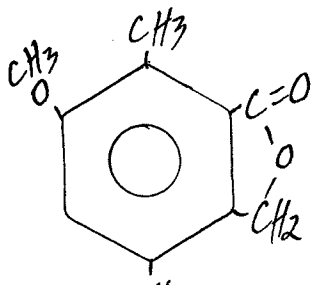
(V1)



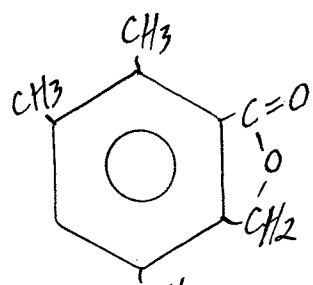
(V)



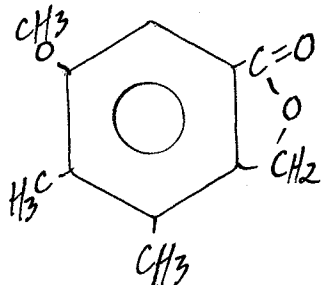
(V11)



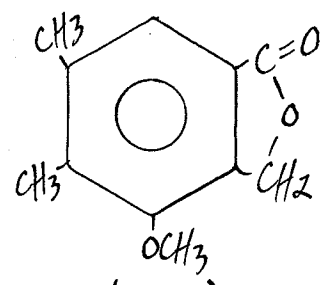
(LXX11)



(LXX1X)



(LXXV11)

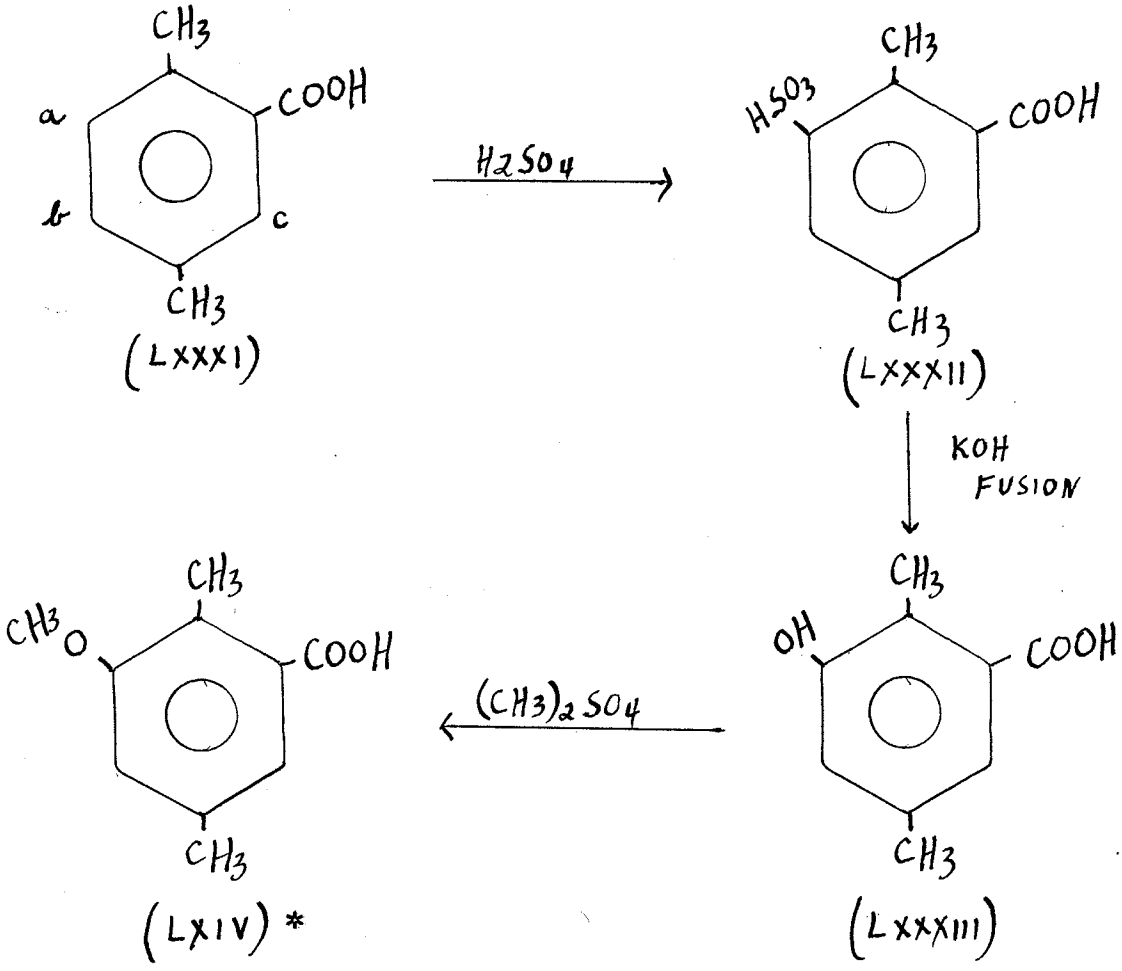


(LXXX)

The phthalide (LXV), prepared synthetically from 2,5-dimethyl-3-methoxybenzoic acid (LX1V), melted at 169.5 - 179.5°, and mixed melting points and infra red spectra showed this compound to be identical with isomer (LXX11). Compound (LXX11) was derived from the chloromethylphthalide (1V) of melting point 178.0 - 179.5°. In this way then, the orientation of phthalide (1V) is definitely established. Because of the fact that only one chloromethyl isomer is produced from the simple phthalide 3-methyl-5-methoxyphthalide (11), it follows that the chloromethylphthalide of structure (V) is not produced in the original condensation reaction, thus confirming the theoretical predictions already made by a careful consideration of the rules dealing with phthalide formation.

Similarily, phthalide (LX111) as derived from 2,3-dimethyl-5-methoxybenzoic acid (LX11), melted at 179.5-180.5° and was shown to be identical to compound (LXX1X), thus definitely establishing the orientation of chloromethyl-phthalide (V1) of melting point 134.0 - 135.0°. Of course once the orientation of this particular phthalide is established, it follows that the chloromethylphthalide corresponding to the melting point of 152.5 - 154.0° must have the structure as shown for (V11).

The synthesis of 2,5-dimethyl-3-methoxybenzoic acid (LX1V) was carried out as follows:-



(LXXX1) (LXXX11) (LXXX111) (LX1V) *

2,5-Dimethylbenzoic acid (LXXX1) was heated with fuming sulphuric acid to give the sulphonic acid (LXXX11). After conversion to the sodium salt, this acid on alkali fusion produced phenol (LXXX111). Methylation with dimethyl sulphate gave the required 2,5-dimethyl-3-methoxybenzoic acid (LX1V).

There are three possible positions where the sulphonic acid substituent may enter when the above aromatic acid (LXXX1) is sulphonated. If attack took place at carbon c so as to yield after fusion and methylation an

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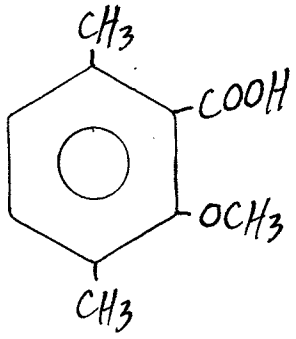
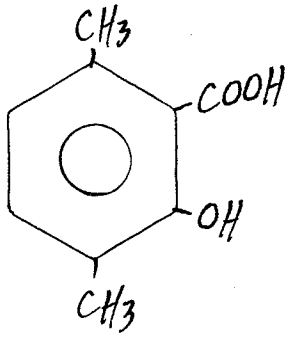
* Confirmation of the structure of (LX1V) and (LX11) could also be provided by NMR spectroscopy.

acid of structure (LXXXIV),



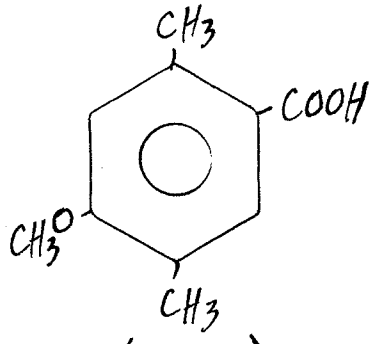
(LXXXIV)



(LXXXV)

no phthalide formation would be possible because no position ortho to the carboxyl group is vacant. However, a phthalide was produced in this reaction. Also a ferric chloride test on the substituted salicylic acid (LXXXV) should produce a vivid colour change. No colour reaction was observed. The structures corresponding to (LXXXIV) and (LXXXV) can therefore be ruled out.

If the sulphonic acid group had entered position b in acid (LXXXI), one would then obtain for the final product the known 4-methoxy-2,5-dimethylbenzoic acid (LXXXVI),



(LXXXVI)

first prepared by Gattermann (30),(31),(32) and synthesized for our purposes by modifications of this method.* These modifications, which were described by Adams and his co-workers, (1), (2), employ zinc cyanide as both a convenient source of anhydrous hydrogen cyanide and as a catalyst. When hydrogen chloride is introduced into the reaction mixture, hydrogen cyanide and zinc chloride are formed "in situ". Zinc chloride appears to be an ineffective condensing agent for mono-phenols or their alkyl ethers. In these cases aluminum chloride must be used, and it may be introduced along with zinc cyanide.

The methoxydimethylbenzoic acid which was produced through the sulphonation, alkali fusion and methylation of 2,5-dimethylbenzoic acid (LXXXl), was not identical to the corresponding known acid made as described above by the modified Gattermann method. Hence, the sulphonic acid substituent could only have entered position a when compound (LXXXl) was sulphonated and therefore possesses structure (LXXXll).

The synthesis of 2,3-dimethyl-5-methoxybenzoic acid (LXll) was carried out in a similar manner to the previously discussed acid. The steps involved are as follows:

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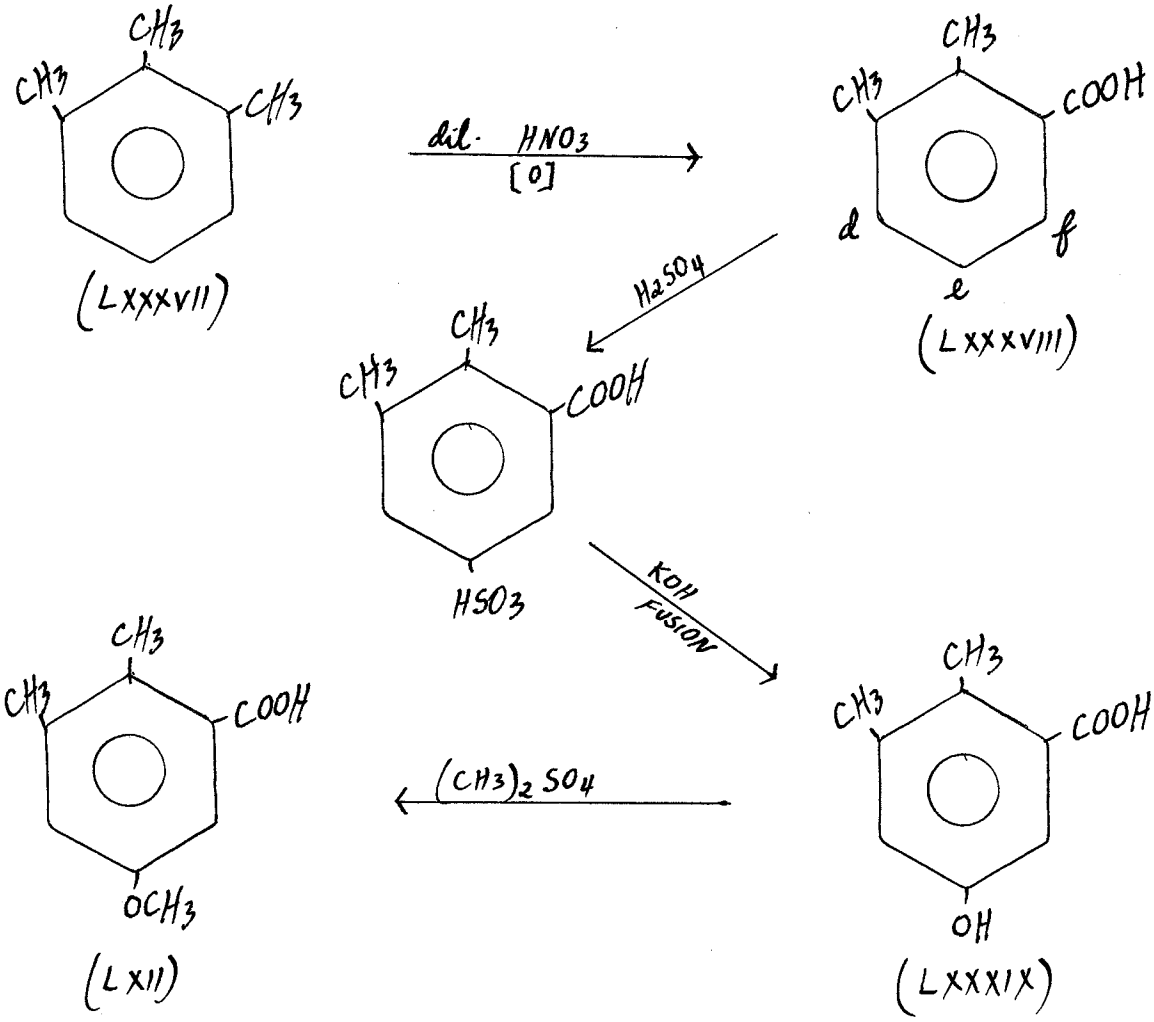
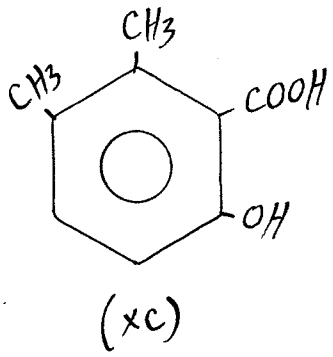
* A good review on the Gattermann reaction is given by W.E.Truce, Organic Reactions, Vol.lX, P.37.



