

THE ACTION OF FORMALDEHYDE AND HYDROCHLORIC ACID
ON 5-METHOXY-m-TOLUIC ACID
AND 3,5-DIMETHOXY-p-TOLUIC ACID
RESPECTIVELY

THE ACTION OF FORMALDEHYDE AND HYDROCHLORIC ACID
ON 5-METHOXY-m-TOLUIC ACID
AND 3,5-DIMETHOXY-p-TOLUIC ACID
RESPECTIVELY

BY GEORGE EWEN CAMERON, B. Sc.,
MANITOBA, 1936.

A THESIS SUBMITTED TO THE COMMITTEE ON
POST-GRADUATE STUDIES
OF THE UNIVERSITY OF MANITOBA
IN CANDIDACY FOR THE DEGREE OF
MASTER OF SCIENCE

1939.

CONTENTS

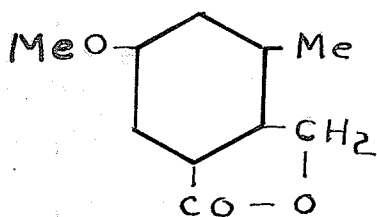
	<u>Page.</u>
<u>NOMENCLATURE</u> - - - - -	1
<u>INTRODUCTION</u> - - - - -	2
i. The Normal Reaction - - - - -	2
ii. Exceptions to the Normal Reaction - - - - -	4
iii. Practical Value of the Normal Reaction - - - - -	7
<u>PRELIMINARY OUTLINE OF EXPERIMENTAL RESULTS</u> - - - - -	9
i. The Reaction involving 5-Methoxy-m-toluic acid - - - - -	9
ii. The Reaction involving 3,5-Dimethoxy-p-toluic acid - - - - -	11
<u>DISCUSSION</u> - - - - -	13
i. The Nature of the Chloroproducts I and V - - - - -	13
ii. The Theoretical Isomerism of Product I - - - - -	25
iii. The Reaction of Product I with Alcoholic Sodium Hydroxide - - - - -	28
iv. The Mechanism of Formation of Products I and V - - - - -	32
v. The Nature of the Non-chlorinated Products II, III, IV and VI - - - - -	54
<u>EXPERIMENTAL</u> - - - - -	
i. Outline of Preliminary Preparations - - - - -	65
ii. Preparation of 5-Sulpho-m-toluic acid - - - - -	66
iii. Preparation of 5-Hydroxy-m-toluic acid - - - - -	67
iv. Preparation of 5-Methoxy-m-toluic acid - - - - -	68
v. Preparation and Isolation of Products I, II, III and IV - - - - -	69
vi. Outline of Experiments with Products I, II, III and IV - - - - -	73

CONTENTS - Cont'd.

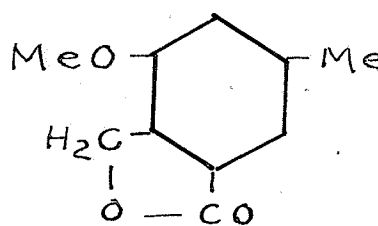
	<u>Page.</u>
vii. Analysis of Product I - - - - -	75
viii. Analysis of Product II - - - - -	77
ix. Reaction of Product I with Alcoholic Sodium Hydroxide - -	79
x. Preparation of Crude s-Dichloromethyl Ether - - - -	80
xi. Reaction of s-Dichloromethyl Ether with 5-Methoxy-m-toluic acid - - - - -	81
xii. Preparation and Isolation of Products I and V - - -	83
xiii. Outline of Experiments with Products I and V - - -	84
xiv. Analysis of Product V - - - - -	85
xv. List of Products obtained - - - - -	86
<u>SUMMARY</u> - - - - -	88

NOMENCLATURE.

In order to avoid confusion in the systematic naming of the compounds referred to in this paper, the following system has been adopted: in naming toluic acid derivatives, the nuclear substituent groups are numbered as usual, beginning with the acid carboxyl group: in naming the phthalides corresponding to these acids, the original numbering of the groups is retained; where it becomes necessary to differentiate between isomeric phthalides, the nomenclature employed by Meldrum (J. C. S., 1911, 99, 1716.) is utilized. Following this system, the respective structures for the α - and β -phthalides of 5-methoxy-m-toluic acid are represented as shown below.



α -Isomer.



β -Isomer.

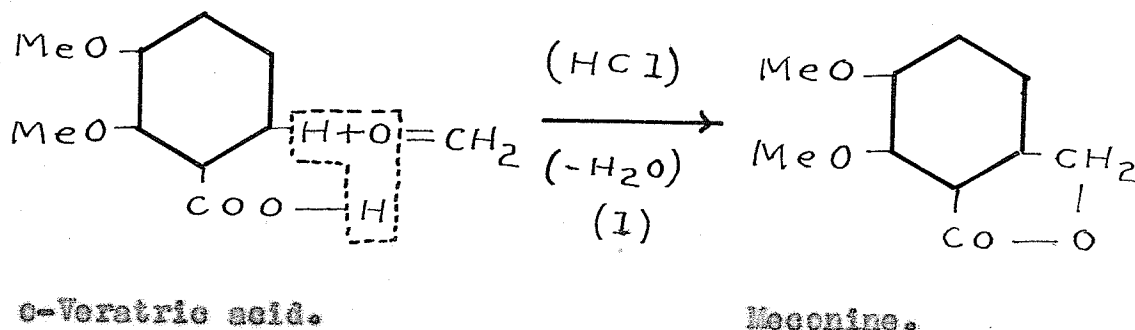
In cases where the methyl groups present in a compound remain intact throughout a reaction, the symbol Me is used for convenience, in place of CH₃.

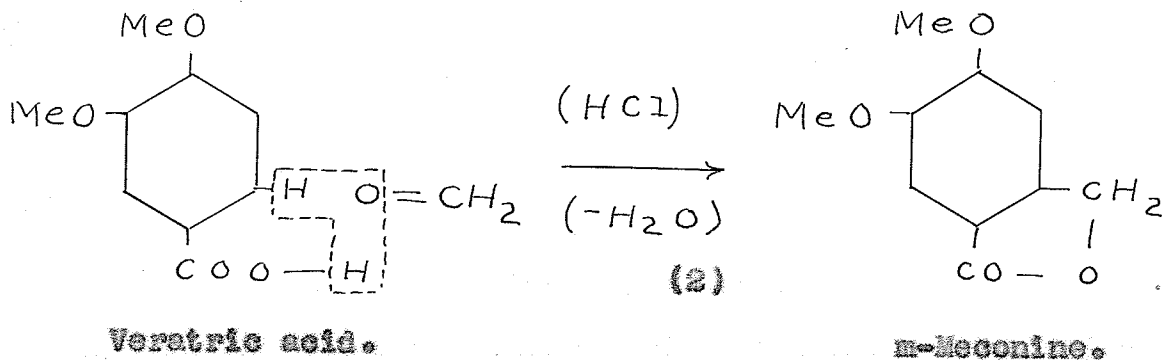
INTRODUCTION.

THE NORMAL REACTION.

The action of formaldehyde on phenols, phenolic ethers, and aromatic acids and their derivatives has been studied by several investigators, under varying experimental conditions. Thus, phenols and phenolic ethers condense with formaldehyde in the presence of cold aqueous alkali, to yield the corresponding benzyl alcohols (Manasse, Ber., 1894, 27, 2411; Lederer, J. Pr. Chem., 1894, 11, 50, 225).

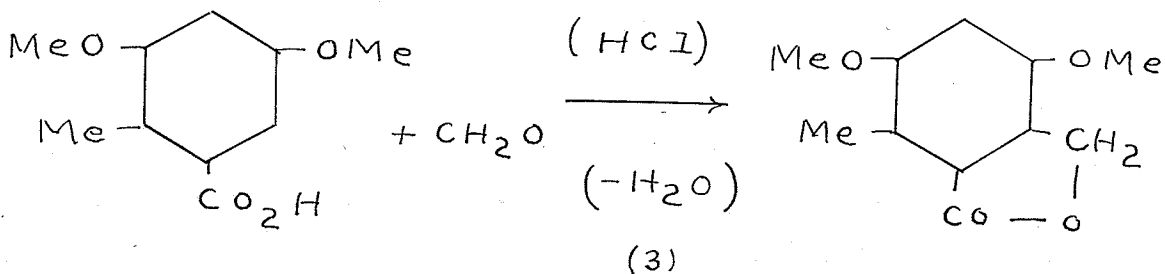
On the other hand, Perkin, Edwards and Stoylo (J. C. S., 1925, 127, 195.) found that the veratric acids do not condense at all with cold aqueous formaldehyde, but that on boiling with excess of formaldehyde and concentrated hydrochloric acid, the corresponding meconine is formed, in moderately good yield. This synthesis of meconine is notable in that it represents the first successful application of this method to the preparation of a phthalide, and the reactions involved may be indicated as follows:





This type of reaction, in which formaldehyde and hydrochloric acid are used to convert an aromatic acid to the corresponding phthalide, will be referred to, henceforth, simply as the normal reaction. This designation is merely for convenience, and is not intended to have any theoretical significance. The mechanism of this reaction is generally considered to involve the elimination of the elements of water between the formaldehyde and the aromatic acid, the methylene group of the former becoming part of the phthalide ring, as illustrated above.

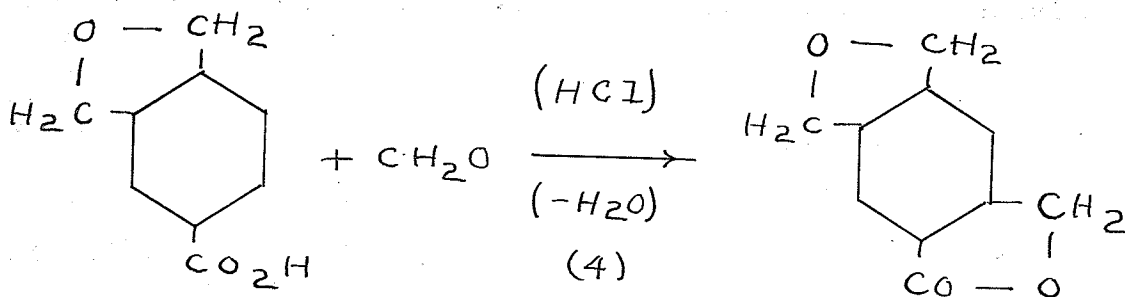
Mitter, Sen and Paul (J. Ind. Chem. Soc., 1927, 4, 525.) claim to have brought about the normal reaction, using cresorcellenic acid (3,5-dimethoxy-o-toluic acid), thereby preparing the corresponding phthalide, according to the reaction,



However, these authors give no experimental details for their application of this method, although they give full details in connection with the other method which they employed, involving the used of chloral hydrate. The latter method will be referred to later.

EXCEPTIONS TO THE NORMAL REACTION.

Perkin, Edwards and Stoylo (loc. cit.) made an unsuccessful attempt to prepare the methylene ether of 4,5-dihydroxyphthalide by the action of formaldehyde on piperonylic acid, according to the reaction,

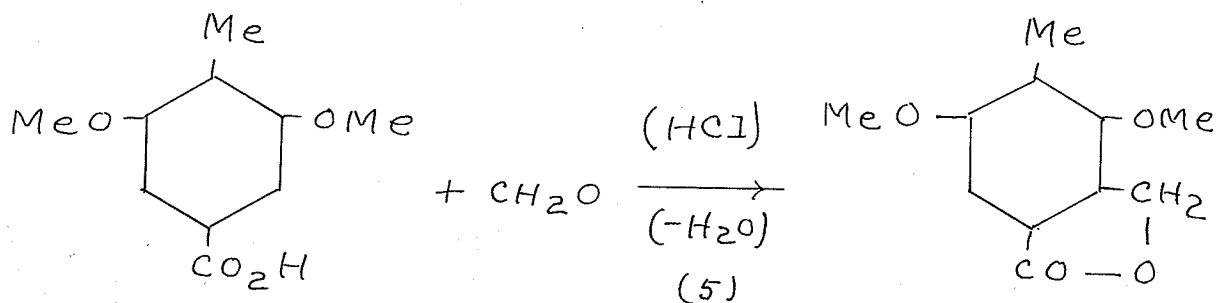


Even after long boiling, this reaction did not occur, and only a small yield of an easily crystallizable substance, of high molecular weight, was obtained. From this it would appear that the case of piperonylic acid represents an exception to the normal reaction. However, it should be noted at this point that the product obtained was not reported to contain chlorine. For this reason, the reaction involved may be only of minor importance in connection with the present investigation, in which the formation of chlorinated

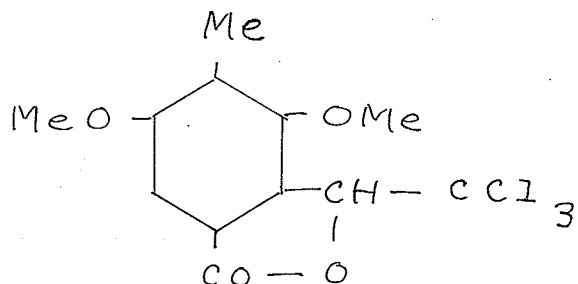
products is of particular interest.

