

A STUDY OF THE CONDENSATION OF
FORMALDEHYDE AND AROMATIC ACIDS IN THE PRESENCE OF
HYDROGEN CHLORIDE

**A Study of the Condensation of
Formaldehyde and Aromatic Acids in the Presence of
Hydrogen Chloride**

By M. M. Yan

**A Thesis Presented to the Committee on Post-
Graduate Studies of the University of Manitoba in Partial
Fulfilment for the Degree of Master of Science
1942.**

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To DR. E. H. CHARLESWORTH, in
earnest appreciation of his
patient interest and excellent
advice during this research,
the thanks of the writer are
most sincerely offered.

The writer wishes to express his thanks to the National Research Council for an award of a Bursary which made this work possible.

The writer is also indebted to the Research Committee of the University of Manitoba for a grant towards the purchase of many required chemicals.

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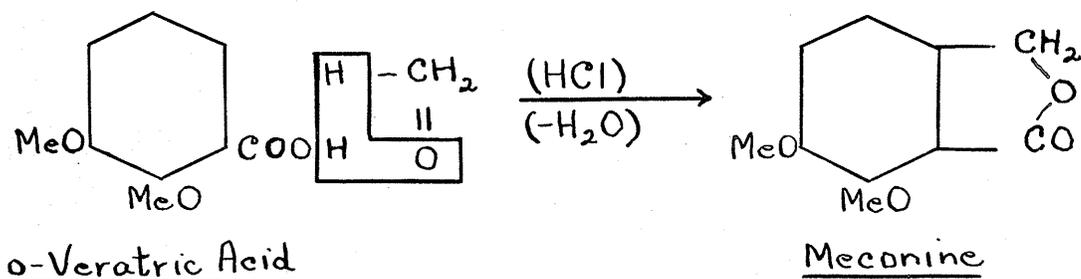
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INTRODUCTION

Aromatic acids respond to the action of boiling formaldehyde and concentrated hydrochloric acid in one of four ways: (1) no reaction; (2) phthalide formation; (3) chlorocompound formation; (4) resin formation.

The present investigations were undertaken with two objects in view: firstly, to establish the nature of the chloroproduct resulting from the action of formaldehyde and hydrochloric acid on 5-methoxy-m-toluic acid; and secondly, to study the action of the same condensing agents on a variety of other acids, with a view to elucidating the peculiarities of structure essential to phthalide formation.

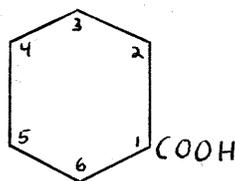
In 1925, Perkin, Edwards and Stoye (13) prepared the phthalide meconine, by boiling o-veratric acid with formaldehyde and concentrated hydrochloric acid. The reaction involved may be indicated as follows.



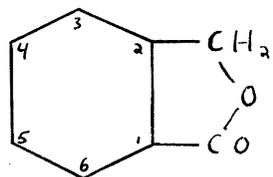
The striking simplicity of this condensation encouraged later workers to employ this method of phthalide production. These efforts met with success in several instances, but in other cases the required phthalide did not result. Thus Perkin, Edwards and Stoye failed to obtain

the phthalide corresponding to piperonylic acid. Charlesworth and Robinson (2), using the same method on 3:5-dimethoxy-p-toluic acid, obtained not a phthalide but an unknown chlorinated product. Raistrick, Robinson, and Fodd (15) met similar failure with 5-methoxy-m-toluic acid, a chloroproduct again being obtained (private communication). Table (I), on page 3, summarizes the results of all such previous investigations involving the condensation of aromatic acids and formaldehyde in the presence of concentrated hydrochloric acid.

NOTE: In order to avoid confusion, it is necessary to mention the system of nomenclature employed. In designating the acid derivatives, the nuclear substituent groups are named in a counter-clockwise direction, beginning with the acid carboxyl group (a). In naming the phthalide the system indicated in (b) is followed.



(a)



(b)

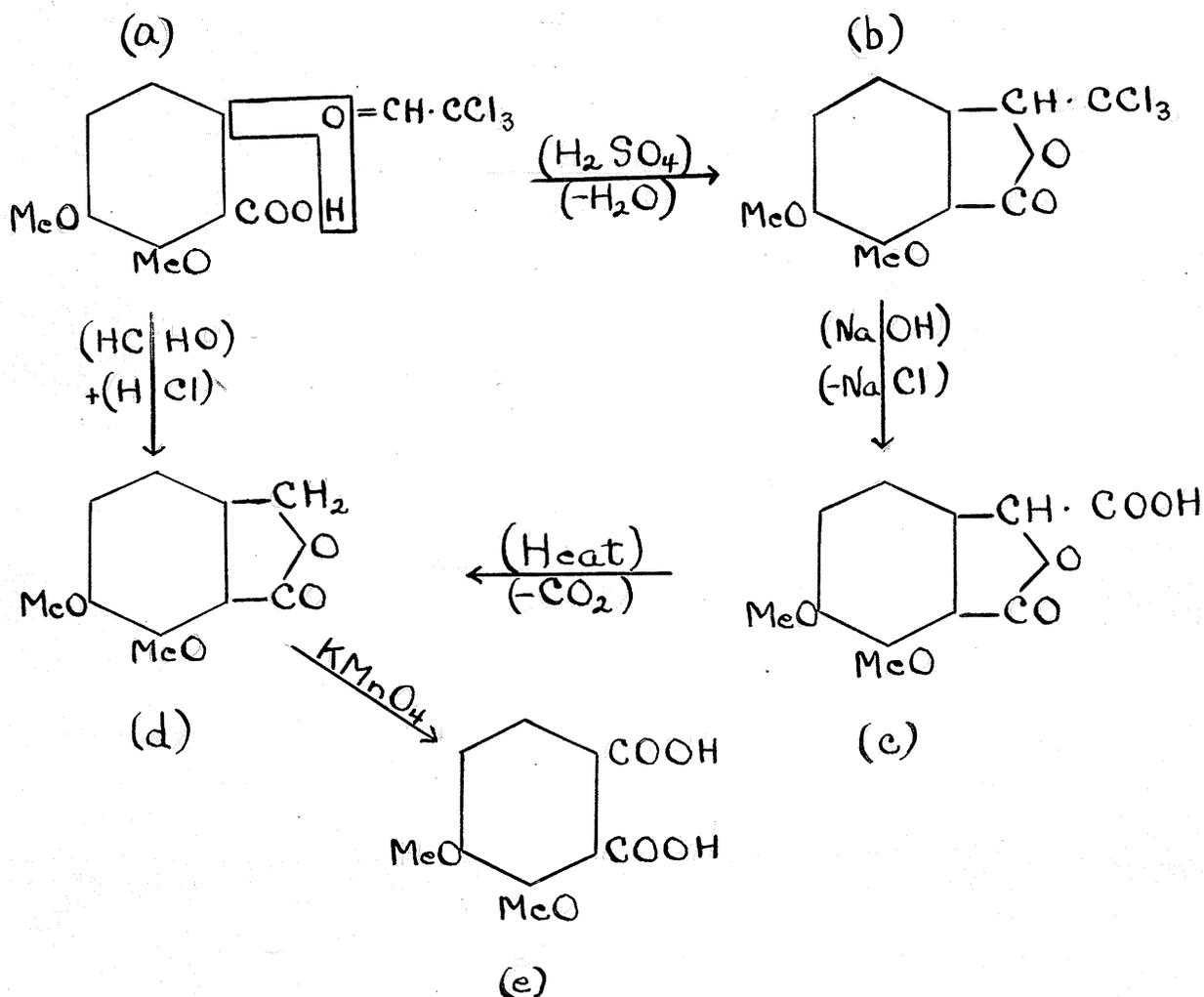
In cases where the methyl group is present in the compound, the symbol "Me" is used for convenience in place of "CH₃", and "OMe" in place of "OCH₃".

TABLE I

CONDENSATIONS WITH FORMALDEHYDE AND HYDROCHLORIC ACID

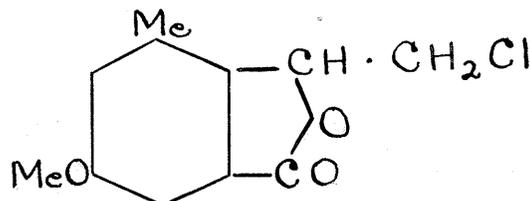
<u>ACID</u>	<u>PRODUCT</u>	
Benzoic	No result	(17)
o-Methoxybenzoic	No result	(17)
p-Methoxybenzoic	No result	(17)
2:3-Dimethoxybenzoic (o-veratric acid)	5:6-Dimethoxyphthalide (meconine)	(13)
3:4-Dimethoxybenzoic (veratric acid)	4:5-Dimethoxyphthalide (m-meconine)	(13)
2:4-Dimethoxybenzoic	4:6-Dimethoxyphthalide	(17)
1-Bromo-2:3-Dimethoxy- benzoic	6-Bromo-4:5-dimethoxy- phthalide	(16)
4:5-Methylenedioxy-benzoic (piperonylic acid)	No result	(13)
5:6-Methylenedioxy-benzoic (o-piperonylic acid)	5:6-Methylenedioxy- phthalide	(21)
3:4:5-Trimethoxybenzoic (trimethyl gallic acid) (a) with acetic (b) without acetic	3:4:5-Trimethoxy-6- chloromethylphthalide 3:4:5-Trimethoxyphthalide Methyl ester of trimethyl gallic acid	(12) (12) (17)
3-Methoxy-4:5-methylene- dioxybenzoic (myristicinic acid) (a) with acetic (b) without acetic	A chloromethylphthalide A phthalide	(12) (12)
m-Toluic	No result	(17)
p-Toluic	No result	(17)
5-Methoxy-o-toluic	3-Methoxy-6-methyl- phthalide	(17)
5-Methoxy-m-toluic	Chlorocompound	(1)
3:5-Dimethoxy-o-toluic	6-Methyl-3:5- dimethoxyphthalide	(19) (17)
3:5-Dimethoxy-p-toluic	Chlorocompound	(1) (2)

The practical value of this condensation lies in the fact that a variety of substituted phthalic acids, so widely used in anthraquinone syntheses, can generally be produced by oxidation of the corresponding phthalides. Prior to the synthesis of meconine by Perkin, Edwards, and Stoye, the classical Fritsch series (4) was the only available practical method of obtaining phthalides from their parent acids. The procedure consisted of condensing the acids with chloral hydrate in 95% sulphuric acid. Thus, applying this reaction to *o*-veratric acid (a), Fritsch obtained the corresponding trichloromethylphthalide (b). This was then decomposed with aqueous alkali to yield the carboxylic acid (c), which on decarboxylation gave meconine (d). Meconine, on permanganate oxidation produced the required phthalic acid (e).