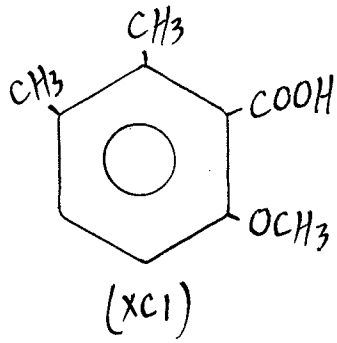
The mono-carboxylic acid (LXXXVlll) was produced from hemimellitene (LXXXVll) on oxidation with dilute nitric acid. This acid was sulphonated and the sodium salt of the sulphonic acid thus formed was subjected to an alkali fusion to yield the phenol (LXXXlX), which on methylation produced the required acid (LXll).

As in the previous case, the sulphonic acid substituent can enter three possible positions. If substitution of compound (LXXXVlll) took place at carbon f, the two final products formed would be 2,3-dimethyl-6-hydroxybenzoic acid (XC) and 2,3-dimethyl-6-methoxybenzoic

acid (XC1).

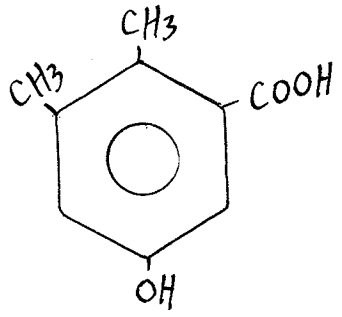


(xc)

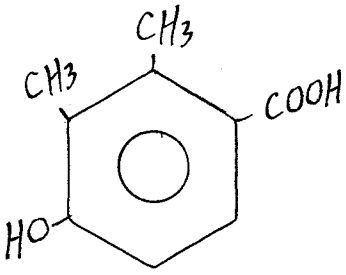


(XC1)

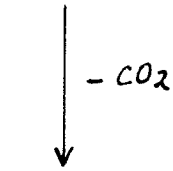
The substituted salicylic acid (XC) would be expected to produce a vivid colour reaction with ferric chloride solution; this however was not observed when this treatment was carried out. Also it would be impossible for compound (XC1) to produce a phthalide as no vacant ortho position exists next to the carboxyl substituent. However, a phthalide was produced. Substitution at carbon f can therefore be ruled out. It is a relatively simple matter now, to decide whether carbon d or e was attacked. If acids (LXXX1X) and (XC11), which represent the two remaining possibilities are decarboxylated, 3,4-dimethylphenol (XC111) and 2,3-dimethyl-phenol (XC1V) would be produced. These two substituted phenols, shown below, are solids and are commercially available. The original phenolic acid prepared synthetically was shown to be identical to compound (XC111) after decarboxylation, so that it is position e on acid (LXXXV111) which is in fact attacked on sulphonation.

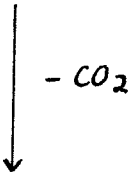


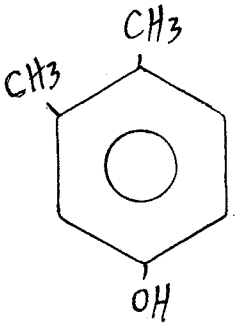
(LXXXIX)



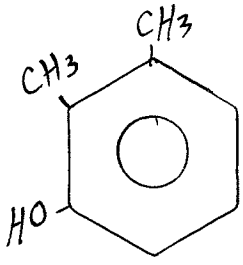
(XCII)







(XCIII)

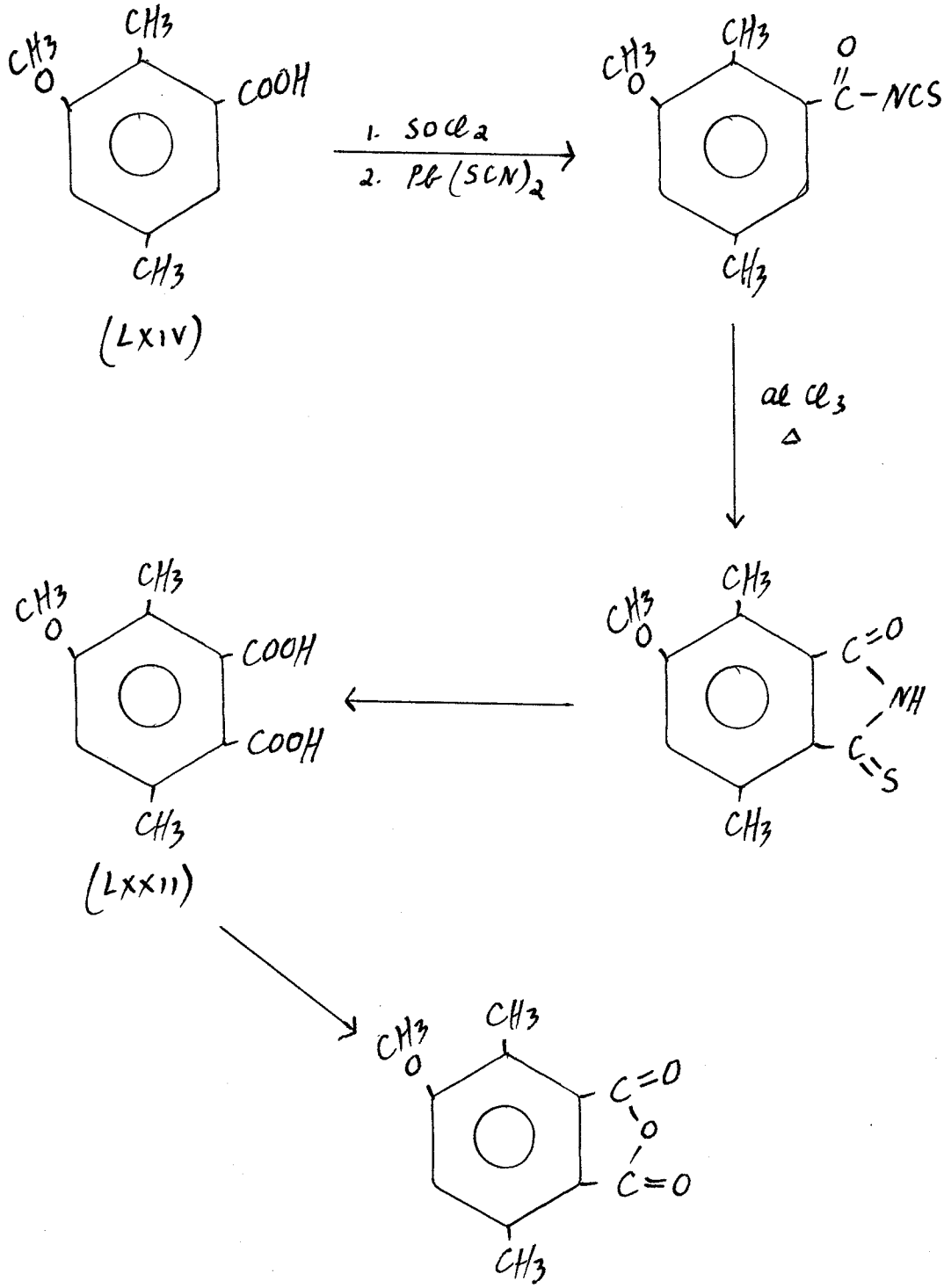


(XCIV)

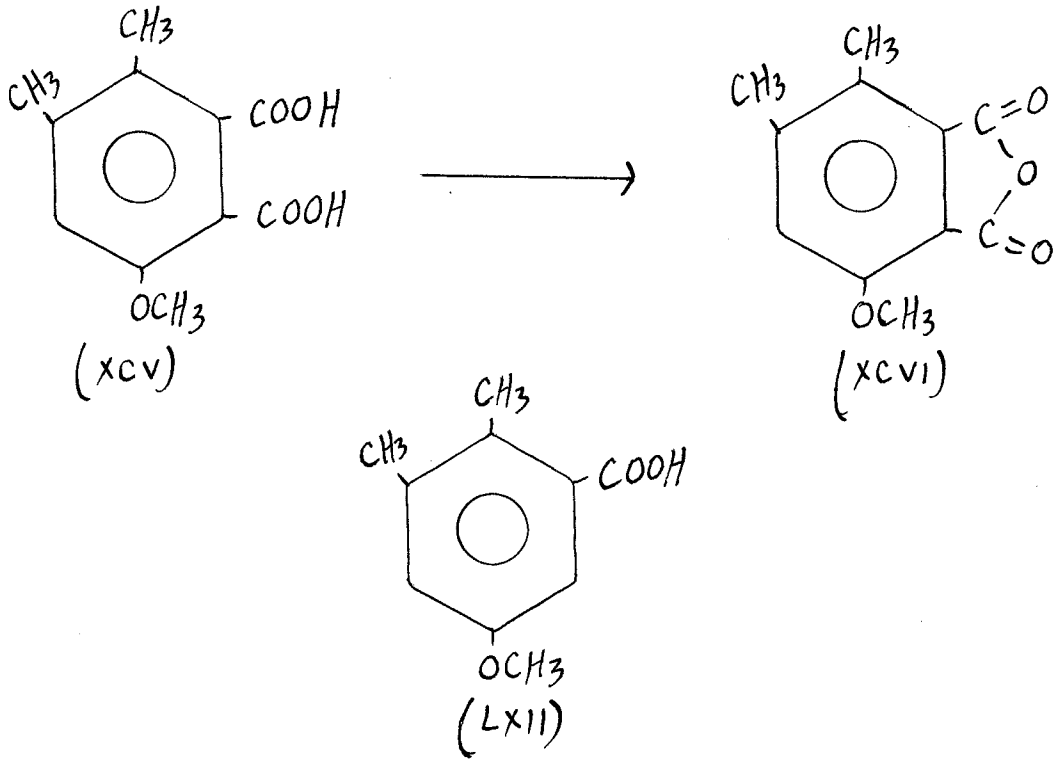
In 1960, a very interesting paper by Smith and Kan (69) was published. It dealt in part with a simple reaction for converting substituted benzoic acids to phthalic acids. The acids are converted through their chlorides by reaction with lead thiocyanate to acyl isothiocyanates which are cyclized to monothio-phthalimides or -homophthalimides by treatment with aluminum chloride in carbon disulphide. The cyclization of benzoyl isothiocyanates appears to require the presence of an activating meta substituent.

Applying this series of reactions to 2,5-dimethyl-3-methoxybenzoic acid (LXIV) for example, one should obtain

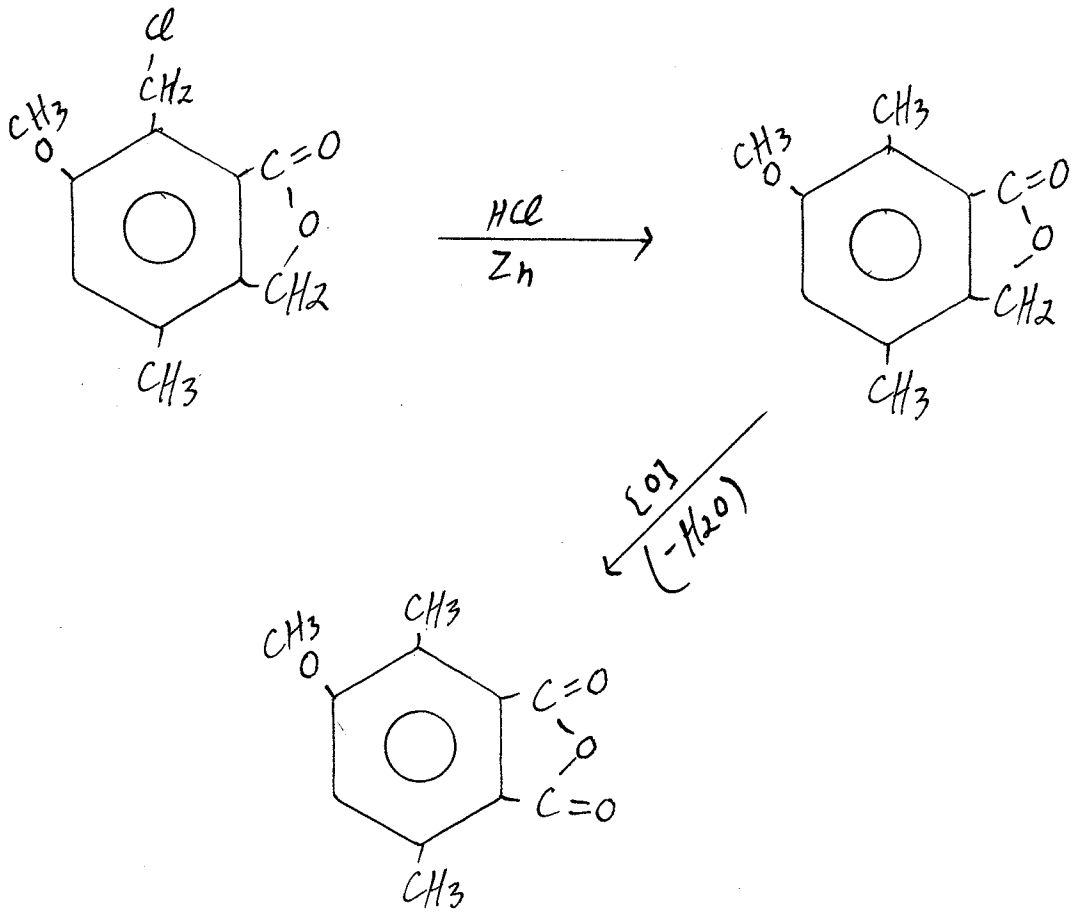
3,6-dimethyl-4-methoxyphthalic acid (LXXll). This acid could in turn be converted very easily into its anhydride.