Certain other reactions, which result in the production of compounds containing chlorine, have been reported. Two reactions of this type, involving certain methoxyl derivatives of the m- and p-toluic acids, respectively, have been studied by the writer, and the results thus obtained are presented and discussed in this paper.

In the course of an investigation involving the preparation of a dimethoxymethylphthalic acid, Charlesworth and Robinson (J. C. S., 1934, 1531.) attempted to use the method of Perkin, Edwards and Stoye, to convert 3,5-dimethoxy-p-toluic acid to the corresponding phthalide, by the normal reaction, as shown below.

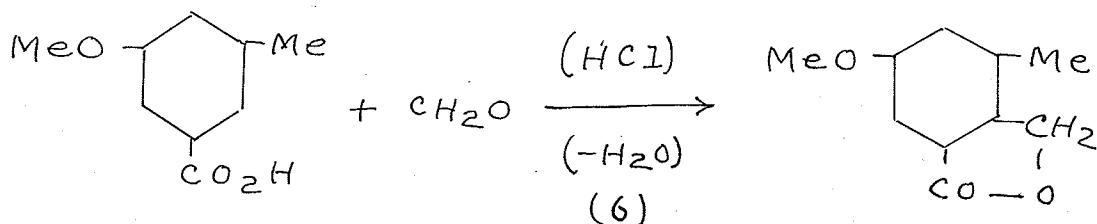


However, no such reaction was found to occur, since the phthalide was not obtained. On the other hand, an unidentified product, which melted at 131° and contained chlorine, was isolated from the mixture. Furthermore, this substance was not identical with 3,5-dimethoxy-4-methyl-trichloromethylphthalide, a compound having the structure,



A study of the reaction producing the unidentified chloro-product has been included in this paper, at the suggestion of Dr. Charlesworth, who very kindly provided the writer with a small quantity of the required 3,5-dimethoxy-p-toluic acid.

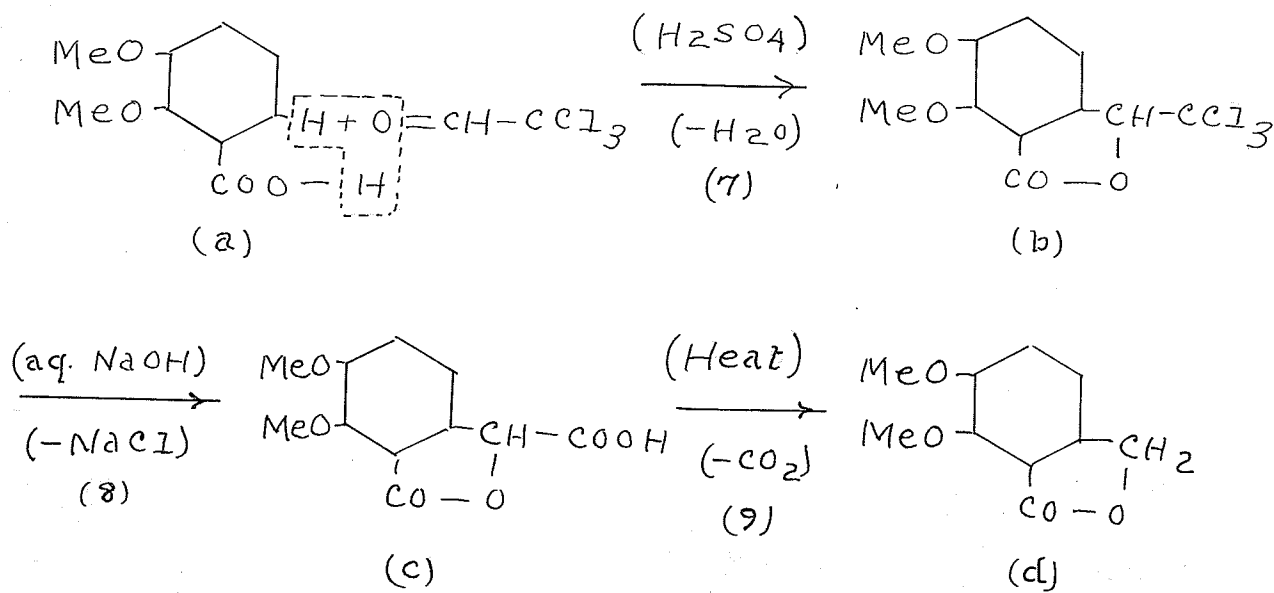
In order to carry out a synthesis of helminthosperin (4,5,8-trihydroxy-2-methylanthraquinone), Haistrick, Robinson and Todd (J. C. S., 1933, 121, 498.) found it necessary to prepare 3-methyl-5-methoxyphthalide, from the corresponding 5-methoxy-m-toluic acid. In this case, again, the method of Perkin and co-workers was tried without success, and an unidentified chloro-product, which did not seem to be the trichlorophthalide, was obtained (private communication). This product is not referred to in their paper. A study of this reaction has also been included in the present investigation. Of course, if the normal reaction had occurred, it would have been readily formulated as indicated below:



PRACTICAL VALUE OF THE NORMAL REACTION.

Before proceeding to a discussion of the results obtained in the present work, it seems appropriate to point out the practical value of the normal reaction, as a method of preparing phthalides.

Prior to the synthesis of the meconines by Perkin et al., already described, the only available practical method of obtaining these compounds from their parent acids consisted in condensing the acids with chloral hydrate in strong sulphuric acid (Fritsch, Ann., 1898, 301, 51.). Thus, applying this reaction to *o*-veratric acid (a, below), Fritsch obtained the corresponding trichloromethylphthalide (b). This was then decomposed with aqueous alkali, yielding a carboxylic acid (c), which on decarboxylation gave the required meconine (d). The steps involved in the process are indicated below:



The yield of mesonine obtained by this method is very low. The direct preparation in a single step, using the acid formaldehyde condensation (page 1) instead, is obviously a superior method, being more convenient and more efficient in actual practice. On the other hand, the formaldehyde method seems to be more restricted in application, as far as can be deduced from the information available.

PRELIMINARY OUTLINE OF EXPERIMENTAL RESULTS.

REMARKS.

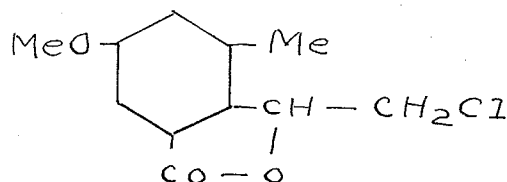
Since the complete report of this work is somewhat lengthy, it will be deferred until later, and only a brief outline of the results obtained will be presented at this point, in order to provide a basis for the theoretical discussion.

With reference to the previous work carried out in connection with the reactions referred to in the title, it may be mentioned that the results here obtained are in agreement with those reported, on the one hand, by Charlesworth and Robinson, and on the other, by Raistrick, Robinson and Todd, insofar as the normal reaction did not occur in these cases, and certain hitherto unknown chloroproducts were obtained. However, in the present work certain additional non-chlorinated products were also obtained, and these are also described briefly, below.

THE REACTION INVOLVING 5-METHOXY-m-TOLUIC ACID.

A chloroproduct (I, m. p., 175-176°) was obtained from the reaction involving 5-methoxy-m-toluic acid, formaldehyde and concentrated hydrochloric acid. The evidence obtained from analysis, from general physical and chemical properties, and from consideration of certain general

properties of compounds analogous to the methoxy-toluic acids, indicates that this compound probably has the structure indicated below:



I

m. p., 175-176°.

Found: Cl, 16.32%. (Mean of two determinations)

(C₁₁H₁₁O₃Cl requires Cl, 15.67%).

A non-chlorinated product (II, m. p., 247-248°) was also obtained from the above reaction. The general properties of this substance were investigated, and an attempt was made to determine its empirical formula by elementary analysis. However, since the results of this analysis did not agree with any formula expected on theoretical grounds,¹ the true formula of the substance is still in doubt.

A small quantity of another non-chlorinated product (III, m. p., 263-264° d.) was isolated from the above reaction. This substance is closely similar to II in general properties, and there is a theoretical possibility that these two compounds are structurally isomeric. The amount of III isolated was insufficient for conclusive analysis.

A third non-chlorinated product (IV, m. p., 94-96°) was obtained from the same reaction, above, but could not be isolated in sufficient quantity for analysis. However, the general properties observed indicate that this product is the known, normal phthalide. (See equation 6, page 6). The structure shown on page 6 represents the known α -phthalide, m. p., 105.5°. The β -phthalide, m. p., 135.5°, is also known, and its structure has already been indicated (page 1). The melting-point of product IV, 94-96° (not very sharp, however), together with the other evidence available, suggests that it may be a mixture of the α - and β -isomeric phthalides.

THE REACTION INVOLVING 3,5-DIMETHOXY-p-TOLUIC ACID.

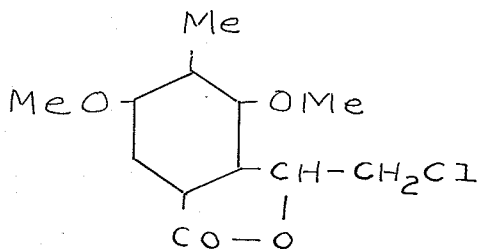
A chloroproduct (V, m. p., 128-130°) was obtained from the reaction involving 3,5-dimethoxy-p-toluic acid, formaldehyde and concentrated hydrochloric acid. The probable structure of this compound is indicated below, the evidence from analysis and general properties being in agreement with this structure.

V.

m. p., 128-130°.

Found: Cl, 13.13%.
(One determination).

(C₁₂H₁₃O₄Cl requires Cl, 13.84%).



A non-chlorinated product (VI, m. p., 246-250°) was also obtained from the above reaction. As in the case of product II, the general properties of this substance, together with certain theoretical considerations, suggest a possible structural formula. In this case, however, analysis of the small amount of sample available did not yield concordant results, therefore no conclusion could be reached as to structure.

CONCLUDING REMARKS.

A complete report of the experimental evidence obtained in connection with the six products described above is given in the experimental section.

Certain other products, which were obtained from various accessory experiments, are more conveniently described in connection with the theoretical discussion.

All the products which have been obtained in this work are colourless solids.

DISCUSSION.

THE NATURE OF THE CHLOROPRODUCTS I AND V RESPECTIVELY.

Introduction.

For reference in connection with the discussion which follows, the general properties of the chloroproducts I and V are summarized in table I, page 14.

The Nature of Product I.

In order to arrive at a possible structure for product I, it was necessary, at first, to make certain assumptions, and then to test the product in such a manner as to verify or disprove these assumptions.

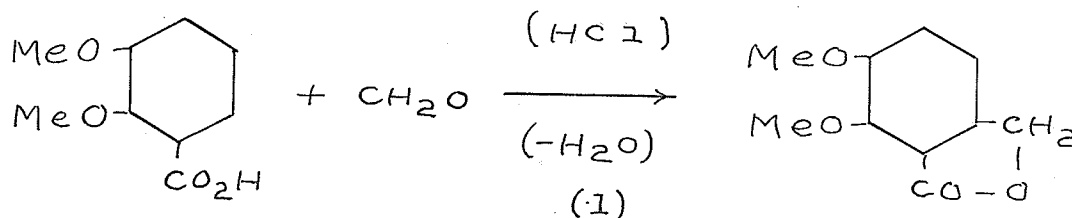
It has already been mentioned (page 2) that the veratric acids yield corresponding meconines, under conditions similar to those involved in the formation of product I. From this it is evident that a boiling solution of formaldehyde and hydrochloric acid has no effect on nuclear-substituted methoxyl groups, and likewise, that if any CH group of the benzene ring were attacked, it would probably be that one in the ortho-position to the carboxyl group.

In the case of 5-methoxy-m-toluic acid, therefore, the methoxyl group should remain intact: any reaction involving the nucleus should occur at the ortho-position, and therefore the meta-substituted methyl group should not readily be attacked. Thus far, then, it is clear that product I probably contains, unchanged, the original methyl and methoxyl groups of the parent acid.

TABLE I

PROPERTIES	PRODUCT I	PRODUCT V
M. P. - - -	175-176° - -	128-130°
Appearance - -	Col'less needles from alcohol. -	Col'less needles from alcohol.
Solubility:		
Water - - -	Insol. - -	Insol.
Alcohol - -	Sol. hot. - -	Sol. hot.
Ether - - -	Sol. - - -	Insol.
Acetone - -	Sol. - - -	Sol.
Glac. acetic acid	Sol. - - -	Sol.
Ethyl acetate -	Sol. - - -	Sl. sol.
Benzene - -	Sol. - - -	Sol.
Petr. ether -	Sol. hot. - -	
Chloroform -	Sol. - - -	
Carb. tetrachlor.	Sol. hot. - -	Insol.
Carb. disulphide	Sol. hot. - -	
With moist litmus	Neutral. - -	Neutral.
" aq. NaHCO ₃	No reaction. -	No reaction.
" aq. NaOH -	Insol., no action.	Insol., no action.
" aq.,alc. FeCl ₃	No colour. -	No colour.
" conc. H ₂ SO ₄	Sol., no decomp.	Sol., no decomp.

