A STUDY OF THE ACTION OF FORMALDEHYDE IN THE PRESENCE OF CONCENTRATED HYDROCHLORIC ACID ON CERTAIN AROMATIC ACIDS

A STUDY OF THE ACTION OF FORMALDEHYDE IN THE PRESENCE OF CONCENTRATED HYDROCHLORIC ACID ON CERTAIN AROMATIC ACIDS

By

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To DR. E. H. CHARLESWORTH

for his excellent advice and for his infinitely patient guidance which made work a pleasure, the thanks of this writer are most sincerely offered.

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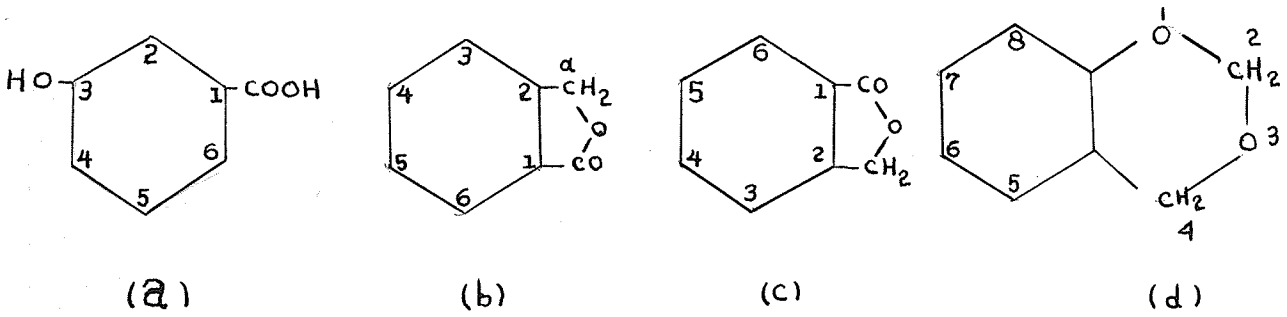
INTRODUCTION

Prior to 1925, the standard method of preparing phthalides was the Fritsch (7) reaction. In 1925, Perkin, Edwards and Stoyle (19) succeeded in preparing the phthalide meconine directly by the action of hydrochloric acid and formaldehyde on O-veratic acid. As this was a much shorter proceedure, attempts were made to use this reaction as a general method of preparing phthalides. However, it was found that phthalides were not always formed. Among the various cases encountered, were (1) no reaction at all, (2) phthalide formation, (3) chlorocompound formation, (4) polymer or resin formation or (5) combinations of the latter cases.

The present investigations were undertaken to determine the nature of the products resulting from the reaction of hydrochloric acid and formaldehyde with 3-hydroxy-p-toluic acid and from the reaction of the same condensing agents on 2:4-dimethoxybenzoic acid. These reactions had been carried out by previous investigators, but the results obtained were somewhat doubtful. In addition, in this work other similar reactions were investigated in an attempt to determine the conditions necessary for phthalide formation.

The following system of nomenclature is used. In designating the aromatic acid derivatives, the carbon atoms in the benzene nucleus are numbered in a counter-clockwise

direction, starting from the carbon to which the carboxyl group is attached (a). In naming phthalides, the system indicated in (b) and (c) are followed, while the system indicated in (d) is followed in naming dioxanyl phthalides.

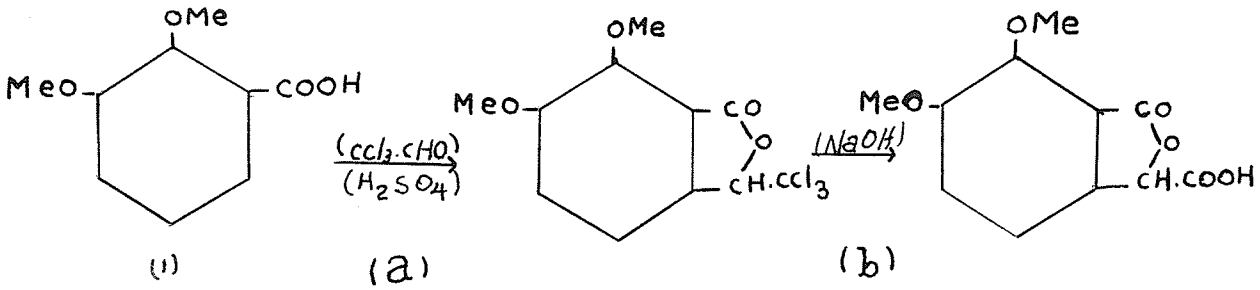


(a) (b) (c) (d)

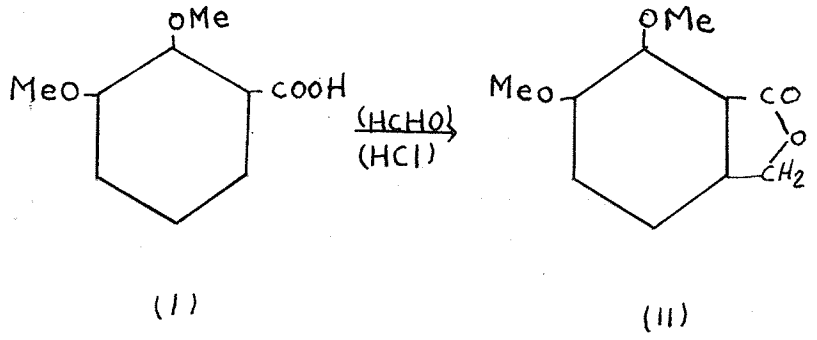
For convenience, the symbol "Me" is used in place of "CH_3", and "OME" in place of "OCH_3". The Perkin, Edwards, and Stoyle reaction is sometimes referred to as the "hydrochloric acid-formaldehyde condensation", or simply as the "condensation", and the Fritsch reaction, as the "chloral hydrate condensation."

The Fritsch reaction consists in treating the aromatic acid with chloral hydrate and sulfuric acid (a) to first form the trichloromethylphthalide. This is converted to the carboxyphthalide by warming with 20% aqueous sodium hydroxide (b). Decarboxylation (c) yields the phthalide. Thus, the preparation of meconine (II) from O-veratric Acid (I)

by the Fritsch reaction would proceed as follows:



To prepare meconine by the hydrochloric acid-formaldehyde method, a mixture of o-veratric acid (I), hydrochloric acid, and formaldehyde is merely heated over wire guaze for a few minutes. This is a direct step from the aromatic acid to the phthalide, thus:



It has been shown by the work of Stephen, Gladding and Short (25), King and King (10), and others, that phthalide formation by the hydrochloric acid-formaldehyde condensation does not result by direct reaction of the aromatic acid with the hydrochloric acid and formaldehyde. Intermediate compounds are formed. A Chloromethyl group must first be introduced into the benzene nucleus. Stephen, Gladding and Short (25) have shown how this takes place.

They treated the aromatic compound, in the presence of zinc chloride as a dehydrating agent, with the product obtained by the action of hydrochloric acid on paraformaldehyde, which was found to consist of s-dichloromethyl ether (III) and a small amount of monochloromethyl ether (IV) formed from the methyl alcohol present as an impurity in the commercial paraformaldehyde. Stephen, Gladding and Short (25) suggest that the formation of s-dichloromethyl ether takes place as follows:

$$2\ HCHO + 2\ HCl \longrightarrow \underset{(III)}{(CH_2Cl)_2O} + H_2O \qquad (III)$$

while the formation of the monochloromethyl ether may be represented by

$$2\ CH_3OH + HCl \longrightarrow \underset{(IV)}{CH_3O \cdot CH_2Cl} \qquad (IV)$$

Chloromethyl derivatives may be obtained from both these products, but the reaction with the monochloromethyl ether is much slower. A possible explanation of the facts is indicated by the following scheme.

$$(CH_2Cl)_2O + 2\ C_6H_6 \longrightarrow 2\ C_6H_5 \cdot CH_2Cl + H_2O$$

$$CH_3O \cdot CH_2Cl + C_6H_6 \longrightarrow C_6H_5 \cdot CH_2Cl + CH_3OH.$$

In support of this, Stephen, Gladding and Short (25) found that substituting zinc chloride monohydrate, which forms zinc chloride at 27°, for zinc chloride, in the reaction of the aromatic compound with the monochloromethyl ether, the reaction rate increased due to the following reactions:

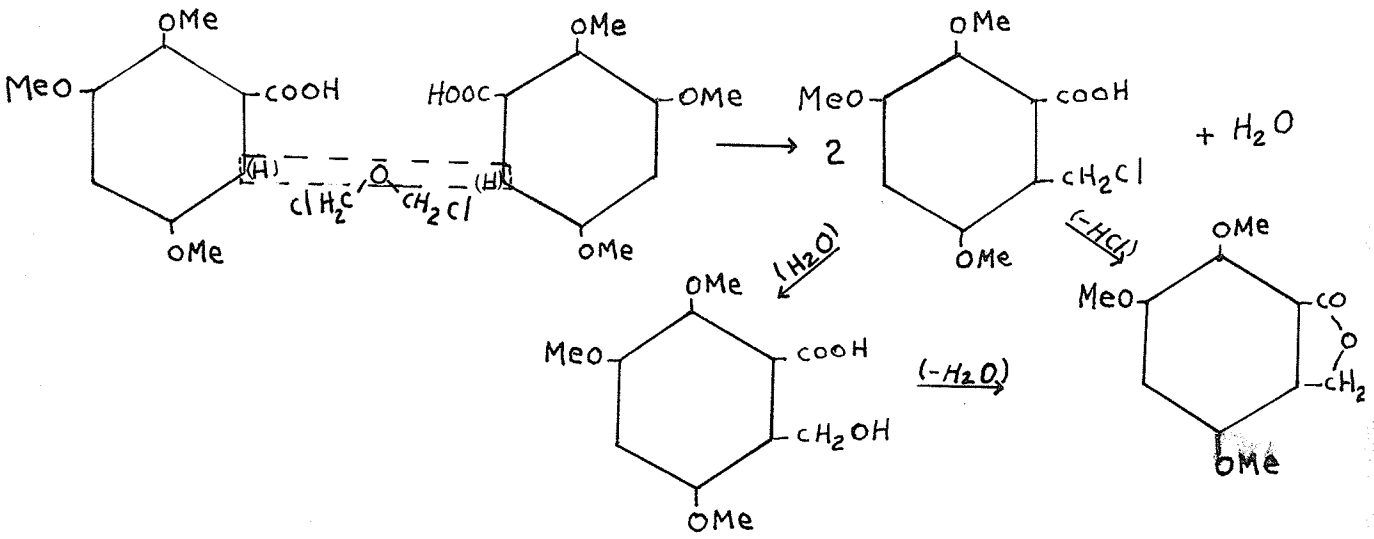
$$CH_3O.\ CH_2Cl + H_2O \longrightarrow CH_3OH + CH_2Cl.OH$$

$$2\ CH_2Cl.\ OH \longrightarrow (CH_2Cl)_2O + H_2O$$

Thus, the water liberated from the zinc chloride monohydrate hydrolyzed the monochloromethyl ether to the dichloromethyl ether.

On the basis of the above reactions, Yan (29) and Sinder (23) showed how phthalide formation can take place in the reaction of an aromatic acid with hydrochloric acid and formaldehyde. The hydrochloric acid and formaldehyde react to form s-dichloromethyl ether (III), which introduces a chloromethyl group into the aromatic nucleus. For phthalide formation to occur, the chloromethyl group must be introduced ortho to the carboxyl group. The final reaction may take place in one of two ways. The chloromethyl group and the carboxyl group may lose hydrogen chloride directly to form the phthalide, or hydrolysis of the chloromethyl group may take place first to form the carboxybenzyl alcohol, the lactone ring then forming by a loss of water between the alcohol and

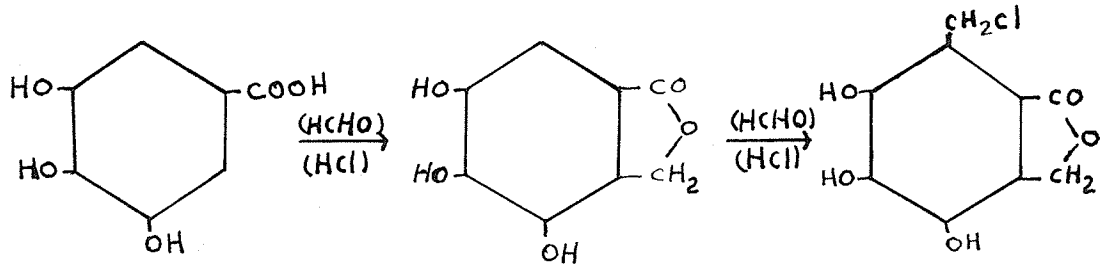
the carboxyl groups:



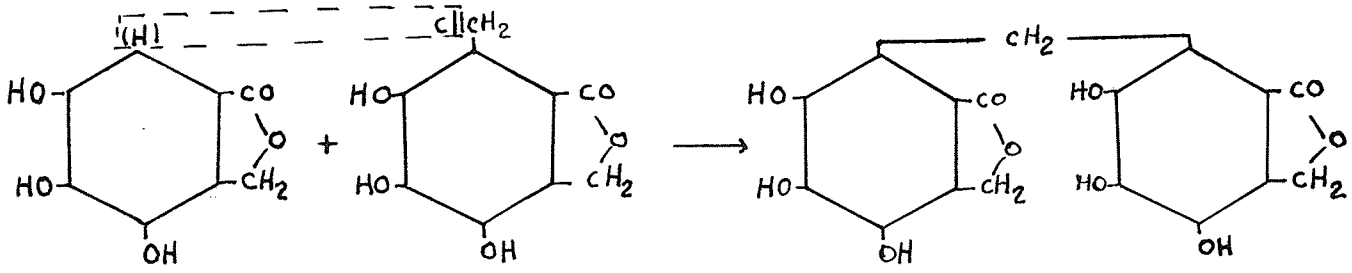
Evidence in support of the latter mechanism may be found in the work of Stoermer and Behn (26) who used formaldehyde to introduce the $-CH_2OH$ group into the aromatic nucleus of such compounds as o-nitrophenol and o-chlorobenzene. They suggested that the introduction of the chloromethyl group was the first stage of the reaction, with subsequent formation of the alcohol. This would indicate that the chloromethyl derivative is an unstable intermediate. However, a number of chloromethyl derivatives, in which the chloromethyl group introduced was not ortho to the carboxyl group, have been isolated. It is only in alkaline solution that the chloromethyl group is easily hydrolyzed to the alcohol. Since phthalide formation takes place in an acid medium, it is likely in these cases that the lactone ring is formed by direct loss of hydrogen chloride.