If these reactions were repeated on 2,3-dimethyl-5-methoxybenzoic acid (LXll), one would obtain the corresponding phthalic acid (XCV). This acid could again be converted quite easily to its anhydride (XCVl).



The orientation of these two anhydrides are therefore fixed by this method. There are three anhydrides formed from the three chloromethylphthalides produced in the condensation reaction with 5-methoxy-3-methylbenzoic acid, as previously outlined. For example, taking 3,6-dimethyl-5-methoxyphthalide as a convenient example, one obtains the following anhydride.



By a comparison of mixed melting points of the known anhydrides and those produced as outline immediately above, definite orientation could be assigned to the three chloromethylphthalides. (see table 2, page 46).

EXPERIMENTAL

Preparation of 5-Methoxy-3-methylbenzoic Acid

Two methods were used in the synthesis of this acid.

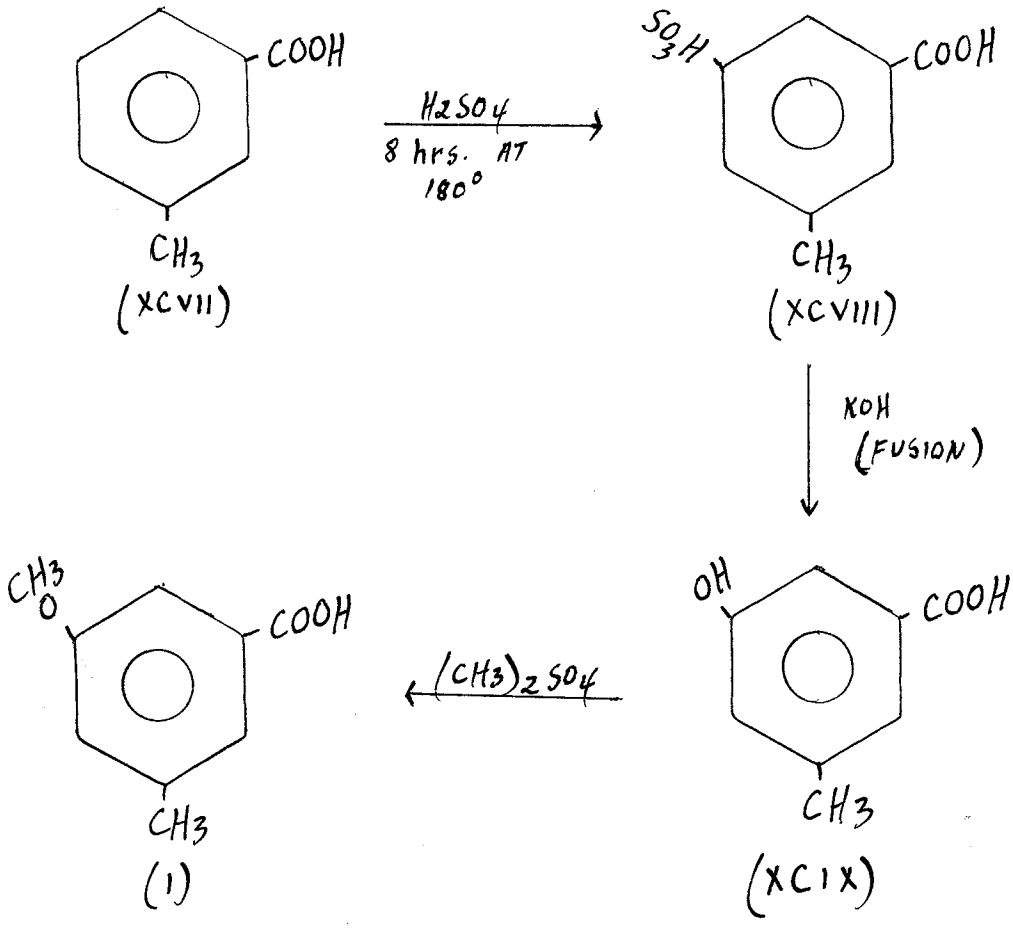
Method 1

Most of the acid required for this investigation was synthesized from 3-methylbenzoic acid (XCVll), obtained from the Aldrich Chemical Company, Milwaukee, and which gave subsequently through the 5-sulpho-(XCVlll) and 5-hydroxy-3-methylbenzoic acids (XClX) the required 5-methoxy-3-methylbenzoic acid (l). A small amount of 3-methylbenzoic acid was originally prepared by hydrolysis of 3-cyanotoluene in accordance with the directions given by Cohen (22).

a) Sulphonation of m-toluic acid

The 3-methylbenzoic acid obtained above was sulphonated by the method of Meldrum and Perkin (50). 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-sulpho-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.



b) 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 the 5-hydroxy-3-methylbenzoic acid was very badly contaminated with an oily substance

which could not be removed. This oily material was probably due to some oxidation of the phenol.

The crude 5-sulpho-3-methylbenzoice acid (XCVlll) obtained from 60 grams of the 3-methylbenzoic acid was thoroughly dried as outlined above. Potassium hydroxide pellets (285 g), with water (8-10 ml) were heated in a nickel crucible to a temperature of 180 - 200°. All the crude sulpho-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 water (700 ml). The solution was neutralized with dilute sulphuric acid, and made slightly alkaline with 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, when a thick, light brown precipitate settled. Normally, only one crystallization from water was necessary to get a relatively pure product which melted at 207.0 - 208.5°.

c) Methylation of 5-hydroxy-3-methylbenzoic acid

The method used was essentially that of Tambor (72),

and utilized by Anderson (16). 5-Hydroxy-3-methylbenzoic acid (20g) was dissolved in sodium hydroxide solution (100 ml, 20%) in a three neck flask. While the solution was cooled and stirred in an atmosphere of nitrogen, dimethyl sulphate (35 g) was added in three portions over 15 minutes. The reaction mixture was stirred ½ hour longer, then sodium hydroxide (5g) 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, a little charcoal, being used to remove coloured impurities, 5-methoxy-3-methylbenzoic acid (13 - 15 g) was obtained as fine white needles which melted at 135 - 136°.

An attempt was made to improve the yield and also to shorten the time require in the preparation of the hydroxy acid (XClX) above. The method used involved the conversion of the sulphonic acid directly into its sodium salt. The sodium salt thus isolated, could be dried in an oven, and this material was much easier to handle and gave no trouble in the alkali fusion step. By this procedure, an increase in yield of the 5-methyl-3-hydroxybenzoic acid (1) of from 20 - 30% was obtained.

M-toluic acid (60 g) was heated with fuming sulphuric acid (20% SO_3) for three hours at 120 - 130°. The dark solution was cooled, and poured into cold water (1200 ml). The acid solution was partially neutralized by adding carefully and in small portions solid sodium bicarbonate (60 g). Sodium chloride (150 g) was then added and the solution heated until it dissolved. This mixture was placed in the cold for a standing period of one to two days, at which time a light brown precipitate had formed. The crude sodium salt was filtered by suction using a sintered glass funnel, then washed with a saturated sodium chloride solution. The precipitate was dried in an oven at 110°. Yield 75 grams.

The alkali fusion was carried out as follows: The dry sodium salt of the sulphonic acid obtained above was added to a KOH (320 g) - H_2O (3 ml) melt at 170 - 180°. This would require approximately ten minutes. There was no splattering or frothing and in this respect is a great improvement over the first method. The solution was then taken to 270° and held there for ½ hour. The procedure followed now was identical to that outlined by the method above. Yield of 5-methyl-3-hydroxybenzoic acid was 30 grams (50%) based on 60 grams of the starting m-toluic acid.

Method 2

A smaller amount of 5-hydroxy-3-methylbenzoic acid

was prepared from ethyl acetopyruvate (55), much according to details given by Meldrum and Perkin (50) and outlined by Yan (76). Although this method produced 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 Edwards, Perkin and Stoyle (24) as modified by Rây and Robinson (64). 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.

I Condensation time 2 minutes or less.

5-Methoxy-3-methylbenzoic acid (4 g), concentrated hydrochloric acid (25 ml), aqueous formaldehyde (10 ml, 37%) 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 (11)

Cold water was added to the filtrate obtained above, when a white precipitate settled. This mixture was allowed to stand in the cold over night at which time the precipitate was filtered and washed with water. Repeated crystallization from ethyl alcohol (95%) finally produced the 5-methoxy-3-methylphthalide (11) which melted at 105 - 106°. Yields would range from 0.7 - 0.9 grams.

Analysis

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

Found C, 66.89%; 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 diphenylmethane resin type compound. This material was not examined further.

b) Isolation of the two chloromethylphthalides of melting point 134.0° - 135.0° (V1) and 152.5 - 154.0° (V11)

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 remove coloured impurities. The dry white crystals were subjected to small portions, (approximately 5 ml), of boiling ethyl alcohol while the crude product was still on the filter funnel. This was continued until all of the more soluble material (A) was gone, usually 4 to 6 portions of ethyl alcohol were necessary. This 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 which melted at 152.5 - 154.0° was obtained. Approximate yields were 0.6 grams.

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 which melted at 134.0 - 135.0°. Yields ranged from 0.9 to 1.1 grams.

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 15 minutes and longer

Isolation of the chloromethylphthalide of melting point 178.0 - 179.5° (IV)

The procedure followed here was identical to that in part 1, except, of course, for the length of time the condensation was continued. The 5-methoxy-3-methylphthalide (11) was recovered as before. In this case, however, the

two chloromethylphthalides isolated from the yellowish precipitate were the 134.0 - 135.0° (A) and the 178.0 - 179.5° (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), isomer (C) being the less soluble. Yields of this latter compound ran as high as 2.1 grams.

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%

When the condensation was continued for one hour or longer, a white precipitate began to settle out of solution. This proved to be more of the 178.0 - 179.5° isomer in a relatively pure state.

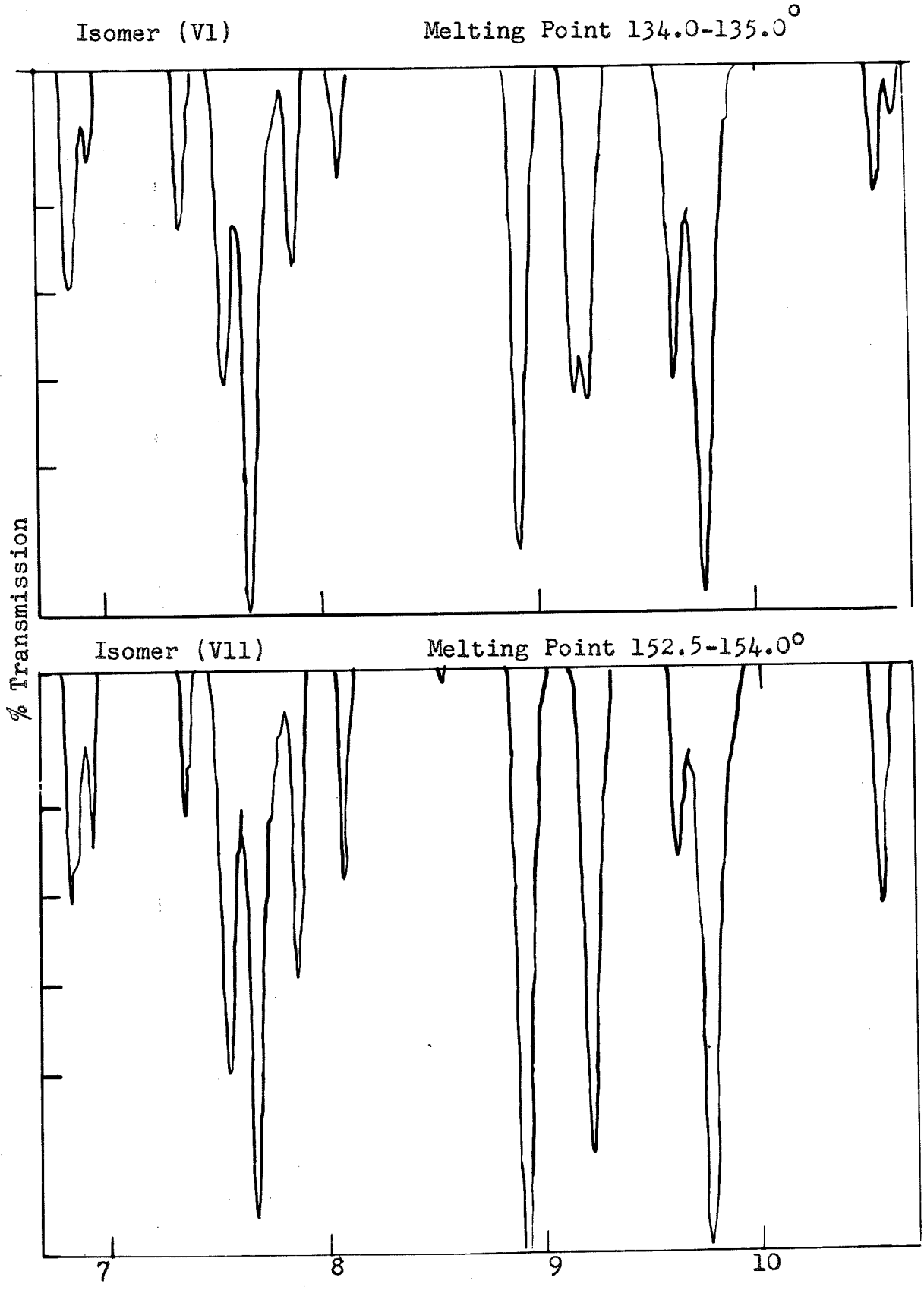
Infra red spectra were obtained for the three chloromethylphthalides A (Vl), B (Vll) and C (lV) isolated previously. These were taken on a Perkin - Elmer model 21 spectrophometer and are represented on pages 95 and 96.

sample cell size - 0.5 mm.

reference cell size (CCl_4) - 0.5 mm.