On the other hand, in the reactions with the veratric acids, referred to above, it was found that the acid carboxyl group had been attacked and converted to the phthalide, thus:

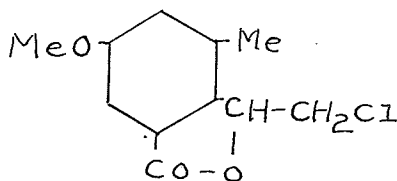


This change clearly involves the loss of acid properties due to the carboxyl group. Thus the product would be neutral to litmus, inactive to sodium bicarbonate solution and possibly insoluble in aqueous alkali. Product I exhibits these properties, differing in this respect from the parent acid, and suggesting the formation of a phthalide structure.

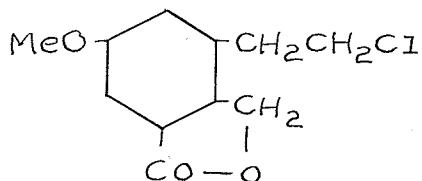
However, product I also contains chlorine. Evidently this chlorine could be present as a nuclear substituent, or substituted in the 3-methyl group, or finally, in the methylene group of the supposed phthalide ring. At this stage it seems rather pointless to speculate on its true position, since this can readily be determined by further experiment. However, since theoretical considerations indicate that the mechanism of the reaction would probably be essentially the same, regardless of the position of the substituted chlorine,

the final possibility referred to above has been adopted, as a basis for discussion. Most of the theories of formation suggested for product I will be found equally useful even if this assumption is shown to be incorrect. In a general way, it will be seen from the discussion to follow that substitution in the phthalide ring seems probable.

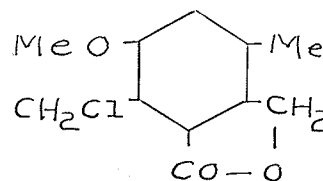
Now, experimental evidence shows clearly that both formaldehyde and hydrochloric acid are involved in the reaction. Moreover, two definite products -- s-dichloromethyl ether, $(\text{CH}_2\text{Cl})_2\text{O}$, and chloromethyl ether, $\text{CH}_3\text{OCH}_2\text{Cl}$, respectively -- have been isolated from a mixture of commercial formaldehyde and hydrogen chloride (Stephen, Gladding and Short, J. C. S., 1920, 117, 520.), and a third product, chloromethyl alcohol, ClCH_2OH , has been suggested by several authors, as being a possible intermediate compound involved in such reactions (Grassi-Crisaldi and Maselli, Gazzetta, 1898, 28, ii, 477; Stephen, Gladding and Short, ref. given). The existence of chloromethyl alcohol is still in doubt, but that of the other two compounds has been definitely established. Since each of these compounds contains the chloromethyl group, it seems logical to expect that in the present case, since a mixture of formaldehyde and hydrochloric acid has apparently produced a chloro-substituted phthalide, the substituent might be the chloromethyl group itself. According to this view, then, product I might have the structure represented by formula (a), (b) or (c), shown below.



(a)



(b)



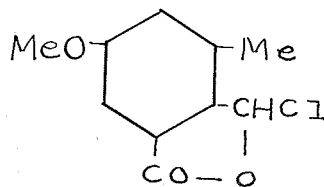
(c)

$C_{11}H_{11}O_3Cl$ requires Cl, 15.67%.

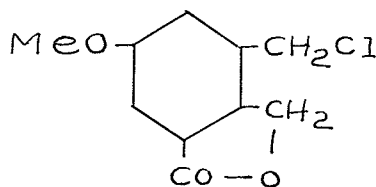
(Found for Product I: Cl, 16.32%).

Two chlorine determinations of product I gave an average value of 16.32%, showing approximate agreement with the formulae above. Reliable carbon and hydrogen estimation and molecular weight determination could not be carried out, for reasons indicated in the experimental section.

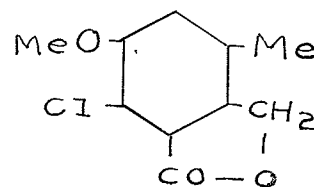
The degree of accuracy of the method employed for chlorine estimation (chlorine removed by method of Stepanow and estimated by Volhard's titration; see Thorpe and Whiteley, "Organic Chemical Analysis," page 52) seems to be a matter of controversy. However, the results obtained establish the fact that only one atom of chlorine can be present in the molecule of product I. On the other hand, it is evident that these results are not sufficiently accurate to eliminate the possibility that product I has one of the simpler structures (d), (e) or (f), indicated below:



(d)



(e)



(f)

$C_{10}H_9O_3Cl$ requires Cl, 16.71%.

(Found for Product I: Cl, 16.32%).

However, in view of the evidence already cited in connection with certain chloromethyl compounds, and considering the difficulty of formulating a plausible reaction which would produce (d), (e) or (f) under the present conditions, the formation of such structures seems rather improbable. Furthermore, reactions yielding the hypothetical compounds (a), (b) and (c), involving chloromethyl substitution, can be formulated in a plausible manner, as will be shown. For these reasons, then, the possible structures (d), (e) and (f) will not be considered further.

Thus far it has been pointed out that the available theoretical evidence is in favour of structure (a), (b) or (c) rather than (d), (e) or (f), but that the method of analysis here employed is not sufficiently accurate to confirm this view. In general, however, either structure (a), (b) or (c) may be considered to represent product I. The question arises, which of these is correct? While there is no

decisive evidence available in this connection, the various points in favour of each may be summarized below.

In favour of (a), if preliminary phthalide formation be assumed, and there is some evidence to indicate that this is the case, it seems that the methylene group of the phthalide ring would be more readily attacked than the nuclear-substituted methyl group.

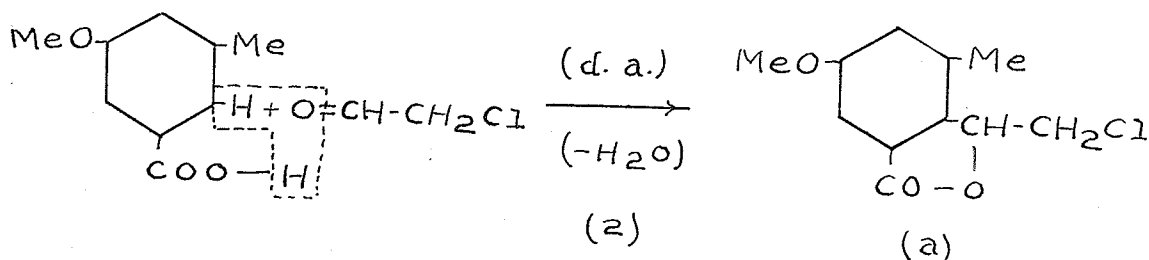
In favour of (b) it may be pointed out that, so far, only the toluic acid derivatives (5-methoxy-m-toluic, 3,5-dimethoxy-p-toluic acids) have been found to yield chloroproducts, while none of the benzoic acid derivatives (piperonylic, o-veratric, veratric acids) do so. This suggests that the substituted methyl group may be essential to the reaction, and therefore, may even be directly involved.

The only evidence in favour of structure (c) appears to be the fact that either chloromethyl ether or *o*-dichloromethyl ether, in the dry state, can bring about chloromethyl substitution in the nucleus of an alkyl-substituted benzene derivative (Stephen et al., ref. given, page 16). Incidentally, the different experimental conditions in the present case would be expected to influence the course of such a reaction, if it occurs at all; and the action of these chloro-ethers on substituted aromatic acids, such as the toluic acids under consideration, is not known.

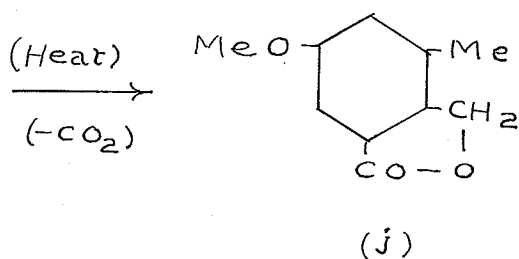
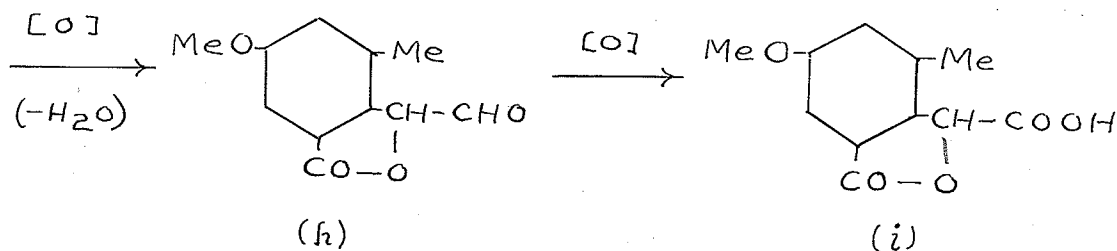
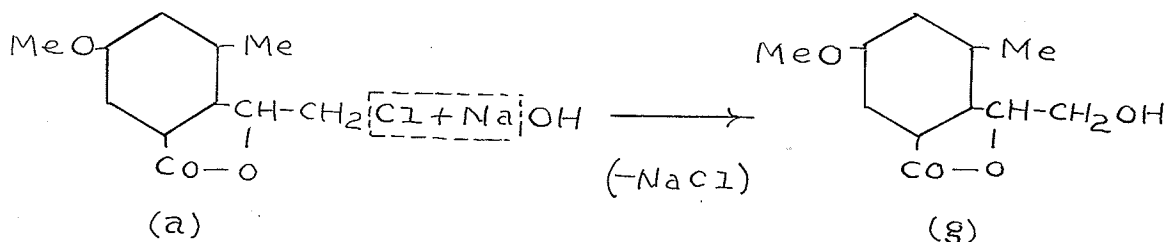
The possibility that the chloromethyl group might occupy position (4) in the nucleus may be disregarded, since the 3,5-dimethoxy-*p*-toluic acid, in which this position is already occupied by the methyl group, yields a chloro-product (V) clearly analogous to I, under identical experimental conditions.

However, considering the present lack of information regarding the behaviour of many other aromatic acids, it can only be stated at present that structure (a) appears to be somewhat more probable than either (b) or (c).

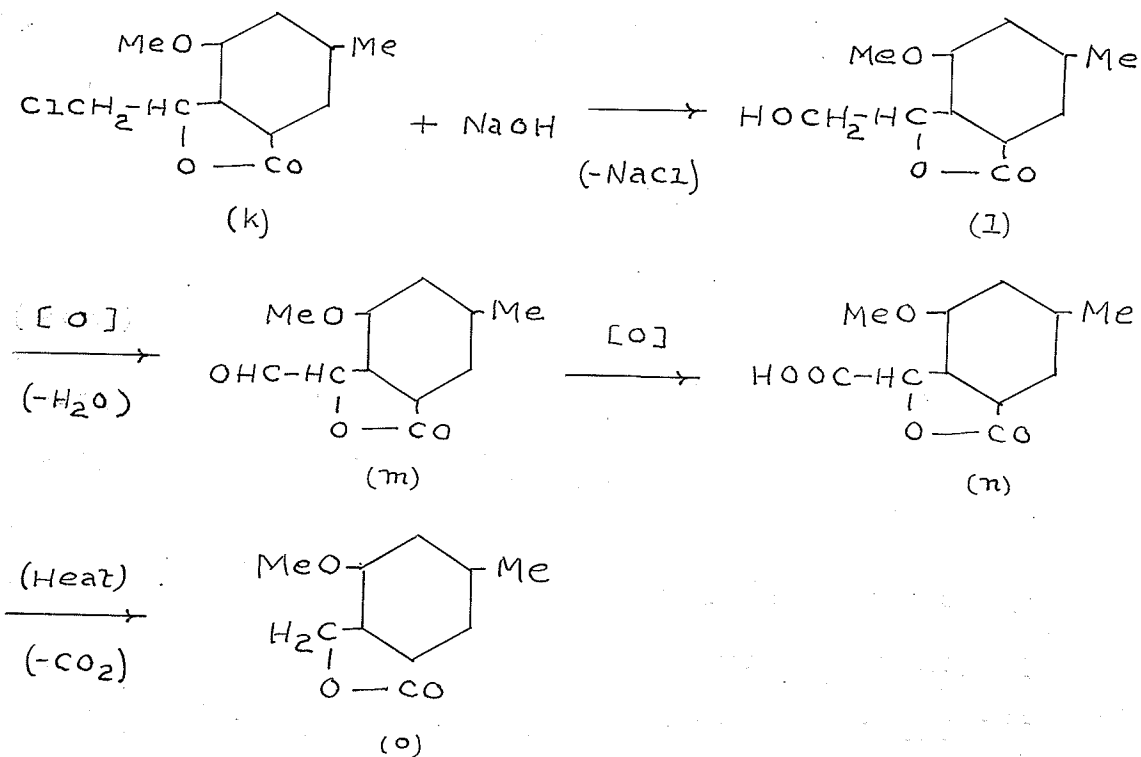
Finally, it should be pointed out that farther experimental work, along the lines suggested below, should lead to a solution of this problem. Thus, if product I can be produced from chloroacetaldehyde and 5-methoxy-*m*-toluic acid, according to the reaction,



structure (a) would then be indicated. Similarly, oxidation of the alcohol (g, below) theoretically obtainable from (a) by treatment with alkali, should yield the corresponding aldehyde (h), acid (i) and finally, by decarboxylation, the phthalide (j), as indicated below.