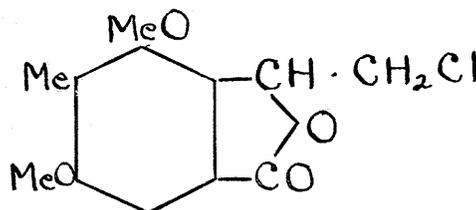


The action of formaldehyde and concentrated hydrochloric acid on *o*-veratric acid is a direct step from (a) to (d). This is obviously much superior to the Fritsch method. It must be remembered, however, that the formaldehyde method is more limited in its application, since phthalides are not always formed.

G. Cameron (1), in a study of the chlorinated condensation product from 5-methoxy-*m*-toluic acid, suggested the chloromethyl structure 5-methoxy-3-methyl- α -chloromethylphthalide as indicated.



In analogy with the formula indicated above, the same author designated the structure of the chlorocompound from 3:5-dimethoxy-*p*-toluic acid, as 3:5-dimethoxy-4-methyl- α -chloromethylphthalide.

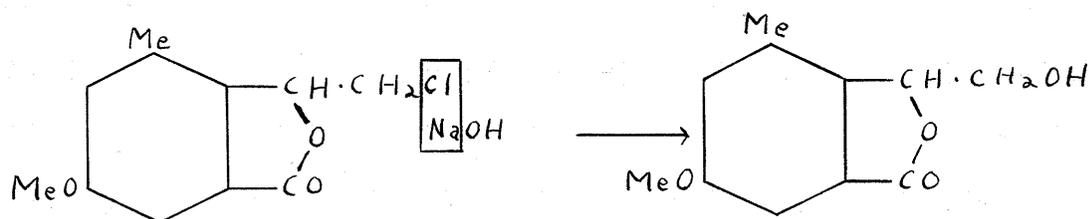


These formulae were, however, based purely on theoretical considerations, with little supporting evidence.

Cameron also obtained small amounts of chlorine free

condensation products with rather indefinite melting points. He suggested that some of these were the normally expected phthalides, but again without experimental verification.

Cameron treated the chlorocompound from 5-methoxy-m-toluic acid with alcoholic caustic soda, hoping to produce an alcohol as indicated below.



A non-chlorinated compound of melting point 135°-140° was isolated. The amount obtained was, however, insufficient for conclusive analysis, so leaving the structure of this substance uncertain. Attempts by the author to reproduce these results have failed, the original chlorocompound being recovered in each case.

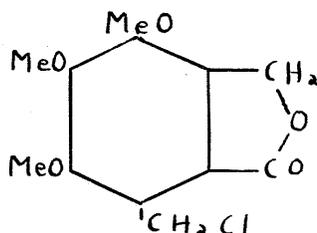
Rennie (17) first undertook a systematic endeavor to determine the characteristics of an aromatic acid essential to phthalide formation. From his results (see table I, page 3; and table II, page 11), Rennie drew the conclusion that the presence of the carboxyl group in the aromatic nucleus hinders phthalide formation, while substituents such as methyl and methoxyl encourage this tendency.

If Rennie's conclusion is correct, gallic acid trimethyl ether, possessing one carboxyl and three methoxyl groups, should produce a phthalide on boiling with formaldehyde and concentrated hydrochloric acid. Yet Rennie was

unable to detect any phthalide whatsoever.

A careful search through the literature revealed a new paper by P. K. Paul (12) on this subject. On treating gallic acid trimethyl ether and myristicinic acid with formaldehyde and concentrated hydrochloric acid, he obtained the corresponding phthalides. No details, however, are given regarding the phthalide of trimethyl gallic acid.

Paul, following Bay and Robinson's modification (16) of Perkin, Edwards, and Stoye's original method, used acetic acid in addition to formaldehyde and hydrochloric acid. Under these conditions, he found that gallic acid trimethyl ether produced 3:4:5-trimethoxy-6-chloromethylphthalide shown below. A similar product was obtained from myristicinic acid.



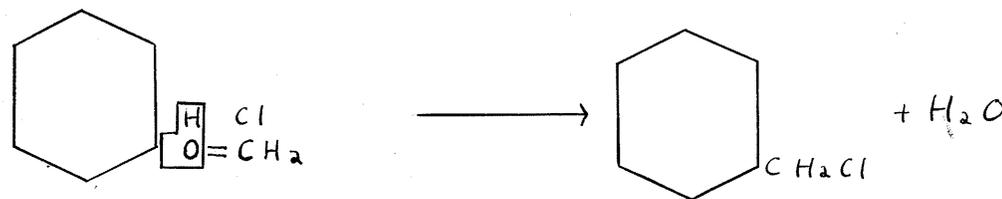
An attempt by the author to reproduce Paul's result failed. While a reaction did occur, no crystalline product could be isolated. Since Paul gives no details regarding the phthalide from trimethylgallic acid, the production of the simple phthalide is definitely in doubt. However, the series of reactions and analyses which Paul describes for his chloromethylphthalide of trimethyl gallic acid, leaves no doubt as to its production, despite the writer's failure to reproduce these results.

Thus it can be said that gallic acid trimethyl ether does not constitute an exception, but rather lends support, to Rennie's conclusion that phthalide formation is hindered by carboxyl and encouraged by methyl and methoxyl.

Extensive investigations by Stephen, Gladding and Short (19), and R. Quellet (14), have shown that the regular action of formaldehyde and hydrochloric acid on aromatic compounds is that of nuclear chloromethylation. Paul's formula indicating a nuclear chloromethyl substituent is, therefore, completely justified.

The work of Stephen, Gladding, and Short, is important in connection with the present investigations, since it deals with the mechanisms of the reactions involved in treating an aromatic compound with formaldehyde and concentrated hydrochloric acid.

It is very unlikely that chloromethylation results by direct reaction with the original reagents as shown below.



More probably, the hydrochloric acid and formaldehyde first react to form an intermediate, which then condenses with the aromatic compound. By passing gaseous hydrogen chloride up a tower packed with glass beads, meanwhile allowing 40% formaldehyde to percolate down, Stephen, Gladding, and Short,

were able to isolate the two compounds, s-dichloromethyl ether and mono-chlorodimethyl ether.

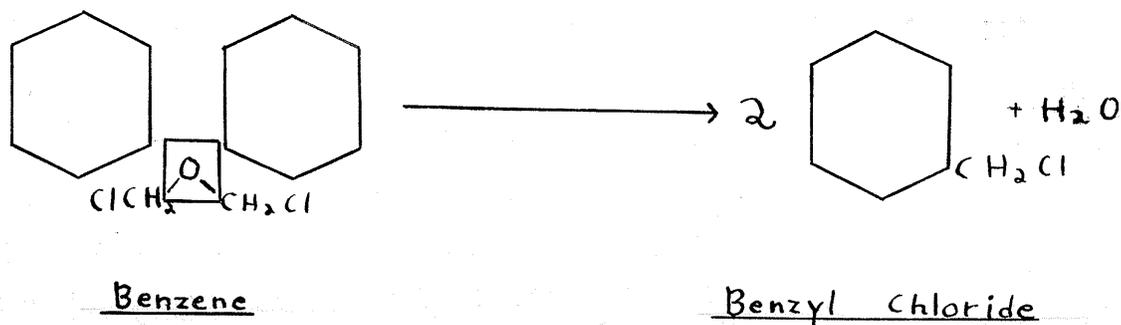
The formation of the s-dichloromethyl ether involves the reaction indicated below.



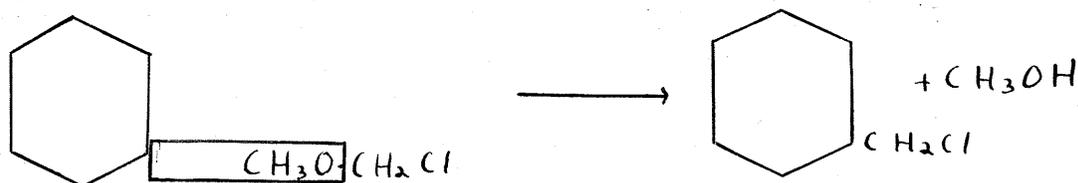
The production of the mono-chlorodimethyl ether is accounted for by the fact that commercial aqueous formaldehyde has some methyl alcohol. The formation of this compound may, therefore, be indicated as shown below:



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



The mono-chlorodimethyl ether may react directly as shown below:



or the following reactions may take place:



The s-dichloromethyl ether thus produced, reacts with the aromatic compound as before.

Stephen, Gladding, and Short, also found that the formation of the chloromethyl derivatives in this manner was usually accompanied by a secondary reaction which predominated at temperatures above 35° and produced diphenylmethane derivatives as in the case of certain Friedel-Crafts reactions. This they believed to be due to further condensation of the chloromethyl derivative with the unchanged reagent present.



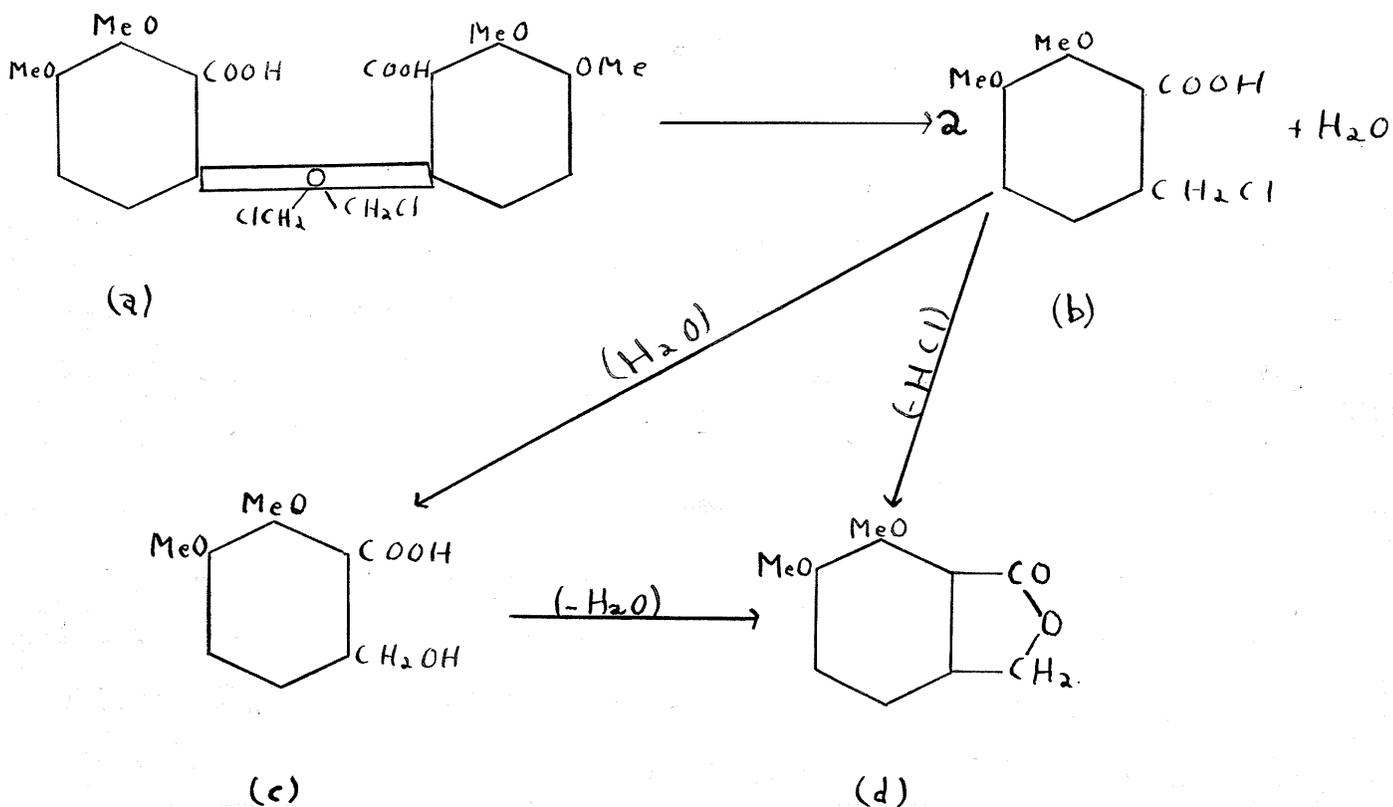
Quelet (14) also, frequently reported the production of such diphenylmethane derivatives.