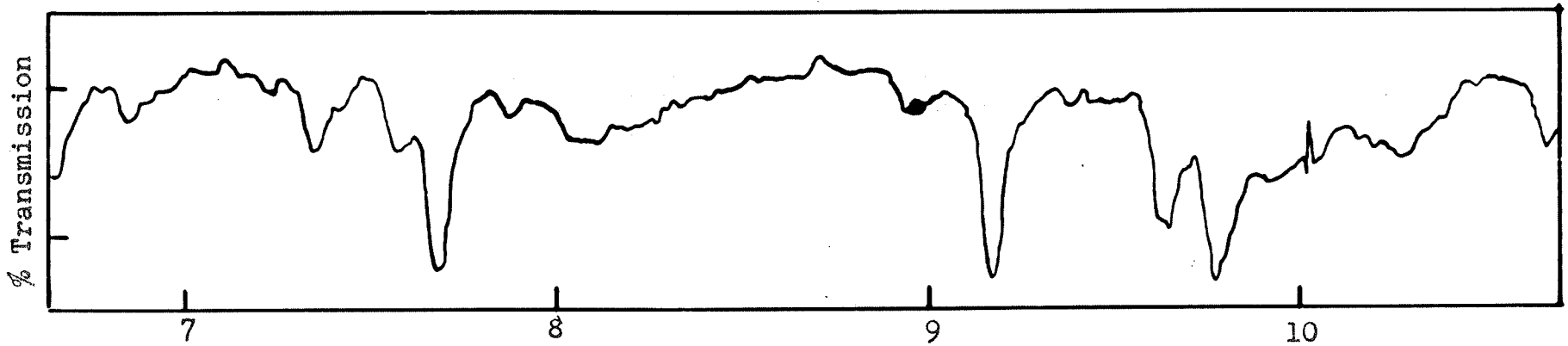
Saturated solutions of the three phthalides were prepared by dissolving these compounds in hot carbon tetrachloride, and then allowing the solutions to cool to room temperature. Excess material was filtered off and a

Infra Red Spectra of Chloromethylphthalides
- A(V1) and B(V11) in Carbon Tetrachloride



Infra Red Spectrum of Chloromethylphthalide
C(1V) in Carbon Tetrachloride.

Melting Point 178.0-179.5°



Wavelength (microns)

small amount of carbon tetrachloride was then added to each of the clear filtrates.

The chloromethylphthalide C proved to be only slightly soluble in carbon tetrachloride so that concentrated solutions could not be obtained. For this reason, spectrum C was not as clear as those for A and B. However, the three 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 μ and 9.23 μ), single peak in B (9.23 μ)
2. double peak in A (10.56 μ and 10.66 μ), single peak in B (10.56 μ)
3. small peak at B (8.55 μ), not present in A.

Some differences to be noted between the spectra of compound C and either A or B are:

1. no peak in C at 6.91 μ
2. no peak in C at 8.90 μ

Fritsch Synthesis (26)

1. Preparation of 5-methoxy-3-methylphthalide (11)

The method followed here was essentially that of Meldrum (49).

a) 5-Methoxy-3-methyl-α-trichloromethylphthalide (L11)

5-Methoxy-3-methylbenzoic acid (5 g), chloral hydrate (5 g), 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 for 36 hours, a gummy substance formed in the solution. This crude material was collected and washed with aqueous alcohol (50%). Crystallization from methyl alcohol (charcoal) produced white crystals of 5-methoxy-3-methyl-α-trichloromethylphthalide, (4.4 g) which melted at 114.5 - 116.0°. Concentration of the filtrate gave a second crop of crystals (0.5 g).

b) 5-Methoxy-3-methyl-α-carboxyphthalide

5-Methoxy-3-methyl-α-trichloromethylphthalide (4.8 g) and ethyl alcohol (6.0 ml, 95%) were heated together until the alcohol began to boil. Much heat was evolved when aqueous sodium hydroxide solution (25 ml, 15%) was added, producing a dark violet colouration. The solution was kept at 50 - 60° when a red precipitate began to form. After one hour, this solid was collected and the filtrate which contained a mixture of 5-methoxy-3-methyl-α-carboxyphthalide and 3-methoxy-5-methyl-α-carboxyphthalide was saved. The red solid collected above was dissolved in water and coloured impurities removed with a little charcoal. The aqueous solution was acidified with dilute hydrochloric acid, giving a yellow oil, and then cooled overnight. Fluffy white crystals then formed. These were

collected and recrystallized from acetic acid to yield 5-methoxy-3-methyl-α-carboxyphthalide (0.4 g) which melted at 168 - 170°.

c) 5-Methoxy-3-methylphthalide (11)

5-methoxy-3-methyl-α-carboxyphthalide (0.21 g) and naphthalene (0.7 g) 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 (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 1 (a), showed no depression in melting point.

A second method for this decarboxylation was attempted and proved very successful. This involved heating the dry acid phthalide in an oil bath held at 190 - 200°. Effervescence continued for 15 minutes. The dark residue was taken up in hot ethyl alcohol and treated with charcoal to remove coloured impurities. On cooling the required 5-methoxy-3-methylphthalide precipitated out.

Although the yields of product formed are comparable in both methods, the simple phthalide is produced

more easily by this latter procedure.

2. Preparation of 3-methoxy-5-methylphthalide (111)

a) 3-Methoxy-5-methyl-α-carboxymethylphthalide

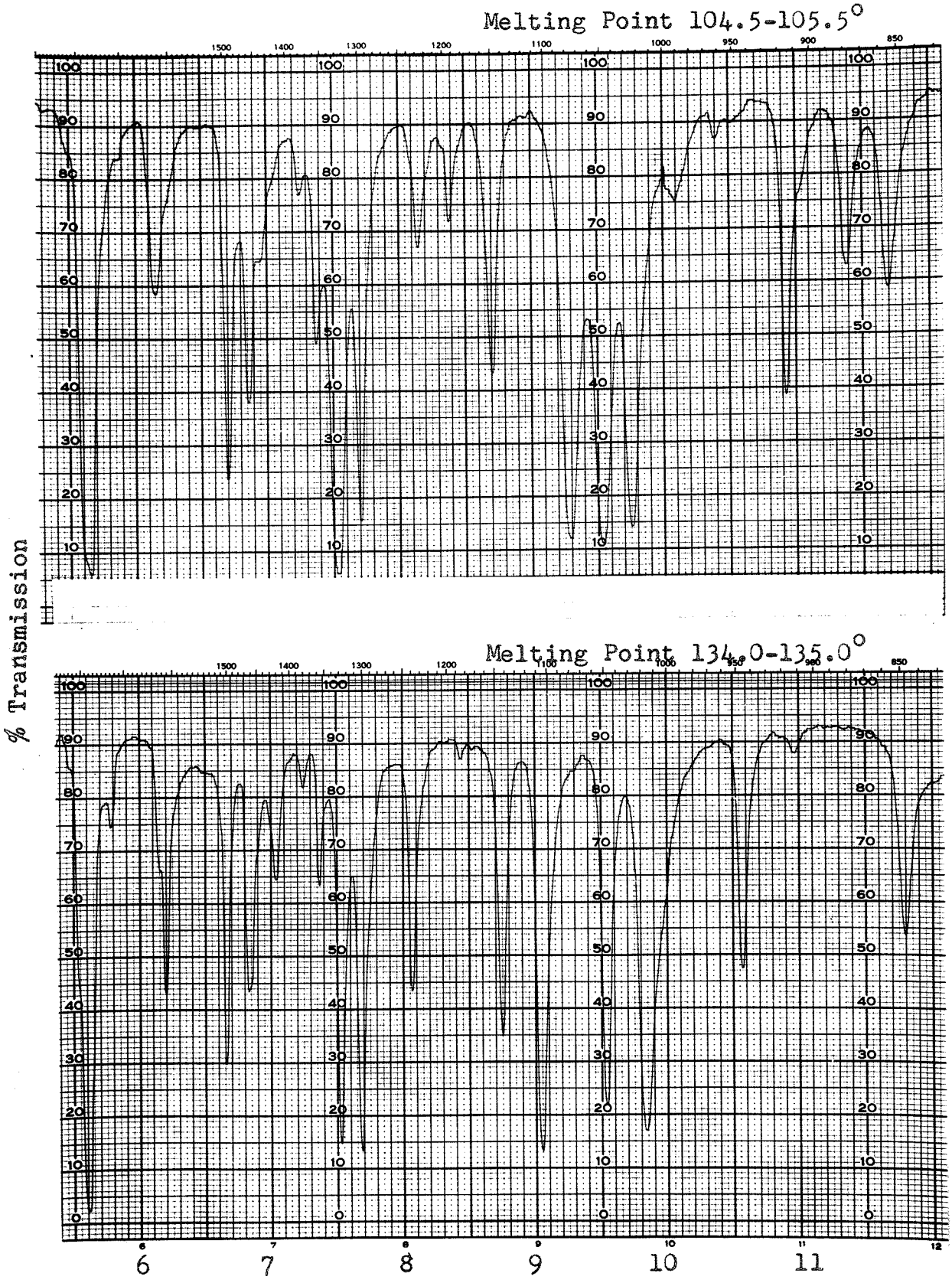
The solution saved from above (1 (b)) which contained a mixture of 5-methoxy-3-methyl-α-carboxyphthalide and 3-methoxy-5-methyl-α-carboxyphthalide was acidified with dilute hydrochloric acid and made slightly alkaline with solid sodium hydroxide. The solution was boiled to remove alcohol, cooled and acidified with concentrated hydrochloric acid. An orange precipitate formed when left in the cold overnight. This solid was recrystallized from glacial acetic acid (charcoal), and represents a mixture of two isomeric organic acids which can be separated by their calcium salts. In most cases, however, it was found that the 3-methoxy-5-methyl-α-carboxymethylphthalide would separate without converting to the calcium salt. This latter compound (3.1 g) was recrystallized from glacial acetic acid and melted at 186.0 - 187.0°.

b) 3-Methoxy-5-methylphthalide (111)

Both methods outlined above were used successfully in the decarboxylation of the α-carboxyphthalide to form phthalide (111). The melting point of this substance was 134.0 - 135.0°.

Infra red spectra of these two isomeric simple phthalides (11) and (111) in carbon tetrachloride are reproduced on page 101.

Infra Red Spectra of the Simple Phthalides (11) and (111) in Carbon Tetrachloride



Formation of the Three Chlorine-free Phthalides (LXXll), (LXXlX) and (LXXX)

The method used in these reductions was similar to that outlined by Holmes and Trevoy (38) in their reduction of 5,6-dimethoxy-3-chloromethylphthalide to 5,6-dimethoxy-3-methylphthalide, but with slight modifications.

1. Preparation of 3,6-dimethyl-5-methoxyphthalide (LXXll)

3-Methyl-5-methoxy-6-chloromethylphthalide (3.5 g) of melting point 178.0 - 179.5°, zinc dust (3.7 g), concentrated hydrochloric acid (10 ml) and ethyl alcohol (75 ml, 95%) were refluxed overnight. Excess hydrochloric acid was added until all the zinc had dissolved. The solution was cooled, and a thick white precipitate formed on addition of cold water (75 ml). The solid was collected, washed well with water and allowed to dry. Crystallization from ethyl alcohol (95%) produced white crystals (3.2 g) which melted at 169.5 - 170.0°. Sodium fusion on this material gave a negative test for chlorine.

Analysis:

Calculated for $C_{11}H_{12}O_3$:- C, 68.7%; H, 6.26%

Found: C, 68.3%; H, 6.15%

2. Preparation of 5,6-dimethyl-3-methoxyphthalide (LXXIX)

The procedure was identical to that above except that 5-methyl-3-methoxy-6-chloromethylphthalide which melted at 134.0 - 135.0° was used. Melting point of the corresponding chlorine free phthalide was 179.5 - 180.5°. Yields ran from 85 to 95%.

Analysis:

Calculated for $C_{11}H_{12}O_3$:- C, 68.7%; H, 6.26%

Found: C, 68.5%; H, 6.29%

3. Preparation of 4,5-dimethyl-3-methoxyphthalide (LXXX)

Procedure is identical to that outlined above except that 5-methyl-3-methoxy-4-chloromethylphthalide which melted at 152.5 - 154.0° was used. The melting point of the chlorine free phthalide after reduction was 174.0 - 175.5°. Yields are similar to those above.

Analysis:

Calculated for $C_{11}H_{12}O_3$:- C, 68.7%; H, 6.27%

Found: C, 68.5%; H, 6.19%

Formation of the Three Phthalic Anhydrides Produced from (LXXII), (LXXIX) and (LXXX)

1. Preparation of 3,6-dimethyl-4-methoxyphthalic acid (LXXII)

3,6-Dimethyl-5-methoxyphthalide (3.0 g) from above, was dissolved in potassium hydroxide solution (100 ml,6N)

by heating with frequent stirring. After cooling, finely powdered potassium permanganate (3.8 g) 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 of 3,6-dimethyl-4-methoxyphthalic acid was formed. This relatively pure product (2.1 g) was collected, washed well with water and allowed to dry. The melting point was 180.5 - 182.0°. There was vigorous effervescence when a little of this material was added to sodium bicarbonate solution.