Since both isomeric forms of the acid, and also those of the phthalide are known (Meldrum, J. C. S., 1911, 99, 1716.) it should be a simple matter to identify them, if formed as products of the above reaction. If this were the case, of course, structure (a) would be indicated, and the above formulation would then apply to the formation of the α -isomeric alcohol, acid, etc., from the parent α -chloromethylphthalide. Similarly, formation of the corresponding β -isomers, from the hypothetical β -chloromethylphthalide (k, below) would be represented as follows:

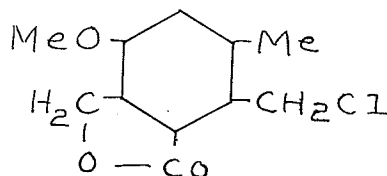


Conversely, if a different carboxylic acid were obtained, and if this likewise yielded the phthalide on decarboxylation, either structure (b) or (c) would then be indicated (page 17), and the true position of the carboxyl group would have to be ascertained by further experiment.

In any one of the cases outlined above, separation of two structurally isomeric alcohols, aldehydes, acids or phthalides would indicate corresponding isomerism in the original chloroproduct. The topic of isomerism will be considered further later in the discussion.

Incidentally, it will be noted that the structure (c) already indicated (page 17) would not appear to be

capable of showing the type of α - β isomerism here referred to. However, if preliminary phthalide formation were involved in its production, it might be assumed that the isomeric β -phthalide would yield a corresponding structure, in which the chloromethyl group would occupy position (2) instead of (6), as indicated below:



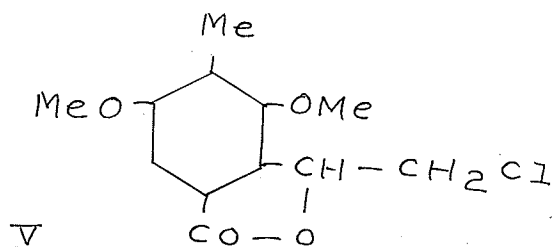
Derivative of the β -phthalide,
corresponding to (c), page 17.

Other experimental evidence in support of the general structure of product I is still lacking. Thus, complete carbon and hydrogen estimation, methoxyl determination and the preparation of suitable derivatives would be necessary, before the true structure could be definitely established.

The Nature of Product V.

By similar reasoning to that given in the preceding, it may be shown that the probable structure of V is that

indicated below:



$C_{12}H_{13}O_4Cl$ requires 13.84%, for Cl.

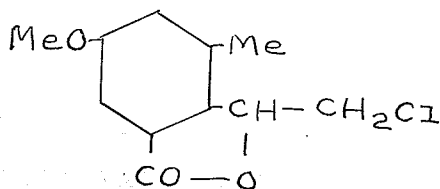
(Found: Cl, 13.18%).

(One determination).

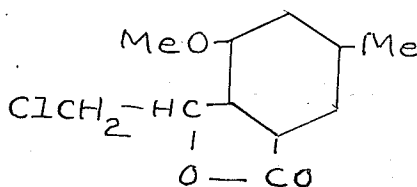
In the case of product V, it is evident that no α - β isomerism, of the type suggested for product I, is possible, as shown by the structure suggested above.

THE THEORETICAL ISOMERISM OF PRODUCT I.

It is evident, from the structural formula tentatively adopted for product I (formula a, page 17), that it should be capable of existing in two distinct, structurally isomeric forms. These would be termed the α - and β -isomers, respectively, according to the system of naming employed by Meldrum, who was the first to isolate and study the normal isomeric phthalides of 5-methoxy-m-toluic acid (see ref., page 1). As already mentioned, the α - and β -forms of product I would then have the structures shown below:



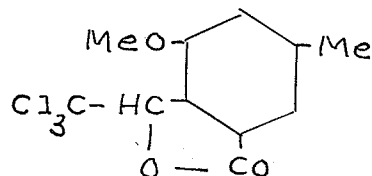
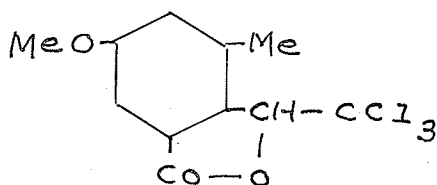
α -isomer.



β -isomer.

Although Meldrum prepared both the normal α - and β -phthalides of 5-methoxy-m-toluic acid, and the corresponding isomeric carboxylic acids, he was unable to obtain the corresponding isomers of the trichloromethylphthalide. However, he considered the existence of these isomers to be highly probable, and believed that the mixture he used in the hydrolysis (see below) was a mixture of the α - and

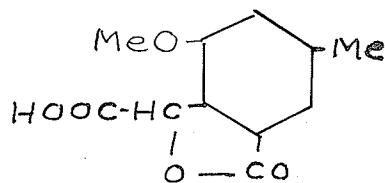
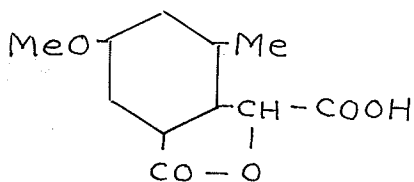
β -forms. In this way he accounts for the formation, from such a mixture, of the more easily separated isomeric phthalides, by hydrolysis of the trichloromethylphthalides and subsequent decarboxylation of the isomeric acids obtained. The structures assigned by Meldrum to these hypothetical α - and β -trichloromethylphthalides, and to the corresponding acids and phthalides which he discovered, are shown below:



α -Methyl- β -methoxy-

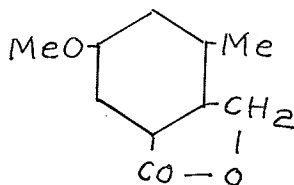
β -Methyl- β -methoxy-

α -trichloromethylphthalide. β -trichloromethylphthalide.

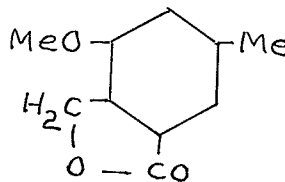


α -carboxymethylphthalide.

β -carboxymethylphthalide.



3-Methyl-5-methoxy-
 α -phthalide.



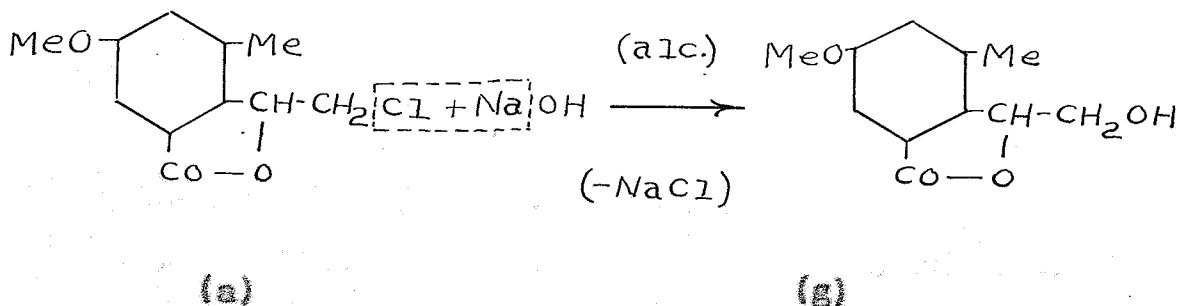
3-Methyl-5-methoxy-
 β -phthalide.

At present, the suggested isomerism of product I (page 25) is purely a theoretical assumption, since shortage of material did not permit investigation of this problem. Since no direct experimental evidence of isomerism is available, the formula of the α -isomer is used in this paper merely for the sake of uniformity, and is not intended to indicate whether this product is actually the α - or β -isomer, or a mixture of the two forms. At present, the formula for the β -chloromethylphthalide would serve equally well.

THE REACTION OF PRODUCT I WITH ALCOHOLIC SODIUM HYDROXIDE.

Introduction.

The structure adopted for product I suggests that it might react with alcoholic sodium hydroxide in the following manner:



In view of this possibility, a small amount of product I was treated with alcoholic caustic soda, and the details of procedure are given in the experimental section. However, the significant results obtained are outlined below.

A non-chlorinated product (II, m. p., 135-140°) was isolated in small amount from the reaction mixture. A few general properties of this product are shown in table II (page 29), along with those normally expected for the hypothetical alcohol referred to above (g). The properties of the known β -phthalide are also given in the table, for purposes of comparison.

TABLE II

<p>PROPERTIES OBSERVED FOR PRODUCT IX.</p>	<p>PROPERTIES EXPECTED FOR A COMPOUND OF STRUCTURE (g).</p>	<p>PROPERTIES OF THE KNOWN 3-METHYL- 5-METHOXY- β-PHTHALIDE.</p>
<p>M. P., 135-140°.</p> <p>Minute flakes from water.</p> <p>Sol. hot water.</p> <p>Sol. hot alc.</p> <p>Neutral to moist litmus.</p> <p>Inactive to aq. NaHCO₃.</p> <p>Insol. in, inactive to aq. NaOH.</p> <p>No colour with aq., alc. FeCl₃.</p>	<p>M. P., below 175°.</p> <p>Sol. water (?)</p> <p>Sol. alcohol (?)</p> <p>Neutral to moist litmus.</p> <p>Inactive to aq. NaHCO₃.</p> <p>Inactive to aq. NaOH.</p> <p>No colour with aq., alc. FeCl₃.</p>	<p>M. P., 135.5°.</p> <p>Col'less scales from acetone and alcohol.</p> <p>Sol. hot alc.</p> <p>Neutral to moist litmus.</p> <p>Inactive to aq. NaHCO₃.</p> <p>Inactive to aq. NaOH.</p> <p>No colour with aq., alc. FeCl₃.</p>

The Nature of Product IX.

The exact nature of product IX remains unknown as yet, since the quantity obtained was insufficient for analysis. However, since it cannot be product I, it is clear that a reaction involving sodium hydroxide and product I does occur. Since it is neutral to litmus, inactive to aqueous sodium bicarbonate and insoluble in alkaline solution, it probably does not contain the acid carboxyl group. Since no colour is produced with ferric chloride, it is not likely to be a phenol.¹ Unlike product I, it is soluble in hot water, which might be expected if substitution of a hydroxyl group for chlorine had occurred. Similarly, such a substitution, other things being equal, usually tends to lower the melting-point of this type of compound, so that product IX might be expected to have a melting-point lower than that of the chloroproduct I (175-176°), as indicated in the table. Incidentally, since the hypothetical alcohol (g) referred to above should be capable of existing in two isomeric forms, it may be that IX is actually a mixture of the α - and β -isomers, in which case the observed melting-point would probably be rather indefinite, a conclusion in agreement with the above results.

It is obvious, of course, that the above evidence is altogether too incomplete to indicate the nature of product IX. Nevertheless, it is evident that many possible structures related to I are practically eliminated,

¹ Any non-carboxylic phenol here possible should give this test.

including the corresponding carboxylic acids and the α -phthalide. Since the only likely, known compound remotely resembling IX is the β -phthalide, the latter has been included in the above table. However, it will be seen that the properties of IX are in general agreement with those expected for the alcohol (g). Furthermore, the formation of a primary alcohol by the reaction suggested is simple, and agrees with that of analogous compounds, while the formation of either the α - or β -phthalide, or both, from the same materials, would be more difficult to explain on theoretical grounds.

THE MECHANISM OF FORMATION OF PRODUCTS I AND V.

Introduction.

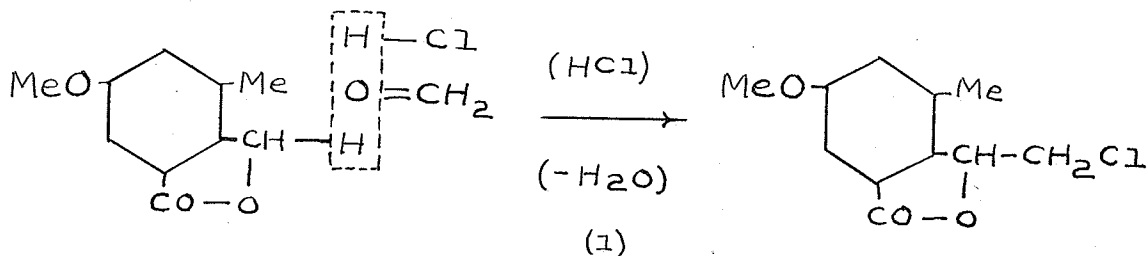
Before discussing the probable nature of the reactions referred to in the title, it should be mentioned that experimental results indicate quite clearly that the same general mechanism of formation is concerned in both reactions. For this reason it will be convenient, in the discussion which follows, to employ the somewhat simpler formula of product I, all the reasoning involved being considered to apply with equal force to the formation of V, unless otherwise indicated.