Rennie (17) and Cameron (1), after having tried the action of formaldehyde and hydrochloric acid on aromatic acids, treated some of the same acids in various other ways, employing such condensing agents as s-dichloromethyl ether, anhydrous zinc chloride, and zinc monohydrate. Heptane was introduced in some cases as recommended by Quelet. Such modified condensations with aromatic acids are indicated in Table II, page 11. It is to be noted that all these modifications were of no advantage, as the results were identical in every way to those produced by the use of formaldehyde and hydrochloric acid alone.

TABLE II

<u>ACID</u>	<u>REAGENTS</u>	<u>PRODUCT</u>
Benzoic	$(\text{CH}_2\text{Cl})_2\text{O} \neq \text{ZnCl}_2$	No reaction
o-Methoxybenzoic	$(\text{CH}_2\text{Cl})_2\text{O} \neq \text{ZnCl}_2$	No reaction
p-Methoxybenzoic	$\text{HCHO} \neq \text{HCl} \neq$ $\text{ZnCl}_2 \cdot \text{H}_2\text{O}$	No reaction
p-Toluic	$(\text{CH}_2\text{Cl})_2\text{O} \neq \text{ZnCl}_2$	No reaction
m-Toluic	$\text{HCHO} \neq \text{HCl} \neq \text{ZnCl}_2$ \neq heptane	No reaction
5-Methoxy-m-toluic	$(\text{CH}_2\text{Cl})_2\text{O} \neq \text{HCl}$	Chlorocompound
2:4-Dimethoxybenzoic	$(\text{CH}_2\text{Cl})_2\text{O} \neq \text{ZnCl}_2$	4:6-Dimethoxyphthalide
3:4:5-Trimethoxybenzoic	$(\text{CH}_2\text{Cl})_2\text{O} \neq \text{ZnCl}_2$	Methyl ester of trimethyl gallic acid

Using the mechanism suggested by Stephen, Gladding, and Short, for the introduction of the chloromethyl group into the aromatic nucleus, it is not difficult to explain the formation of phthalides from aromatic acids by the action of formaldehyde and concentrated hydrochloric acid. The first step in phthalide production is the introduction of the chloromethyl group by interaction of the aromatic acid (a) with s-dichloromethyl ether. The chloromethyl carboxylic acid (b) can form the phthalide in one of two ways. It may directly lose HCl to form the phthalide (d), or the $-\text{CH}_2\text{Cl}$ group may be hydrolysed to $-\text{CH}_2\text{OH}$ to produce the carboxylic benzyl alcohol (c), which lactonizes with loss of water in the normal way to form the phthalide (d).



Evidence in support of the latter mechanism is found in the work of Stoermer and Behn (19) who used formaldehyde to introduce the -CH₂OH group into the nucleus of such compounds as *o*-nitrophenol and *o*-chloronitrobenzene. They suggested that the introduction of the chloromethyl group was the first stage of the reaction, with subsequent formation of the alcohol.

DISCUSSION OF EXPERIMENTAL RESULTS

A summary of the results obtained in this investigation is given below.

TABLE III

<u>ACID</u>	<u>REAGENTS</u>	<u>PRODUCT</u>
m-Methoxybenzoic	HCHO ∇ HCl (CH ₂ Cl) ₂ ^o	No result No result
p-Methoxybenzoic (anisic acid)	HCHO ∇ HCl ∇ SnCl ₂ ∇ heptane	No result
o-Toluic	HCHO ∇ HCl (CH ₂ Cl) ₂ ^o	Trace of methyl-o-toluate Trace of methyl-o-toluate
Phenylacetic	HCHO ∇ HCl HCHO ∇ HCl ∇ acetic	No result No result
Phthalic	HCHO ∇ HCl HCHO ∇ HCl ∇ acetic	No result No result
5-Hydroxy-m-toluic	HCHO ∇ HCl	Bakelite type product
5-Methoxy-m-toluic	HCHO ∇ HCl HCHO ∇ HCl ∇ acetic	Chloromethylphthalide Chloromethylphthalide
3-Hydroxy-p-toluic	HCHO ∇ HCl	Crystalline product m. p. 165.5 ^o
3-Methoxy-p-toluic	HCHO ∇ HCl HCHO ∇ HCl ∇ acetic	5-Methoxy-4- methylphthalide 5-Methoxy-4- methylphthalide
3:4:5-Trimethoxy- benzoic (trimethyl gallic acid)	HCHO ∇ HCl HCHO ∇ HCl ∇ acetic	Resin Resin

Rennie (17) studied the action of formaldehyde and hydrochloric acid on m- and p-toluic acid, and on o- and p-methoxybenzoic acid. To complete these two series, the

behaviour of *o*-toluic and *m*-methoxybenzoic acid was investigated. Both these acids showed no tendency to react with either formaldehyde and hydrochloric acid, or *s*-dichloromethyl ether. In each case most of the acid originally employed was recovered unchanged. In the case of *o*-toluic acid, there did form a small amount of an oil smelling strongly of wintergreen. This was probably methyl-*o*-toluate formed by the action of methyl alcohol present in the formalin. Rennie similarly, in his gallic acid trimethyl ether condensations, noted the formation of the solid methyl ester of trimethyl gallic acid.

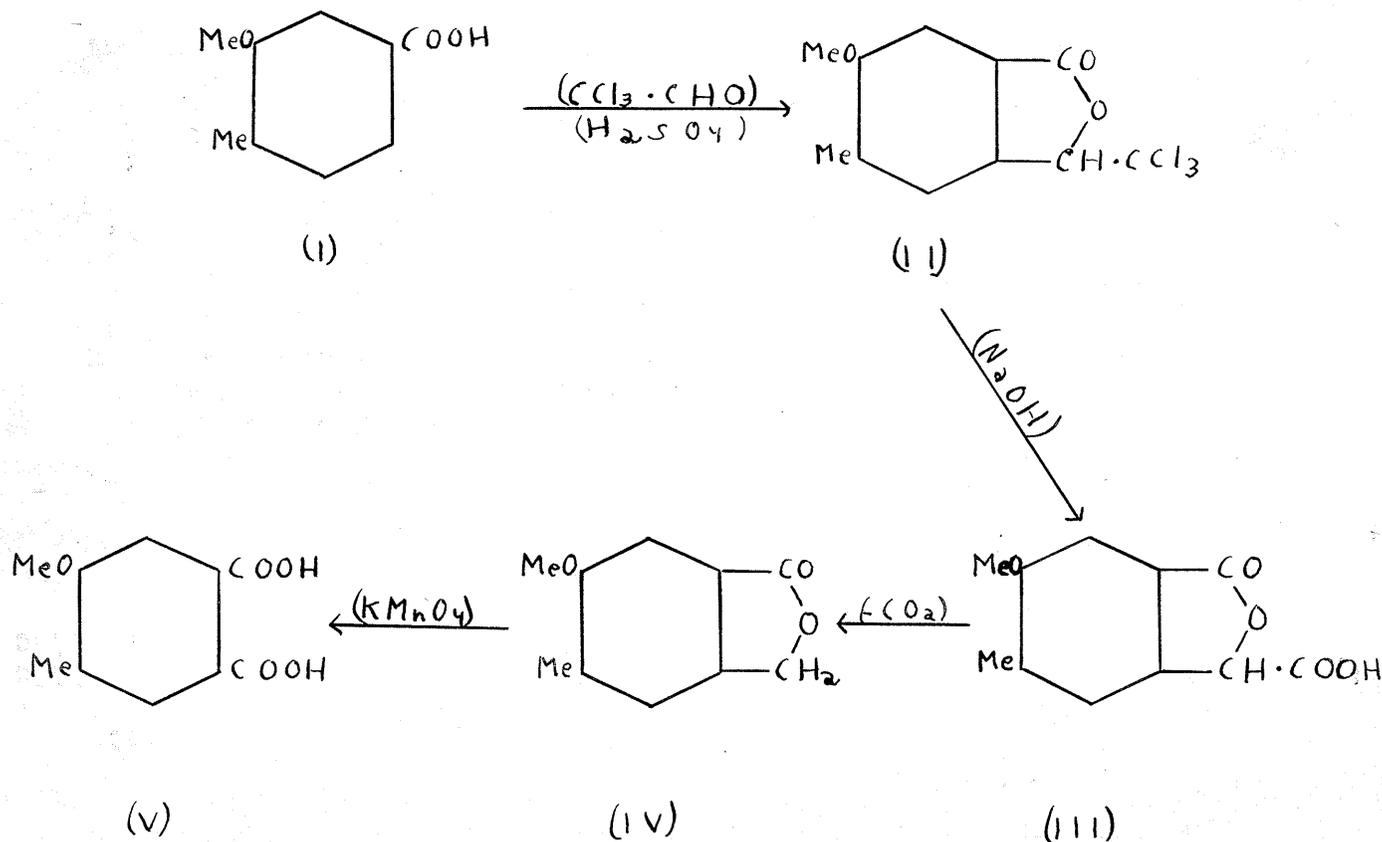
A method employed by Quelet (14) for successful production of the chloromethyl derivative of anisaldehyde, was applied to anisic acid. Hydrogen chloride gas was passed through a cold mixture of anisic acid, formaldehyde, zinc chloride, and heptane, for 1½ hours. However, no reaction occurred, the anisic acid remaining undissolved and being recovered unchanged at the end of the experiment.

The action of formaldehyde-hydrochloric solution on phenylacetic acid was investigated in the hope that the $-\text{CH}_2\cdot\text{COOH}$ group would not hinder phthalide production in contrast to benzoic acid, where carboxyl directly attached to the nucleus definitely prevents phthalide formation. However, no condensation took place.