Analysis:

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

Found: C, 58.4%; H, 5.41%

It was found that purification by crystallization of these different phthalic acids could not be carried out, as all the acids were immediately converted into their anhydride form with even a small amount of warming. For this reason, it was decided not to attempt the isolation of the free acids, but rather the corresponding anhydrides which could then be purified easily by recrystallization.

2. Preparation of 3,6-dimethyl-4-methoxyphthalic anhydride

Attempted recrystallizations of 3,6-dimethyl-4-methoxyphthalic acid in both ethyl alcohol (95%) and

glacial acetic acid produced a product melting at 185.0-186.5° which no longer effervesced in bicarbonate solution.

Analysis on anhydride thus formed:

Calculated for $C_{11}H_{10}O_4$:- C, 64.1%; H, 4.85%

Found: C, 63.9%; H, 5.10%

3. Preparation of 3,4-dimethyl-6-methoxyphthalic anhydride

5,6-Dimethyl-3-methoxyphthalide (3.0 g) was dissolved in hot potassium hydroxide solution and oxidized with permanganate or outlined previously. The final product (1.2 g), which did not effervesce in bicarbonate solution was recrystallized from glacial acetic acid and a little charcoal to remove coloured impurities and melted at 229.5 - 231.5°.

Analysis:

Calculated for $C_{11}H_{10}O_4$:- C, 64.1%; H, 4.85%

Found: C, 63.8%; H, 4.98%

Some unreacted starting material was also isolated from the reaction.

4. Preparation of 4,5-dimethyl-3-methoxyphthalic anhydride

4,5-Dimethyl-3-methoxyphthalide was treated as outlined in the previous two cases. Crystallization from glacial acetic acid produced white crystals of 4,5-dimethyl-3-methoxyphthalic anhydride which melted at 174.0 - 175.5°.

Analysis:

Calculated for $C_{11}H_{10}O_4$:- C, 64.1%; H, 4.85%

Found: C, 63.8%; H, 4.74%

Attempted Decarboxylation of 3,6-Dimethyl-4-Methoxyphthalic Acid (LXXIII)

All attempts to decarboxylate this dicarboxylic acid with copper chromite in quinoline proved unsuccessful, the final product isolated always being the corresponding anhydride.

3,6-Dimethyl-4-methoxyphthalic acid (1.9 g), quinoline (30 ml) and copper chromite (0.02 g) were mixed together and put into an oil bath at 185 - 200° for one hour with occasional stirring. The solution was filtered hot to remove some copper chromite and allowed to cool. Acidification with dilute hydrochloric acid produced a thick white precipitate. This solid did not effervesce in bicarbonate solution and was shown by mixed melting point determinations to be the corresponding 3,6-dimethyl-4-methoxyphthalic anhydride.

Reaction of 5-Methoxy-3-Methylphthalide (11) with Hydrochloric Acid, Formaldehyde and Glacial Acetic Acid

When this reaction was carried out on simple phthalide (11) for various heating periods, only one chloromethylphthalide was ever isolated. This was 5-

methoxy-3-methyl-6-chloromethylphthalide (IV). No evidence of the other chloromethylphthalides (VI) or (VII) was found.

1. Heating time 2 minutes

5-Methoxy-3-methylphthalide (0.13 g), produced by the Fritsch synthesis (26), concentrated hydrochloric acid (3 ml), glacial acetic acid (3 ml) and formaldehyde (1.5 ml, 37%) were heated for length of time necessary to dissolve the phthalide, approximately two minutes. The clear solution was put into an ice bath immediately to insure no further reaction. Water was added (9 ml) and the mixture allowed to cool overnight. The white precipitate which had formed was collected and washed with water. Repeated crystallizations from ethyl alcohol (95%) gave a product which melted at 103.0 - 104.5°. A sodium fusion test gave negative results for chlorine. Mixed melting point determinations showed this material to be unreacted starting material. From these results it can be concluded that no reaction had taken place.

2. Heating time 90 minutes

5-Methoxy-3-methylphthalide (0.85 g), concentrated hydrochloric acid (10 ml), glacial acetic acid (10 ml) and formaldehyde (7 ml, 37%) were heated for 1½ hours. A white precipitate began to form after 15 minutes. The

solution was allowed to cool overnight where the white solid was collected and washed with water. Repeated crystallizations from ethyl alcohol (95%) produced a product (0.6 g) which melted at 177.5 - 179.0°. Sodium fusion on this material gave a positive test for chlorine. Infra red spectra and mixed melting point determinations showed the product to be 5-methoxy-3-methyl-6-chloromethylphthalide (IV).

These same results were obtained when the heating period was reduced to 20 minutes. In this case some unreacted starting material was also isolated.

Reaction of 3-Methoxy-5-Methylphthalide (III) with Hydrochloric Acid, Formaldehyde and Glacial Acetic Acid

When this reaction was carried out with the simple phthalide (III), only two isomeric chloromethylphthalides were produced. These were 3-methoxy-5-methyl-6-chloromethylphthalide (VI) and 3-methoxy-5-methyl-4-chloromethylphthalide (VII). None of the higher melting 5-methoxy-3-methyl-6-chloromethylphthalide (V) was isolated from the different condensations.

1. Heating time 2 minutes

3-Methoxy-5-methylphthalide (2.0 g), produced by the Fritsch synthesis (26), concentrated hydrochloric acid (10 ml), glacial acetic acid (10 ml) and formaldehyde

(4.5 ml, 37%) were heated just long enough to dissolve the phthalide; a period of about 2 minutes being required. The clear solution was placed in an ice bath immediately to insure no further reaction. On cooling, a thick white precipitate (A) formed. This was filtered and thoroughly washed with water. The filtrate from precipitate (A) was diluted in water and cooled, when a second solid (B) separated.

Precipitate A

This solid was recrystallized from ethyl alcohol (95%) and coloured impurities were removed with the use of a little charcoal. The dry white material was placed on a suction flask and subjected to 2 or 3 portions of hot ethyl alcohol, approximately four or five millileters alcohol to each portion. The solutions containing the more soluble material were combined, cooled and the precipitate (0.4 g) thus formed, melted at 152.5 - 154.0°. Sodium fusion indicated the presence of chlorine. Infra red spectra and mixed melting point determinations showed this product to be identical to 3-methoxy-5-methyl-4-chloromethylphthalide (VII).

Precipitate B

This solid, on repeated crystallizations from ethyl alcohol (95%), gave a product (0.32 g) which melted at 132.5 - 134.0°. Tests for chlorine were positive;

infra red spectra and mixed melting points showed this compound to be identical to 3-methoxy-5-methyl-6-chloromethylphthalide (VI).

2. Heating time 2 hours

3-Methoxy-5-methylphthalide (1.0 g), concentrated hydrochloric acid (6 ml), glacial acetic acid (6 ml) and formaldehyde (3 ml, 37%) were heated together for 2 hours. A white solid began to settle after 15 minutes. At the completion of the reaction, the hot solution was filtered. The insoluble material (C) was washed with water, and the filtrate cooled thus producing a white solid (D).

Precipitate C

When this material was subjected to fractional crystallizations with ethyl alcohol as outlined above, a white product was isolated which proved to be the chloromethylphthalide (VII) of melting point 152.5 - 154.0°.

Precipitate D

Similarily, when this solid was subjected to fractional crystallization with ethyl alcohol, the material isolated proved to be the chloromethylphthalide (VI) melting at 134.0 - 135.0°.

Condensation of 2,5-Dimethyl-3-Methoxybenzoic Acid (LXIV) with Formaldehyde in Acid Solution

1. Preparation of 2,5-dimethyl-3-methoxybenzoic acid

a) Sulphonation of 2,5-dimethylbenzoic acid

After various methods were attempted, the following procedure proved to be the most successful. This involved converting the sulphonic acid directly into its sodium salt. By this procedure the sulphonic acid could be handled much more easily and also the alkali fusion in the next stage of the synthesis was carried out very smoothly.

2,5-Dimethylbenzoic acid (11 g) was heated for two hours at 100 - 110° with stirring in a fuming sulphuric acid solution made from H_2SO_4 (15 ml, 98%) and H_2SO_4 (35 ml, 20% SO_3). A sample poured into water gave no precipitate at the end of the reaction. The solution was cooled, and poured cautiously into cold water (200 ml). The solution was again cooled and the acid partially neutralized by adding carefully and in small portions 10 grams of sodium bicarbonate; then sodium chloride (25 g) was added and the mixture heated until solution was complete. The clear liquid was cooled in an ice bath where a brown solid began to settle. This sodium salt of 2,5-dimethyl-3-sulphobenzoic acid (LXXXII) was collected on a sintered glass funnel and washed with a small quantity of a filtered saturated sodium chloride solution, then dried

in an oven. The yield of the dry salt was 15 grams.

b) Preparation of 2,5-dimethyl-3-hydroxybenzoic acid (LXXXIII)

Potassium hydroxide (80 g) with a few drops of water was heated to 180° in a nickel crucible. The dry sodium salt of 2,5-dimethyl-3-sulphobenzoic acid (14 g) was added at this temperature and then heated at 300° for 30 minutes. At the end of the heating period, the clear solution was cooled and leached with water (300 ml). The aqueous solution was neutralized cautiously with dilute sulphuric acid. The solution was then made slightly alkaline with solid potassium hydroxide, cooled, and the precipitated sodium sulphate removed. A little charcoal was added and the solution then concentrated to about one third the original volume. On cooling, a second batch of the inorganic salt formed and was removed. Acidification with concentrated hydrochloric acid produced the required 2,5-dimethyl-3-hydroxybenzoic acid (5.8 g), which when recrystallized from water, melted at 163 - 165°.

Analysis

Calculated for $C_9H_{10}O_3$:-	C, 65.0%;	H, 6.03 %
Found:	C, 65.0%;	H, 5.99 %

Neutralization Equivalent

Calculated for $C_9H_{10}O_3$: -	166
Found:	163

c) Preparation of 2,5-dimethyl-3-methoxybenzoic acid (LXIV)

2,5-Dimethyl-3-hydroxybenzoic acid (5.2 g) was dissolved in sodium hydroxide solution (35 g, 20%) and the clear liquid then cooled in an ice bath. Dimethyl sulphate (10 g) was added over a period of 10 minutes and the reaction mixture was stirred an additional 30 minutes. Sodium hydroxide (5 g) was then added and the solution was refluxed for 20 minutes to destroy any excess dimethyl sulphate. The mixture was cooled and the crude acid which was precipitated by acidification with concentrated hydrochloric acid was filtered, washed well with water and dried. Recrystallization from aqueous ethyl alcohol produced white crystals of 2,5-dimethyl-3-methoxybenzoic acid (2.3 g) which melted at 143.5 - 144.0°.

Analysis

Calculated for $C_{10}H_{12}O_3$:- C, 66.8%; H, 6.68%

Found: C, 67.0%; H, 6.74%

2. Preparation of 3,6-dimethyl-5-methoxyphthalide (LXV)

2,5-Dimethyl-3-methoxybenzoic acid (1.5 g), concentrated hydrochloric acid (11 ml), glacial acetic acid (11 ml) and formaldehyde (9 ml, 37%) were heated on a steam cone for 45 minutes. No solution took place. The flask was then cooled and the precipitate collected and well washed with water. Recrystallization from ethyl

alcohol produced white crystals of 3,6-dimethyl-5-methoxyphthalide which melted at 169.0 - 170.0°. Yield was 1.3 grams.

Analysis

Calculated for $C_{11}H_{12}O_3$:- C, 68.7%; H, 6.25%

Found: C, 68.4%; H, 6.24%

A mixed melting point determination between this material and the chlorine free phthalide (LXXll) formed previously by the reduction of 3-methyl-5-methoxy-6-chloromethyl-phthalide with zinc and hydrochloric acid showed no depression.

Condensation of 2,3-Dimethyl-5-Methoxybenzoic Acid (LXll) with Formaldehyde in Acid Solution

1. Preparation of 2,3-dimethyl-5-methoxybenzoic acid

a) Oxidation of 1,2,3-trimethylbenzene

The oxidation with dilute nitric acid on 1,2,3-trimethylbenzene was first reported by Jacobsen (40). However he gave no experimental procedure. After many attempts at this oxidation under various conditions the following method proved to be the most satisfactory. It appears impossible however, to stop the reaction at the required stage without some dicarboxylic acid being formed in addition to the mono-carboxylic acid.

1,2,3-Trimethylbenzene (60 ml) was heated under

reflux with a solution of nitric acid (50 ml, 70%) in water (140 ml) for about 20 hours, a stirrer operating throughout this heating period. The solution was then poured into cold water (400 ml) and allowed to cool for a few hours, when the crude 2,3-dimethylbenzoic acid, in the form of an orange oil, solidified. This crude acid was separated from the aqueous solution and dissolved in 10% sodium hydroxide solution (200 ml). After chilling the dark red solution, any unreacted starting material was removed by extraction with a little ether. The aqueous solution was now heated gently with decolourizing carbon and filtered. The warm filtrate was added with stirring to a solution of concentrated hydrochloric acid (45 ml) in water (55 ml). The acid solution was cooled overnight when a brown solid formed. The solid was recrystallized from aqueous ethyl alcohol, more charcoal being used to remove coloured impurities and the required 2,3-dimethylbenzoic acid (8 g), which melted at 139 - 141° was collected. Although Jacobsen gives a value of 144° for this material, it was felt that further purification was unnecessary and that this material was sufficiently pure for synthetic purposes.