The chloro-product I is of special interest, since it represents a deviation from the normal reaction, and its probable structure, in the light of the evidence here obtained, has already been indicated (page 10).

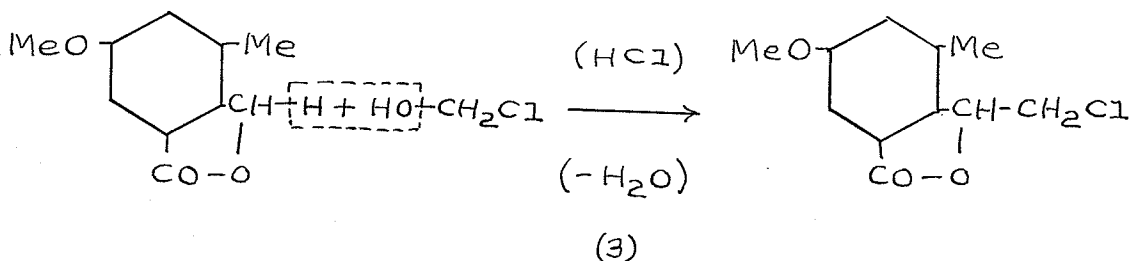
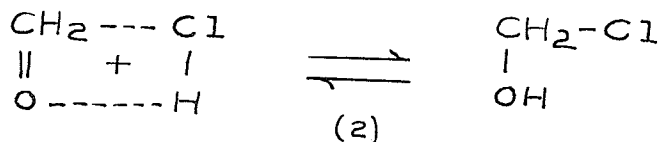
Since such a chloro-product does form, it is evident that the hydrochloric acid must take part in the reaction, in the process contributing its chlorine to the product. However, hydrochloric acid alone has no effect on 5-methoxy-m-toluic acid, since the former reagent precipitates it unchanged from an alkaline solution. This indicates, therefore, that formaldehyde is also essential to the reaction.

Two Theories of Formation.

Supposing that the present reaction involves the preliminary formation of the phthalide, by the normal reaction; then substitution of the chloromethyl group, to give product I, might occur in at least two different ways -- either by direct reaction with the original reagents, as shown below,



-- or through the medium of an unstable, intermediate compound, chloromethyl alcohol, produced by an independent reaction involving formaldehyde and hydrochloric acid, as follows:



Of course, to both of the theories suggested above, there is a common objection, namely, that no such unsubstituted phthalide has definitely been isolated from the reaction, either in the present work or in any previous investigation (page 6). However, there is some evidence, to be mentioned later, that further study of a non-chlorinated product (IV, m. p., 94-96°) may show it to be a mixture of the α - and β -phthalides (known α -phthalide, m. p., 105.5°; known β -phthalide, m. p., 135.5°). In view of this possibility, therefore, this objection may be discounted, for the present.

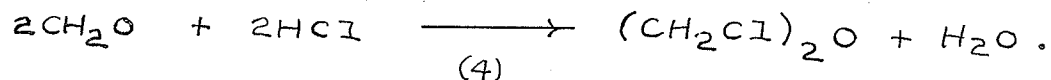
It now remains to consider which of the two theories of chloromethyl substitution, suggested above, is the more probable. It would seem logical to accept the first explanation, if it were not for certain apparent objections. In the first place, there is considerable indirect evidence (to be described) for the formation of chloromethyl alcohol, in the manner suggested by equation (2), above: in the second place, the theory represented by equation (1) would require a condensation reaction involving three different compounds simultaneously, whereas, in the other case, only two compounds would be involved in the final reaction. Incidentally, it seems logical to suppose that the preliminary formation of a chloromethyl group would facilitate its substitution in another compound. In general, therefore,

it would appear that the second explanation, represented by equations (2) and (3), is the more probable alternative. Adopting this conclusion for the present, then, it becomes necessary to examine the evidence, already mentioned, in support of chloromethyl alcohol formation under the present conditions.

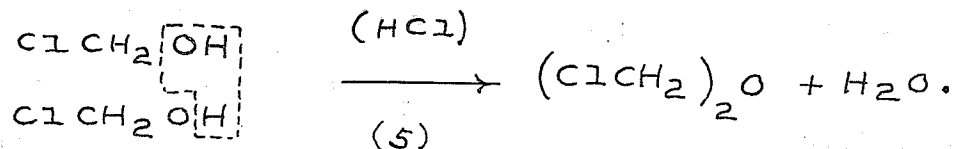
Chloromethyl Alcohol.

The simplest compound which might form, theoretically, by direct addition of hydrogen chloride to formaldehyde, would be chloromethyl alcohol (formaldehyde hydrochloride), the reaction being represented as in equation (2), above. The conception of such a reaction occurring is not a new one. The name chloromethyl alcohol was given to a product obtained from paraformaldehyde and hydrogen chloride by Grassi-Crisaldi and Maselli (Gazzetta, 1898, 28, 11, 477). A compound of this name and formula is listed in Beilstein, but no specific physical properties by which it might be recognized are given there, and therefore it has apparently never been isolated in a pure condition. If such is the case, of course, its existence must still be considered doubtful. There is also certain indirect evidence available, however. Stephen, Gladding and Short (J. C. S., 1920, 117, 520.) isolated two definite compounds from a mixture obtained by treating commercial formaldehyde with gaseous hydrogen

chloride. One of these proved to be *s*-dichloromethyl ether, and this fact suggested that the following reaction had occurred:

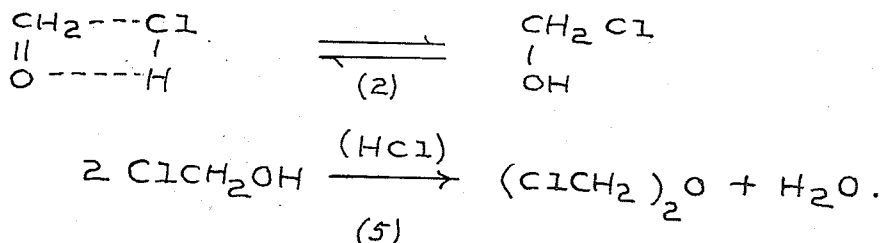


These authors did not suggest an actual mechanism for this reaction, however. Nevertheless, in discussing a related reaction, they suggested, first, that chloromethyl alcohol may exist in the presence of water, and second, that it may condense in the presence of a dehydrating agent, to give the dichloromethyl ether, as shown below:



This theoretical reaction is based on extensive research, and is well supported by indirect experimental evidence, as will be shown.

It now becomes clear that if the two possible reactions (2) and (5) which have been considered are combined, they provide a simple mechanism by which to explain reaction (4), as shown:

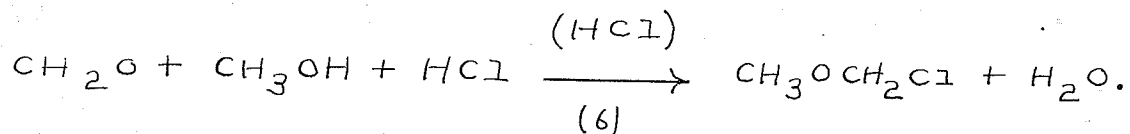


Since the dichloromethyl ether is actually obtained under the conditions described, it seems quite possible that the above explanation is correct, and that chloromethyl alcohol may exist under such conditions.

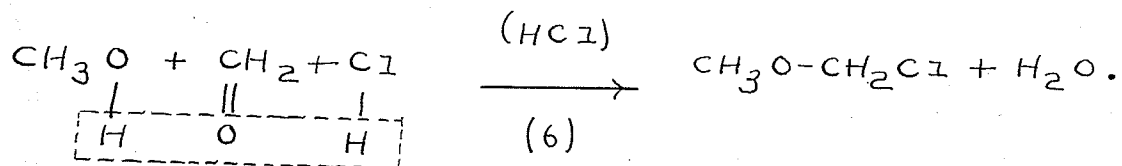
It should be noted, however, that the dichloromethyl ether was obtained using gaseous hydrogen chloride in a reaction tower packed with pumice, the gas introduced at the bottom coming into contact with the formaldehyde percolating downwards from the top. It was found difficult to prepare it by simply passing the gas into cold formaldehyde solution, because of the separation of paraformaldehyde which resulted. Furthermore, hydrolysis of the dichloromethyl ether yields formaldehyde. These facts seem to indicate that the above reactions are reversible, the equilibrium concentration of each reactant depending, for one thing, on the proportion of water present. According to this view, then, the use of strong hydrochloric acid in place of hydrogen chloride gas would tend to reverse reaction (5) above, due to the greater amount of water present. On the other hand, water is not directly concerned in reaction (2), and its influence here should be less marked. Under the present experimental conditions, therefore, one would not expect the dichloromethyl ether to be formed in any appreciable amount, but there is still experimental evidence that chloromethyl alcohol may be

present in the solution.

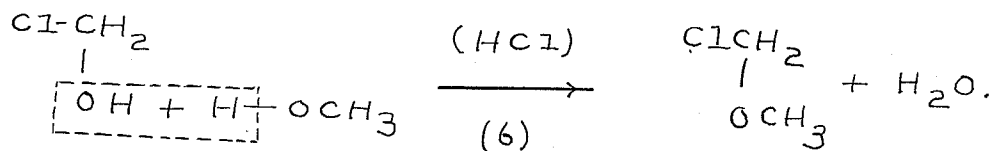
It has been mentioned above that the mixture of formaldehyde and hydrogen chloride used by Stephen et al. yielded another product, in addition to *o*-dichloromethyl ether. This other product was found to be the corresponding monochloromethyl ether ($\text{CH}_3\text{OCH}_2\text{Cl}$). The authors accounted for its presence by suggesting that the small amount of methyl alcohol, present in the commercial formaldehyde which they used, had reacted as follows:



Ordinarily, this reaction might be supposed to involve simultaneous reaction of the three compounds, as shown below,



In this case, however, preliminary formation of chloromethyl alcohol would simplify the reaction, which might then be formulated as involving two compounds, thus:



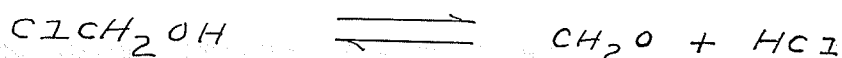
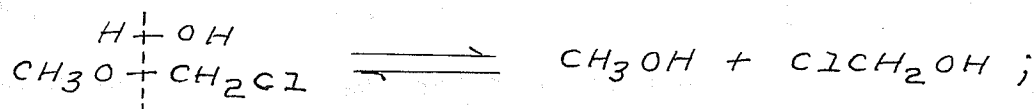
As in the formation of the dichloromethyl ether (page 36),

the presence of water would tend to reverse this reaction, and this would be expected to occur if the strong acid were used in place of hydrogen chloride.

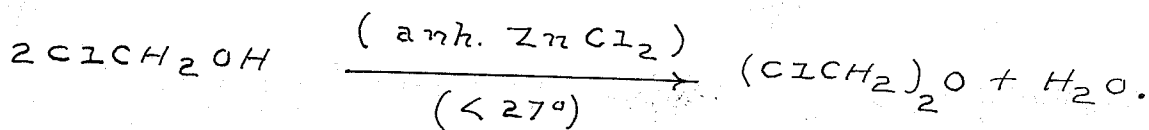
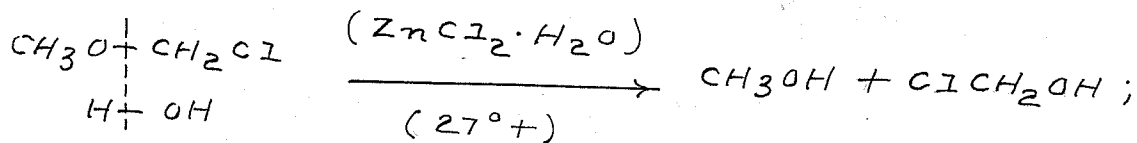
In connection with the above reaction, of course, the argument for chloromethyl alcohol formation would be parallel to that already outlined for chloromethyl substitution in the phthalide derivative (page 34). Furthermore, Stephen and co-workers suggest that chloromethyl alcohol is produced in the course of hydrolysis of the monochloromethyl ether. Since this hydrolysis is simply the reverse of the above reaction, it seems logical to assume that the reaction itself should involve the same intermediate compound.

The formation of *s*-dichloromethyl ether, already described, is more conclusive evidence, however, since in this case the reaction cannot be formulated reasonably at all, without assuming the intermediate reaction. Apparently this is the case because the formation of an ether requires that at least one of the reactants should contain an oxygen atom linked to two independent groups, one of which may be a hydrogen atom. In the formation of chloromethyl ether, the methyl alcohol fulfils this condition; in the case of the dichloromethyl ether, it becomes necessary to assume the formation of such a compound, and the evidence indicates chloromethyl alcohol.