Phthalic anhydride similarly, was not attacked, all of the original anhydride being recovered as phthalic acid.

3-Methoxy-*p*-toluic acid (I) condensed readily with hydrochloric acid and formaldehyde, yielding the correspond-

ing 5-methoxy-4-methylphthalide (IV) in good yield. The identity of this new phthalide was definitely established by its synthesis from 3-methoxy-p-toluic acid by the Britsch reaction (4). The phthalide was successfully oxidized by cold alkaline permanganate to 5-methoxy-4-methylphthalic acid.



This series marks the first recorded preparation of 5-methoxy-4-methylphthalide and 5-methoxy-4-methylphthalic acid.

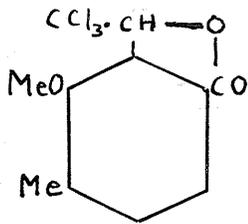
Meldrum and Kapadia (7) have prepared 5-methoxy-4-methyl- α -trichloromethylphthalide (II), and 5-methoxy-4-methyl- α -carboxymethylphthalide (III), by a similar procedure. They have definitely proven their structure to be that indicated above. The structure of the phthalide (IV) and the phthalic acid (V) is, therefore, also firmly established.

The reasons for the orientation assumed by Meldrum

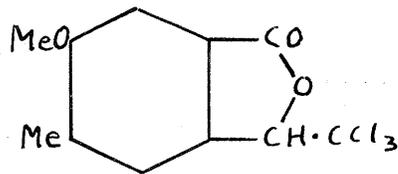
and Kapadia for the compounds mentioned are quite conclusive. On condensation with chloral hydrate, the $-\text{CHOH}\cdot\text{CCl}_3$ group may enter one of three positions in the nucleus of 3-methoxy-p-toluic acid. Ring closure of these types would produce the compounds (II), (VI), (VII).

The linking of the $-\text{CHOH}\cdot\text{CCl}_3$ group meta to the methoxyl group as indicated in formula (VII), was ruled out of consideration for the following reasons. The trichlorophthalide (II), on reduction with zinc and acetic acid gave 3-methoxy-4-methyl-6- $\beta\beta$ -dichloroethylbenzoic acid (VIII). The reduction product, on treatment with concentrated sulfuric acid, yielded the phenylacetic acid (IX). The compound (IX) was oxidized with potassium permanganate to 3-hydroxy-4-methylphthalic acid (X) of melting point 245° . This acid was not identical with the known acid 3-hydroxy-4-methylisophthalic acid (XII), melting point 270° , which would have resulted from this series of reactions had the original $-\text{CHOH}\cdot\text{CCl}_3$ entered meta to the methoxyl as in (VII).

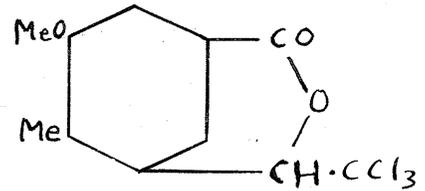
Hence the chloral hydrate molecule must have attached itself to the position ortho or para to the methoxyl group. Final orientation was determined by treatment of (IX) with chloral hydrate and 100% sulfuric acid. After four days, two products were obtained, one with chlorine, and one without chlorine. The first was a polymer of chloral. The second was the known 3-hydroxy-4:6-dimethylbenzoic acid (XI). The structure of the original chloral hydrate condensation product was thus definitely fixed as (II). The orientation of the phthalide resulting from the formaldehyde condensation is, therefore, quite certainly as indicated in (IV).



(VI)

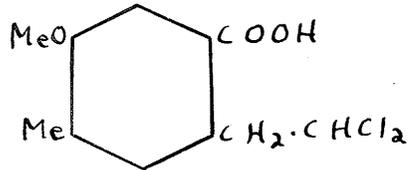


(II)



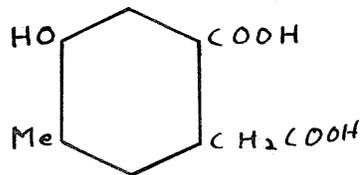
(VII)

(reduction)
(Zn+acetic)



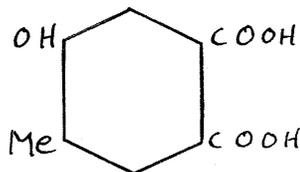
(VIII)

(hydrolysis)
(conc. H₂SO₄)



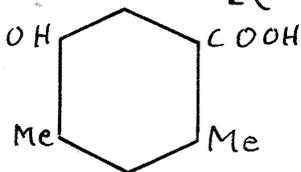
(IX)

(KMnO₄)



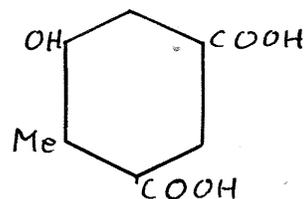
(X)

(CCl₃-CHO)
(100% H₂SO₄)



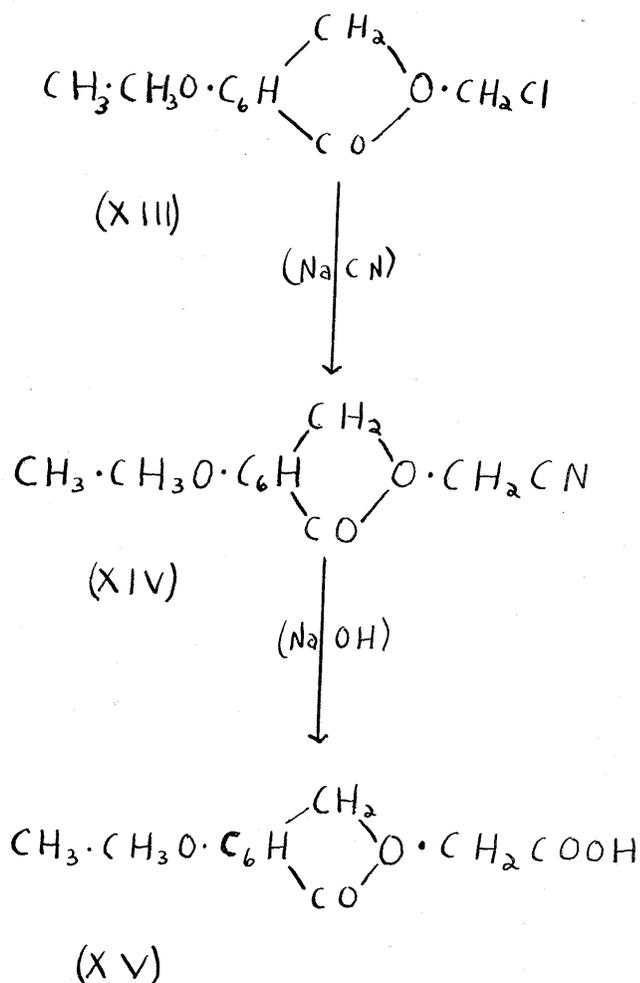
(XI)

(same)
(steps)



(XII)

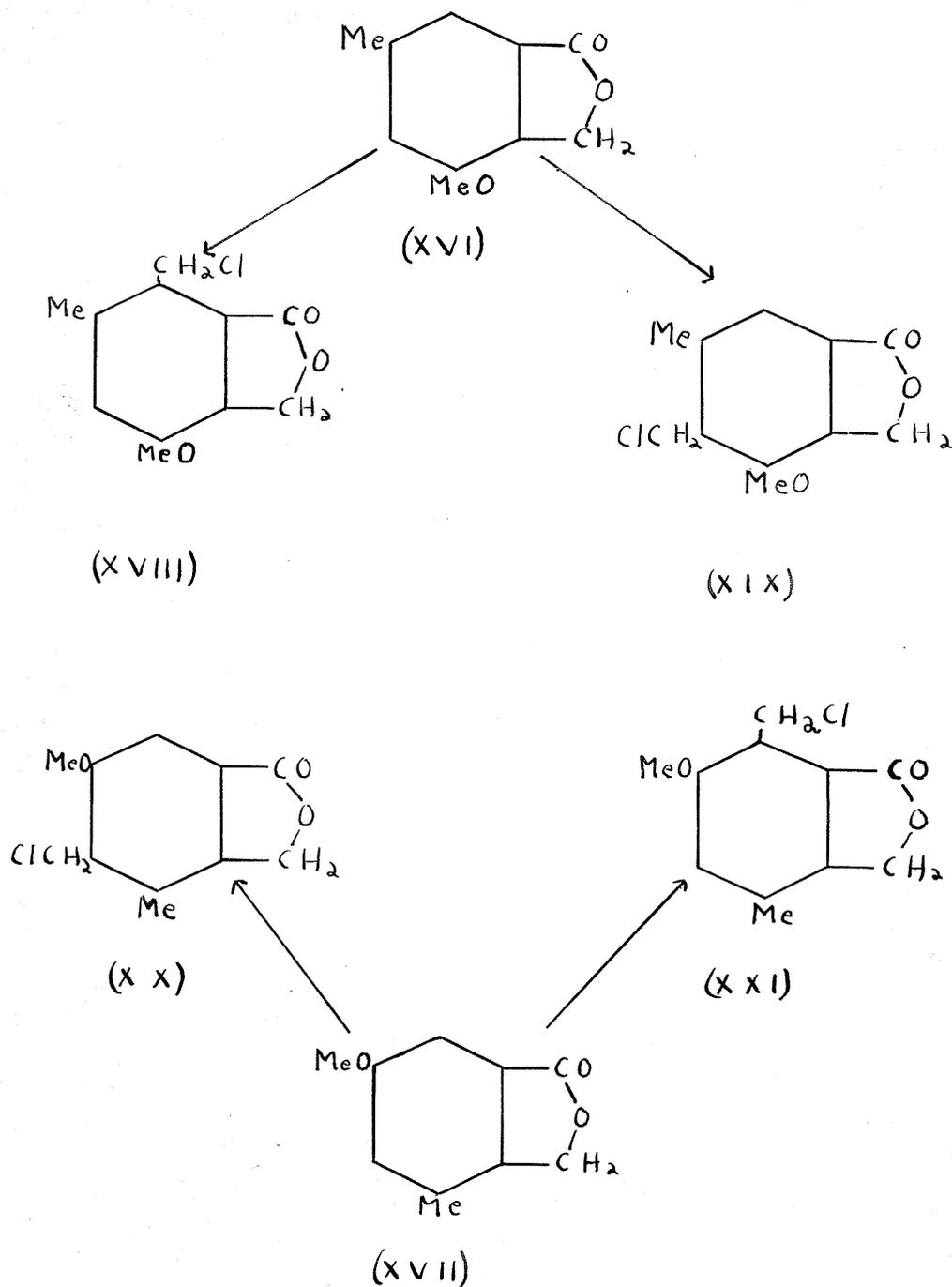
5-Methoxy-m-toluic acid gave the crude chlorocompound in fair yield. Purification, however, was extremely difficult, and the best product obtainable melted within a range of two degrees (177°-179°). This impurity of the chloroproduct led to a rather low chlorine analysis.