The aqueous solution from above which had been separated from the crude 2,3-dimethylbenzoic acid contained some crude 3-methylphthalic anhydride along with the

corresponding phthalic acid.

b) Sulphonation of 2,3-dimethylbenzoic acid

The sulphonation was carried out exactly as outlined above for 2,5-dimethylbenzoic acid. The yields of the sodium salt of the required 1,2-dimethyl-5-sulphobenzoic acid were approximately 16 grams when 12 grams of starting material were used.

c) Preparation of 2,3-dimethyl-5-hydroxybenzoic acid (LXXXIX)

This alkali fusion was carried out exactly as outlined above for 2,5-dimethyl-3-sulphobenzoic acid. The yields of the required 2,3-dimethyl-5-hydroxybenzoic acid were comparable to those obtained for the first acid. The crude material was recrystallized from water and melted at 179.0 - 179.5°.

Analysis

Calculated for $C_9H_{10}O_3$:-	C, 65.0%;	H, 6.03%
Found:	C, 64.6%;	H, 6.04%

Neutralization Equivalent

Calculated for $C_9H_{10}O_3$:-	166
Found:	161

d) Preparation of 2,3-dimethyl-5-methoxybenzoic acid (LXII)

2,3-Dimethyl-5-hydroxybenzoic acid (0.6 g) in a

three necked flask fitted with a mercury stirrer, water condenser and dropping funnel, was dissolved in 20% sodium hydroxide solution (10 ml) and the mixture heated to 80°. Dimethyl sulphate (2.5 g) was then added and the solution stirred an additional 30 minutes. Sodium hydroxide pellets (0.5 g) were added and the solution refluxed for 20 minutes, then cooled and filtered. Acidification of the clear filtrate with concentrated hydrochloric acid produced crystals of 2,3-dimethyl-5-methoxybenzoice acid (0.47 g), which melted at 102 - 103° after recrystallization from aqueous ethyl alcohol.

Analysis

Calculated for $C_{10}H_{12}O_3$:-	C, 66.8%;	H, 6.68%
Found:	C, 66.7%;	H, 6.68%

2. Preparation of 5,6-dimethyl-3-methoxyphthalide (LX111)

2,3-Dimethyl-5-methoxybenzoic acid (0.4 g), concentrated hydrochloric acid (5 ml), glacial acetic acid (5 ml) and formaldehyde (4 ml, 37%) were heated on a steam cone where solution took place almost immediately. A white precipitate began to form after heating for a few minutes, and after thirty minutes the solution was filtered hot, and the solid thus collected washed thoroughly with water and dried. Recrystallization from ethyl alcohol produced 5,6-dimethyl-3-methoxyphthalide (0.3 g) which melted at 179.5 - 180.5°.

Analysis

Calculated for $C_{11}H_{12}O_3$:- C, 68.7%; H, 6.25%

Found: C, 68.5%; H, 6.38%

A mixed melting point determination between this material on the chlorine free phthalide (LXXIX) formed previously by the reduction of 3-methoxy-5-methyl-6-chloromethylphthalide with zinc and hydrochloric acid showed no depression.

Decarboxylation of 2,3-Dimethyl-5-Hydroxybenzoic Acid (LXXXIX)

All attempts to produce the dimethylphenol by a decarboxylation of 2,3-dimethyl-5-hydroxybenzoic acid in quinoline and copper chromite proved unsuccessful. This product was finally formed when the acid was subjected to a more drastic treatment with soda lime.

Finely powdered soda lime (5.0 g) which was heated in an oven (120°) was intimately mixed in a combustion tube with a dried sample of 2,3-dimethyl-5-hydroxybenzoic acid (0.5 g). An equal volume of soda lime was added in addition, the tube then heated over a Meker burner for one hour. The tube, which was tilted so that liquids formed could not flow back onto the hot portion, was fitted with a condenser consisting of a long glass tubing. After cooling, the dark solid residue was thoroughly shaken with ether and filtered. The clear ether solution was dried (Na_2SO_4)

and the ether removed leaving a small amount of residue. This material, which melted at 62 - 63°, did not effervesce in bicarbonate solution and mixed melting point determinations showed it to be 3,4-dimethylphenol.

Preparation of 2,5-Dimethyl-4-Methoxybenzoic Acid (LXXXVI) by the Modified Gattermann Reaction

The zinc cyanide required for this reaction was prepared by a method outlined by Adams and Levine (1) but modified slightly by Borkowski (7).

To a solution of sodium cyanide (49 g) in water (65 ml) was added magnesium chloride solution until no more precipitate of magnesium hydroxide and carbonate formed. It was found necessary to use double the quantity of magnesium chloride suggested by Adams and Levine. The precipitate was filtered immediately and the filtrate added at once to a solution of zinc chloride (135 g) dissolved in ethyl alcohol (600 ml, 98%). The solution was allowed to stand for 15 or 20 minutes and then filtered. The white precipitate was slightly sticky but when dried overnight in vacuum over anhydrous calcium chloride, gave a powdery white solid. Yields from several preparations ran from 35 to 45 grams.

1. Preparation of 2,5-dimethyl-4-hydroxybenzaldehyde

This reaction was carried out using a modification

of the Adams and Levine (1) method as suggested by Adams and Montgomery (2).

The apparatus used was as follows; a three necked flask (1000 cc) was fitted with a good reflux condenser, a mechanical stirrer with a mercury seal and a wide mouth inlet tube. To this inlet tube was attached a safety bottle which in turn was attached to a sulphuric acid trap leading to a generator producing hydrogen chloride. To the top of the condenser was connected a tube leading into a wash bottle containing sulphuric acid from which a tube lead to a safety bottle and then to the surface of a sodium hydroxide solution.

2,5-Dimethylphenol (30 g), zinc cyanide (50 g) and dry benzene (150 ml) were introduced into the flask, the stirrer started and dry hydrogen chloride gas passed rapidly into the cooled solution. The solution immediately took on a pink colouring. After one hour, finely ground anhydrous aluminum chloride (45 g) was added as quickly as possible, turning the solution orange in colour. The flask was now warmed in a water bath held at 40 to 45°. In about 20 minutes a thick orange precipitate formed and the hydrogen chloride gas was passed through for an additional 30 minutes. The stirrer was kept in operation all this time. At the end of this heating period, the benzene layer is decanted and discarded. The remaining orange solution was poured carefully in a 10% hydrochloric

acid solution (1000 ml), where after 10 minutes a thick white precipitate of the imide hydrochloride separated. This mixture was refluxed for half an hour, thus causing a rapid decomposition with the formation of a dark oily product. The solution was then steam distilled when benzene and unreacted starting material were carried over. Sodium chloride (10 g) was dissolved in the hot filtrate and then the solution was cooled in an ice bath where a thick white precipitate formed. This crude 2,5-dimethyl-4-hydroxybenzaldehyde was collected and recrystallized from benzene and a little charcoal to remove coloured impurities and the final product (16 g) melted at 130 - 132°. Clemo et al. (21) give a value of 133°.

2. Preparation of 2,5-dimethyl-4-methoxybenzaldehyde

A solution of methyl sulphate (56 g), methyl alcohol (100 g) and potassium hydroxide (25 g) was gradually added to a hot solution of 2,5-dimethyl-4-hydroxybenzaldehyde (29.1 g) in 10% methyl alcoholic-potassium hydroxide (100 ml) and, after a further 30 minutes of heating, the alcohol was removed and the residue diluted with water and extracted with ether. The extract was dried (Na_2SO_4) and fractionated; 2,5-dimethyl-4-methoxybenzaldehyde (23.5 g), b.p. 147 - 149° /12 mm, was obtained and rapidly solidified to a practically colourless, crystalline mass, which melted at 32 - 33°. Clemo et al.(21)

gives a value of 34°.

The red coloured filtrate from above obtained after the extraction with ether was acidified with dilute hydrochloric acid when a thick white precipitate formed when cooled in an ice bath. This material (3.2 g), which melted at 126° proved to be unreacted starting material.

3. Preparation of 2,5-dimethyl-4-methoxybenzoic acid (LXXXVI)

The methoxy-aldehyde from above was converted to the corresponding acid by a neutral oxidation similar to that outlined by Barger and Field (3) in their oxidation of aconitine to oxonitin.

Potassium permanganate (35 g), finely pulverized, was heated to boil in acetone (200 ml) for 5 minutes when 2,5-dimethyl-4-methoxybenzaldehyde (23.5 g) was added. The solution was refluxed for 10 minutes, when a heavy precipitate settled and the purple coloured solution turned dark brown. More acetone (100 ml) was added, and reflux contained an additional 30 minutes, after which the hot solution was filtered and the precipitate thus collected, washed with acetone. This dark solid which is a mixture of the oxidized product and manganese dioxide was suspended in water, and a current of sulphur dioxide (generated by dropping concentrated sulphuric acid on sodium sulphate) was passed through the solution, thus destroying the manganese dioxide and leaving suspended

in the now clear solution a thick white precipitate of the required 2,5-dimethyl-4-methoxybenzoic acid. More product is obtained by concentrating the acetone filtrate from above and adding water. Total yield after recrystallization from aqueous acetic acid was 14.6 grams, which melted at 163.5 - 165.0°. Clemo et al. (21) reported an identical value.

Attempted Condensation of 3-Methylbenzoic Acid

Condensation attempts with this material has already been shown (65) to yield no phthalide. However, the reaction was repeated now with addition of glacial acetic acid to insure uniformity in this series of reactions.

3-Methylbenzoic acid (5 g), concentrated hydrochloric acid (35 ml), glacial acetic acid (35 ml) and formaldehyde (12 ml, 37%) were heated on a steam cone for three hours. The clear solution was cooled where a thick white precipitate was formed. This material, 4.8 grams, was collected and washed well with water, and melted at 109.5 - 110.5°. There was much effervescence in bicarbonate solution. This product was shown by the mixed melting point method to be unreacted starting material.

Attempted Condensation of 3,5-Dimethylbenzoic Acid

1. Preparation of 3,5-dimethylbenzoic acid

1,3,5-Trimethylbenzene (25 g), nitric acid (50 ml, 70%) and water (120 ml) were refluxed for 19 hours. At the end of the reaction time the solution was cooled and a thick precipitate which had formed was collected and washed with water. The solid was then dissolved in sodium bicarbonate solution and extracted with ether so as to remove unreacted starting material. The bicarbonate solution was acidified (dilute HCl) giving a white precipitate. Repeated crystallizations from aqueous ethyl alcohol gave a product (12 g) which melted at 164.5-165.5°. Geuther and Frolich (33) quote a value of 166.0°.

2. Attempted condensation of 3,5-dimethylbenzoic acid

3,5-Dimethylbenzoic acid (4 g), concentrated hydrochloric acid (25 ml), glacial acetic acid (25 ml) and formaldehyde (10 ml, 37%) were heated on a steam cone for 3 hours. At the conclusion of the reaction, the solution was cooled and the solid thus formed collected and washed well with water. The precipitate was recrystallized from aqueous ethyl alcohol, a little charcoal being used to remove colour impurities. This material, 3.1 grams, which melted at 164.0 - 165.0° showed much effervescence with bicarbonate solution

indicating the carboxyl group was still free. Mixed melting point determinations showed this product to be unreacted starting material, i.e. no ring closure had taken place.

Condensation of 3-Methoxyphthalic Acid with Formaldehyde in Acid Solutions

1. Preparation of 3-methoxyphthalic acid

a) Methylation of 2,3-dimethylphenol

2,3-dimethylphenol (30 g), water (300 ml) and sodium hydroxide (15 g) were heated in a round bottom flask equipped with a mercury stirrer and water condenser until the phenol dissolved. Dimethyl sulphate (53 g) was then added to the hot solution during a period of 15 minutes. A milky solution was produced with an orange oil floating on top. The mixture was stirred for an additional 30 minutes. Sodium hydroxide pellets (6.0 g) were then added and the solution refluxed for a further 30 minutes. After cooling, the oil was separated and dried overnight with anhydrous calcium sulphate. Yield of the clear methyl ether of 2,3-dimethylphenol was 26.4 grams, which boiled at 198°. Moschner (52) gives a value of 199°.

b) Oxidation of 3-methoxy-1,2-dimethylbenzene

The procedure followed for this neutral oxidation

reaction is similar to that outlined by Fosdick and Fancher (27) in their oxidation of 4-methoxy-m-xylene to 4-methoxyisophthalic acid.

3-Methoxy-o-xylene (19 g) in water (600 ml) in a three necked flask equipped with a mechanical stirrer and a reflux condenser was heated to boiling and a hot solution of potassium permanganate (90 g) in water (600 ml) was added over a period of three hours. The solution was then filtered to remove the brown manganese dioxide precipitate. The clear filtrate was cooled and acidified (conc. HCl), then concentrated to about one third of the original volume. On standing overnight at room temperature, the white solid which had formed was collected and dissolved in hot water. On cooling, a solid (E), which effervesced in bicarbonate solution was collected. The filtrate was acidified (conc. HCl) and placed in the cold overnight, when stout prisms of 3-methoxyphthalic acid which melted at 170 - 171° were collected. Bentley et al. (5) give a value of 173 - 174°.

Precipitate (E) from above, gave a neutralization equivalent equal to 167. Calculated value for a monocarboxylic acid is 166. Hence this solid represents an incomplete oxidation. Fractional crystallization using hot water produced two isomers. The first with a melting point of 109 - 111° presumably is 2-methoxy-6-methylbenzoic acid. Gibson (34) gives a value of 112°. The second gave

a melting point of 140 - 142° and would represent 2-methyl-3-methoxybenzoic acid. Fieser et al. (28) give a value of 145 - 146°.

2. Preparation of 5-methoxy-6-carboxylphthalide

3-Methoxyphthalic acid (0.92 g), concentrated hydrochloric acid (30 ml), glacial acetic acid (30 ml) and formaldehyde (20 ml, 37%) were heated on a steam cone for three hours. The clear solution was then concentrated to near dryness when a thick white precipitate formed. This solid was collected and well washed with water. Crystallization from water produced white needle shaped crystals (0.16 g) which melted at 260 - 261°. Neutralization equivalent and combustion results showed this material to be 5-methoxy-6-carboxylphthalide. These results are almost identical to those reported by Buehler et al. (13).