Hydrolysis of chloromethyl ether yields methanol, formaldehyde and hydrochloric acid. Applying the present theory to this reaction, it might be represented thus:



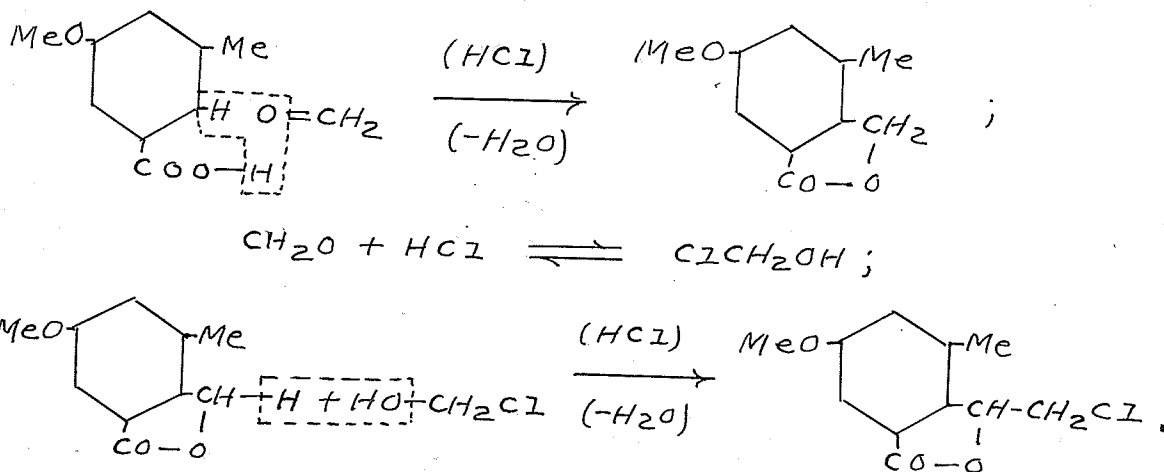
Stephen and co-workers produced evidence that chloromethyl alcohol is the intermediate compound involved in this hydrolysis, by using zinc chloride monohydrate in place of water. In this case, they finally obtained *s*-dichloromethyl ether, instead of formaldehyde and hydrogen chloride. Since the hydrated zinc salt liberates its water of crystallization at 27°, and since the reaction was induced by heating to this temperature, these results indicated that the water had been used up in the first stage of the reaction, to produce chloromethyl alcohol, as indicated below. When the temperature again fell below 27°, the anhydrous zinc salt left over would then bring about self-condensation of the alcohol, by removal of the elements of water. This interpretation of the reaction may be summed up as follows:



From the above formulation, it is evident that hydrolysis of chloromethyl ether is simply a regeneration of the chloromethyl alcohol previously utilized in its formation. The course of the reaction, from this point, depends on the experimental conditions, as already explained

The Second Theory of Formation.

It has been shown that, if the first stage in the formation of product I be the formation of the simple phthalide, by the normal reaction, a different type of condensation would then be necessary to bring about substitution of the chloromethyl group, and the theory of chloromethyl alcohol formation therefore represents an attempt to provide the different type of reagent required. The evidence in support of this theory has been outlined above. For reasons already given, then, (page 34) the second theory of formation suggested for product I (page 33) seems the more probable alternative, and may now be summarized as indicated below:

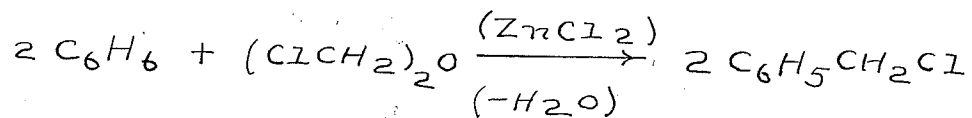


The final reaction, above, seems plausible, since one would expect the (CO₂) group of the phthalide ring to be that part of the molecule most readily attacked. The theory is still open to the same objection already mentioned, however, since it should be possible to isolate the phthalide from the reaction mixture. Likewise, further experiment is necessary to determine whether product I can be obtained in this way, starting with the phthalide instead of the toluic acid. Until this has been attempted, the above formulation must be considered merely a speculation. By analogy with the meconines, already referred to (page 2), such a reaction would seem to be improbable. However, no conclusion can be drawn from the behaviour of the latter compounds, since their preparation from the veratric acids yields no chloro-products at all.

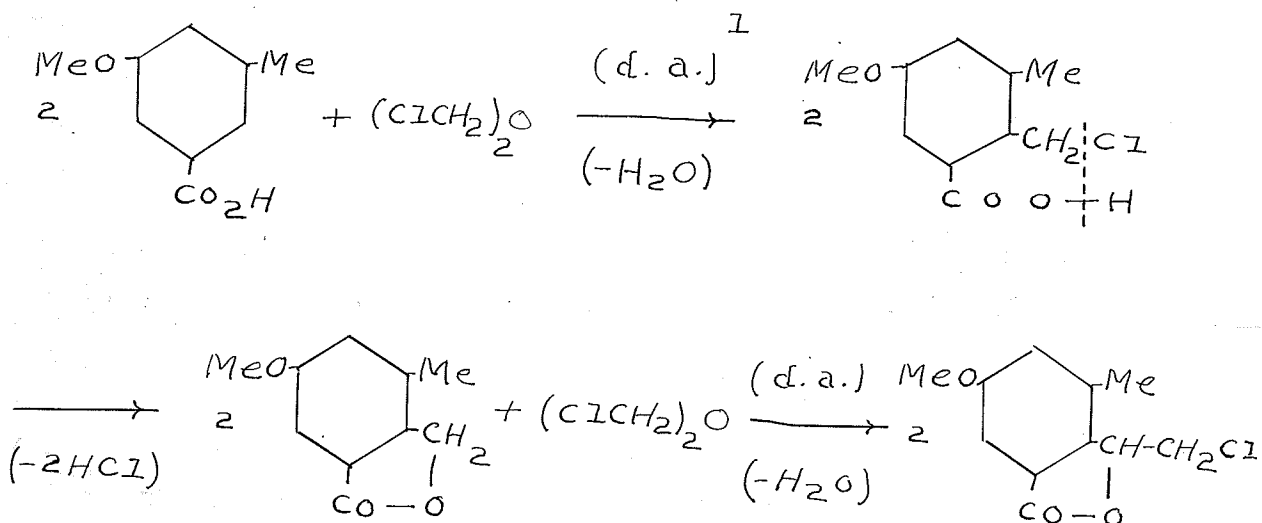
s-Dichloromethyl Ether.

Another possibility to consider is the self-condensation of chloromethyl alcohol, in the manner already mentioned (page 36), to produce s-dichloromethyl ether. Of course, it has already been pointed out that such a reaction seems unlikely to occur under the present conditions. Nevertheless, it is interesting to note that, if it could reasonably be assumed, introduction of the chloromethyl group into the aromatic nucleus would then appear likely.

since such a reaction would correspond closely to that investigated by Stephen et al., as indicated below:



As this type of reaction requires practically anhydrous reagents, it could only occur to a very limited extent, if at all, in the present case. With the teluic acid under consideration, the probable reactions involved might be represented thus:



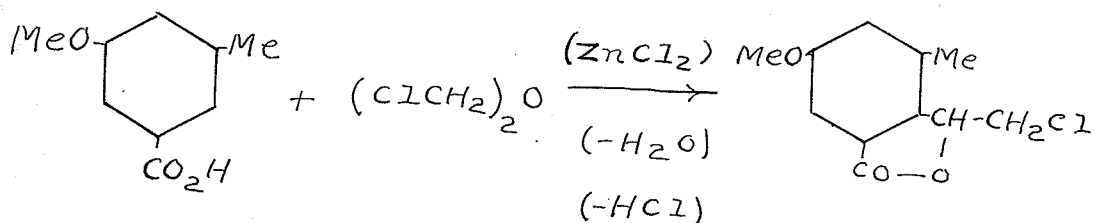
It is evident that the mechanism of formation of the unsubstituted phthalide, as shown above, is more complicated, and also less likely to occur, than the

¹ Dehydrating agent.

normal reaction, under the present conditions. Even if one supposed a small amount of dichloromethyl ether to exist in the presence of free water, this amount would hardly seem to be sufficient to account for a yield of 20% of the theory, in the case of product I, or of 24% for product V, as actually obtained.

The Action of Dry *s*-Dichloromethyl Ether on
5-Methoxy-*m*-toluic acid.

In the course of the present work an attempt was made to prepare product I by treating 5-methoxy-*m*-toluic acid with dry *s*-dichloromethyl ether, with anhydrous zinc chloride as the dehydrating agent, in the hope of bringing about the reaction,



The various intermediate reactions possibly involved in this change have been suggested (page 43).

This method of preparing the chloro-product, if successful, would have twofold importance: from the theoretical point of view, it would demonstrate that

s-dichloromethyl ether, which may be used to introduce the chloromethyl group into the benzene nucleus, may also be used to form the chloromethyl⁽¹⁾phthalide group, when treated with an aromatic acid under similar conditions; again, it might be possible to obtain a more satisfactory yield of the chloroproduct by this method, rather than by the present method. The optimum experimental conditions would have to be determined by trial experiments, of course.

The results obtained from this experiment are reported in the experimental section. However, the important evidence obtained may be indicated briefly at this point. Considerable heat was developed, and copious quantities of hydrogen chloride were evolved. Two products were isolated in rather crude form from the mixture (VII, m. p., 165-175°, and VIII, m. p., +240°), both in small amounts. The quantity of VII obtained was only sufficient for a single test by the sodium fusion method, and this test gave no positive indication of chlorine, while several such tests, made on product VIII, all gave negative results for chlorine.

It will be seen that these results provide some evidence in favour of the above reaction. The heat-production indicates that some reaction took place, while the evolution of hydrogen chloride and the formation of the two different products VII and VIII, the respective

melting-points of which approximate those of products I and II (175-176° and 247-248° respectively), suggests that such a reaction may occur, and that VII may be identical with I, and VIII with II. However, since no chlorine could be detected in the small quantity of product VII examined, the evidence is contradictory in this respect, and further experiment is necessary before any definite conclusions can be reached.

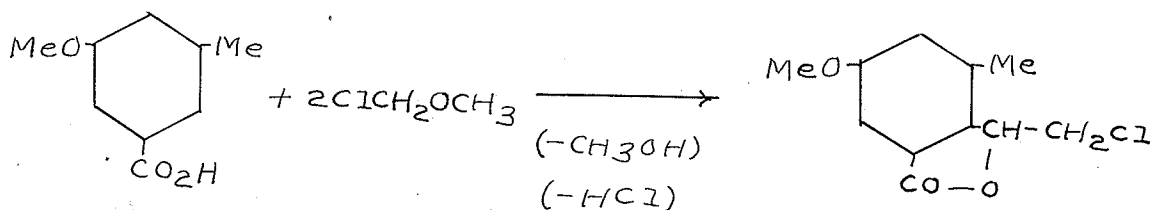
A few general properties of products VII and VIII are shown in the table below, the corresponding properties of products I and II being indicated also, for comparison.

TABLE III

PRODUCT VII.	PRODUCT I.	PRODUCT VIII.	PRODUCT II.
M. P., 165-175°.	M. P., 175-176°.	M. P., + 240°.	M. P., 247-248°.
Amorphous from alc.	Needles from alc.	Microcrystalline from 75% acetic acid.	
Insol. water. Sol. hot alc.			
Sol. hot glac. acetic acid.	Sol. glac. acetic acid.	Sol. hot glac. acetic acid.	
Cl absent (?)	Cl present.		
		Cl absent.	

Chloromethyl Ether.

Chloromethyl ether, already referred to as a product of the reaction involving commercial formaldehyde and hydrogen chloride, may be considered as a possible intermediate compound involved in the formation of product I, from the same reagents. In this case, the reaction might be represented thus: ¹



This would clearly be analogous to the theoretical reaction involving the dichloromethyl ether (page 44), methanol being a by-product of the reaction instead of water. The mode of formation of the chloromethyl ether has already been considered, and the probable intermediate stages involved in the above reaction would also correspond to those suggested for the dichloromethyl ether (page 43). Since it has already been shown that the latter is not likely to form in appreciable amount under the present conditions, the same reasoning can be applied in this case, hydrolysis of the ether, if formed at all, being supposed to occur as suggested (page 40). Participation of chloromethyl ether in the reaction giving product I must be

¹ Improbable under present conditions. See footnote 2, page 43.

considered as even less probable than that of *s*-dichloromethyl ether, since only a little of the methyl alcohol essential to its formation is present in the solution.

Theories of Reaction Summarised.

considering the general lack of definite experimental evidence, no definite conclusions as to the exact mechanism of the reaction can be drawn from the above discussion. However, to sum up the various theories of formation suggested, it may be considered as probable:

- (a) that a preliminary reaction occurs between form-
aldehyde and hydrochloric acid;
- (b) that the product of this reaction is chloromethyl
alcohol;
- (c) that the latter does not react directly with
5-methoxy-*m*-toluic acid to give product I in a
single step;
- (d) that a second intermediate product is formed;
- (e) that this may be the normal phthalide of 5-methoxy-
m-toluic acid, produced by the normal reaction,
but is not likely to be
 - (i) *s*-dichloromethyl ether, formed by self-
condensation of chloromethyl alcohol, or

(ii) chloromethyl ether, produced by interaction of chloromethyl alcohol and methanol present as impurity;

(f) that, since the normal phthalide may be formed by a preliminary reaction, it may then react simultaneously with formaldehyde and hydrochloric acid, to give product I directly, but is more likely to react with chloromethyl alcohol, present as the other intermediate product, to give product I.