In many cases, neither the Fritsch reaction nor the

hydrochloric acid-formaldehyde condensation form phthalides. For example, Alimanchandri and Meldrum (1) were unable to prepare the phthalide of trimethoxy gallic acid by the Fritsch reaction. Similarly, in the present work, it was found impossible to form the phthalide of 2-hydroxy-4-methoxybenzoic acid. The hydrochloric acid-formaldehyde reaction is limited by the fact that chloromethyl derivatives or polymeric condensation products may result. The formation of the chloromethylphthalide may be represented as follows:



while resin formation may take place by a condensation of the chloromethyl derivatives to form diphenylmethane types of compounds,



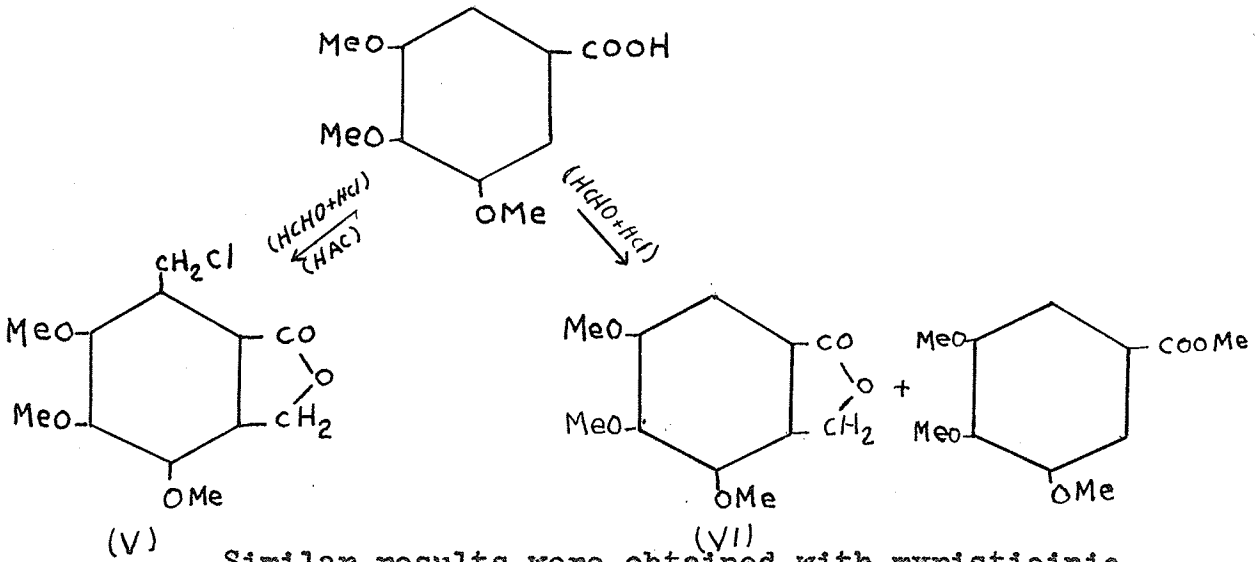
Despite the limitations of the hydrochloric acid-formaldehyde condensation, the simplicity of this reaction as compared to the longer Fritsch reaction, or chloral hydrate

condensation, as it is sometimes termed, led to attempts to prepare other phthalides by the shorter method.

A large number of these attempts were successful. Following the preparation of meconine by Perkin, Edwards and Stoyle (19), Mitter, Sen and Paul (14), applying the hydrochloric acid-formaldehyde method to 3:5-dimethoxy-o-toluic acid obtained 6-methyl-3:5-dimethoxyphthalide. More recently, Rennie (22), working with some of the simpler aromatic acids, in an attempt to establish some general course of reaction for the hydrochloric acid-formaldehyde condensation obtained the phthalide of 5-methoxy-o-toluic acid. Continuing this investigation, Yan (29) prepared the phthalide of 3-methoxy-p-toluic acid by the same method.

Very early in the attempts to prepare phthalides by the method of Perkin, Edwards and Stoyle (19), it was found that the reaction was limited in its application. Raistrick, Robinson and Todd (21) failed to obtain a phthalide from 5-methoxy-m-toluic acid. Instead, they obtained a chlorine-containing compound, undoubtedly a chloromethyl derivative. Similar chloromethyl derivatives were obtained by Charlesworth and Robinson (6) and by Cameron (4). Stephen, Gladding and Short (25), working with aromatic compounds such as phenol, anisole, dimethylaniline, found the formation of chloromethyl derivatives to be accompanied by the production of resinous diphenylmethane derivatives. This latter reaction was found to be influenced by the type of dehydrating agent employed, and by the temperature. Sulfuric acid, instead of zinc chloride

as dehydrating agent formed larger quantities of diphenylmethane derivatives. Traces of metals such as iron, zinc and mercury caused the same results. In their experiments they had to keep the temperature below 35° to keep resin formation to a minimum. The course of the reaction was also found to be influenced by the reaction medium. Thus, Paul (20) obtained the chloromethylphthalide (V) on condensing trimethyl gallic acid with hydrochloric acid and formaldehyde, if, in addition, acetic acid were added to the reaction mixture. Without acetic acid the ordinary phthalide (VI) was formed, together with the methyl ester of trimethyl gallic acid.



Similar results were obtained with myristicinic acid. 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 acid was omitted. Yan (29), however, found that the presence of acetic acid did not alter the products of the

hydrochloric acid-formaldehyde condensation with the exception of the reaction of 5-methoxy-m-toluic acid. This acid, when condensed in the presence of acetic acid, produced what was probably a simple phthalide, whereas none of this product was formed in the absence of acetic acid. The work of King and King (10) is of interest here. In their investigations of phthalide formation by the action of hydrochloric acid and formaldehyde on trimethylgallic acid, they found that the course of the reaction was also influenced by the concentration of the hydrochloric acid. Using a large excess of hydrochloric acid resulted in the formation of 6-chloromethyl-3:4:5-trimethoxyphthalide (V), while a simple phthalide (VI) was obtained by considerably decreasing the amount of hydrochloric acid.

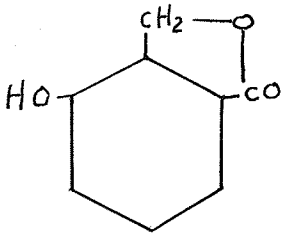
Extensive work on phthalide formation has been done by Charlesworth, Rennie, Sinder and Yan (5). In addition to preparing phthalides by the ordinary condensation with hydrochloric acid and formaldehyde, they produced the phthalides of m-meconine and of 3-methoxy-m-toluic acid by the use of hydriodic acid instead of hydrochloric acid. Attempts to use higher aldehydes, such as paraldehyde, propionic and butyric aldehydes in place of formaldehyde, were unsuccessful probably because of polymerization of the aldehyde before condensation with the aromatic acid could occur.

The same authors attempted to condense benzoic, o-toluic, m-toluic, p-toluic, o-methoxybenzoic, p-methoxybenzoic, phenylacetic, and phthalic acids with hydrochloric acid and

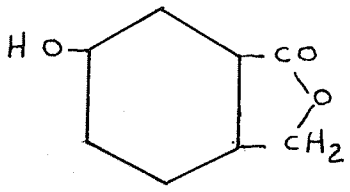
formaldehyde. However, under the conditions employed, in each case there was no sign of any reaction.

Recently Buehler, Powers and Michels (2) published a paper on the reaction of hydrochloric acid and formaldehyde with m-hydroxybenzoic acid. This is of interest since this reaction was also investigated in the present work. Their paper marks the first recorded preparation of a simple phthalide by the condensation of hydrochloric acid and formaldehyde with a phenolic acid. These authors obtained two products, one a simple phthalide (VII), melting at 254° and the other a dioxane derivative (IX) of the simple phthalide, melting at 176°. This formation of the dioxane derivative constitutes a sixth course which may be taken by the Perkin, Edwards and Stoyle reaction.

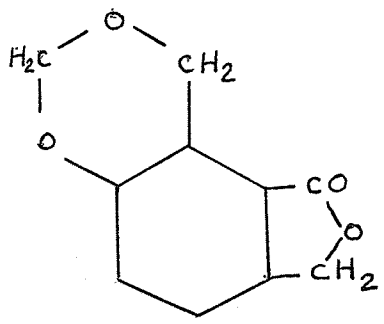
The reaction was carried out by passing hydrogen chloride gas for two hours through a mixture of hydrochloric acid, formaldehyde, sulfuric acid and m-hydroxybenzoic acid, at a temperature of 30° - 40°. The phthalide formed could have one of two structures. Since the reactive positions are ortho and para to the hydroxyl group, the chloromethyl group could enter to produce either a 5-hydroxyphthalide (VIII) or a 3-hydroxyphthalide (VII).



(VII)

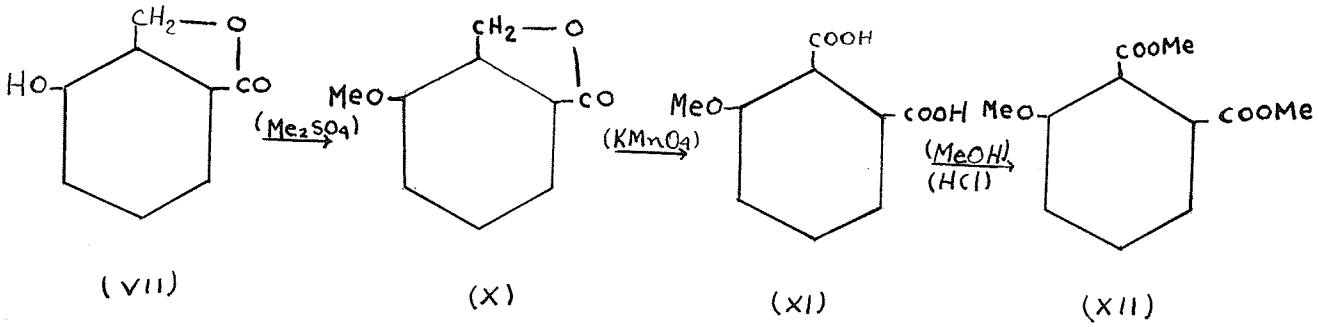


(VIII)



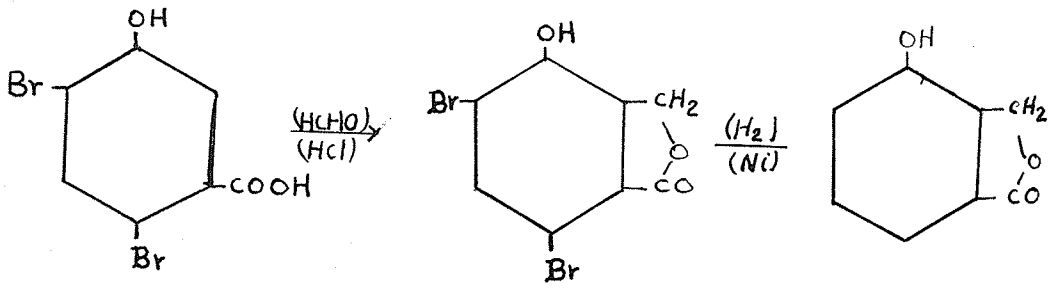
(IX)

The evidence obtained by these authors indicates the 3-hydroxyphthalide structure. The hydroxyphthalide was methylated with methyl sulfate in alkaline solution to produce the methoxyphthalide (X). This method of methylating phthalide derivatives will be discussed later. Oxidation of the methoxyphthalide gave the known 3-methoxyphthalic acid (XI), which, with methyl alcohol and hydrochloric acid, gave known dimethyl-3-methoxyphthalate (XII):



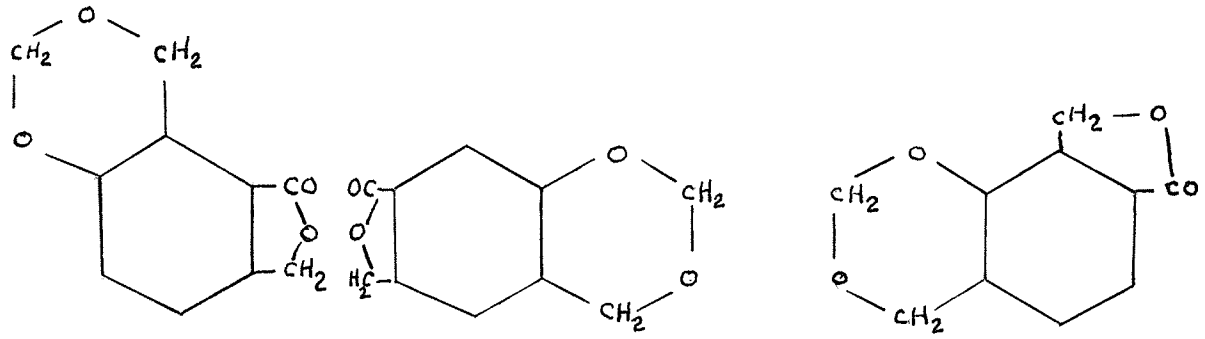
(VII) (X) (XI) (XII)

Further proof was obtained by synthesizing the phthalide when the positions, with the exception of the 2-position, ortho and para to the hydroxyl group were blocked. Thus, m-hydroxybenzoic acid was brominated to form 4:6-dibromo-m-hydroxybenzoic acid (XIII). This was then treated with hydrochloric acid and formaldehyde to form the phthalide derivative. The bromine was removed by shaking with nickel and hydrogen to form the 3-hydroxyphthalide (VII):



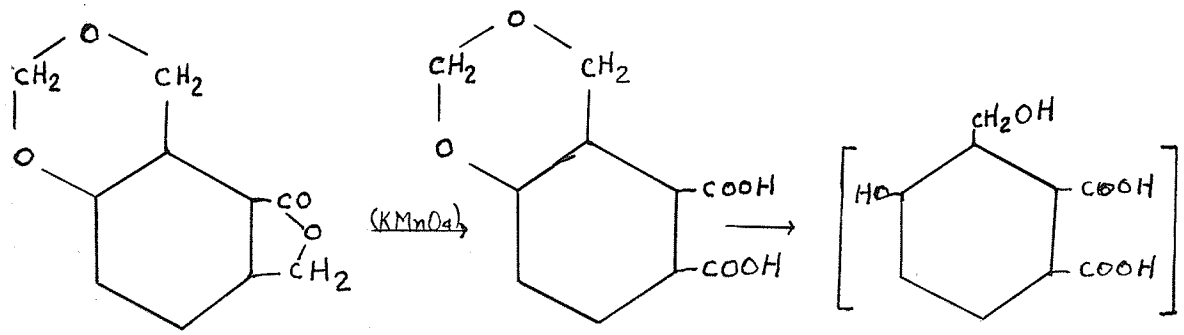
(XIII) (XIV) (VII)

The structure of the dioxane derivative (IX) was investigated by Buehler, Harris, Shacklett and Block (3). The three structures possible are shown below:

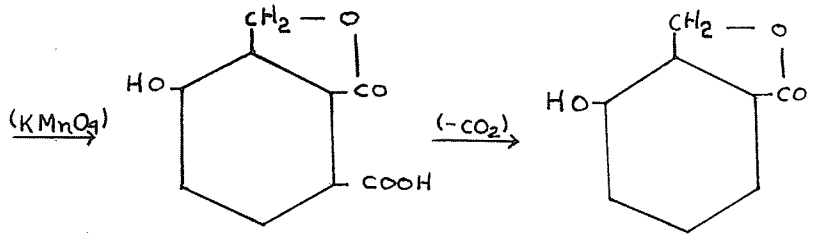


(IX) (XV) (XVII)

Oxidation with dilute potassium permanganate led to the formation of a product which the authors found reconcilable only on the basis of formula (IX):

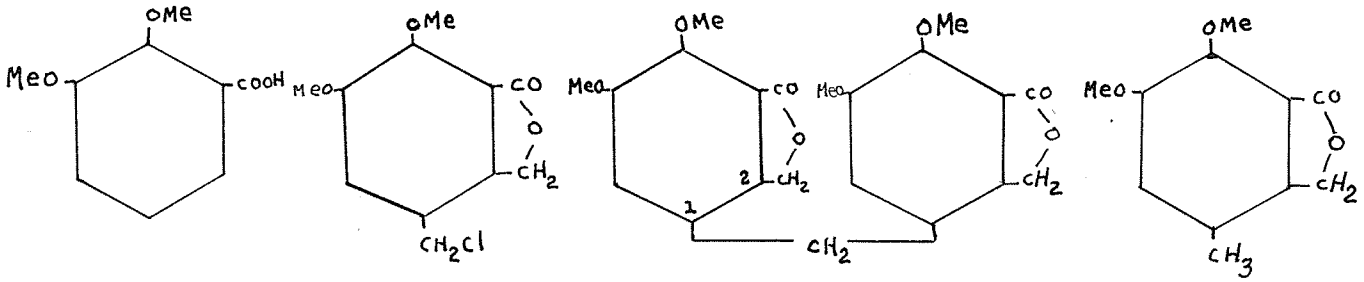


(IX)



(VII)

Further significant work on phthalide formation has been done by Manske and Ledingham (11). On boiling 2:3-dimethoxybenzoic acid (I) with hydrochloric acid and formaldehyde, they produced the chloromethylphthalide (XX) and some bis-(3-carboxy-2-hydroxymethyl-4:5-dimethoxybenzyl) ether dilactone (XXI). However, on reduction of (XX) by heating overnight with zinc and alcoholic hydrochloric acid, the phthalide, 3-methyl-5:6-dimethoxyphthalide (XXII) was obtained:



(I) (XX) (XXI) (XXII)

Below is a table of the results of these and similar investigations.