Attempted Condensation of 2-Methoxyterephthalic Acid with Formaldehyde in Acid Solution

1. Preparation of 2-methoxyterephthalic Acid

a) Methylation of 2,5-dimethylphenol

The procedure used in this methylation is identical to that outlined above. Yields of the methyl ether of 2,5-dimethylphenol ran from 85 - 95% with a boiling point of 196 - 197°. Jacobsen (39) gives a value of 194°.

b) Oxidation of 2-methoxy-1,4-dimethylbenzene

The oxidation procedure is identical to that described previously. It should be noted however, that when the two methyl groups are not ortho to one another, the oxidation proceeded more smoothly with no evidence of incomplete oxidation products. For example, in this particular reaction, when the solution was acidified with concentrated hydrochloric acid after the removal of the manganese dioxide, a thick precipitate formed immediately. This solid was recrystallized from ethyl alcohol (95%), a little charcoal being used to remove coloured impurities and gave a product which melted at 288° (dec.). Neutralization equivalent and combustion results showed this material to be the required 2-methoxyterephthalic acid. Yields ran from 30 to 40 %. Various melting points are listed in Beilstein (4); 274 - 276°, 277 -279°, 281°, depending upon the different investigators.

2. Attempted Condensation of 2-methoxyterephthalic acid

2-Methoxyterephthalic acid (4 g), concentrated hydrochloric acid (25 ml), glacial acetic acid (25 ml) and formaldehyde (14 ml, 37%) were heated on a steam cone for 2½ hours and then refluxed over a low flame for an additional 30 minutes. The terephthalic acid did not go into solution. At the end of the heating period the

mixture was filtered hot. Insoluble solid (H) was collected and thoroughly washed with water. The filtrate was cooled in an ice bath thus yielding a second crop of crystals (K) which were collected and washed with water. Both (H) and (K) effervesced in bicarbonate solution and were eventually shown to be the same compounds. Neutralization equivalents and mixed melting point determinations showed these solids to be unreacted starting material.

Attempted Condensation of 5-Methoxyisophthalic Acid with Formaldehyde in Acid Solution

1. Preparation of 5-methoxyisophthalic acid

a) Methylation of 3,5-dimethylphenol

The method used for the methylation of this material is identical to that outlined above for 2,3-dimethylphenol. Yields of the methyl ether of 3,5-dimethylphenol were very high. Boiling point of this colourless oil was 195 - 196°. Gattermann (29) quotes a value of 194.5°.

b) Oxidation of 5-methoxy-1,3-dimethylbenzene

The method used was identical to that described previously for 3-methoxy-1,2-dimethylbenzene. Again, because the methyl substituents were not ortho to one another, no trouble was encountered when isolating the isophthalic acid. The acid was collected and recrystallized from methyl alcohol. Yield of product which melted at 266.5

268.0° was 58% of starting material. Again, various values are listed in the literature depending upon the experimentors. Grey and Bonner (36) list a value of 269 - 270°. Kruber and Schmitt (43) give a value of 270°. A value of 265° is listed in Chemical Abstracts (20).

2. Condensation attempt on 5-methoxyisophthalic acid

5-Methoxyisophthalic acid (1 g), concentrated hydrochloric acid (20 ml), glacial acetic acid (20 ml) and formaldehyde (10 ml, 37%) were heated on a steam cone for 3 hours and then refluxed mildly for an additional 30 minutes. The clear solution was cooled in an ice bath and the resulting precipitate (0.7 g) washed well with water and then dried. Neutralization equivalent and mixed melting point determinations showed the solid to be unreacted starting material.

Oxidation of 4-Methoxy-1,2-Dimethylbenzene

1. Methylation of 3,4-dimethylphenol

This reaction carried out by the methylation method previously described, produced the methyl ether of 3,4-dimethylphenol which boiled at 202 - 203°. Moschner (52) gives a value of 204 - 205°.

2. Oxidation of 4-methoxy-1,2-dimethylbenzene

An attempt was made to produce 4-methoxyphthalic acid by the neutral permanganate oxidation of the

corresponding o-xylene as outlined in the previous preparations. However, in this case only one methyl group was oxidized, no phthalic acid being produced.

4-Methoxy-o-xylene was oxidized as outlined previously for 3-methoxyphthalic acid. When the clear filtrate was acidified after removal of the brown manganese dioxide precipitate, a thick white solid was formed. This was collected and dissolved in a small quantity of hot ethyl alcohol (98%). The solution was cooled and a thick precipitate melting at 176 - 177° was produced on the addition of cold water. This material effervesced in warm bicarbonate solution and neutralization equivalents gave a value of 167. Calculated value for a monocarboxylic acid is 166, indicating only one methyl substituent had been oxidized. Analytical results definitely substantiated this finding. Charlesworth et al. (18) reported the melting point of the isomeric 5-methoxy-2-methylbenzoic acid as 146 - 147°. Presumably then, it is the methyl substituent para to the methoxy group which is oxidized. Schall (67) gives a melting point of 176° for 4-methoxy-2-methylbenzoic acid.

Condensation of 3,5-Dimethoxybenzoic Acid (LXIX) with Formaldehyde in Acid Solution

1. Preparation of 3,5-dimethoxybenzoic acid

a) Preparation of 3,5-dihydroxybenzoic acid

This preparation was carried out as outlined in

Organic Syntheses (53). The sulphonation and alkali fusion steps proceeded without any difficulty. The product produced had a melting point of 224 - 226°. A value of 227 - 229° is given in Organic Syntheses.

b) Methylation of 3,5-dihydroxybenzoic acid

3,5-Dihydroxybenzoic acid (10 g) was dissolved in a solution of NaOH (12 g) in water (50 ml) and the resulting orange solution cooled. The flask was equipped with a mechanical mercury stirrer, condenser and dropping funnel. Dimethylsulphate (32 g) was added over a period of 20 minutes and stirring was continued for an additional 45 minutes. Sodium hydroxide (5 g) was then added and the solution refluxed for 20 minutes, then cooled and filtered. The filtrate was acidified (dilute HCl) producing a thick white precipitate which was collected and washed with water. Crystallization from aqueous acetic acid and a little charcoal to remove coloured impurities produced the required 3,5-dimethoxybenzoic acid (7.1 g) which melted at 178.0 - 179.5°. Bülow et al. (14) quotes a value of 180 - 181°.

2. Condensation of 3,5-dimethoxybenzoic acid

3,5-Dimethoxybenzoic acid (1 g) was heated on a steam cone for 3 hours in a solution of concentrated hydrochloric acid (17 ml), glacial acetic acid (17 ml) and formaldehyde (10 ml, 37%). The acid did not dissolve

and no reaction appeared to have taken place. At the end of this heating period, the mixture was filtered hot, the solid (0.85 g) thus collected was washed with water and dried. It was insoluble in all the organic solvents tried. Partial purification was carried out as follows; the solid was placed in boiling ethyl alcohol (98%) for a couple of minutes and then filtered hot. By this method a relatively good sample melting at 297 - 300° was obtained. It did not effervesce in bicarbonate solution indicating no free carboxyl groups, nor did it give a test for chlorine. A solution made by boiling a sample in glacial acetic acid was placed under a microscope where the solid definitely showed to be amorphous. These preliminary tests as well as combustion analysis indicate a biphenylmethane type compound.

Analysis

Calculated for $C_{21}H_{20}O_8$:- C, 63.1%; H, 5.00%

Found: C, 62.4%; H, 4.83%

The condensation reaction was repeated with the following variation. The reaction mixture was stirred at room temperature for 10 minutes and the insoluble material was then collected, washed with water and dried. It effervesced in bicarbonate solution and to purify this solid, it was put into boiling alcohol and the solution filtered immediately. The insoluble material

proved to be the amorphous material previously described. The alcoholic filtrate was cooled, and the solid thus produced was collected and washed with water and dried. Mixed melting point determinations showed this solid to be unreacted starting material.

A large quantity of the amorphous material was produced when the formaldehyde-acid filtrate from above was cooled.

It would appear then, that the simple phthalide or its chloromethyl derivative is impossible to isolate under these conditions.

Attempted Condensation of 4,5-Dimethoxyphthalic Acid (LXX) with Formaldehyde in Acid Solution

1. Preparation of 4,5-dimethoxyphthalic acid

a) Condensation of 3,4-dimethoxybenzoic acid

The condensation was carried out exactly as described by Edwards, Perkin and Stoyle (24) and utilized by Sinder (68).

The crude 4,5-dimethoxyphthalide was washed with sodium bicarbonate solution in order to remove unreacted acid and then recrystallized from water, and gave a melting point of 156 - 157°. This is the same value reported by Sinder.

b) Oxidation of 4,5-dimethoxyphthalide

The procedure followed here was similar to that outlined by Edwards et al. (24).

4,5-Dimethoxyphthalide (9.6 g) was heated in a solution of sodium hydroxide (10 g) in water (250 ml) in order to dissolve the phthalide. The clear liquid was cooled, and carbon dioxide gas from a Kipp generator was passed through for 10 minutes. Sodium bicarbonate (1.0 g) was added, then potassium permanganate (9 g) and the solution heated on a steam cone until the permanganate colour had been removed (approximately 25 minutes), a current of carbon dioxide being passed through the solution the whole time. The clear liquid was cooled, filtered and acidified (dil. HCl) and then concentrated to about one third of the original volume. The resulting liquid was cooled overnight and a thick precipitate formed when the side of the beaker was scratched with a stirring rod. The product effervesced in bicarbonate solution and on recrystallization from water with a little charcoal to remove coloured impurities, white crystals of 4,5-dimethoxyphthalic acid (5.1 g) which melted at 200.0 - 201.5° (dec.) were produced. Edwards et al. give a value of 203.0°.

2. Condensation attempt on 4,5-dimethoxyphthalic acid (LXX)

4,5-Dimethoxyphthalic acid (3.0 g), concentrated

hydrochloric acid (20 ml), glacial acetic acid (20 ml) and formaldehyde (10 ml, 37%) were heated on a steam cone for 3 hours. After the first 2 hours excess hydrochloric acid (10 ml) and formaldehyde (5 ml) was added. The solution was cooled slightly and evaporated from a suction flask until only a white solid was left. This precipitate was washed thoroughly with water, collected and dried. The solid, which effervesced in bicarbonate solution was recrystallized from water to yield a white solid (2.1 g) which melted at 199 - 201°. This material was shown by the mixed melting point method to be unreacted starting material.

Attempted Chloromethylation of 3,6-Dimethyl-5-Methoxyphthalide (LXXll)

The chlorine free 3,6-dimethyl-5-methoxyphthalide obtained by reduction of the corresponding 3-methyl-5-methoxy-6-chloromethylphthalide (isomer lV) was heated with formaldehyde in acid solution in an attempt to produce a chloromethyl derivative of the former phthalide.

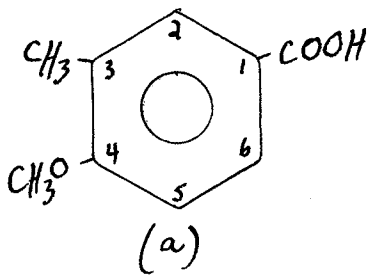
3,6-Dimethyl-5-methoxyphthalide (0.32 g), concentrated hydrochloric acid (4 ml), glacial acetic acid (4 ml) and formaldehyde (3 ml) were heated on a steam cone for 2 hours, when a white solid began to settle. The solution was then refluxed on an open flame

an additional 2 hours, then filtered hot. The solid was collected and washed well with water, then recrystallized from ethyl alcohol thus producing white crystals (0.29 g) which melted at 168.5 - 169.5°. Mixed melting point determinations showed this to be unreacted starting material.

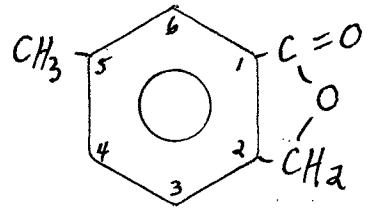
APPENDIX

Numbering and nomenclature of rings

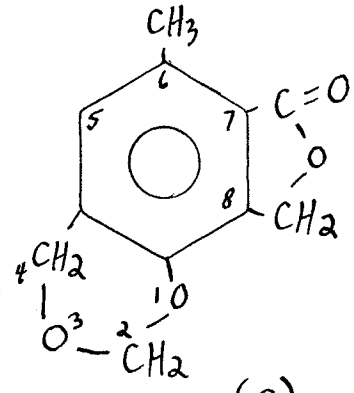
In order to avoid confusion in the systematic naming of the compounds referred to in this paper, the following system has been adopted.



(a)



(b)



(c)

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 for example, (a) represents 3-methyl-4-methoxybenzoic acid.

In naming phthalides, the system indicated by (b) is followed, that is, (b) represents 5-methylphthalide.

The dioxane ring structures have two rings numbered, for example, (c) is the lactone of 8-hydroxy-methyl-1,3-benzodioxan-6-methyl-7-carboxylic acid.