This difficulty of purification was, however, overcome in the following manner: the relatively crude chlorocompound (XIII) was converted to the nitrile (XIV) by boiling with alcoholic NaCN; the nitrile was then hydrolyzed with aqueous alkali to a phenylacetic acid (XV). Purification of the phenylacetic acid was a relatively simple matter. Analysis of the pure phenylacetic acid confirmed the structure of the chloro-

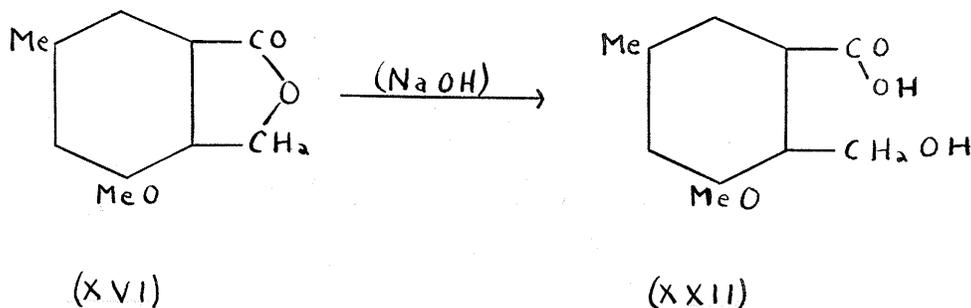
compound as 3-(or 5)-methoxy-5-(or 3)-methyl- α -chloromethyl-phthalide.

The orientation of the substituent groups is as yet in doubt. The phthalide ring may close in one of two positions (XVI), (XVII), and each of these phthalides can be chloromethylated in two ways. The four existing possibilities are shown below.



In one condensation with 5-methoxy-*m*-toluic acid, Ray and Robinson's modification (16) of Perkin, Edwards, and Stoye's method (13) was used. In the presence of the added acetic acid, the higher melting products obtained by Cameron were eliminated, making it easier to obtain the chloro-product in pure form.

Moreover, a substantial quantity of a non-chlorinated low melting product (131°-133°) was obtained. The melting point roughly agreed with the figure 135.5° given by Meldrum (6) for 3-methoxy-5-methylphthalide (XVI).



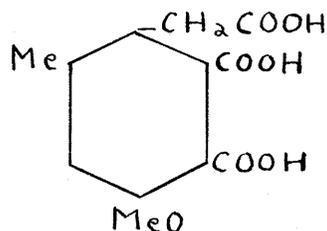
In support of this proposed structure, the compound, while insoluble in boiling water, slowly dissolved in alkali showing the presence of a lactone ring which opened in base to form the alkali soluble carboxybenzyl alcohol (XXII).

If the chloromethyl group of the chloro-compound was introduced only after all of the 5-methoxy-*m*-toluic acid had been converted to a simple phthalide (XVI), it should be possible to obtain the pure non-chlorinated phthalide by shortening the condensation period. Efforts in this direction, however, proved fruitless. Even a $\frac{1}{2}$ hour heating period produced a mixture of simple phthalide and chloromethylphthalide. Apparently phthalide production and chloromethylation proceeded simultaneously.

Later work will include the purification and complete analysis of this low melting product. If it proves to be Meldrum's phthalide, the structure of the chlorocompound will be narrowed to formulae (XVIII) and (XIX).

Final decision between these various formulae rests on the success of oxidative experiments on the phenylacetic acid derived from the chlorocompound.

Oxidation of the phenylacetic acid with cold alkaline permanganate produced a crude acid melting at 235°-238°. It was not found possible to purify this acid further, but analysis showed it to be a tricarboxylic acid of the type indicated in formula (XXIII).



(XXIII)

Identification of this tricarboxylic acid would completely orientate the substituents of the chlorocompound. No record, however, was found of any acid of this type. Proof of the structure of this acid would require further oxidative degradations or elaborate synthetic methods.

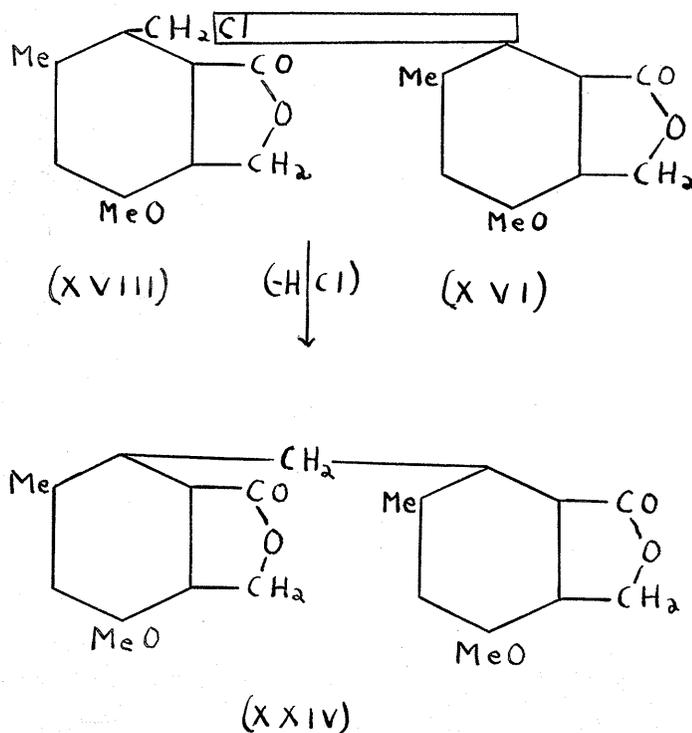
More drastic oxidation of the chlorocompound itself, might produce recognizable fragments which would establish complete orientation.

A fair amount of Cameron's high melting non-chlorinated product was obtained from the condensations not

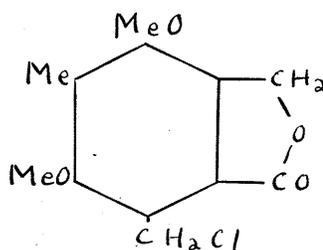
employing acetic acid. Since, however, the use of acetic acid eliminated this substance, the present writer was not much concerned with it.

It was thought at first that the product might simply be a polymer of formaldehyde produced on long boiling with hydrochloric acid. However, when formaldehyde and hydrochloric acid were heated alone for 5 hours, none of the high melting product separated. This, therefore, is not a formaldehyde polymer.

As mentioned previously (page 10), the chloromethylation of organic compounds by means of formaldehyde and hydrochloric acid is frequently accompanied by a secondary reaction producing diphenylmethane derivatives. The high melting product is quite likely a substituted diphenylmethane derivative (XXIV), probably formed from phthalide (XVI) and chloromethylphthalide (XVIII) in some such manner as indicated below.



In analogy with the formulae indicated (XVIII), (XIX), for the chlorocompound from 5-methoxy-*m*-toluic acid, the chlorinated compound obtained by Charlesworth and Robinson (2) from 3:5-dimethoxy-*p*-toluic acid, would have the structure 3:5-dimethoxy-4-methyl-6-chloromethylphthalide (XIV).



(XIV)

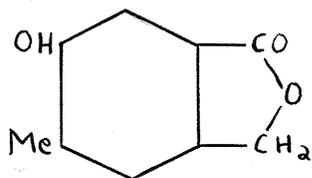
Conversion of this chloromethyl compound to the corresponding phenylacetic acid by way of the nitrile, would confirm this structure.

Two hydroxy carboxylic acids were condensed with formaldehyde and hydrochloric acid. 5-Hydroxy-*m*-toluic acid gave a bakelite-like product from which no crystalline material could be isolated. Stephen, Gladding, and Short (18), obtained a similar bakelite type product by the action of formaldehyde-hydrochloric solution on phenol.

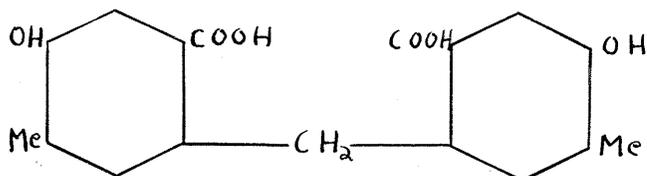
3-Hydroxy-*p*-toluic acid gave a non-chlorinated product melting at 165.5°. Analysis ruled out the possibility of the substance being the normal hydroxyphthalide (XVI), and suggested the diphenylmethane structure of the type indicated in (XVII).

Suginota-Shunso (20) has obtained *o*-*p*-dihydroxydiphenylmethane by steam distillation of the resin resulting from the treatment of phenol with formaldehyde in the presence of

hydrochloric acid. The resin finally resulting was produced by polymerization of these diphenylmethane units.



(XXVI)