Table I

Condensation with Hydrochloric Acid and Formaldehyde

Acid	Product
2:3-dimethoxybenzoic	5:6-dimethoxyphthalide (19)
3:4-dimethoxybenzoic	4:5-dimethoxyphthalide (19)
4:5-methylenedioxybenzoic	no reaction (19)
5-methoxy-o-toluic	3-methoxy-6-methylphthalide (22
5-methoxy-m-toluic	A chloromelhylphthalide (4) and (29)
3:5-dimethoxy-o-toluic	6-methyl-3:5-dimethoxy-phthalide (22)
3-methoxy-p-toluic	4-methyl-5-methoxyphthalide (29
m-hydroxybenzoic	3-hydroxyphthalide and (2), a dioxamylphthalide (3)

A number of investigators have made suggestions as to the influence of nuclear substituents groups on the course of the reaction of an aromatic acid with hydrochloric acid and formaldehyde. Rennie (22) suggested that the carboxyl group hinders, while methyl and methoxyl groups aid the introduction of the chloromethyl group. On the basis of the work of King and King (10), Yan (29) suggests that the conditions under which the reaction is carried out are also important in determining the nature of the reaction. Definite information on the effect of nuclear substituent groups has been obtained by Vavon, Bolle, and Calin (28) who measured the rate of halogenmethylation of various substituted aromatic compounds. They

found the rate is increased by $-CH_3$, C_2H_5, $-C_3H_7$, $-OCH_3$, $-OC_3H_7$; while it is decreased by -Cl, -Br, -I, $-CH_2Cl$, -COOH, $-NO_2$. It is, of course, obvious that the reaction will be influenced by anything that will affect the introduction of chloromethyl groups into the aromatic nucleus.

DISCUSSION OF EXPERIMENTAL RESULTS

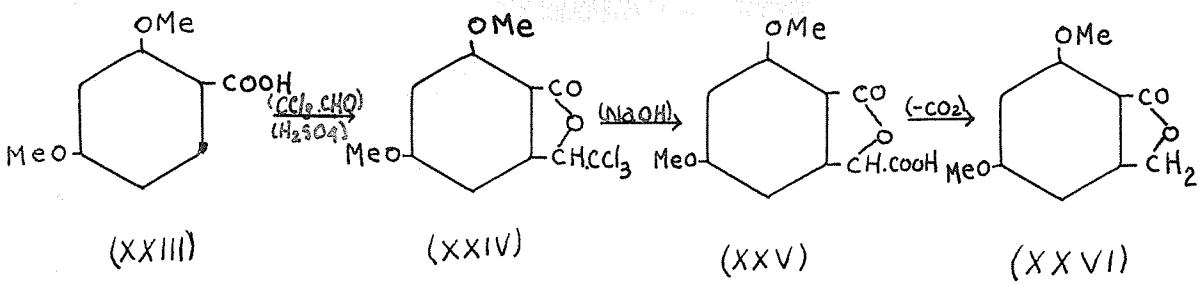
The results obtained in this work are summarized in the table below, which indicates the products formed from the various reactions studied.

TABLE II

ACID	PRODUCT
2:4-dimethoxybenzoic	two non-crystalline polymeric solids
2-hydroxy-4-methoxybenzoic	non-crystalline solid
3-hydroxy-p-toluic acid	dioxanylphthalide (XXX)
m-hydroxybenzoic	3-hydroxyphthalide and dioxanylphthalide (XVII)
Gallic acid	diphenylmethane type compound (XXXVI)
Salicylic acid	non-crystalline solid
5-hydroxy-m-toluic acid	non-crystalline solid

I. Condensations With 2:4-Dimethoxybenzoic Acid.

The first investigation of the reaction of 2:4-dimethoxybenzoic acid (XXIII) with hydrochloric acid and formaldehyde, was undertaken by Rennie (22), who reported the formation of a simple phthalide (XXVI). Evidence for the structure of this phthalide was obtained by oxidation to the dicarboxylic acid, and also by comparing with the compound formed by applying the Fritsch reaction to 2:4-dimethoxybenzoic acid. In the course of this investigation Rennie reported the formation of the trichloromethylphthalide (XXIV), the carboxyphthalide (XXV), and the phthalide (XXVI), formed by the Fritsch reaction as follows:



(XXIII) (XXIV) (XXV) (XXVI)

Sinder (23), however, was unable to repeat Rennie's work. It was, therefore, decided to undertake a further investigation of the action of hydrochloric acid and formaldehyde on 2:4-dimethoxybenzoic acid.

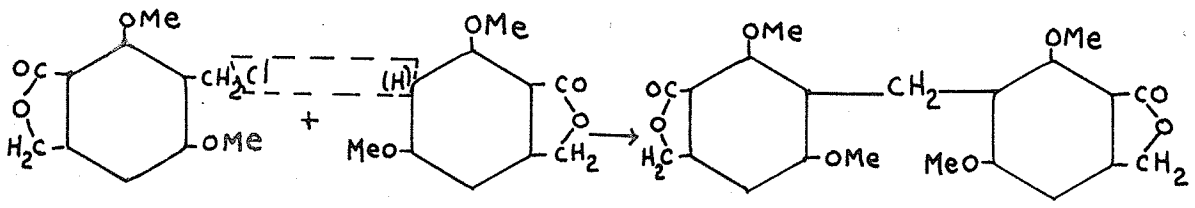
Rennie gave 100°-101° as the melting point of the 2:4-dimethoxybenzoic acid employed in the condensation. Likewise, Sinder's product melted at 103°-104°. However, the literature value was found to be 107°-108°. Undoubtedly the acid was incompletely methylated. In this investigation care was taken to prepare a completely methylated acid. The methylation was carried out according to Tambor (27), instead of by Graebe's method (8) which Rennie employed. However, contrary to Tambor's statement that the two methylations, one for each hydroxyl group, produced the required dimethoxy compound, the acid obtained gave a heavy blue color with ferric chloride and melted far below the literature value.

A careful search through the literature revealed a paper by Niemstein (15) on the methylation of 2:4-dimethoxybenzoic acid by the action of diazomethane on the acetyl-derivative of the acid. Though the reaction conditions were varied, the attempt to completely methylate the aromatic acid

by this method gave the same results as obtained by Tambor's method.

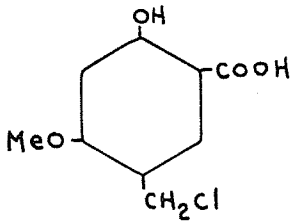
The 2:4-dimethoxybenzoic acid was finally prepared by repeatedly methylating 2:4-dihydroxybenzoic acid by Tambor's method. After four methylations a product was obtained which melted at 107°-108°, and gave an almost imperceptible color with ferric chloride.

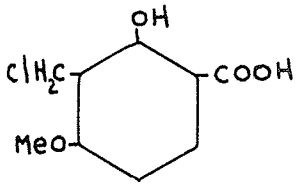
The condensation with hydrochloric acid and formaldehyde, however, did not yield the phthalide. Instead, a non-crystalline mass was obtained, consisting of two different products, neither of which contained either chlorine or free carboxyl groups. It was suspected that they might be diphenylmethane types of compounds. However, it was not possible to obtain them in crystalline form, and an analysis of the impure products did not conform to any proposed structures, though a molecular weight determination indicated that one of the products was probably a diphenylmethane type dimer (XXVII) formed as follows:



(XXVI) (XXVII)

Since Rennie had worked with an impure acid, the possibility remained that the products be obtained were the result of the condensation of the 2-hydroxy-4-methoxybenzoic acid with the hydrochloric acid and formaldehyde. However, a condensation with this acid yielded an entirely different product than that reported by Rennie. It did not appear to be crystalline, contained no halogen, and had an indefinite melting point. This indicated a diphenylmethane type of structure. Also, the product contained free carboxyl groups, showing that a lactone ring had not formed. The chloromethyl group probably entered one of the positions meta to the carboxyl group as show below:





This compound could then have condensed with some of the free acid to form the halogen-free diphenylmethane type of compound.

It is significant that on treating the 2-hydroxy-4-methoxybenzoic acid with chloral hydrate in the Fritsch reaction, a compound also containing free carboxyl groups was obtained. This indicates that the orientating influences affect introduction of the aldehyde group of chloral and the chloromethyl group in the same manner.

An attempt was made to prepare the phthalide of 2:4-dimethoxybenzoic acid by means of the Fritsch reaction. Condensation with chloral hydrate gave the trichloromethylphthalide (XXIV), melting at approximately the temperature given by Rennie. However, further treatment according to the Fritsch reaction did not yield either the carboxylic acid (XXV) or the phthalide (XXVI).

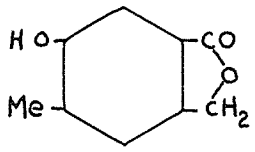
The original compounds left by Rennie were investigated. All, with the exception of the trichloromethylphthalide, appeared to be non-crystalline and had indefinite melting points. It is significant that by mixing the two products in proper proportions, obtained in this investigation by the condensation of 2:4-dimethoxybenzoic acid with hydrochloric acid and formaldehyde, a mixture identical in physical properties with Rennie's condensation products was obtained. Rennie's products were brown rather than white. This suggested the possibility that they may have decomposed on standing. However, the products obtained in the present investigation were colored almost the same shade of brown and did not appear to change color on standing.

It can, therefore, be concluded that it is not possible to produce the simple phthalide of 2:4-dimethoxybenzoic acid by condensation with hydrochloric acid formaldehyde in the ordinary manner, or by the Fritsch reaction. Since, however, in the former reactions, compounds resulted which did not contain free carboxyl groups it is conceivable that the phthalide did form,

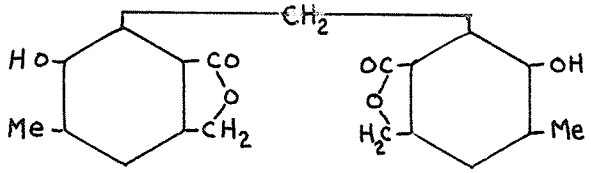
only to be further chloromethylated and react to form phthalide derivatives.

II. Condensation With 3-Hydroxy-p-Toluic Acid.

The action of hydrochloric acid and formaldehyde on 3-hydroxy-p-toluic acid was first studied by Yan (29). White, needle-shaped crystals, melting sharply at 165.5°, which did not contain any chlorine or free carboxyl groups, were obtained. Yan's analysis did not conform to either the phthalide derivative (XXVIII) or the diphenylmethane type of dimer (XXIX).



(XXVIII)



(XXIX)

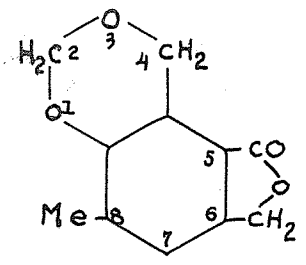
However, since there was fair analytical agreement with the latter structure, it was concluded that this was the product formed, although the melting point seemed on the low side for a substance of this nature.

The condensation of 3-hydroxy-p-toluic acid with hydrochloric acid and formaldehyde was repeated in this investigation. The 3-hydroxy-p-toluic acid was prepared by sulfonating p-toluic acid, followed by alkali fusion, according to the method of Meldrum and Perkin (12), and also by the hydrolysis of p-toluic nitrile with subsequent sulfonation and fusion. The hydrochloric acid-formaldehyde condensation product obtained was found to be identical with that described by Yan, melt-

ing sharply at 165°. Analysis and solubility tests confirmed the identity of the two products. However, molecular weight determinations ruled out the diphenylmethane type of structure suggested by Yan. Also, it is very unusual for a compound of this type to have a melting point as low as 165°, or to be soluble in alcohol, acetone, or ether.

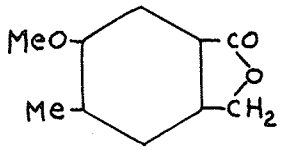
The work of Buehler, Harris, Shacklett and Block (3) described above, throws new light on the problem. On condensing m-hydroxybenzoic acid with hydrochloric acid and formaldehyde, they found that a dioxane type phthalide derivative (IX) formed, in addition to the normal phthalide (VII). The dioxane derivative melted sharply at 175°-176° while the corresponding sample phthalide melted at 254°.

Thought it is not possible to differentiate definitely, by analysis alone, between a dioxane and a diphenylmethane structure (XXIX) for the condensation product of 3-hydroxy-p-toluic acid, the crystalline appearance and the solubility indicate the dioxane derivative (XXX). Only one dioxane structure is possible, as shown below:



(XXX)

If the condensation product were a simple phthalide, it should have been possible to convert it to the methoxy derivative (XXXI).



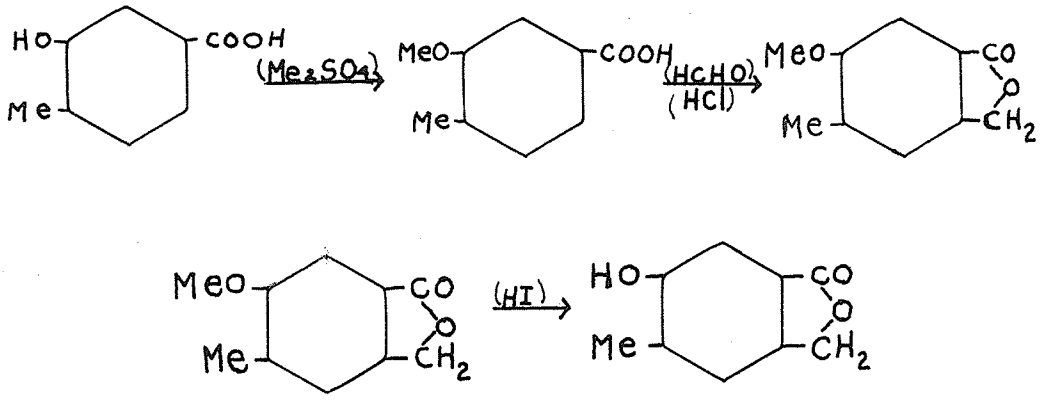
(XXXI)

The methoxy derivative had previously been prepared by Yan (29). Its structure was therefore known. Formation of this phthalide by methylation of the condensation product from 3-hydroxy-p-toluic acid would confirm the structure of the condensation product. Since the latter contained the phthalide ring which opened up in alkali to yield the carboxybenzyl alcohol, it was decided not to use methyl sulfate in the methylation. Instead, the reaction was attempted by means of methyl iodide and silver oxide according to directions given by Irvine (9). However, even after prolonged treatment, the entire original product was recovered unchanged. On the basis of a simple phthalide or diphenylmethane type structure, such resistance to methylation is inexplicable. However, this is to be expected if the condensation product has the dioxane structure (XXX).