In general, it should be noted that these tentative conclusions could be arrived at by similar reasoning, even if structure (b) or (c) suggested for product I (page 17) were shown to be correct.

General Remarks.

At the present time, only five different aromatic acids have been treated with formaldehyde and hydrochloric acid, in the manner described in this paper. These include the derivatives of benzoic acid (piperonylic, o-veratric and veratric acids, investigated by Ferkin and co-workers) and the two toluic acids (5-methoxy-m-toluic acid, referred to by Charlesworth and Robinson; 3,5-dimethoxy-p-toluic acid, mentioned by Raistrick and co-workers). For references to

these, see Introduction, pages 2 -- 6, inclusive.

Of these five, only the toluic acids yielded chloro-products, while the *o*-veratric and veratric acids each produced the normal phthalide, and only piperonylic acid gave neither normal phthalide nor chloro-product.

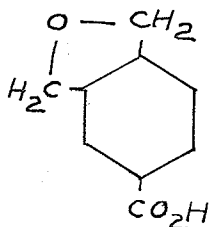
A third toluic acid, cresercollenic acid (3,5-dimethoxy-*o*-toluic acid) has been reported as giving the normal phthalide (Mitter, Sen and Paul; ref., page 3), but since no details of procedure were given in this case, it is not known whether the experimental conditions were uniform with those in the other cases, mentioned above.

Disregarding cresercollenic acid for the moment, then, certain tentative conclusions can be drawn from the information available. In the first place, the fact that, so far, only the toluic acids yield chloro-products, suggests that the nuclear-substituted methyl group may be essential to the reaction in some way, as already pointed out. On the other hand, the directing effect of the different substituents, and their respective positions in the nucleus, would be expected to influence the course of the reaction, apart from the obvious case in which occupation of both ortho-positions would prevent phthalide formation. In considering this factor, it is interesting to note that the two toluic acids, which yield the chloro-products, differ from the three benzoic acids, which do not, in regard to

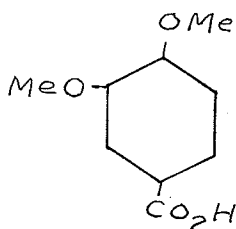
the arrangement of the substituent groups, with reference to the carboxyl group. Thus, in each tolnic acid, both meta-positions are occupied and both ortho-positions are unoccupied, while in none of the benzoic acids is this the case.

Incidentally, it will be noted that crescerellenic acid, like the benzoic acids mentioned, does not fulfil these conditions.

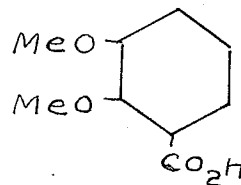
The structures of the six acids referred to above are shown below:



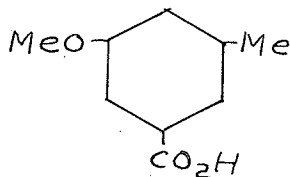
Piperonylic acid.



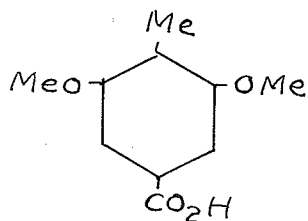
Veratric acid.



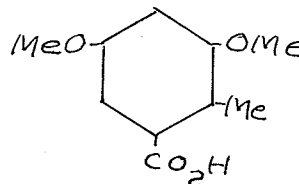
o-Veratric acid.



5-Methoxy-m-tolnic acid.



3,5-Dimethoxy-p-tolnic acid.



Crescerellenic acid.

Although the conditions noted above may be essential to the formation of the chloro-products, no such generalizations can be made until information is available on many other similar aromatic acids. From the results so far obtained, it might be supposed that any aromatic acid of the type referred to, having methyl or methoxyl groups substituted in the 3,5- or 3,4,5- positions, other positions being free, would yield such chloro-products on treatment with formaldehyde and hydrochloric acid. Thus α -resorcylic acid (3,5-dimethoxy-benzoic acid) and the trimethyl ether of gallic acid would form chloro-products, while benzoic acid itself would not. Since these compounds are readily available, further investigation of the problem might well begin with them, and the results obtained would indicate whether the factors mentioned above have any importance in this connection.

Other acids which might give chloro-products would include mesitylenic acid (3,5-dimethylbenzoic acid), α -isodarylic acid (3,4,5-trimethylbenzoic acid) and 4,5-dimethoxy-m-toluic acid, to mention only a few.

The effect of substituting other simple radicals in place of the methyl or methoxyl groups might also be investigated.

In connection with the theory of the reaction, it would be of interest to consider it from the standpoint

of the modern electronic theory, when further experimental data are available.

THE NATURE OF THE NON-CHLORINATED
PRODUCTS II, III, IV AND VI.

Introduction.

In view of the general lack of information regarding the non-chlorinated products obtained in this work, a detailed discussion of the subject is not possible at present. In any case, the main object of this investigation has been the identification and study of the chloroproducts I and V respectively. However, the probable nature of the non-chlorinated products may be discussed briefly, in the light of such evidence as has been obtained.

The general properties of the non-chlorinated products II and III, both obtained from the reaction involving 5-methoxy-m-toluic acid, and also those of product VI, from the reaction involving 3,5-dimethoxy-p-toluic acid, are summarized in table IV, page 56. The corresponding properties of product IV, from 5-methoxy-m-toluic acid, are shown in table V, page 63, along with those of the known 3-methyl-5-methoxy- α -phthalide, for purposes of comparison. All these products are colourless, more or less crystalline solids.

Quantitative analysis of product II for carbon and

hydrogen has been carried out, and the analytical results will be referred to below. Shortage of time and material did not permit of conclusive analysis of products III and IV, and the results obtained from repeated analyses of VI were found to be discordant, apparently because of impurities present in the sample, as suggested by the melting-point observed (246-250°).

General Indications.

Inspection of table IV reveals a general similarity in products II, III and VI, in appearance, solubility and general chemical properties. The respective melting-points of these products are all high, all being above 240°. On the other hand, product VI (table V), melting below 100°, differs markedly from these in appearance and solubility.

From these facts it may be concluded that the three similar products are all probably formed by similar reactions, while the remaining product, IV, represents a special case of some sort. Furthermore, it seems significant that IV was obtainable in much larger quantities than any of the other reaction-products. Unfortunately, it was only discovered in the final stages of the experimental work, and there was not sufficient time to purify it on a larger scale.

None of these products contain chlorine, but none of them remotely resemble the original materials used in

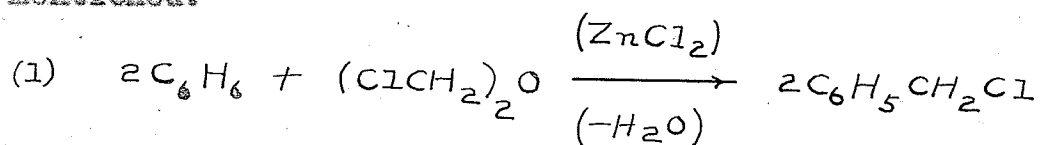
TABLE IV

PROPERTIES.	PRODUCT II.	PRODUCT III.	PRODUCT VI.
M. P. - - - -	247-249°.	263-264°d.	246-250°.
Appearance - -	Microcryst. from 75% acetic acid.		
Solubility:			
Water - - - -	Insol. - - - -		Insol.
Alcohol - - - -	Sl. sol. hot. - -		Insol.
Ether - - - -	Insol. - - - -		Insol.
Acetone - - - -	Sl. sol. hot. -		Sl. sol. hot
Glac. acetic acid	Sol. hot. - - -		Sol. hot.
Ethyl acetate -	Insol. - - - -		Sl. sol. hot
Benzene - - - -	Insol. - - - -		Sol. hot.
Petr. ether - -	Insol. - - - -		
Chloroform - -	Sol. hot. - - -		Sol. hot.
Carb. tetrachloride	Insol. - - - -		Insol.
Carb. disulphide	Insol. - - - -		
With moist litmus	- -	Neutral.	
" aq. NaHCO ₃ -	- -	No reaction.	
" aq. NaOH -	- -	Insol., no reaction.	
" aq., alc. FeCl ₃	- -	No colour.	
" conc. H ₂ SO ₄ -	- -	Sol., no decomposition.	

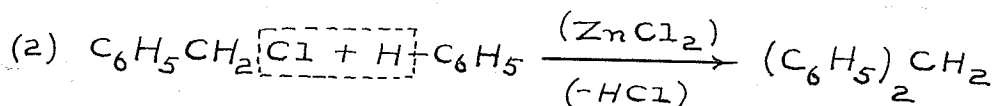
their preparation. Obviously, then, they are actually produced in the course of the reaction.

Products II and III.

In the paper by Stephen, Short and Gladding, already referred to (page 35), the following reaction is mentioned:



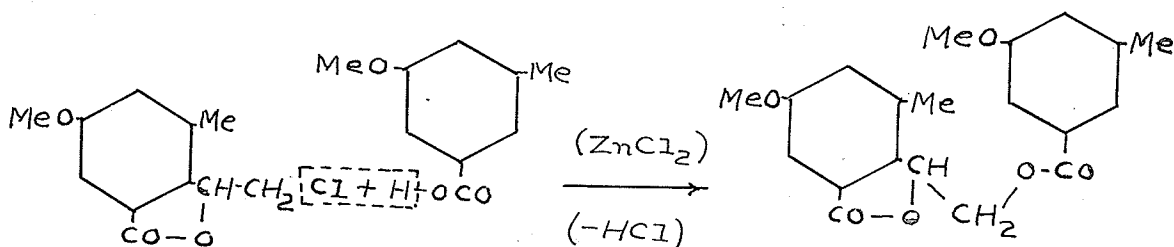
These authors also showed that a secondary reaction occurs, in this case involving elimination of hydrogen chloride, between the benzyl chloride produced and the original benzene, thus:



It will be seen that this is similar to the ordinary Friedel-Crafts reaction, with anhydrous zinc chloride replacing the usual aluminium chloride.

It has also been mentioned that an attempt was made, in the present work, to obtain the chloroproduct I by a reaction corresponding to that indicated above (reaction 1), using 5-methoxy-n-toluic acid in place of benzene. The results of this experiment have already been outlined and discussed (page 44). The non-chlorinated product VIII obtained (see table III, page 46) by this

method may be a secondary reaction-product, corresponding to the diphenylmethane produced as above (reaction 2). This secondary reaction would then be formulated as shown below, assuming that the chloroproduct I had actually been formed as the primary product:



This explanation would seem probable if it had been definitely established that product I is actually formed in the experiment with *s*-dichloromethyl ether. Further investigation of this reaction is obviously necessary before the problem can be solved. The experimental conditions would seem to favour the secondary reaction in this case, and possibly only a small proportion of the chloroproduct would remain unchanged, if formed at all. Reference to table III shows that the observed properties of product VIII are in good agreement with those of product II, obtained as described, thereby suggesting that II may be a secondary product of the type shown above, and possibly having the structure indicated, above. Incidentally, proof that the above reaction occurs

might be useful accessory evidence regarding the nature of the primary reaction giving product I, as obtained from the acid-formaldehyde mixture.

There is other indirect evidence that product II has this structure, and therefore, that it is formed by the reaction suggested. It has already been mentioned that there is a possibility that the phthalide of 5-methoxy-m-toluic acid may be formed as an intermediate product, by way of the normal reaction. Reference to table IV, above, shows that neither II nor III can possibly be the known α -phthalide; similarly, neither of them can be the β -phthalide, or any of the corresponding carboxylic acids, considering their general properties. By this reasoning, then, practically all the likely, known compounds may be eliminated, and it appears increasingly probable that product II or III, or both, are secondary products of the type referred to.

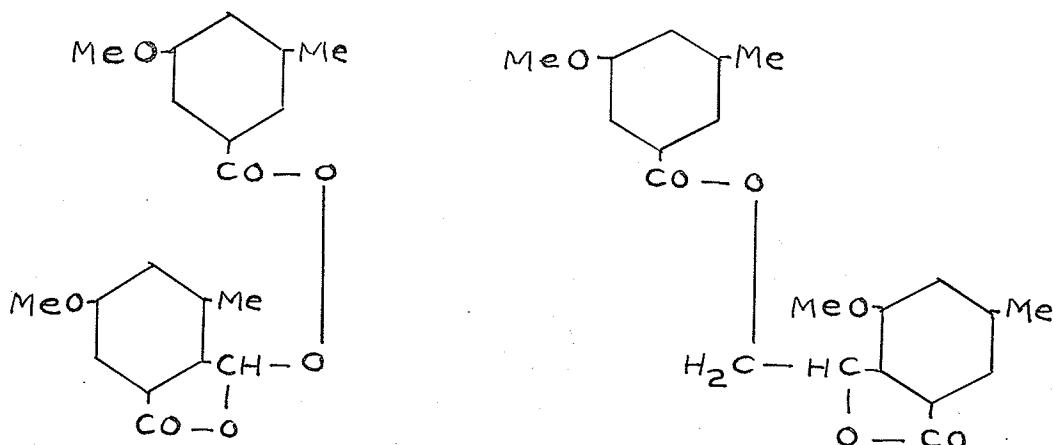
It is interesting to note that both of these products have almost the same properties, the only differences noted being those of meltingpoint and, to a slight extent, of solubility in alcohol. This suggests the possibility that they may be structural isomers, corresponding to the hypothetical α - and β -chloromethyl-phthalides (page 25). If this were the case, the structures of the two isomers would be those indicated

4



(100-10)

below, still assuming them to be secondary reaction-products:



α -isomer.