Table 3

Condensation of Aromatic Acids with Formaldehyde in Acid Solution

Benzoic acid	no reaction (65)
o-Toluic acid	no reaction (18)
m-Toluic acid	no reaction (65), "P*"
p-Toluic acid	no reaction (65)
o-Methoxybenzoic acid	no reaction (65)
m-Methoxybenzoic acid	5-methoxyphthalide (15)
p-Methoxybenzoic acid	no reaction (65) (18)
o-Hydroxybenzoic acid	dimer or resin (75)
m-Hydroxybenzoic acid	3-hydroxyphthalide and dioxanylphthalide (75) (12) (11)
p-Hydroxybenzoic acid	diphenylmethane derivative (25)
3,5-Dimethylbenzoic acid	no reaction "P"
5-Methoxy-2-methylbenzoic acid	3-methoxy-6-methyl-phthalide (18)
5-Methoxy-3-methylbenzoic acid	5-methoxy-3-methyl-phthalide "P", 3-methoxy-5-methyl-4-chloromethylphthalide "P", 3-methoxy-5-methyl-6-chloromethyl-phthalide "P", 5-methoxy-3-methyl-6-chloromethylphthalide "P" (18)
3-Methoxy-4-methylbenzoic acid	5-methoxy-4-methyl-phthalide (18)
2,3-Dimethoxybenzoic acid	5,6-dimethoxyphthalide and 5,6-dimethoxy-3-chloromethylphthalide (24), (48)

3,4-Dimethoxybenzoic acid	4,5-dimethoxyphthalide (24) (64) (68)
2,4-Dimethoxybenzoic acid	dimer or resin (68) (75)
3,5-Dimethoxybenzoic acid	bis-(2-carboxy-3-hydroxymethyl-4,6-dimethoxybenzyl) ether dilactone "P"
2,5-Dimethy-3-methoxybenzoic acid	3,6-dimethyl-5-methoxyphthalide "P"
2,3-Dimethy-5-methoxybenzoic acid	5,6-dimethyl-3-methoxyphthalide "P"
3,5-Dimethoxy-2-methylbenzoic acid	3,5-dimethoxy-6-methylphthalide (18) (51)
4,5-Dimethoxy-2-methylbenzoic acid	no substance isolated (48)
3,5-Dimethoxy-4-methylbenzoic acid	3,5-dimethoxy-4-methyl-6-chloromethyl-phthalide (18) (19)
2,3-Dimethoxy-5-methylbenzoic acid	5,6-dimethoxy-3-methylphthalide (48)
2-Bromo-3,4-dimethoxybenzoic acid	6-bromo-4,5-dimethoxy-phthalide (64)
3,4,5-Trimethoxybenzoic acid	3,4,5-trimethoxy-phthalide, 6-chloromethylphthalide and dimer or resin (56) (18) (42)
3,4-Methylenedioxybenzoic acid	no reaction (24) (68)
2,3-Methylenedioxybenzoic acid	5,6-methylenedioxy-phthalide (58)
3-Methoxy-4,5-methylenedioxy-benzoic acid	5-methoxy-3,4-methylene-dioxyphthalide and 6-chloromethylphthalide (56)

3,5-Dimethoxy-4-hydroxybenzoic acid	3,5-dimethoxy-4-hydroxyphthalide and 6-chloromethylphthalide (42)
2-Hydroxy-4-methoxybenzoic acid	dimer or resin (75)
5-Hydroxy-2-methylbenzoic acid	3-hydroxy-6-methylphthalide and dioxanylphthalide (17)
5-Hydroxy-3-methylbenzoic acid	dimer or resin (17) (18)
3-Hydroxy-4-methylbenzoic acid	dioxanylphthalide (16) (17) (18)
3,5-Dihydroxy-4-methylbenzoic acid	3,5-dihydroxy-4-methylphthalide and dimer (16)
3,5-Dihydroxy-2-methylbenzoic acid	dimer or resin (17)
3,4,5-Trihydroxybenzoic acid	dimer or resin (75)
3-Bromobenzoic acid	no reaction (17)
5-Bromo-2-methylbenzoic acid	no reaction (17)
2-Methoxy-p-phthalic acid	no reaction "P"
5-Methoxy-m-phthalic acid	no reaction "P"
3-Methoxy-o-phthalic acid	5-methoxy-6-carboxylphthalide "P"
4,5-Dimethoxy-o-phthalic acid	no reaction "P"

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* "P" - present research

SUMMARY

1. The orientation of the simple phthalide isolated from the condensation reaction with 5-methoxy-3-methylbenzoic acid has been definitely established as 5-methoxy-3-methylphthalide.

2. The orientations of the three chloromethylphthalides isolated from this same condensation reaction has been definitely established as 5-methoxy-3-methyl-6-chloromethylphthalide (m.p. 178.0 - 179.5°); 3-methoxy-5-methyl-6-chloromethylphthalide (m.p. 134.0 - 135.0°) and 3-methoxy-5-methyl-4-chloromethylphthalide (m.p. 152.5 - 154.0°).

3. Three chlorine free phthalides have been prepared by reduction of the previously mentioned chloromethyl-phthalides listed in 2. These are as follows; 3,6-dimethyl-5-methoxyphthalide (m.p. 169.5 - 170.0°); 5,6-dimethyl-3-methoxyphthalide (m.p. 179.5 - 180.5°) and 4,5-dimethyl-3-methoxyphthalide (m.p. 174.0 - 175.5°).

4. Three anhydrides have been prepared by oxidation of the previously mentioned chlorine free phthalides listed in 3. These are as follows; 3,6-dimethyl-4-methoxyphthalic anhydride (m.p. 185.0 - 186.5°);

3,4-dimethyl-6-methoxyphthalic anhydride (m.p. 229.5 - 231.5°) and 4,5-dimethyl-3-methoxyphthalic anhydride (m.p. 208.0 - 209.5°).

5. Infra red absorption spectra were obtained for the two simple phthalides, 5-methoxy-3-methylphthalide (m.p. 104.5 - 105.5°) and 3-methoxy-5-methylphthalide (m.p. 134.0 - 135.0°) as derived from the Fritsch synthesis, as well as for the three chloromethyl-phthalides listed in 2.

6. The orientation of 3,6-dimethyl-5-methoxyphthalide (from 3), was definitely established by mixed melting point determinations with the phthalide produced from 2,5-dimethyl-3-methoxybenzoic acid. The latter substance was prepared by the methylation of the corresponding previously unreported phenol.

7. The orientation of 5,6-dimethyl-3-methoxyphthalide (from 3), was definitely established by mixed melting point determinations with the phthalide produced from 2,3-dimethyl-5-methoxybenzoic acid. The latter substance was prepared by the methylation of the corresponding previously unreported phenol.

8. A new method has been presented for the preparation of 5-methoxy-6-carboxylphthalide. This involved the condensation of 3-methoxyphthalic acid with

formaldehyde in acid solution.

9. A systematic study has been made dealing with the influence of nuclear substituent groups on the course of the reaction of aromatic acids with formaldehyde in acid solution. This study has substantiated the first two rules (listed on pages 48 and 49 and first suggested by Anderson). Apparently, the substituents already in the aromatic nucleus and their position relative to a carboxyl group are all important.

RECOMMENDATIONS FOR FUTURE WORK

1. Examination of the four chloromethylphthalides (lV), (V), (Vl) and (Vll) (see page 2) by the method of Nuclear Magnetic Resonance should distinguish the chloromethylphthalide (V) from the others. In isomers (lV), (Vl) and (Vll) the nuclear proton in each case is ortho to a methyl substituent so that a broadening of the ring proton peak would be expected due to the unresolved coupling to the methyl protons. There is no such coupling possible in structure (V). One should also be able to distinguish compound (Vll) from (lV) and (Vl) because in this case the nuclear proton peak of isomer (Vll) should be at a lower magnetic field due to the influence of the ortho carboxyl substituent.

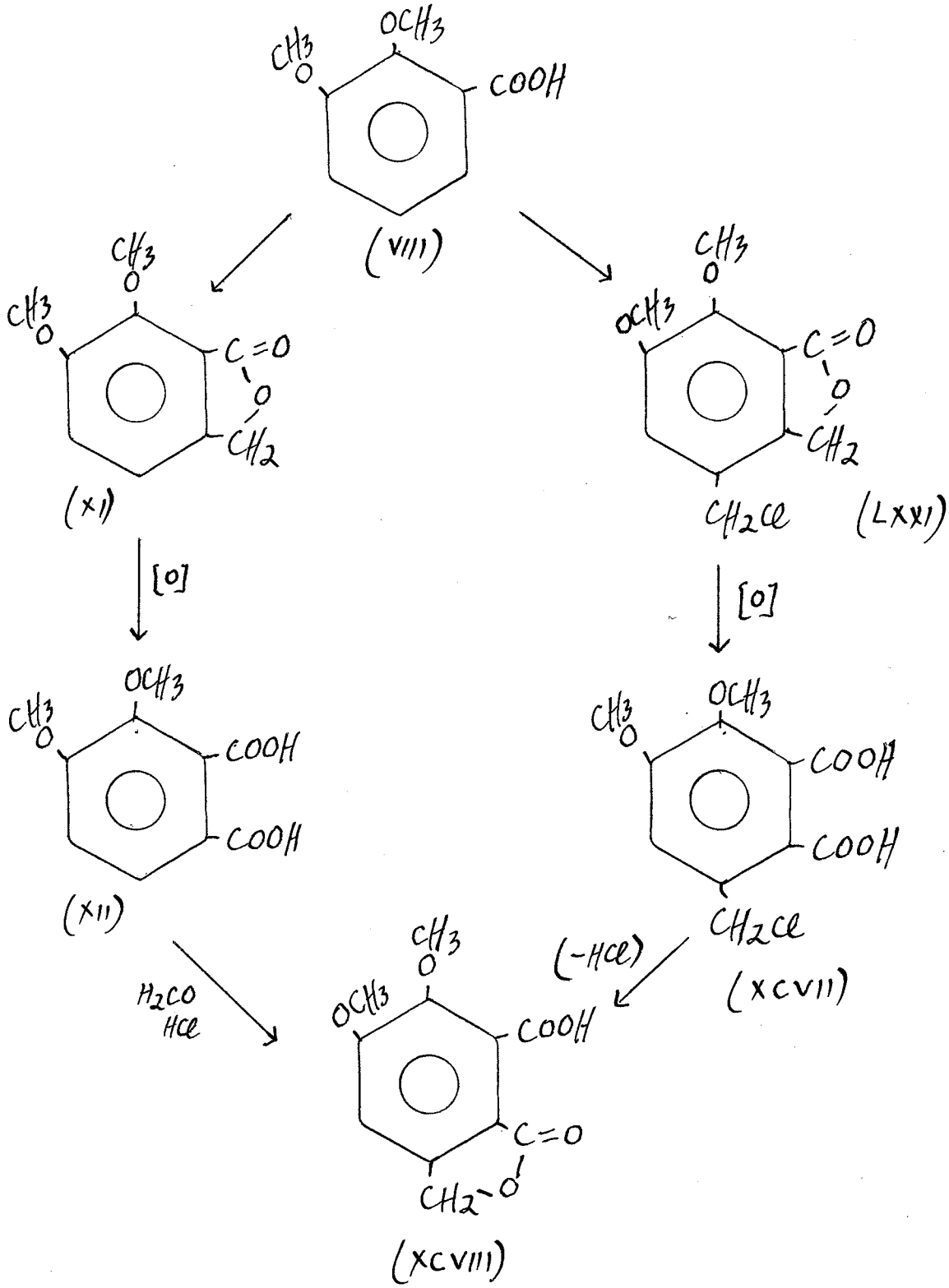
2. As indicated previously, it would be of great interest to study the results obtained when dimethoxy-dicarboxylic acids are heated with formaldehyde in acid solution when these substituents are situated at different positions in the benzene ring.

3. A more thorough examination should be undertaken in order to confirm the structure of the biphenylmethane compound derived from the condensation of 3,5-dimethoxybenzoic acid with formaldehyde in acid solution.

4. The work of Smith and Kan (69), outlined on pages 82 to 85, requires more investigation. This appears to be an excellent method for introducing a carboxyl substituent into the aromatic nucleus.

5. An interesting series of reactions can be carried out to show the part played by the chloromethyl substituent in these condensation reactions. This can be done as follows; o-veratric acid (Vlll), when heated under different conditions with formaldehyde in acid solution produced the simple phthalide (Xl) in one case and the chloromethyl derivative (LXXl) in the other, as already indicated in the "Discussion of Experimental Results". These two phthalides would then be oxidized to open the lactone rings and so produce phthalic acids (Xll) and (XCVll). The theory states that for phthalide formation to take place, a chloromethyl substituent must enter the benzene nucleus ortho to a carboxyl group. If this is true, an intermediate similar to (XCVll) is formed, but is normally never isolated in condensation reactions. However, compound (XCVll) as produced below, should be quite stable and therefore isolable, and by heating this material in acid solution, the phthalide (XCVlll) would be expected to form on loss of hydrogen chloride. If the theory is correct, this phthalide (XCVlll)

should be identical to that produced when compound (XII) is subjected to condensation conditions.



6. As already indicated in the "Literature Survey", it is possible to produce either the simple phthalide, or the chloromethylphthalide, depending upon the amount of hydrochloric acid used in the condensation reaction. King and King (42) were able to isolate only the chloromethylphthalide derivative when trimethylgallic acid (XX) was heated with formaldehyde in acid solution under normal condensation conditions. This is to be expected considering the three strong ortho-para directing methoxyl substituents. However when the amount of hydrochloric acid was reduced, only the simple phthalide of trimethylgallic acid (XXll) was isolated.

   It would be instructive to repeat this reaction using 5-methoxy-3-methylbenzoic acid (l) in place of trimethylgallic acid. With excess hydrochloric acid, one simple and three chloromethylphthalide derivatives were isolated from the reaction mixture (see page 38). If it is true that the chloromethyl derivatives are in fact produced through the simple phthalides (ll) and (lll), then by adding only a small quantity of hydrochloric acid, these simple phthalides should be the only isolatable products. It would also be interesting to know, if possible, which of the two simple phthalides is first produced.

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