Since the methylation was unsuccessful, a further attempt was made to produce the hydroxy phthalide (XXVIII) by some standard method. 3-hydroxy-p-toluic acid was methylated according to Tambor's method (27). This was then condensed with hydrochloric acid and formaldehyde according to Yan (29).

It is to be noted that, in addition to the simple phthalide (XXXI), an amorphous product, melting at approximately 95°, was obtained. The phthalide was de-methylated by means of hydrogen iodide according to "Organic Synthesis" (17) in the hopes that the resulting product might be identical with that obtained from the condensation of 3-hydroxy-p-toluic acid with hydrochloric acid and formaldehyde.,

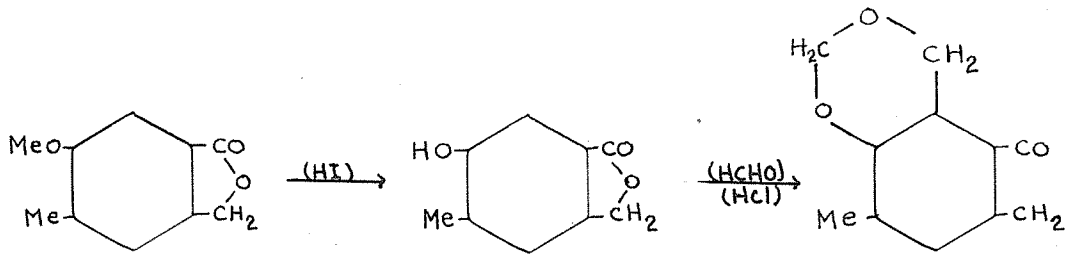
These reactions may be represented by the following scheme:



Thus, the final product should be 4-methyl-5-hydroxyphthalide. A search through the literature did not reveal any record of this compound. However, since the product differed in melting point, solubility and physical appearance with that obtained by condensing 3-hydroxy-p-toluic acid with hydrochloric acid and formaldehyde, further confirmatory analysis was not attempted.

Thus, all the evidence rules out the possibility of Yan's condensation product from 3-hydroxy-p-toluic acid being the simple phthalide. The structure of this product might be confirmed as follows. The hydroxyphthalide (XXVIII) could be

prepared by demethylating 5-methoxy-4-methylphthalide (XXXI). Further treatment with formaldehyde and hydrochloric acid, or with paraformaldehyde and sulfuric acid should yield the dioxane derivatide (XXX) as indicated below.



(XXXI) (XXVIII) (XXX)

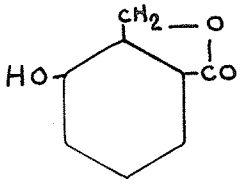
Time has not permitted a trial of this method. Oxidation experiments similar to those carried out by Buehler, Harris, Shacklett and Block (3) might also assist in confirming the structure.

III. Condensations with m-Hydroxybenzoic Acid.

m-Hydroxybenzoic acid was the next acid to be investigated. The present work confirmed most of the results obtained by Buehler, Powers and Michels (2) and Buehler, Harris, Shacklett and Block (3).

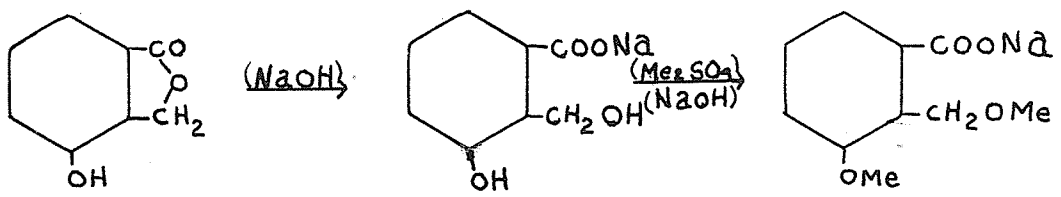
On heating the m-hydroxybenzoic acid with hydrochloric acid and formaldehyde for about five minutes at 65°, a gelatinous, white precipitate formed. At a temperature of 30° no reaction appeared to take place even when the mixture was left overnight, while if heated to 64° and allowed to cool slowly, the product resulted in good yields. The white precipitate

crystallized from dilute acetone in long, white needles which melted at 253°. The needle-shaped crystals contained neither halogen nor free carboxyl groups, and slowly dissolved in aqueous alkali, showing the presence of a lactone ring. Though no carbon and hydrogen analysis was carried out, the properties described above, together with the solubility in various organic solvents, indicate that these needle-shaped crystals were identical with the phthalide (VII) prepared by Buehler, Powers and Michels (2). These authors reported the phthalide as needle-shaped crystals melting at 254°, and showed the structure of the compound to be as follows:



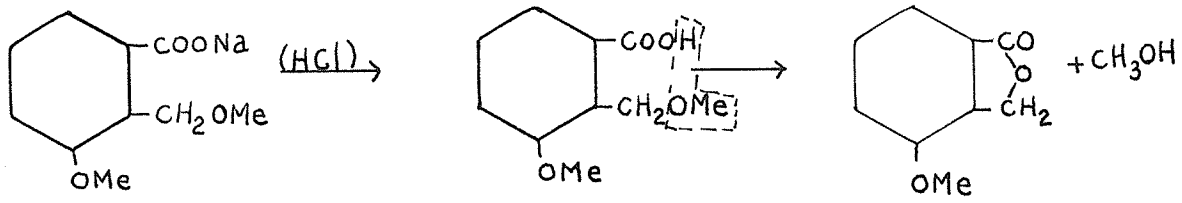
(VII)

In determining the structure of the phthalide, the authors report the formation of a methoxy derivative (X), prepared by methylating the hydroxyphthalide (VII) by the use of methyl sulfate in an alkaline medium. In the present investigation, it was found that even 1% alkali caused the hydroxyphthalide (VII) to dissolve. This indicates opening of the phthalide ring to form the carboxybenzyl alcohol (XXXVII). It is difficult to see why the methyl sulfate did not methylate the hydroxyl group formed as a result of the opening of the lactone ring, as follows:

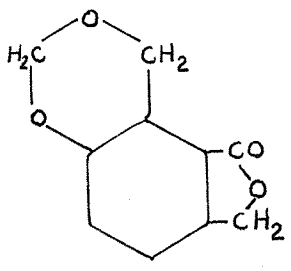


(VII) (XXXVII)

Perhaps this methylation did occur, but the product was unstable in acid solution, and on acidification, methyl alcohol was removed to form the phthalide ring:

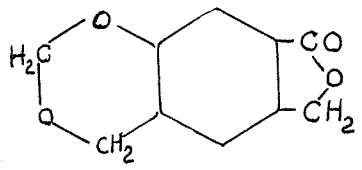


As mentioned previously, Buehler, Powers and Michels (2) obtained, in addition to the simple phthalide, a dioxane derivative (IX) which they reported as needle-shaped crystals melting at 175°-176°. They gave the structure of this compound as shown below:



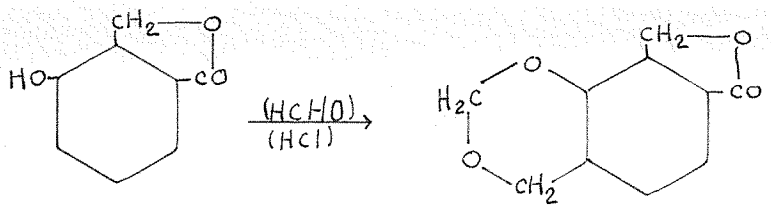
(IX)

This structure was based on the results of oxidation with dilute potassium permanganate as described previously. However, they mention the fact that additional evidence, temporarily withheld from publication, suggested the following structure:



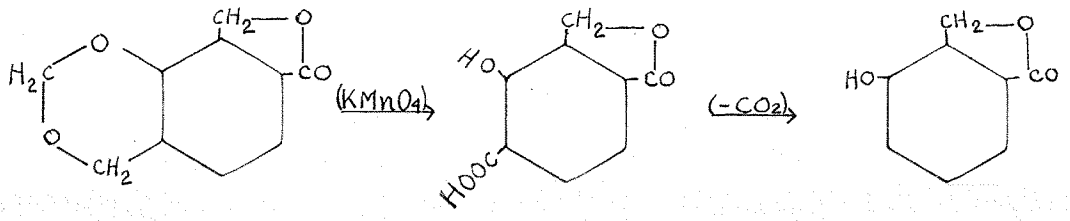
(XV)

In the present investigation, the dioxane derivative was obtained by refluxing the mixture of hydrochloric acid, formaldehyde and m-hydroxybenzoic acid over wire guaze for about eight minutes, when a cloudy precipitate formed. Needle-shaped crystals melting at 173°-173.5° were obtained from dilute acetone. Analysis, molecular weight determinations and solubility tests showed this product to be identical with the dioxane derivative obtained by Buehler, Harris, Shacklett and Block (3). It was found in the present work that it was also possible to prepare this compound by refluxing the simple phthalide (VII) with the formaldehyde and hydrochloric acid over wire guaze for a short while. This indicates that the dioxane ring is formed as a result of further chloromethylation of the aromatic nucleus. The reaction may be represented as follows:



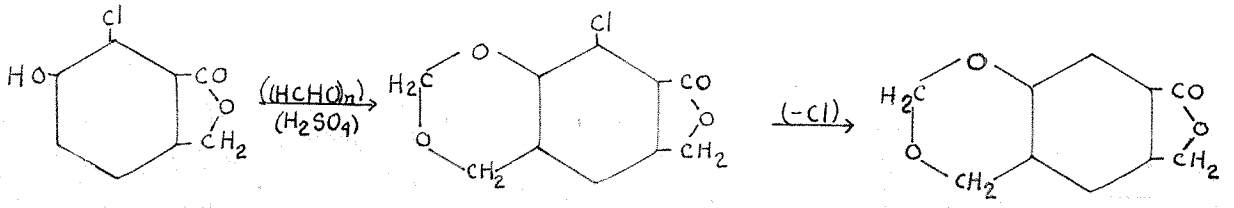
(VII) (XVII)

In order for a dioxane ring to form the second chloromethylation would have to take place ortho to the hydroxyl group. Since there is only one ortho position available, the dioxane derivative can only have the structure shown above (XVII), contrary to the conclusion arrived at by Buehler, Harris, Shacklett and Block (3). It is significant that the results of the oxidation of the dioxanyl phthalide obtained by the above authors could be explained more easily on the basis of (XVII) as follows:



(XVII) (VII)

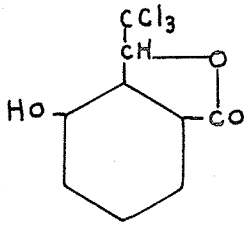
Also it is to be noted that the authors prepared the dioxanyl phthalide (XV) by treating 5-hydroxy-6-chlorophthalide with paraformaldehyde and sulfuric acid as shown below:



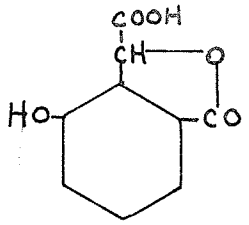
(XV)

This product (XV) was not identical with the original dioxanyl phthalide from m-hydroxybenzoic acid.

An attempt was made to prepare the 3-hydroxyphthalide (VII) by the Fritsch reaction. Treatment with chloral hydrate gave the trichloromethylphthalide (XXXIV) in large star-shaped crystals, melting at 196°-197°. Since the orientating influences for the formation of the trichloromethylphthalide are the same as for the formation of the simple phthalide, the structure of the compound is as shown below. Treatment with alkali, instead of yielding the carboxylic acid (XXXV), produced a small amount of dark red gummy material which had no definite melting point, and could not be crystallized or otherwise purified.



(XXXIV)

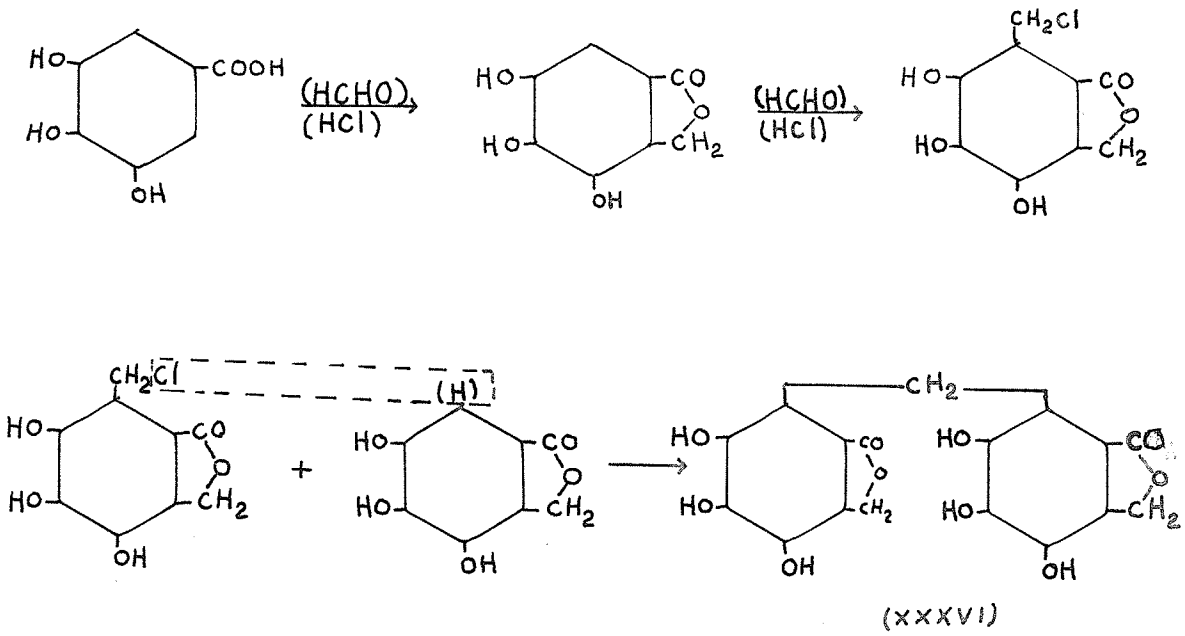


(XXXV)

IV. Condensations With Gallic Acid, Salicylic Acid and 5-Hydroxy-m-Toluic Acid.

The next acid to be investigated was gallic acid. Since Paul (20) and King and King (10) obtained the simple phthalide from the trimethyl ether of gallic acid, it seemed likely that gallic acid would also form the simple phthalide. However, this was not the case. The reaction of this aromatic acid with hydrochloric acid and formaldehyde gave only a product

which had an indefinite melting point and did not appear to be crystalline. Analysis and molecular weight determinations suggested the diphenylmethane type structure (XXXVI). The reaction is represented as follows:



(XXXVI)

The same results were obtained at lower temperatures, though at 30° no reaction took place. It was thought possible that the excess hydrochloric acid used in the condensations might have caused the formation of the dimer. With this in mind, reactions were carried out using molecular quantities calculated to introduce only one chloromethyl group. However, in this case, part of the gallic acid was recovered unchanged while the remainder reacted as before. The same results were obtained regardless of the temperature, providing the temperature was high enough for the acid to react.