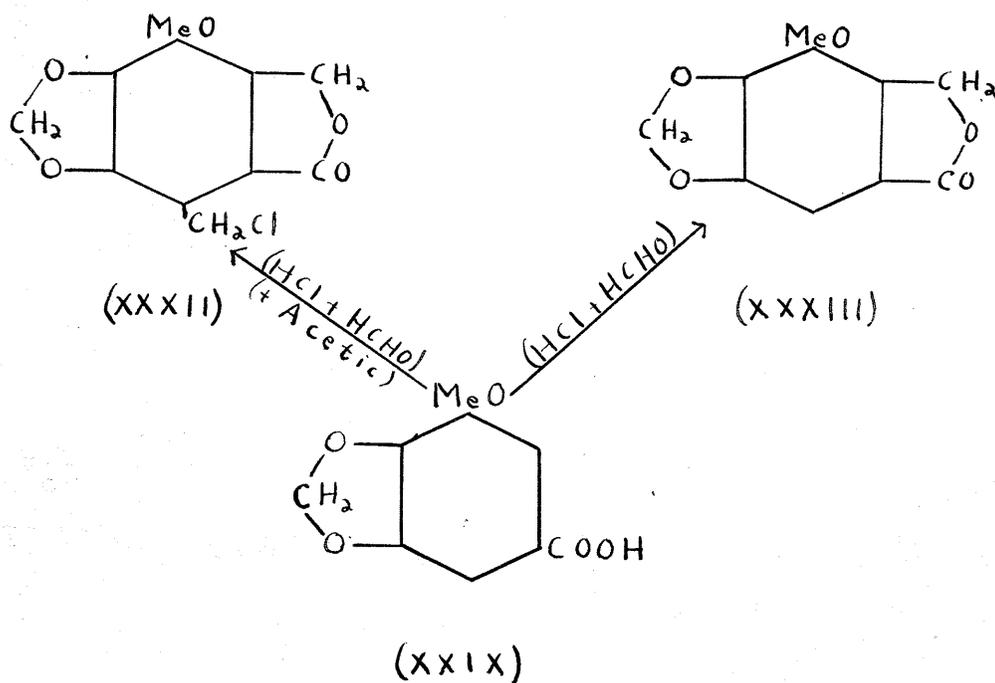
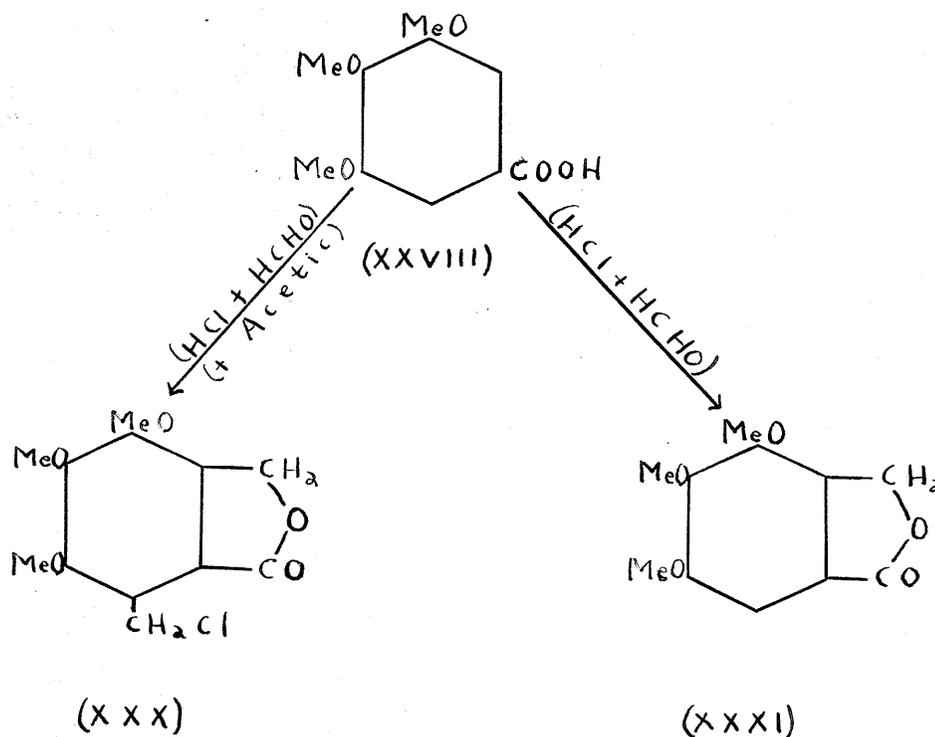
(XXVII)

It is highly probable, therefore, that the condensation product from 5-hydroxy-p-toluic acid is similarly an incompletely polymerized diphenylmethane derivative, that is, a bakelite^{type} in its early stages.

P. K. Paul (12) reported that gallic acid trimethyl ether (XIVIII) and myristicinic acid (XXIX), on condensation with formaldehyde and hydrochloric acid in the presence of acetic gave respectively, 3:4:5-trimethoxy-6-chloromethylphthalide (XXX) and 3:4-(or 4:5)-methylenedioxy-5-(or 3)-methoxy-6-chloromethylphthalide (XXXII). If, however, acetic acid was omitted, the normal phthalides, formulae (XXXI and XXXIII) respectively, were produced.

In the hope of duplicating these results with other aromatic acids, several condensations were attempted using acetic acid. These efforts met with no success. No new chloromethylphthalides were obtained. As can be seen from Table III, page 13, the results in the presence of acetic acid were identical, with one exception, to those obtained using formaldehyde and hydrochloric acid alone. And indeed, in direct contradiction to Paul's experience, 5-methoxy-*m*-toluic

acid, in the presence of acetic, produced what was probably a simple phthalide, where none of this product was formed in the absence of acetic acid.



In conclusion, it is of interest to discuss the results of the present investigation in reference to the effect of the nuclear substituent groups on condensations with formaldehyde in the presence of hydrochloric acid.

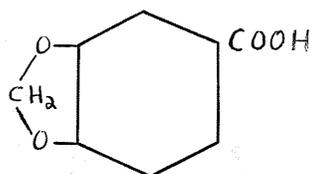
The work of Quelet (14) and others has shown that the nuclear chloromethylation of such compounds as phenolic ethers, aldehydes, hydrocarbons, and halogen derivatives of these compounds, proceeds without difficulty.

On the other hand, the simple aromatic acids such as benzoic acid, the various methoxybenzoic and toluic acids, phenylacetic and phthalic acid, all resisted chloromethylation. From this fact it must be concluded that the presence of carboxyl hinders the introduction of the chloromethyl group into the aromatic nucleus.

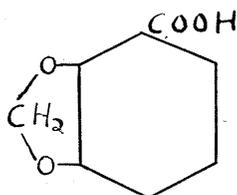
This statement is directly contrary to Stoerner and Behn (19) who claimed that the presence of a substituent carboxyl group ortho to the hydroxyl of phenols, facilitated chloromethylation para to the hydroxyl. However, the authors based this assumption on expected orienting influences rather than on experimental fact.

In the case of aromatic acids possessing more than one nuclear substituent besides the carboxyl, such resistant behaviour to condensation with formaldehyde is not so evident. In fact, all such acids but piperonylic acid, definitely do condense with formaldehyde, although in a few cases the product is resinous in nature. With piperonylic acid, Perkin, Edwards, and Stoye (13), found that even after long boiling phthalide production did not occur, and only a small amount of easily crystallizable matter of high molecular weight was

obtained. This failure of piperonylic acid (XXXIV) to condense is hardly understandable in view of the fact that the very closely related *o*-piperonylic acid (XXXV) readily produces the normal phthalide when heated with formaldehyde and hydrochloric acid in the presence of acetic acid.



(XXXIV)



(XXXV)

However, Perkin, Edwards, and Stoye, give no details regarding the piperonylic acid condensation, so that it is possible that a reaction did occur but isolation of the resulting compound was not effected. To clarify this point, this condensation should be repeated under various conditions employing acetic acid. The added acetic acid may induce phthalide formation.

Granting then, that an aromatic acid with two or more nuclear substituents besides carboxyl will yield a condensation product, the question arises: when is the simple phthalide produced and when the chlorinated compound?

Cameron (1), in drawing his conclusions, knew of only five acids which had been treated with formaldehyde and hydrochloric acid. These included the derivatives of benzoic acid (piperonylic, *o*-veratric and veratric), and the two toluic acids (5-methoxy-*m*-toluic, and 3:5-dimethoxy-*p*-toluic).

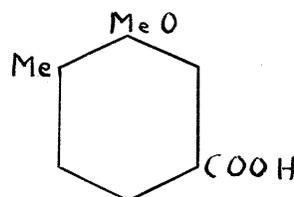
On the basis of this data he suggested two general possible requirements for chlorocompound formation. Firstly, he

noted that only the toluic acids had yielded chloroproducts, suggesting that the nuclear substituted methyl group might be essential to the reaction. Secondly, only those acids having methyl or methoxyl in the 3:5- or 3:4:5-positions produced chloroproducts.

A glance at Table I page 3, and Table III page 13, shows that the first generalization has no basis in fact. None of the toluic acids but 5-methoxy-*m*-toluic and 3:5-dimethoxy-*p*-toluic produce chlorocompounds, and indeed, two benzoic acids, gallic acid trimethyl ether and myristicinic acid, without the methyl group, do produce chloroproducts.

Cameron's second suggestion is closer to the truth. All of the acids producing chloroproducts have methyl or methoxyl in the 3:5- or 3:4:5- positions. However, 3:5-dimethoxy-*o*-toluic acid, which satisfies this condition, does not produce a chloroproduct. Also, trimethyl gallic acid and myristicinic acid yield chloroproducts only in the presence of acetic acid. In the absence of acetic the normal phthalides result.

Paul suggests that "*m*-methoxy-benzoic acid derivatives, having an additional *p*-orienting group, chiefly methoxyl, yield by Ray and Robinson's modification, chloromethylphthalides, provided that the *p*-position to the additional methoxyl group is free."



(X X X V I)

This is true of gallic acid trimethyl ether and syringic acid. However, 3-methoxy-p-toluic acid (XXXVI) indicated above, satisfies these conditions, and yet fails to produce a chloro-compound in the presence of acetic acid.

It is evident, therefore, that chlorocompound formation cannot be attributed solely to the influence of nuclear substituent groups. The conditions under which the condensation is carried out play an equally important part in determining the nature of the compound produced.

EXPERIMENTAL

I.

ATTEMPTED CONDENSATION OF 3-METHOXYBENZOIC ACID
WITH S-DICHLOROMETHYL ETHER

(a) Preparation of m-Methoxybenzoic Acid

A solution of m-hydroxybenzoic acid (5 grams) and sodium hydroxide (4 grams) in water (40 grams), was shaken with dimethyl sulfate (5 c.c.) for $\frac{1}{2}$ hour, when all the sulfate dissolved. The solution was refluxed for 15 minutes to complete the reaction and to destroy excess dimethyl sulfate. Sodium hydroxide (1.5 grams) was then added and the solution refluxed for 4 hours more, in order to saponify any ester which might have been formed.

On cooling and acidification, m-methoxybenzoic acid (4 grams) separated. After washing with warm water it melted at 103° - 105° . A sample on recrystallization from aqueous alcohol melted at 107° - 108° (Beilstein's values range from 105° - 110°).

This same method was employed in all subsequent methylations carried out in this research, unless otherwise stated.

(b) Preparation of s-Dichloromethyl Ether

s-Dichloromethyl ether was prepared essentially as described by Stephen, Gladding, and Short (13). Instead of a tower packed with pumice (as described by these authors), an

air condenser filled with glass beads, as used by Rennie (17), was employed.

40% Formaldehyde (200 grams) was allowed to percolate slowly down the tower, and at the same time a rapid stream of hydrogen chloride gas was passed upwards through the tower. The treated formaldehyde was collected below in a separating funnel.

After the first run through the tower, the formaldehyde separated none of the ether. On the second run through the tower, an oil formed and sank to the bottom of the separating funnel. This oil, which was the required ether, was separated and the formaldehyde solution passed down the tower a third time. More oil was formed. This process was repeated twice more, when no more oil separated. However, the formaldehyde, on standing, produced more of the *s*-dichloromethyl ether.

The total yield of the ether was 30 grams.

An attempt was also made to prepare the *s*-dichloromethyl ether by the action of hydrochloric acid on hexamethylene tetramine as described by Stephen, Gladding, and Short (18). However, the writer was unable to obtain any of the ether by this method. Rennie, similarly, failed to obtain any *s*-dichloromethyl ether by this method.

(c) Description of Attempted Condensation

The method was that of Stephen, Gladding, and Short (18). *m*-Methoxybenzoic acid (10 grams) was mixed with *s*-dichloromethyl ether (10 grams) and the mixture heated over wire gauze for 3½ hours. The acid melted, and settled to the bottom of the flask as a thick oil. On cooling, the oil

crystallized to a brown solid (7 grams). Mixed melting point determinations showed that the solid was unchanged *m*-methoxybenzoic acid.