Salicylic acid likewise yielded a resinous product when refluxed over wire guaze with hydrochloric acid and formaldehyde. The substance did not have a definite melting point, and contained free carboxyl groups, showing that no phthalide ring had formed.

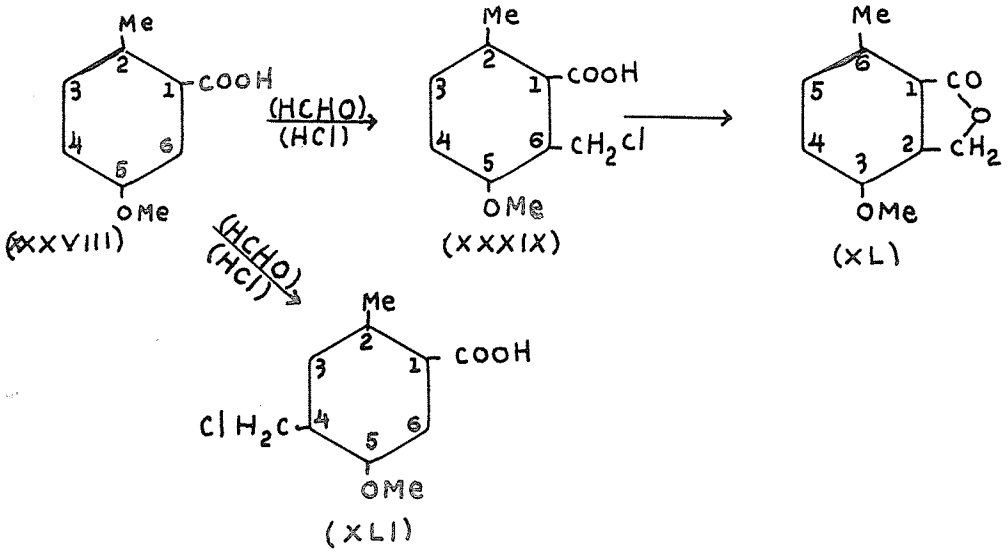
It is to be noted that the condensations with gallic acid and salicylic acid each produced only one product.

The condensation of 5-hydroxy-m-toluic acid with hydrochloric acid and formaldehyde yielded a gummy substance and a white, powdery solid. The latter, which did not appear to be crystalline, contained neither halogen nor free carboxyl groups, and appeared to melt at 172°. This substance was not investigated further.

V. Generalizations.

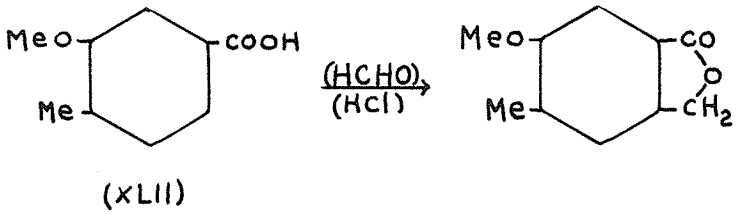
These results and the results of similar investigations may be presented in a more concise form by making certain generalizations. On examining the results of the various hydrochloric acid-formaldehyde condensations studied, it appears that, if a reaction occurs, the first chloromethyl group to be introduced into the benzene nucleus enters the position ortho or para to the ortho and para orientating groups already present in the ring, in such manner as to be also ortho to the carboxyl group if this is possible. The following examples will make this clear. Consider 5-methoxy-o-toluic acid (XXXVIII). The methyl and methoxyl groups activate ortho and para to themselves. There is thus the possibility of

the chloromethyl group entering the 3-,4-, or the 6- position in the benzene nucleus, as shown by (XXXIX) and(XLI) below:

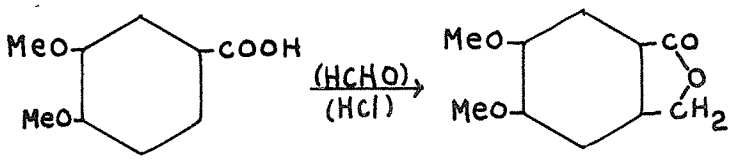


However, consistent with the generalization stated above it enters a position ortho to the methoxyl and also ortho to the carboxyl group, to form 6-methyl-3-methoxyphthalide. In the case of 3-methoxy-p-toluic acid (XLII), the chloromethyl group enters the aromatic nucleus para to the methoxyl group, but ortho to the carboxyl. It is possible that the position ortho to the methoxyl group offers more steric hindrance. Compare, for example, veratric acid (XLIII), which

forms m-meconine (XLIV).



(XLII)



(XLIII) (XLIV)

There is one exception to the above generalization. This is 2:4-dimethoxybenzoic acid which forms what is probably a diphenylmethane type phthalide derivative. The chloromethyl group must enter a position meta to both methoxyl groups in order to form the lactone ring, rather than ortho or para to the methoxyl groups. There are a number of acids, of course, to which the rule cannot be applied, for example, 2-hydroxy-4-methoxybenzoic acid. In such cases, the chloromethyl group enters ortho or para to the orientating groups regardless of the fact that it is not possible to enter ortho to the carboxyl group at the same time.

It is not likely that these are strict rules, since the position which the chloromethyl group enters, of course, must depend on the relative reactivity of the activating groups already present in the benzene nucleus, and on their positions

relative to each other. Groups such as -COOH, $-NO_2$, and halogens, which tend to deactivate the benzene ring will, of course, hinder chloromethylation. It appears that one activating group such as methyl or methoxyl in the ring is not sufficiently strong to oppose the effect of the carboxyl group, consequently chloromethylation will not take place unless there are at least two such groups present in the ring. Rennie (22) arrived at the same conclusion. A single hydroxyl group, however, will overcome the inhibiting effect of the carboxyl group.

It has been shown by Somelet (24) that, by esterifying substituent groups in the ring, which are too active, chloromethylation can be inhibited sufficiently so that resins will not form. In view of this fact, it seems reasonable that by thus altering the activity of the substituent groups, the course of the hydrochloric acid-formaldehyde condensation could be accurately controlled.

EXPERIMENTAL

I. Condensation of 2:4-Dimethoxybenzoic Acid With Hydro-Chloric Acid and Formaldehyde.

(a) Preparation of 2:4-dihydroxybenzoic acid.

The procedure outlined by Niernstein and Clibbens (16) was employed. Resorcinol (100 gm.), sodium bicarbonate (500 gm.), and water (1200 gm.) were refluxed together in a 3-litre round-bottom flask, while carbon dioxide from a Kipp generator was bubbled through the mixture. A reaction appeared to take place after about 5 minutes of heating. After $2\frac{1}{2}$ hours, the solution was cooled and acidified with concentrated hydro-chloric acid. A thick, white precipitate formed in the deep amber solution. This was filtered, washed with a small amount of water, and recrystallized from water (200 cc.). The pure 2:4-dimethoxybenzoic acid, melting at 213°-214° in rapid heat, precipitated as faintly colored pink crystals (60 gm.). Ethereal extractions of the original filtrate yielded only very small amounts of the product. In a subsequent preparation, in which the reaction mixture was allowed to stand overnight before refluxing, a larger yield (76 gm.) was obtained from the same quantity of resorcinol (100 gm.).

(b) Preparation of 2:4-dimethoxybenzoic acid.

Since the method described by Tambor (27) failed to produce the completely methylated 2:4-dihydroxybenzoic acid, an attempt was made to obtain the compound by the action of an ethereal solution of diazomethane on 2:4-diacetylbenzoic acid, as outlined by Niernstein (15). The diazomethane was prepared according to directions given by Owens (18).

(i) Attempted methylation of 2:4-dihydroxybenzoic acid with diazomethane.

1. Preparation of 2:4-diacetylbenzoic acid.

2:4-dihydroxybenzoic acid (100 gm.) dried at 110° for 5 hours, was heated for 3½ hours with acetic anhydride (50 gm.) and zinc chloride (1 gm.) on the water bath, and after cooling, poured with stirring into ice water (200 cc.). An oil formed, which was more dense than the water. The separated oil, after standing for 3 days at -8°, began to crystallize out. Agitating and cooling further at -15° for 2 hours completed the crystallization. The crystals were dissolved in aqueous sodium bicarbonate (100 ml. of 10% solution) and the brown, oily layer, which floated to the surface, was filtered off through a cold filter paper. Snow white crystals (4 gm.) melting at 131.5°-132° were obtained.

2. Preparation of acetylmethylurea.

The method of Owen (18) was employed. Aqueous sodium hydroxide (10%) was added slowly, with shaking, to a solution of acetamide (200 gm.) and bromine (45 cc.) until the red solution was permanently pale yellow, first with cooling by ice, followed by heating on the water bath. The reaction on adding the sodium hydroxide was quite

intense, and a reflux condenser would be advisable. On cooling the almost colorless solution, acetylmethylurea separated in white needles (95 gm.) melting at 177°-178°. Concentrating the filtrate from 1000 cc. to about 500 cc. by evaporation over wire guaze yielded more crystals (15 gm.). Further concentration did not increase the yield.

3. Preparation of Nitrosomethylurea.

Employing the method of Owen (18), acetylmethylurea (110 gm.) was hydrolyzed by refluxing for 3 hours with aqueous hydrochloric acid (200 cc. of 8%). The solution was then cooled in ice, and a saturated solution of sodium nitrite (55 gm.) added from a tap funnel, the stem of the latter being kept below the level of the liquid during the addition. The nitrosomethylurea (75 gm.) which separated as a curdy precipitate was collected and washed with a small quantity of cold water, and dried in a vacuum. Some acetic acid was allowed to remain to stabilize the compound. The nitrosomethylurea was kept at -15° since mild temperature decomposes it. At about 20° it began to turn blue, indicating decomposition while the same effect was noticed on keeping the substance at temperatures below -15°.

The diazomethane was prepared by treating

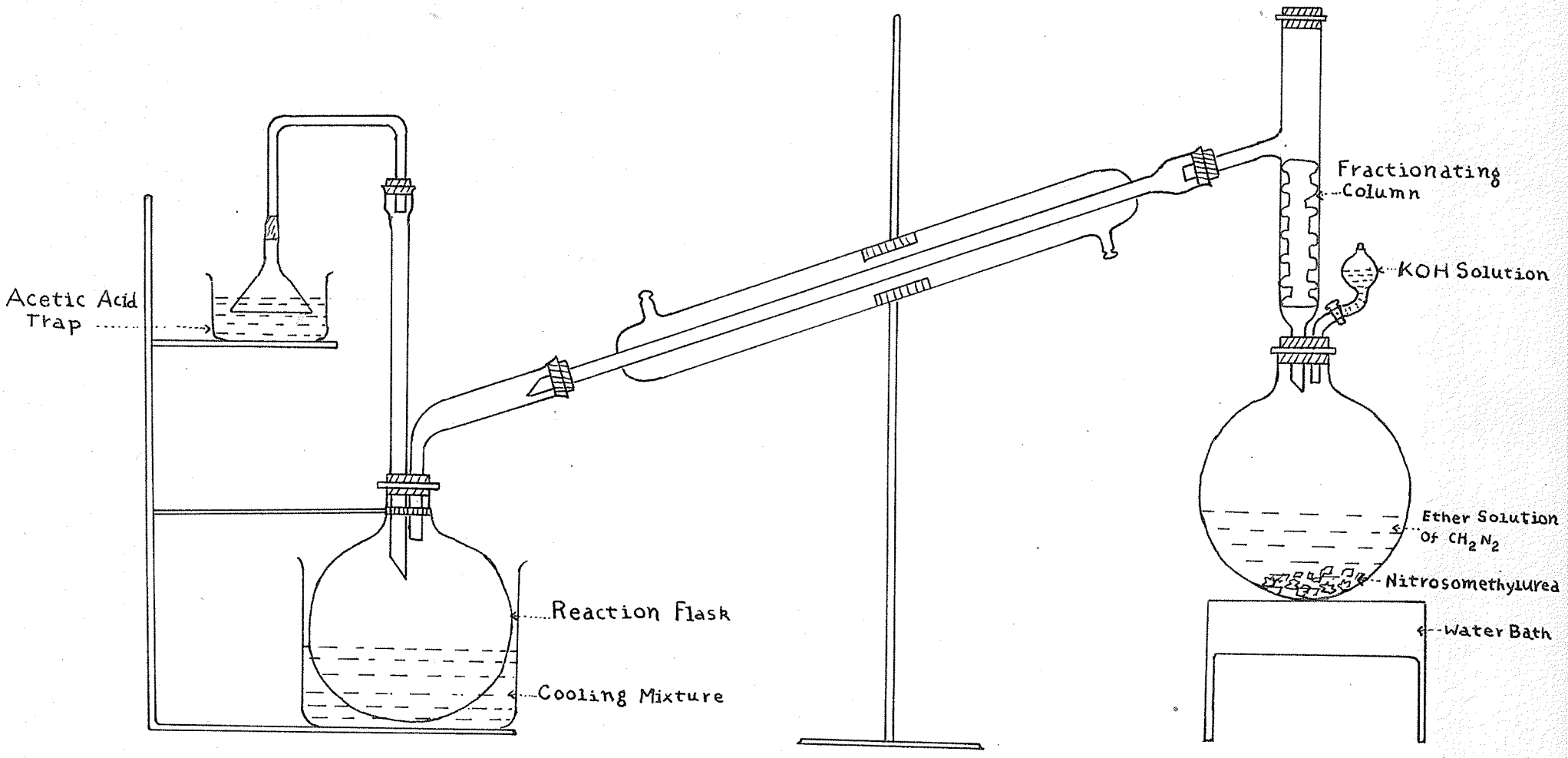

Acetic Acid
Trap
Reaction Flask
Cooling Mixture
Fractionating
Column
KOH Solution
Ether Solution
Of CH_2N_2
Nitrosomethylurea
Water Bath