The same method was employed in all the condensations involving the use of *s*-dichloromethyl ether.

II.

5-METHOXY-*m*-TOLUIC ACID SERIES

(a) Preparation of 5-Methoxy-*m*-Toluic Acid (XLII)

Most of the acid required for this investigation was synthesized from *m*-toluidine by converting the latter substance to the corresponding nitrile, and subsequently through the 5-sulfo- and 5-hydroxy-*m*-toluic acids to 5-methoxy-*m*-toluic acid.

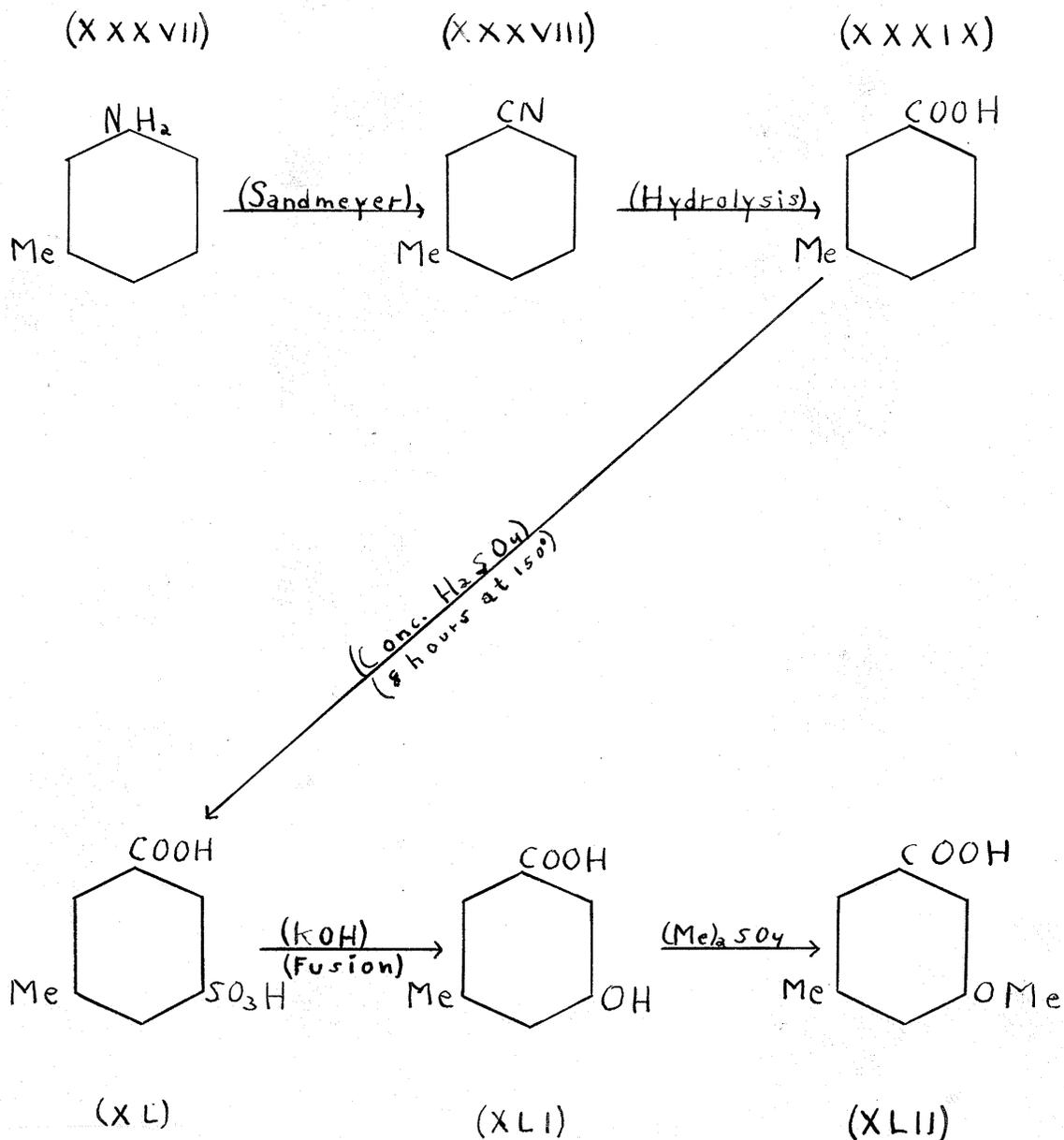
The *m*-toluidine (XXXVII) was first converted to *m*-cyanotoluene (XXXVIII) by the standard Sandmeyer reaction as described by Cohen (3).

The *m*-nitrile was hydrolyzed by boiling with 75% sulfuric in accordance with Cohen's directions (3). Great care was taken at the beginning of the hydrolysis, since the onset of the reaction was very sudden and very violent. To prevent loss of nitrile, it was necessary, at this point, to discontinue heating for a few moments.

Gattersman (5) claims that a purer acid is obtained in better yield, if the heating period is 5 hours at 150°. This method was tried in one hydrolysis, but the results were no better than those obtained by Cohen's procedure.

m-Toluic acid (XXXIX) was sulfonated by the method of Meldrum and Perkin (9). In this connection, it is to be noted that the free 5-sulfo-*m*-toluic acid (XL) did not separate on

merely standing overnight as described by these authors. A three to five day period in the cold was necessary for the complete crystallization of the required sulfonic acid.



The crude black sulfonic acid thus obtained was converted to the corresponding 5-hydroxy-2-toluic acid (XLI) by alkali fusion. Methylation of the hydroxy acid in the usual manner, employing dimethyl sulfate in alkaline solution, gave the required 5-methoxy-2-toluic acid (XLII). Repeated

crystallizations of the calcium salt from water, and of the free acid from aqueous acetic, gave pure white 5-methoxy-*m*-toluic acid (m. p. 134^o).

A smaller amount of 5-hydroxy-*m*-toluic acid was prepared from ethyl acetopyruvate (11), much according to details given by Meldrum and Perkin (9). Although the yields were poorer, the latter method was preferable since it produced a much purer acid in a shorter time.*

(b) 3-(or 5)-Methoxy-5-(or 3)-Methyl-*x*-Chloromethylphthalide (XIII)

The general method followed was that used by Perkin, Edwards, and Stoyke (13), in the preparation of meconine. This procedure was employed in all the formalin condensations with occasional modifications in the period of heating, the proportion of formaldehyde, and the method of separation of the reaction products.

1. Condensation without Acetic Acid

Pure 5-methoxy-*m*-toluic acid (30 grams) was added to 40% aqueous formaldehyde (89 c.c.), the mixture being heated 3 hours on the water bath. A further quantity of concentrated hydrochloric acid (120 c.c.) was added during the heating period to replace the hydrogen chloride which boiled away.

At first, partial solution of the acid occurred, with a brown solid appearing at the surface. This soon changed to an oil which sank to the bottom of the flask. On cooling, yellow lumps of a solid with a toffee-like consistency were formed. This stickiness of the solid reaction product was generally observed in the various formalin condensations, with consequent difficulty in purification.

*See Addenda, page 43A, number 2.

The resulting solid (47 grams) was well washed with water and sodium bicarbonate solution. Since acidification of the alkaline washings never produced free 5-methoxy-m-toluic acid, it was evident that all the acid employed was entirely converted into condensation product.

The crude solid was extracted with six 70 c.c. portions of boiling 95% alcohol, the extracts being filtered hot. A relatively small amount of an insoluble chlorine free, high melting (275°-285°) white powder was left. This substance was not investigated any further.

The hot alcoholic extracts, on cooling, separated white crystals. The first fraction was in general very impure. Successive fractions improved in quality. Total yield from the first extraction was 13.5 grams.

Repeated and laborious fractional crystallization produced the chloromethyl derivative in fine white needles melting from 177°-179° (Cameron 175°-176°). It was found impossible to raise the melting point above this figure. Mixed melting point determinations with Cameron's chloroproduct proved the identity of the two compounds.

Analysis

Calculated for $C_{11}H_{11}O_3Cl$: Cl, 15.67; CH_3O , 13.7; molecular weight, 226.5.

Found: Cl, 14.75; CH_3O , 14.7; molecular weight (by Rast's method), 214.*

*NOTE:

Chlorine was determined by a semimicro method as described by Suchards and Bobranski in "Semimicro-Methods for

the Elementary Analysis of Organic Compounds," page 39.

Methoxyl estimations were made by E. P. Clark's semimicro method (J. Am. Chem. Soc., 51, 1479, 1929).

2. Condensation with Acetic Acid

Perkin, Edwards, and Stoyie's method as modified by Ray and Robinson (16) was tried in one condensation.

5-Methoxy-m-toluic acid (4 grams), fuming hydrochloric acid (25 c.c.), and 40% aqueous formaldehyde (6.2 c.c.) were* heated for 3 hours under reflux on the steam bath, when the reaction mixture turned yellow. On cooling, a crystalline precipitate settled out, with none of the gumminess of the crude solid obtained in the absence of acetic acid.

The precipitate was washed well with water and extracted with three portions of boiling 95% alcohol. No insoluble material was left.

The first extract yielded 1.4 grams of white crystals melting at 131.5°-133°. The second extract produced 1.6 grams of white crystals melting at 166°-173° with, however, much previous softening. The third extract separated 0.6 grams of the chloromethyl derivative in the form of needlelike crystals melting at 176°-178°.

Similar condensations were made using various heating periods from $\frac{1}{2}$ hour to 3 hours. However, the results were always the same, irrespective of the length of the heating period.

(c) Cyanomethylphthalide (XIV)

The chloromethyl compound (0.9 grams) was heated with KCN (0.4 grams) in 95% alcohol (10 c.c.) on a steam bath under reflux for 4 hours when the reaction was complete. The

*See Addenda, page 43A, number 1.

reaction product (0.8 grams) was obtained on diluting the reaction mixture with water. It crystallized from 95% alcohol in soft white leaflets melting at 179° - 181.5° .

Analysis

Calculated for $C_{11}H_{11}O_3CN$: N, 6.43%.

Found: N, 6.10%.

(d) Phenylacetic Acid (XV)

The above chloromethylphthalide (0.5 grams) was boiled under reflux with 10% NaOH (10 c.c.) for 7 hours. The alkaline solution was filtered to get rid of the higher insolubles. On acidification, pure white crystals (0.3 grams) resulted. On recrystallization from water and alcohol the acid melted at 218° - 219° .

Analysis

Calculated for $C_{11}H_{11}COOH$: acid equivalent, 236; C, 61.03; H, 5.17.

Found: acid equivalent, 234; C, 61.3; H, 5.30.

(e) Tricarboxylic Acid (XVIII)

Pure phenylacetic acid (0.7 grams) was dissolved in 10% NaOH (20 c.c.) and powdered potassium permanganate (0.77 grams) was added. The mixture was allowed to stand for 48 hours in the cold with occasional shaking.