Fig 1

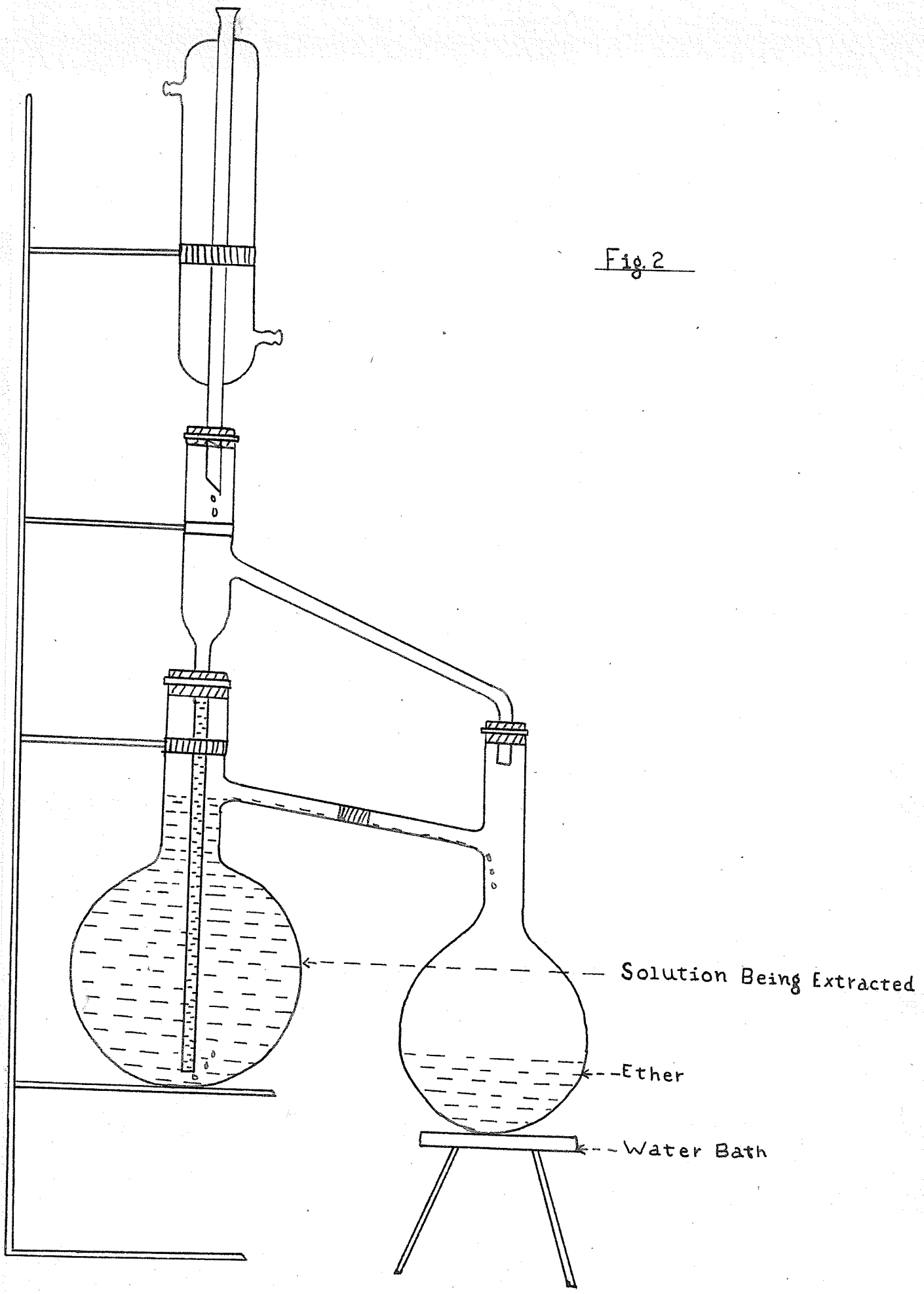
a mixture of nitrosomethylurea and ether with aqueous potassium hydroxide as described below.

4. Description of attempted methylation.

The apparatus used is shown in fig. 1. Aqueous potassium hydroxide (30 cc. of 50%) was added slowly into a solution of nitrosomethylurea (10 gm.) in ethyl alcohol (10 cc.) and ether (100 cc.) in a round bottom flask. The flask was cooled with a mixture of ice and salt. The dizaomethane which formed colored the solution a deep yellow. The ethereal solution of diazomethane was then slowly distilled over a water bath into another round bottom flask containing 2:4-diacetyl-benzoic acid (3 gm.) dissolved in ethyl alcohol and piperidine (3.7 cc.) also dissolved in ethyl alcohol (6 cc.). A fractionating column with a smooth surface was used to separate the diazomethane, since sharp corners aid the decomposition of the gas. The reaction flask containing the 2:4-diacetylbenzoic acid was cooled by an ice-salt mixture, and contained a trap leading into glacial acetic acid to decompose any diazomethane which might have escaped. The ethereal solution was distilled until the condensing ether was colorless.

It is to be noted that diazomethane is an insidious poison. Careless working with the gas may not give noticeable effects for some time. But this leads to a supersensitivity, and then

Fig. 2



even careful working with the poison causes fever attacks resembling asthma and which may last for several weeks. Care was therefore taken to have the apparatus air-tight. Needless to add, the entire reaction was carried out in a fume-chamber.

The reaction flask containing the solution of diazomethane and 2:4-diacetylbenzoic acid was allowed to stand for 24 hours at room temperature. At first, the reaction was rapid as shown by rapid evolution of nitrogen. By the end of 18 hours, very little nitrogen was given off though the solution was slightly yellow, indicating the presence of excess diazomethane. The alcohol was then removed and the solid dissolved in warm aqueous alkali and refluxed for 30 minutes on the water bath. The solution was freed from piperidine by exhaustive extraction with ether for 3/4 hours in the apparatus shown in fig. 2. Acidification of the cooled solution with concentrated hydrochloric acid precipitated a mixture of brown and white crystals, melting at approximately 145°. The mixture which had a sweetish odor, as if an ester had formed, gave a heavy coloration with ferric chloride, indicating the presence of free hydroxyl groups. As piperidine and sodium hydroxide both interfere with the ferric chloride test, the test could not be made before this point. Varying the temperature from -12° to 30° or sub-

stituting methyl alcohol for ethyl alcohol did not alter the results. Since identical results could be obtained by the much simpler method given by Tambor (27), the above process of methylation was discarded, and a modification of Tambor's method employed as described below.

(ii) Methylation of 2:4-dihydroxybenzoic acid with methyl sulfate.

2:4-Dihydroxybenzoic acid (70 gm.) was dissolved in ethyl alcohol (110 cc.) in a litre flask equipped with a dropping funnel, reflux condenser and stirrer. To the boiling solution was added, drop by drop with stirring, sodium hydroxide (31.5 gm. in 226 cc. water). The mixture was refluxed for about 10 minutes to be certain that the carboxyl group was protected against esterification. Dimethyl sulfate (77 cc.) was then added in the same manner, and the solution refluxed for 45 minutes. The brown, oily layer which formed was almost completely hydrolyzed by refluxing with solid sodium hydroxide (40 gm.) for 30 minutes. The solution was cooled slightly, and the sodium sulfate filtered off, after which alkali and methylsulfate were added as before. The brown oily layer which formed was hydrolyzed with a small quantity of solid sodium hydroxide (6 gm.). The sodium sulfate was filtered off to prevent bumping, and the filtrate boiled down to a smaller volume. Alcohol (100 cc.) was added and the mixture treated once more with alkali and methyl sulfate. Similarly a fourth methylation was

carried out. The hot mixture (800 ml.) was then acidified with concentrated hydrochloric acid, and allowed to cool to room temperature, when the partially methylated compound rose to the surface as a hard, brown cake and was removed mechanically. On further cooling at -15°, the completely methylated acid was precipitated in white crystals. Recrystallization from dilute alcohol gave white needles (26 gm.) melting at 107°-108°. Only a very faint trace of color was produced with ferric chloride, showing the methylation was practically complete. Since this method of methylation is tedious and somewhat expensive, it might be worthwhile to determine whether carrying out the reaction at different temperatures might produce the completely methylated acid in two methylations.

(c) Description of condensation.

2:4-Dimethoxybenzoic acid (5 gm.) was mixed with concentrated hydrochloric acid (25 cc.) and aqueous formaldehyde (20 cc. of 40%) in a 200 cc. round bottom flask equipped with a reflux condenser. The mixture was refluxed over wire guaze for 10 minutes. The solid acid turned pink and then purple almost immediately but approximately the same crystalline shape was retained. On cooling the mixture, the condensation product turned dark brown and became brittle. Adding cold water to the solution precipitated more of this substance. The solid was filtered off, washed with water, heated with sodium bicarbonate solution to remove any unchanged acid and finally heated with ethyl alcohol (95%). This treatment changed the color of the

solid to a light brown. The alcohol was filtered off and cold water added in drops to the filtrate when a semi-colloidal solution formed. This was coagulated by a few drops of concentrated hydrochloric acid to form a slightly grey gelatinous precipitate (1 gm.). This was filtered off and washed with water. Both the residue (a) from the alcohol extraction (4gm.) and the product extracted by the alcohol (b) had to be dried in a vacuum dessicator since temperatures as low as 80° seemed to decompose the moist material. Neither of the products had definite melting points. Product (a) did not show any signs of melting, and at 210° began to decompose, turning dark red and evolving carbon dioxide. In addition, this material was found to be insoluble in cold or hot water and in the common organic solvents such as absolute alcohol, acetone, and ether. Consequently, it was not possible to obtain it in crystalline form. These properties indicated a substance of high molecular weight, possibly a dimer. Sodium fusion showed the absence of halogen, and, since carbon dioxide was not evolved on slight warming with a solution of sodium bicarbonate it was concluded that free carboxyl groups were also absent. This meant that the phthalide ring must have formed. Tests with ferric chloride could not detect any hydroxyl groups. The molecular weight of the crude substance was determined by Rast's method. The difficulty in dissolving the product (a) in liquid camphor was overcome by mixing with camphor and melting and solidifying the latter. On melting the camphor once more, the material dissolved to give an amber colored solution.

Analysis of product (a) after extraction with hot water, ether, acetone, and alcohol:

Found: C = 68.6%; H = 7.1%; Molecular weight = 386

Calculated for $C_{21}H_{20}O_8$ (XXVII): C = 63.0%; H = 5.0%; Molecular weight = 400

Calculated for $C_{10}H_{10}O_4$ (XXVI): C = 62.0%; H = 5.2%; Molecular weight = 194

Though the carbon and hydrogen analysis of the crude material does not conform to any of the proposed structures, the molecular weight indicates a molecule of the size represented by the diphenylmethane type (XXVII). It is very likely that product (a) contained some of product (b) as an impurity which could not be removed even by "recrystallization."

Product (b) was similar in many respects to product (a). No definite melting point was observed, but, on application of heat, the material changed appearance very peculiarly, melting to a reddish jelly at 110°-117°, and then slowly decomposing as the temperature was raised, until at 240° a red color developed and the decomposition with evolution of carbon dioxide became rapid. The material (b) was insoluble in hot or cold water, but was quite soluble in alcohol, acetone and ether. Halogen, free carboxyl groups, and hydroxyl groups were found to be absent. Analysis, after reprecipitation from alcohol:

Found: C = 69.8%
H = 6.7%

This analysis is not in agreement with either of the structures proposed for product (a).

Mixtures of product (a) and (b) in varying proportions produced material which appeared to have a different temperature of decomposition for each mixture. More of product (b) tended to lower this temperature. It is significant that the apparent solubility also was altered.

Varying the conditions of the above condensation did not vary the nature of the products, except that longer heating at higher temperatures produced more of product (b).

II. Condensation of 2-Hydroxy-4-Methoxybenzoic Acid With Hydrochloric Acid and Formaldehyde.

(a) Preparation of 2-hydroxy-4-methoxybenzoic acid.

The 2-hydroxy-4-methoxybenzoic acid was easily prepared by methylating 2:4-dihydroxybenzoic acid by Tambor's method (27). To the boiling solution of 2:4-dihydroxybenzoic acid (55 gm.) in ethyl alcohol (65 cc.) in a litre round bottom flask, was slowly added sodium hydroxide (27 gm.) dissolved in water (108 cc.). The mixture was refluxed for 10 minutes and then methyl sulfate (66 cc.) added in the same manner as the alkali. The refluxing was continued for 45 minutes and then solid sodium hydroxide (6 gm.) added, and the refluxing continued for 1 hour longer to hydrolyze any ester which may have formed. The alkaline solution was concentrated to half its volume, cooled, the small amount of precipitate which formed, removed, and the solution acidified with concentrated hydrochloric acid. The precipitated 2-hydroxy-4-methoxybenzoic acid was purified by recrystallization from aqueous acetone. On slowly adding water to the hot acetone solution of the acid, a brown oil

separated out and settled to the bottom of the solution. The clear solution was siphoned off and allowed to cool, when the pure 2-hydroxy-4-methoxybenzoic acid precipitated as short faintly pink needles (13.6 gm.), melting at 156°-157°. The brown oil, which solidified on cooling, accounted for the remainder of the 2:4-dihydroxybenzoic acid.

(b) Description of condensation.

The same procedure as used in the case of 2:4-dimethoxybenzoic acid was followed. 2-Hydroxy-4-methoxybenzoic acid (16.5 gm.) was mixed with concentrated hydrochloric acid (80 cc.) and 40% formaldehyde (80 cc.) in a 500 cc. round bottom flask. After being heated for a few minutes, the liquid turned milky. However, the solid did not appear to go into solution but rose to the surface, retaining its needle-like crystalline shape, but becoming stringy and turning a darker brown. The liquid was boiled for a total of 5 minutes and then allowed to cool, and the stringy solid, which became brittle on cooling, was filtered and washed with cold water. The final product did not appear to have a crystalline structure, indicating a large molecule, and was found to be readily soluble in acetone and alcohol, and insoluble in cold or hot water. The entire substance dissolved in aqueous sodium bicarbonate with evolution of carbon dioxide. On acidification a gelatinous precipitate formed. Sodium fusion of this precipitate showed absence of halogen while a dark blue color was given with ferric chloride, showing the presence of hydroxyl groups. Further indication that the condensation product was a large molecule was given by the lack of a definite melting point. As the

material was heated it turned brown, and at 220° began to decompose with evolution of carbon dioxide, possibly accompanied by melting.

(c) Attempted methylation of condensation product.

The possibility existed that formation of 2:4-dimethoxybenzoic acid could be accomplished easier by methylating the hydrochloric acid-formaldehyde condensation product of 2-hydroxy-4-methoxybenzoic acid and converting the methylated product back to 2:4-dimethoxybenzoic acid. With this in view, the methylation described below was attempted.

Tambor's method (27) was employed, the condensation product (18 gm.) dissolved in ethyl alcohol (28 cc.) being treated with aqueous sodium hydroxide (7.2 gm. in 28.7 cc. water) and methyl sulfate (17.6 cc.). However, the result was the formation of a brown, taffy-like substance which produced a deep purple color with ferric chloride, showing the presence of free hydroxyl groups.

III. Application of Fritsch Reaction to 2:4-Dimethoxybenzoic Acid.

(a) Preparation of 2:4-dimethoxy-d-trichloromethyl-phthalide (XXIV).

2:4-Dimethoxybenzoic acid (15.0 gm.) was mixed with powdered chloral hydrate (18.8 gm.) in a 200 cc. round bottom flask. Sulfuric acid (82.7 cc. concentrated with 4 cc. water) was added, the flask stoppered, and the contents mixed. On standing for a few hours at room temperature a brown milky solution formed. After 24 hours at room temperature this was slowly poured onto chopped ice when a greyish-white precipitate formed. This was filtered and repricipitated from dilute ethyl

alcohol. From the cold alcoholic filtrate a light-brown taffy-like substance precipitated. Treating this substance once more with chloral hydrate and sulfuric acid formed a greyish white precipitate as before. However, on standing for a day, this precipitate changed back into the original amorphous state.

The trichloromethylphthalide (XXIV) was reprecipitated from 30% acetic acid, and now melted at 212°-213°.