Sulfur dioxide was then passed in until all of the manganese dioxide had dissolved. The cooled solution was filtered and acidified with hydrochloric acid, when sodium chloride separated. This was removed by filtration. The ether

extract of the mother liquor, after drying over anhydrous sodium sulfate, separated 0.5 grams of the tricarboxylic acid with melting point 235° - 238° .

The acid was insoluble in methyl acetate, heptane, chloroform, and carbon tetrachloride, and soluble in water and acetone. It was not found possible, however, to purify the acid further.

Analysis

Calculated for $C_{12}H_{12}O_7$: C, 53.7%; H, 4.44%; acid equivalent, 89.3.

Found: C, 55.2%; H, 4.38%; acid equivalent 84.4.

The high carbon and low equivalent weight can be ascribed to the presence of unoxidized phenylacetic acid (XV).

III.

3-METHOXY-P-TOLUIC ACID SERIES

A substantial quantity of pure 3-hydroxy-p-toluic acid was made available through the courtesy of Dr. H. Charlesworth. The acid was prepared according to the directions given by Meldrum and Perkin (8). Methylation with dimethyl sulfate proceeded smoothly. Recrystallization of the crude acid from ethyl acetate gave pure 3-methoxy-p-toluic acid (I) melting at 153° (Reilstein value 156°).

(a) Preparation of 5-Methoxy-4-Methylanthralide (IV) by the Formaldehyde Condensation

Pure 3-methoxy-p-toluic acid (4.5 grams), 40% aqueous formaldehyde (13 c.c.), and concentrated hydrochloric acid (19 c.c.), were heated on the water bath for 4 hours and then

over wire gauze for $\frac{1}{2}$ hour. Additional hydrochloric acid (10 c.c.) was added during the heating period. Well formed prisms (5 grams) separated on cooling. Recrystallization from alcohol produced glistening white needles (3.3 grams) melting at 144° .

Analysis

Calculated for $C_{10}H_{10}O_3$: C, 67.41; H, 5.61.

Found: C, 67.51; H, 5.88.

(b) Preparation of 5-Methoxy-4-Methylphthalide by the Fritsch Method (4)

1. 5-Methoxy-4-Methyl- α -Trichloromethylphthalide (II)

5-Methoxy-p-toluic acid (16.5 grams) was shaken with chloral hydrate (20.5 grams) and sulphuric acid (90 c.c. sulfuric with 5 c.c. water) and the whole heated to 70° - 80° for $\frac{1}{2}$ hour when the mixture turned a dark green. After 40 hours standing at room temperature the reaction mixture was diluted with cold water. A heavy green oil separated and soon solidified to a pasty green mass. The solid was collected and washed well with water. Charcoal treatment followed by recrystallization from aqueous alcohol resulted in shining white crystals (21 grams) melting at 129° . Meldrum and Kapadia (7) give a melting point of 132° .

Analysis

Calculated for $C_{11}H_9O_3Cl_3$: Cl, 36.04.

Found: Cl, 35.80.

2. 5-Methoxy-4-methyl- α -Carboxyphthalide (III)

5-Methoxy-4-methyl- α -trichloromethylphthalide (20 grams) was heated for 1 hour on the water bath with 20% aqueous sodium hydroxide (102 c.c.). The acid separated as a brick red sodium salt. This was collected, dissolved in water and treated with charcoal. The filtrate from the charcoal treatment produced on acidification long yellow needles (11 grams), which, after one recrystallization from alcohol, melted at 221° with decomposition. A value of 222° is recorded by Meldrum and Lapedia (7).

Analysis

Calculated for $C_{11}H_{10}O_5$: C, 59.46; H, 4.55.

Found: C, 59.40; H, 4.71.

3. 5-Methoxy-4-Methylphthalide (IV)

For decarboxylation of the above acid a method used by Charlesworth and Robertson (2) was first tried. 5-Methoxy-4-methyl- α -carboxyphthalide (4.5 grams) was mixed with quinoline (15 c.c.) and copper chromite (0.4 grams). The mixture was heated on the oil bath at 170° - 180° until all of the carbon dioxide had been evolved. The quinoline solution was decanted from the catalyst into dilute hydrochloric acid when a gummy mass separated. It was found impossible, however, to obtain the phthalide in crystalline form.

A much simpler method was adopted with more success. The dry acid (3.5 grams) was heated in a test-tube at 220° - 230° for 5 minutes and then gradually heated to 260° within

a period of another 10 minutes when carbon dioxide evolution ceased. The hot melt, on solidification, was taken up in hot alcohol (10 c.c.). The phthalide (2.5 grams) separated from the alcohol in yellow needles melting at 145°.

The identity of this phthalide with that produced directly by the formaldehyde condensation was proven by mixed melting point determinations and by analysis.

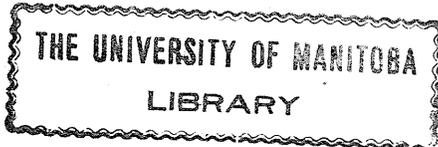
Analysis

Calculated for $C_{10}H_{10}O_3$: C, 67.41; H, 5.61.

Found: C, 67.81; H, 5.80.

4. 5-Methoxy-4-Methylphthalic Acid (V)

5-Methoxy-4-methylphthalide (1 gram) was dissolved in 10% caustic potash (20 c.c.), by long shaking and warming. To the cold solution the theoretical amount of potassium permanganate (1.2 grams) was gradually added with cooling. After 36 hours standing at room temperature the oxidation was complete. Following acidification with hydrochloric acid, the phthalic acid was extracted with ether, and the ether extract dried over anhydrous sodium sulfate. Evaporation of the ether left white crystals of phthalic acid (0.6 grams). On recrystallization from water the acid melted at 165.5°-167°.



Analysis

Calculated for $C_{10}H_{10}O_5$: acid equivalent, 105.0;

C, 57.14; H, 4.77.

Found: acid equivalent, 106.2; C, 57.34; H, 4.86.

IV.

3-HYDROXY-P-TOLUIC ACID

3-Hydroxy-p-toluic acid (4 grams) was heated with 40% formaldehyde (11 c.c.) and concentrated hydrochloric acid (16 c.c.) for 3 hours over wire gauze. A further quantity of concentrated hydrochloric acid (5 c.c.) was added during the heating period.

The acid did not appear to go into solution, but nevertheless, a reaction occurred. The solid reaction product was separated by filtration and treated with sodium bicarbonate to remove any unchanged acid. However, no unchanged acid was detected.

Recrystallization of the solid from ethyl alcohol produced fine white needles (2.4 grams) melting sharply at 165.5°. Sodium fusion and quantitative analysis showed no halogen.

Analysis

Found: C, 63.4; H, 4.86.

Calculated for $C_{17}H_{16}O_6$ (XXVII): C, 64.6; H, 5.06.

Calculated for $C_9H_8O_3$ (XIVI): C, 65.9; H, 4.88.

The analysis is in fair agreement with the diphenylmethane type of structure (XXVII) suggested for the condensation product.

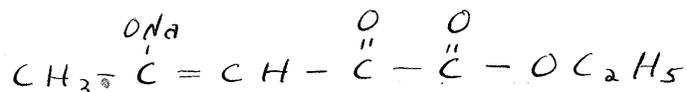
There was also formed in this condensation, a small amount of a white powder whose melting point exceeded 290°. However, the relative insolubility of this substance in

alcohol, made the separation of the main reaction product a comparatively simple matter.

Shortening of the condensation period to $1\frac{1}{2}$ hours, eliminated this high-melting product with no decrease in yield or purity of the main condensation product. A small amount of unchanged acid present, was easily removed by treatment with sodium bicarbonate solution.

ADDENDA

1. Insert the words "glacial acetic acid (25 c.c.)".
2. Sodium (39.5 grams) was dissolved in absolute alcohol (600 c.c.) in a 5 litre flask fitted with a reflux condenser and a mercury seal stirrer. To this solution of sodium ethylate, a mixture of ethyl oxalate (250 grams) and acetone (99.3 grams), both dried over calcium chloride, was gradually added during a period of 2 hours with constant stirring, when the whole became semi-solid owing to the separation of the sodium derivative of ethyl acetoxypruvate (XLIII).



(XLIII)

The yellow mass was washed out of the flask by shaking with absolute alcohol (200 c.c.) and filtered by 3 hours suction on a Buchner funnel. It was then stirred for 2 hours with glacial acetic acid (500 c.c.) and the resulting yellow crystalline product, containing 6.79% sodium, was collected, washed with ether, and ground up with water and excess dilute sulfuric acid, when a colorless crystalline precipitate (201 grams), melting at 88°-90°, separated. Meldrum and Perkin (9) give a melting point of 89° and suggest a structure for this product as indicated in formula (XLIV).

SUMMARY

1. It has been shown that *m*- and *p*-methoxybenzoic acids, *o*-toluic acid, phthalic acid, and phenylacetic acid, do not condense with formaldehyde in the presence of concentrated hydrochloric acid. The use of other condensing media, such as *s*-dichloromethyl ether, zinc chloride, and acetic acid, has been similarly ineffective in promoting condensation of these acids with formaldehyde.
2. An attempt has been made to reproduce the work of P. K. Paul and prepare 3:4:5-trimethoxy-6-chloromethylphthalide and 3:4:5-trimethoxyphthalide, by the action of formaldehyde-hydrochloric solution on trimethyl gallic acid, with and without, respectively, acetic acid, but in both cases only resinous material was produced.
3. Two hydroxy toluic acids have been condensed with formaldehyde in the presence of concentrated hydrochloric acid. 5-Hydroxy-*o*-toluic acid has given a bakelite type material. 3-Hydroxy-*p*-toluic acid has yielded a non-chlorinated crystalline product of melting point 165.5°, for which a substituted diphenylmethane structure has been suggested.
4. The chlorinated condensation product resulting from the action of formaldehyde and concentrated hydrochloric acid on 5-methoxy-*o*-toluic acid has been shown to have the structure 3-(or 5)-methoxy-5-(or 3)-methyl-*o*-chloromethylphthalide. This structure has been established by conversion of the chloromethylphthalide to the corresponding nitrile and phenylacetic

acid, both as yet unrecorded. The phthalide ring of the phenylacetic derivative has been successfully oxidized to yield a new dicarboxyphenylacetic acid.

5. 5-Methoxy-4-methylphthalide has been prepared for the first time by the action of formaldehyde and concentrated hydrochloric acid on 3-methoxy-p-toluic acid. The same phthalide has been successfully oxidized to the hitherto unrecorded 5-methoxy-4-methylphthalic acid.

6. It has been clearly demonstrated that the presence of carboxyl hinders the introduction of the chloromethyl group into the aromatic nucleus, while substituents such as methyl and methoxyl encourage this tendency. In general, aromatic acids having one or more nuclear substituents besides carboxyl, yield phthalides or chloromethylphthalides when treated with boiling formaldehyde and concentrated hydrochloric acid.

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