Analysis:

Found: Cl = 31.8%; molecular weight = 292

Calculated for: $C_{11}H_9O_4Cl_3$ (XXIV): Cl = 34.2%; molecular weight = 312.

Further purification did not change these values. It is to be noted that the product (XXIV) did not have the crystalline shape usually common to trichloromethylphthalides.

(b) Attempted preparation of 2:4-dimethoxyphthalide-α-carboxylic acid (XXV).

2:4-Dimethoxy-α-trichloromethylphthalide (20 grms.) and aqueous sodium hydroxide (94 cc. of 20%) were mixed in a litre beaker and warmed on the water bath. After about half an hour a dark brown solution formed, and yellow flakes began to separate out. At the end of one hour the mixture was cooled, and filtered. The residue was dissolved in the least amount of water and added to the filtrate. On acidification a light-brown precipitate formed. This was reprecipitated from dilute ethyl alcohol yielding a fine brown solid (8 gm.) which did not appear to be crystalline and did not have a definite melting point. On heating this product, at 210° a slight change in color was observed, indicating decomposition. At 239° the decomposition included evolution of carbon dioxide.

Analysis:

Found: C = 46.9%; H = 4.4%

Calculated for $C_{11}H_{10}O_6$ (XXV): C = 55.4%; H = 4.2%

Attempts to deccarboxylate the material by means of quinoline or controlled heating gave a black substance resembling the residue from the decomposition at temperatures above 239°. Obviously, this product was not the desired carboxylic acid (XXV).

IV. 3-Hydroxy-p-Toluic Acid.

(a) Preparation of 3-hydroxy-p-toluic acid.

(i) Preparation of p-toluic acid.

p-Toluic acid was prepared from p-toluic nitrile as described by Cohen ("Practical Organic Chemistry" p. 192). The nitrile (100 gm.) was mixed with sulfuric acid (300 cc. conc. in 200 cc. water), in a litre round bottom flask equipped with a reflux condenser. A clay boiling chip was added and the mixture heated. The reaction proceeded quite slowly at first, but soon became very violent, frothing up into the condenser and causing the loss of some p-toluic nitrile. To prevent this, the p-toluic nitrile should probably be added slowly to the boiling acid. After the reaction had abated, the solution was boiled for 1/2 hour, when the entire liquid became filled with crystals. The reaction mixture was cooled, and the crystals filtered off and washed with cold water (100 cc.). Recrystallization from water produced colorless crystals (111 gm.) melting at 175°.

(ii) Sulfonation of p-toluic acid.

The method used was essentially that outlined by Meldrum and Perkin (12). p-Toluic acid (111 gm.), part obtained by hydrolysis of p-toluic nitrile, and part obtained from Dr. Charlesworth, was mixed with sulfuric acid monohydrate (139 cc. of 20% oleum and 139 cc. of 95.5% sulfuric acid) in a litre round bottom flask and heated in an oil bath at 155° for 10 hours. The cold product was poured into cold water (350 cc.), when the sulfonic acid crystallized out. The crude product was recrystallized from water (333 cc.) forming fine hair-like crystals (158 gm.). On concentrating the filtrate and cooling, a further quantity of the pure sulfonic acid precipitated.

(iii) Alkali fusion of the sulfonic acid.

The method was that described by Meldrum and Perkin (12) except that a larger portion of potassium hydroxide was used. Potassium hydroxide (248 gm.), in a 450 cc. nickel crucible, was moistened with water (14 cc.), and heated to 200°. The sulfonic acid (45 gm.) was added as fast as it could be stirred into the molten alkali, the temperature being kept between 200° and 210°. The mixture was then heated to 260° over a period of about 3 minutes. A thin brown layer had formed on the surface and foaming had begun at 230°. The temperature was kept at 260° for about 25 minutes, when the foaming of the mixture, which

was now quite fluid, had subsided. The mixture was allowed to cool and the almost colorless product leached with hot water (750 cc.), neutralized with 20% sulfuric acid and made slightly alkaline with a few pellets of potassium hydroxide. The potassium sulphate which precipitated from the cooled mixture was filtered off and the filtrate evaporated to 500 cc., cooled, and acidified with concentrated hydrochloric acid, when a heavy white precipitate of 3-hydroxy-p-toluic acid formed. This was filtered and washed with cold water (50 cc.). On stirring the potassium sulfate residues with hot water (300 cc.) filtering, cooling and acidifying the filtrate with concentrated hydrochloric acid, more of the product separated. The total yield of 3-hydroxy-p-toluic acid, melting at 205°, was 22 gm.

(b) Condensation of 3-hydroxy-p-toluic acid with hydrochloric acid and formaldehyde yielding the lactone of 6-hydroxy-methyl-1:3-benzodioxane-8-methyl-5-carboxylic acid.

The same procedure was employed as in the condensation of 2:4-dimethoxybenzoic acid, except that the reaction mixture with 3-hydroxy-p-toluic acid (10 gm.) was heated over wire guaze with hydrochloric acid (40 cc.) and formaldehyde (27.5 cc.) until a definite reaction occurred. The product was recrystallized from ethyl alcohol and yielded white needles (5 gm.) also soluble in acetone, ether, insoluble in hot or cold water and melting at 165°. No halogen or free carboxyl groups could be detected. A

test with ferric chloride was negative. However, this is possibly of no significance, since 3-hydroxy-p-toluic acid also gives a negative test.

Analysis:

Found: C = 63.7%; H = 5.35%; molecular weight = approximately 195

Calculated for $C_{11}H_{10}O_4$ (XXX): C = 64.0%; H = 4.86%; molecular weight = 206

Calculated for $C_9H_8O_3$ (XXVIII): C = 65.9%; H = 4.88%; molecular weight = 164

(c) Attempted methylation of condensation product.

Since the alkaline medium required by Tambor's method would open the lactone ring of the phthalide to form the carboxybenzyl alcohol which might then be methylated, the method described by Irving (9) was employed. The product (1 gm.) of the condensation with 3-hydroxy-p-toluic acid and methyl iodide (21.5 gm.) were mixed in a 150 cc. round bottom flask provided with a reflux condenser. The silver oxide (20 gm.) dried at 200° was added in small quantities at a time, following each addition by slight warming. No reaction appeared to set in. When all the silver oxide had been added, the mixture was refluxed over a water bath for 4 hours.

Extraction with ether yielded only the original condensation product, showing that methylation had not occurred. Varying the amount of silver oxide or of methyl iodide did not alter the results.

(d) Demethylation of 5-methoxy-4-methylphthalide.

(i) Methylation of 3-hydroxy-p-toluic acid.

3-Hydroxy-p-toluic acid (26 gm.) was treated with methyl sulfate (28.6 gm.) and sodium hydroxide (11.7 gm. in 46.8 cc. water) according to the method outlined by Tambor(27). Though no ester was formed during the reaction, the mixture was refluxed with excess sodium hydroxide (3 gm.) to destroy any unreacted methyl sulfate. The 3-methoxy-p-toluic acid (24 gm.), recrystallized from ethyl acetate, melted at 154°.

(ii) Preparation of 5-methoxy-4-methylphthalide.

3-Methoxy-p-toluic acid (24 gm.) was condensed with 40% formaldehyde (69 cc.) and concentrated hydrochloric acid (100 cc.) in the usual manner, as described for 2:4-dimethoxybenzoic acid. The reactants were heated over wire guaze for 25 minutes. After 7 minutes of heating, the frothing, which began when the liquid began to boil, stopped, and the texture of the solid had become gelatinous. After about 12 minutes, most of the solid went into solution, the remainder turning into an amorphous mass. At the end of 25 minutes the solution was filtered and cooled. The phthalide separated in crystalline plates (4 gm.) melting at 140°. The low yield was due to the formation of the amorphous-like solid. This material melted at 95°. Recrystallization failed to change this melting point appreciably. Though it is unlikely, in view of the low melting point, that the substance was a polymer,

it was not investigated further. Undoubtedly, shortening the reaction time to 7 minutes would have entirely eliminated the formation of this substance.

(iii) Description of demethylation.

This demethylation was undertaken with the view in mind that the resultant 5-hydroxy-4-methylphthalide might be identical with the condensation product of 3-hydroxy-p-toluic acid with hydrochloric acid and formaldehyde.

The method employed was similar to that described in "Organic Synthesis" (17). Acetic anhydride (27 cc.) was cautiously added to constant boiling hydriodic acid (27 cc.) in a 250 cc. erlenmyer flask into which a stream of carbon dioxide was directed. There was considerable heat given off, accompanied by spattering, and the mixture turned very slightly brown. Red phosphorous (10.8 gm.) a clay boiling chip, 5-methoxy-4-methylphthalide (3.5 gm.) and the hydriodic acid-acetic anhydride mixture were then mixed in a round bottom flask fitted with a reflux condenser. By means of carbon dioxide, prepared by the action of concentrated hydrochloric acid on marble chips and purified by passing through water to remove hydrochloric acid and through sulfuric acid to remove water, an inert atmosphere was maintained in the reaction flask. The mixture was refluxed gently for 3 hours. The phosphorous was filtered off, washed with water, alcohol, and ether and a further

quantity of water added to the filtrate to destroy excess acetic anhydride, since in the subsequent vacuum distillation the lower boiling acetic acid would be easier to remove. The combined filtrate and washings were evaported in a current of carbon dioxide gas over a water bath under a vacuum of 18 mm. of mercury. A small amount of resinous material separated out, followed by a slightly yellow crystalline precipitate. The crystalline precipitate was filtered from the clear solution, about 3 gms. being obtained. Several recrystallizations of the latter, which at first melted at approximately 163°, raised the melting point to approximately 177°. The substance was soluble in alcohol, acetone, and very soluble in ether.

Comparison of melting point and solubility of the recrystallized material with that of the condensation product of 3-hydroxy-p-toluic acid showed that the two products were not identical.

V. Condensation of m-Hydroxybenzoic Acid with Hydrochloric Acid and Formaldehyde.

(a) Preparation of the lactone of 8-hydroxymethyl-1:3-benzodioxane-7-carboxylic acid (XVII).

m-Hydroxybenzoic acid (5 gm.) was heated with 40% formaldehyde (25 cc.) and concentrated hydrochloric acid (30 cc.) over wire guaze. The m-hydroxybenzoic acid soon dissolved. About 3 minutes later the solution suddenly became milky due to the formation of minute droplets of oil. During this time a small amount of precipitate began to form. Immediately, the milkiness appeared, the reaction mixture was allowed to cool

at room temperature. This caused the oil to precipitate and solidify into a white cake which was apparently amorphous. On further cooling, about a total of an hour, a white somewhat gelatinous precipitate formed. This was recrystallized from dilute acetone to yield fine, white needle-shaped crystals (1.5 gm.) of the dioxanyl derivative (XVII) melting at 173°-173.5°. The product was soluble in alcohol, acetone, ether, slightly soluble in hot water, insoluble in cold water. No halogen or free carboxyl groups could be detected. The lactone ring opened up even in aqueous sodium hydroxide as dilute as 1%.

Analysis:

Found: C = 62.4%; H = 4.64%; molecular weight (By Rast's method) = 211

Calculated for $C_{10}H_8O_4$ (XVII): C = 62.5%; H = 4.18%; molecular weight = 192

Calculated for $C_8H_6O_3$ (VII): C = 64.0%; H = 4.03%; molecular weight = 150.

The non-crystalline material which precipitated along with the phthalide was found to be quite soluble in acetone, and in hot water. Attempts to crystallize this product from these solvents produced only fine droplets of oil dispersed in the solvent. No definite melting point was observed, which is generally characteristic of diphenylmethane types of molecules. This product was not investigated further.

(b) Preparation of 3-hydroxyphthalide (VII).

m-Hydroxybenzoic acid (5 gm.), concentrated hydrochloric acid (30 cc.) and 40% formaldehyde (25 cc.) were mixed in a 250 cc. round bottom flask and kept between 60° and 70° for twenty minutes, with occasional stirring. After 5 minutes a reaction appeared to take place. The m-hydroxybenzoic acid

did not dissolve but merely changed in texture, becoming more gelatinous. Recrystallization from dilute acetone produced long, shiny transparent needle-shaped crystals, melting sharply at 253°, almost insoluble in acetone but soluble in hot water, and containing neither halogen nor free carboxyl groups. The product was quite soluble in cold dilute sodium hydroxide, indicating the presence of the lactone ring. Though no further investigation of this substance was undertaken, its properties, described above, leave no doubt that it was identical with the 3-hydroxyphthalide, melting at 254°, obtained by Buehler, Powers and Michels (2).

(c) Conversion of 3-hydroxyphthalide to the lactone of 8-hydroxymethyl-1:3-benzodioxane-7-carboxylic acid (XVII).

3-Hydroxyphthalide (4 gm.), concentrated hydrochloric acid (20.4 cc.) and 40% formaldehyde (17.0 cc.) were heated together over wire guaze. The mixture did not form a clear solution, but, after about 8 minutes of heating, began to clear, forming an asbestos-like substance. Then without becoming entirely clear, the mixture began to turn milky. The heating was continued for a short while, and the mixture then cooled in cold water. A white, gelatinous precipitate formed, accompanied by an oil which formed a white, amorphous solid. The white, gelatinous precipitate was recrystallized from acetone as follows:

The precipitate was dissolved in a minimum of slightly warm acetone. This was filtered, and to the filtrate cold water added until a precipitate formed. The mixture was heated until this precipitate dissolved, and allowed to cool slowly,

when white, needle-shaped crystals formed, melting at 173° - 173.5°. Mixed melting point determinations showed this product to be identical with the dioxanyl phthalide prepared directly from m-hydroxybenzoic acid.

VI. Application of Fritsch Reaction to m-Hydroxybenzoic Acid.

(a) Preparation of 3-hydroxy-α-trichloromethylphthalide (XXXIV).

m-Hydroxybenzoic acid (15.0 gm.) and powdered chloral hydrate (21.0 gm.) were mixed in a 200 cc. round bottom flask. Warm (50°) aqueous sulfuric acid (90.5 cc. concentrated with 5.1 cc. water) was added and the flask stoppered. The mixture, which changed from a light green to a dark greenish brown, formed an opaque solution. This was shaken and allowed to stand at room temperature for 40 hours. After 40 hours, the mixture was poured onto chopped ice, forming a grey precipitate. Recrystallizing this precipitate from 60% acetic acid (400 cc.) produced the trichloromethylphthalide in fairly large, grey, somewhat rectangular prisms, melting at 196°-197°, with slight softening noticeable at 193°, though the melting point was fairly sharp. The product was soluble in acetone, acetic acid, alcohol, but insoluble in water.

Analysis:

Found: Cl = 40.34%; molecular weight (Rast's method)= 242

Calculated for $C_9H_5O_3Cl_3$ (XXXIV): Cl = 39.79%; molecular weight = 268.

(b) Attempted preparation of 3-hydroxyphthalide-α-carboxylic acid.

3-Hydroxy-α-trichloromethylphthalide (17 gm.) and 20% sodium hydroxide (91.8 cc.) were heated for one hour on a

water bath. The product was a resinous material which could not be crystallized and which did not have a definite melting point. Attempts to hydrolyze the trichloromethylphthalide in an atmosphere of propane produced the same results.

VII. Condensation of Gallic Acid with Hydrochloric Acid and Formaldehyde

Gallic acid (10 gm.), 40% formaldehyde (40 cc.) and concentrated hydrochloric acid (70 cc.) were heated together over wire guaze. After about 2 minutes, a reaction seemed to occur, the gallic acid changing from white to pink. The mixture was cooled and filtered. The solid product obtained was slightly soluble in hot water, somewhat less soluble in alcohol, insoluble in ether. It was not possible to crystallize the material. An attempt was made to purify it by washing with ether, alcohol and cold water and finally reprecipitating from hot water and then from acetic acid. A fine, white, non-crystalline solid (8 gm.) with an indefinite melting point was obtained. No halogen or free carboxyl groups could be detected. Tests with ferric chloride showed the presence of hydroxyl groups. The molecular weight of the product was determined by the ebullioscopic method, using a cottrell pump and pyridine as the solvent.

Analysis:

Found: C = 53.7%; H = 4.13%; molecular weight = 361

Calculated for $C_{17}H_{12}O_{10}$ (XXXVI): C = 54.2%; H = 3.19%; molecular weight = 376

Calculated for $C_8H_6O_5$: C = 52.8%; H = 3.30%; molecular weight = 182.

The analysis roughly agrees with the diphenylmethane structure. The indefinite melting point and solubility also indicate this type of molecule.

Since no carboxyl groups were present, they must have condensed to form the lactone ring. It was hoped therefore that by altering the experimental conditions, the simple phthalide could be formed. With this in view, condensations were carried out at various temperatures. At temperatures below 32° no reaction occurred. On keeping the temperature at 55° for 2 hours, a reaction occured, yielding the same product as obtained above. Thus, the simple phthalide could not be obtained by altering the temperature of the reaction. Since diphenylmethane polymer formation results as a consequence of additional chloromethylation after the phthalide has formed, providing it is possible to form the phthalide, the reaction in which molecular quantities of gallic acid and hydrochloric acid with excess formaldehyde were employed, was investigated. The result was that only part of the gallic acid reacted to form the dimer, while the remainder was recovered unchanged. Altering the temperature did not change these results.

VIII. Condensation of Salicylic Acid with Hydrochloric Acid and Formaldehyde.

Salicylic acid (10 gm.), concentrated hydrochloric acid (70 cc.) and 40% formaldehyde (50 cc.) were heated together over wire guaze. After about 2 minutes a reaction seemed to occur, though at room temperature there was no reaction at all.

The product was a gummy substance when warm, and a brittle amorphous solid when cold. It was insoluble in water or either and slightly soluble in ethyl alcohol. The product was reprecipitated from ethyl alcohol. After cooling for 3 days, the alcoholic solution precipitated the condensation product as a finely divided, snow-white, non-crystalline solid, containing no halogen, and dissolving in sodium bicarbonate solution with evolution of carbon dioxide, thus showing the presence of carboxyl groups. Tests with ferric chloride showed the presence of hydroxyl groups. No definite melting point was observed, the product decomposing at 270° with evolution of carbon dioxide. Since the properties indicated a polymer of high molecular weight, not containing the lactone ring common to phthalides, the investigation was not continued.

IX. Condensation of 5-hydroxy-m-Toluic Acid with Hydro-Chloric Acid and Formaldehyde.

(a) Preparation of 5-hydroxy-m-toluic acid.

The method of Meldrum and Perkin (13) as described by Yan (29) was employed. A solution of sodium (39.6 gm.) in absolute ethyl alcohol (600 cc.) was treated with a mixture of acetone (99.3 gm.) and ethyl oxalate (252 gm.). A small yield of 5-hydroxy-m-toluic acid (7 gm.), melting at 204°-205°, was obtained.

(b) Description of attempted condensation.

5-Hydroxy-m-toluic acid (4 gm.), concentrated hydrochloric acid (12 cc.) and 40% formaldehyde (12 cc.) were heated over wire guaze until boiling began, and then immediately cooled and cold water added. During the heating, an oily

scum developed and the solution turned milky. On cooling and adding water, this resinous material solidified to a semi-solid, and a brownish white precipitate (1.5 gm.) formed. The precipitate which remained suspended in the solution was decanted off, filtered and washed with water. The product, which contained neither halogen nor carboxyl groups did not have a definite melting point but softened to a jelly at 122° and decomposed at 230°. This substance could not be obtained in crystalline form and was not investigated further.

SUMMARY

1. The action of hydrochloric acid and formaldehyde on 2:4-dimethoxybenzoic acid produced non-crystalline derivatives with indefinite melting points, contrary to the results reported by Rennie (22) and probably diphenylmethane dimers in nature. The products obtained from the same reaction by Rennie were examined. They were found to be almost identical to those prepared in the present investigation, being non-crystalline, solid phthalide derivatives with indefinite melting points. It was therefore concluded that 2:4-dimethoxybenzoic acid does not form a simple phthalide when condensed with hydrochloric acid and formaldehyde.
2. The action of hydrochloric acid and formaldehyde on 3-hydroxy-p-toluic acid was investigated. The same product as obtained by Yan (29) was produced. However, analysis and resistance to methylation indicated that the product is the lactone of 6-hydroxymethyl-1:3-benzodioxane-8-methyl-5-carboxylic acid, rather than a diphenylmethane derivative as suggested by Yan (29).
3. The work of Buehler, Powers and Michels (2) regarding the formation of 3-hydroxyphthalide by the condensation of m-hydroxybenzoic acid with hydrochloric acid and formaldehyde, was confirmed.
4. The dioxanyl phthalide obtained by Buehler, Harris, Shacklett and Block (3) by the condensation of m-hydroxybenzoic acid with hydrochloric acid and formaldehyde was

also obtained in the present investigation by the same reaction. Its structure was established as the lactone of 8-hydroxymethyl-1:3-benzodioxane-7-carboxylic acid by converting the simple phthalide, 3-hydroxyphthalide, to the dioxane derivative. Buehler, Harris, Shacklett and Block (3) suggested a somewhat different structure, namely the lactone of 6-hydroxymethyl-1:3-benzodioxane-5-carboxylic acid.

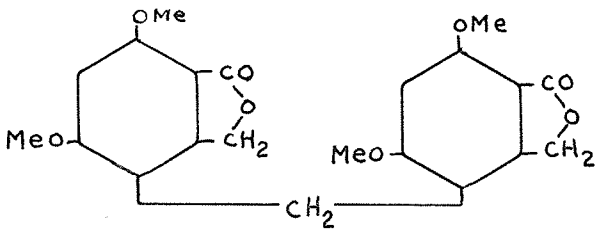
5. 2-hydroxy-4-methoxybenzoic acid and salicylic acid reacted with hydrochloric acid and formaldehyde to form resinous products with free carboxyl groups.
6. Condensation of 5-hydroxy-m-toluic acid and gallic acid with hydrochloric acid and formaldehyde produced non-crystalline phthalide derivatives with indefinite melting points. The product from gallic acid was investigated, and a diphenylmethane structure suggested.
7. The Fritsch reaction was applied to two aromatic acids. 2:4-dimethoxybenzoic acid yielded what was likely an impure trichloromethylphthalide. It was found impossible to carry the reaction beyond this stage, contrary to results reported by Rennie (22). However, examination of Rennie's products showed that similar results had been obtained by Rennie. Similarly m-hydroxybenzoic acid on treatment with chloral hydrate yielded the trichloromethylphthalide. Attempts to convert this to the phthalide resulted in the formation of resinous products.

RECOMMENDATIONS FOR FUTURE WORK

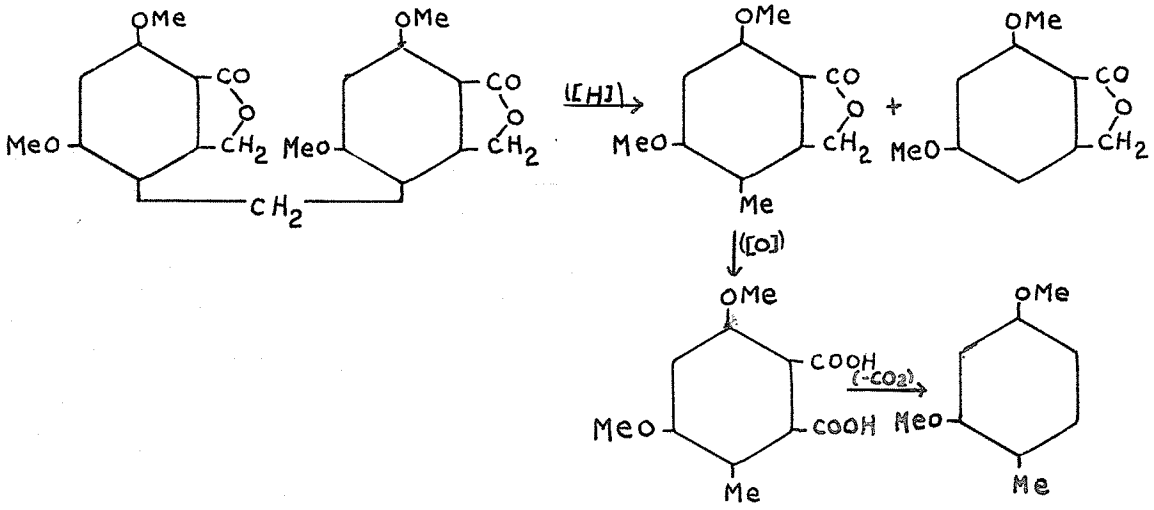
There are a number of individual problems which are still outstanding.

(I) The structure of the compounds resulting from the condensation of 2:4-dimethoxybenzoic acid with hydrochloric acid and formaldehyde.

Very likely the structures of both compounds are of the diphenylmethane type:



A simple means of determining this is suggested by the work of Manske and Ledingham (11), previously mentioned, as follows:

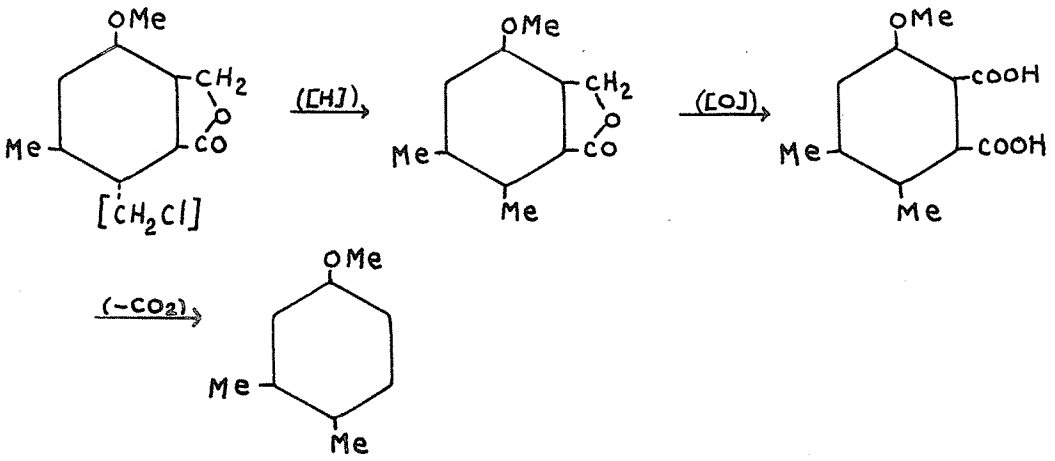


The second, and possibly more complex of the two compounds, might be prepared from the first by further treatment with hydrochloric acid and formaldehyde, and then degraded as shown above.

These same methods might be applied to other polymeric condensation products. By proper choice of oxidizing agent it should be possible to break any lactone ring.

II. The structure of the chloromethylphthalide formed by condensing 3-dimethoxy-m-toluic acid with hydrochloric acid and formaldehyde.

This might be solved as follows:



III. The structure of the condensation product of 3-hydroxy-p-toluic acid with hydrochloric acid and formaldehyde.

Suggestions for determining this structure have been given previously in this report.

IV. A number of aromatic acids did not react in the usual treatment with hydrochloric acid and formaldehyde.

Perhaps they would react if treated as follows:

(1) Hydrochloric acid might be passed through a mixture of the aromatic acid and sulfuric acid at higher temperatures.

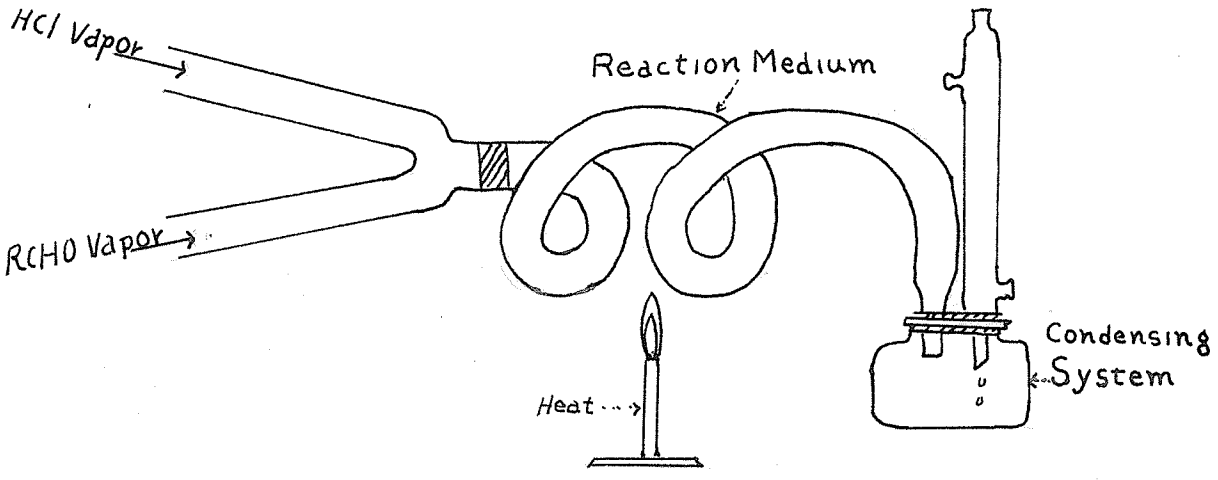
(2) Perhaps try substituting sulfuric acid entirely for hydrochloric acid.

V. Charlesworth, Rennie, Sinder and Yan (5) report unsuccessful attempts to substitute higher aldehydes for formaldehyde.

Perhaps polymerization of the aldehyde could be avoided as follows:

(1) Use sulfuric acid as a dehydrating agent in the condensation, so that the reaction will take place at lower temperatures.

(2) The dichloro ether analogous to §-dichloromethyl ether might be prepared by the method employed by Rennie (22), or if the aldehyde polymerizes, possibly by uniting the vapors of the aldehyde and the hydrochloric acid (since it is possible the aldehyde will not polymerize at high enough temperatures) as follows:



This compound could then be used in place of the aldehyde and hydrochloric acid in condensations with aromatic acids.

VI. Some of the Fritsch reactions were not successful.

It is possible sulfonation is the cause of this. The reactions might be tried using less, or perhaps more, dilute sulfuric acid.

VII. The work of Sommelet[24] suggests new approaches to the hydrochloric acid-formaldehyde condensation with aromatic acids, as follows:

(1) The hydroxyl groups of the aromatic acid might be benzoylated before attempting the condensation.

(2) Acetyl or chloracetyl groups might be substituted for hydroxyl groups in the aromatic acids which give polymeric condensation products.

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