β -isomer.

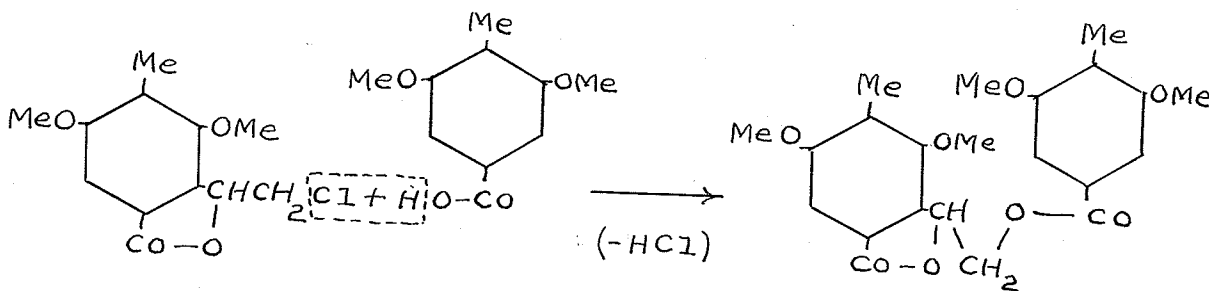
By analogy with the corresponding isomeric phthalides and carboxylic acids, the lower-melting product (II, m. p., 247-248^o) would be the α -form, while the higher-melting substance (III, m. p., 263-264^od.) would be the β -form.

However, the melting-points of these products were not very sharp. In the case of II, the sample turned yellow and sintered slightly, below 247^o, while product III darkened somewhat, below 263^o. These facts also seem to suggest isomerism, since clean separation of such isomers, present only in small amounts, would

probably be somewhat difficult, under such circumstances. The question can only be settled by careful analysis of highly purified samples. In the case of product II, the analytical data obtained do not agree with those calculated from the formula, $C_{20}H_{20}O_6$, representing the structure suggested above. Thus analysis of product II gave carbon, 70.80%, hydrogen, 5.55%; $C_{20}H_{20}O_6$ requires carbon, 67.42%, hydrogen, 5.62%. This discrepancy cannot be definitely accounted for, at present. ¹

Product VI.

Since product VI closely resembles II and III, it seems probable that it is formed by a corresponding secondary reaction, and that it has a structure analogous to that suggested for these products. In this case, no isomerism would be possible, and product VI may therefore have the structure indicated below, its formation from the chloro-product V being represented thus: ²



1,2 See Note, page 64.

Product IV.

The properties of product IV, along with those of the known 3-methyl-5-methoxy- α -phthalide, are indicated in table V, below.

The case of product IV is interesting. It has been pointed out that products II, III and VI do not resemble any of the known compounds, related to the parent toluic acids, which might be expected to form. From this it may be concluded that these may be unknown secondary products, of the type just indicated. On the other hand, product IV has certain properties very different from these, and is therefore not likely to resemble them in structure. However, it shows certain points of resemblance to the known 3-methyl-5-methoxy- α -phthalide, which may be significant. The discrepancy of 10° or so in melting-point may not be a serious objection, since IV may be a mixture of the α - and β -phthalides. Incidentally, the observed melting-point (94-96°) was not very sharp, and a minute amount of sample remained unmelted until about 100° was reached. If the melting-point be disregarded, however, the insolubility of IV in alkali, and its solubility in cold acetone, are properties which disagree with those of the α -phthalide. Further purification, and subsequent analysis of IV could not be carried out, for reasons

TABLE V

PROPERTIES.	PRODUCT IV.	3-METHYL- 5-METHOXY- α-PHTHALIDE.
M. P. - - -	94-96°. - -	105.5°.
Appearance - -	Feathery crystals from water.	Crystals from water.
Solubility:		
Water - - -	Sol. hot. - -	Sol. hot.
Alcohol - - -	Sol. - - -	Sol.
Ether - - -		
Acetone - - -	Sol. - - -	Sol. hot.
Glac. acetic acid	Sol. - - -	
Ethyl acetate -	Sol. - - -	
Benzene - - -	Sol. - - -	
Petr. ether - -	Sol. hot. - -	
Chloroform - -	Sol. - - -	
Carb. tetrachloride	Insol. - -	
Carb. disulphide	Sol. - - -	
With moist litmus	Neutral - -	Neutral.
" aq. NaHCO ₃ -	No reaction. -	No reaction.
" aq. NaOH -	Insol., no action	Sol.
" aq., alc. FeCl ₃	No colour. -	No colour.
" conc. H ₂ SO ₄ -	Sol., no decomp.	Sol., no decomp.

already mentioned (page 55), and it was not possible to make a mixed melting-point determination with a known sample of the phthalide, since no such sample was available.

The fact that a product corresponding to IV was not obtained from the reaction with 3,5-dimethoxy-p-toluic acid has no significance here, since no attempt was made to isolate such a product from the alcoholic mother-liquors left over from crystallization of the chloro-product, this being the procedure which yielded product IV from the m-toluic acid. Only 2.35 grams of the p-toluic acid were available altogether, 1.56 grams of crude material were obtained from the various preparations, and this was entirely used up in the isolation of products V and VI.

NOTE -- Most of the evidence available on products II, III and VI is of a negative character, and is therefore of little value, since various theoretically neutral compounds, thus far unknown, might be derived from theoretical reactions involving the toluic acid derivatives concerned. Disregarding the analyses reported for II, the most serious objection to the structures suggested above seems to be the fact that their formation from the primary chloro-products I and V would involve elimination of HCl in presence of the concentrated acid. However, if product IV is shown to be a mixture of the α - and β -phthalides, as suggested, products II and III might be the corresponding isomeric secondary products, possibly derived from IV by some reaction involving elimination of water. Much more experimental evidence is needed in this connection.

EXPERIMENTAL.

OUTLINE OF PRELIMINARY PREPARATIONS.

In order to obtain the necessary 5-methoxy-m-toluic acid in sufficient quantities for experimental purposes, this material was synthesized from m-toluidine, employing the standard methods already in use for preparing the o- and p-nitriles, the corresponding toluic acids, and the 5-sulpho-, 5-hydroxy- and 5-methoxy-m-toluic acids, respectively.

The m-toluidine was first converted to m-cyanotoluene by the Sandmeyer reaction, following the modern, modified method used with o- and p-toluidine (Org. Syn., III, 33; IV, 96). This method was abandoned after running a few preparations, due to the rather low yields obtained, and the original method of Sandmeyer, as described in Cohen's "Practical Organic Chemistry" (page 191), was used, with more success.

Hydrolysis of the m-nitrile thus obtained was carried out as usual, employing 75% sulphuric acid, the resulting m-toluic acid was sulphonated by the method of Meldrum and Perkin (J. C. S., 1909, 95, 1891.), and the 5-sulpho-m-toluic acid obtained was converted to the corresponding hydroxy-acid,¹ as described by these authors. Methylation of the product in the usual manner, employing

¹ By alkali fusion.

dimethyl sulphate in alkaline solution, gave the required 5-methoxy-*m*-toluic acid.

PRELIMINARY PREPARATIONS.

5-Sulpho-*m*-toluic acid.

The method of Meldrum and Perkin (*loc. cit.*) was used here and in the succeeding preparations described below. A mixture of *m*-toluic acid (50 grams) and concentrated sulphuric acid (150 cc.) was heated under reflux for 8 hours at 130°, on the oil-bath. The product was then cooled, water (100 cc.) was added, and the dark solution was left in the refrigerator overnight. The dark crystals of the sulphonic acid which separated out were removed by filtration through cloth, the material was dried on porous pot and desiccated in vacuo. The crude sulphonic acid thus obtained (yield, 90 grams) was treated with animal charcoal and crystallized from water. The final product obtained was pale yellow in colour, and was not pure enough to give a sharp melting-point. In succeeding preparations of this compound, the treatment with charcoal was omitted, the crude product being used directly in preparing 5-hydroxy-*m*-toluic acid.

5-Hydroxy-m-toluic acid.

Crude 5-sulpho-m-toluic acid (45 grams) was added to moist caustic potash (135 grams) fused in a nickel crucible, the mixture being stirred with a thermometer protected by a brass tube in the usual way. The temperature was raised gradually to 260° and held there for about 10 minutes. After the melt had cooled, the product was dissolved in water and neutralized with sulphuric acid, potassium sulphate was removed and the phenolic solution was concentrated by evaporation. The crude phenol was thrown down on acidifying with strong hydrochloric acid, and a further quantity was obtained by extracting the acid solution with ether. In this run, 11.7 grams of the product were obtained. Several more runs were made, and this yield was much improved. Thus 50 grams of the crude sulphonic acid gave 26 grams of crude 5-hydroxy-m-toluic acid, in a later run.

The crude product obtained as above was purified through the calcium salt. This was accomplished by grinding up the impure 5-hydroxy-m-toluic acid (66.3 grams) in portions with water, to form a paste, which was then digested with pure calcium carbonate until effervescence had ceased. The mixture was diluted, boiled with charcoal, filtered hot, and the calcium salt was recrystallised

from water until pure. Decomposition of this material with dilute hydrochloric acid liberated the free 5-hydroxy-m-toluic acid. Yield, 51.7 grams, m. p., 202-203°.

5-Methoxy-m-toluic acid.

The pure 5-hydroxy-m-toluic acid (20 grams) from the preceding preparation was dissolved in 20% aqueous sodium hydroxide (150 cc.) in a round flask, cooled in ice water. A three-hole cork stopper, equipped with a dropping-funnel and inlet and outlet tubes connected to the gas supply, was inserted in the flask. Gas was passed in, and dimethyl sulphate (40 cc.) was added slowly in three portions, with shaking and cooling. The contents were then diluted with water (50 cc.) and the solution was refluxed over wire gauze for one hour. On acidifying with strong hydrochloric acid in the cold, the crude methyl ether was thrown down. This product was crystallized once from 50% acetic acid, giving a pure white product. Yield of 5-methoxy-m-toluic acid, 12.6 grams, m. p., 131-132°. Two more runs were made, proportional yields being obtained in each case.

THE PREPARATION AND ISOLATION
OF PRODUCTS I, II, III AND IV.

Preparation.

The procedure followed by Perkin et al. in the synthesis of meconine already described (page 2) was used in preparing products I, II, III and IV. These four products were all obtained from the same reaction mixture.

5-Methoxy-m-toluic acid (3.5 grams), obtained as described, was added to 40% aqueous formaldehyde (10 cc.) and concentrated hydrochloric acid (15 cc.), the mixture being heated 4½ hours under reflux on a boiling water-bath, a farther 15 cc. of hydrochloric acid being added in the course of the heating. One more addition of acid (5 cc.) was then made, and the mixture was boiled gently over wire gauze for half an hour. The crude solid obtained on cooling was separated, extracted with hot 95% alcohol, and the products from this treatment were subjected to fractional crystallization from alcohol. In later preparations it was found that the yield of product I was improved when the period of heating the reaction mixture was reduced to about 1½ hours, on the water-bath only.

Changes observed.

On heating the mixture on the water-bath, partial

solution seemed to occur. In about 5 -- 10 minutes a brownish solid appeared on the surface. This soon changed to an oil, which sank to the bottom of the flask. This sequence of changes was observed in every preparation of these products by this method.

Separation of Products.

After extraction of the crude product with alcohol, a small amount of insoluble material remained. This substance, a grayish solid, had a rather indefinite melting-point, about 250-260°. On crystallization from acetic acid (75-80%), a small quantity of a white, non-chlorinated product was obtained (III, m. p., +262-264°d.)

The alcoholic extract, on gradual cooling, yielded several crops of crystalline material, which were collected separately and dried in the usual manner. These portions were still impure, to judge from their appearance under the microscope, and the respective melting-points observed in each case (range of 10°). Further crystallization of these fractions finally yielded two fairly pure products, the lower-melting, more soluble material giving a positive test for chlorine (I, m. p., 175-176°), and the higher-melting, less soluble product, after a final crystallization from 75-80% acetic acid, giving a negative test for chlorine (II, m. p., 247-248°).

The green alcoholic mother-liquors left over from several preparations of I, II and III were finally combined, and the whole solution was diluted with twice its volume of cold water. A voluminous white precipitate was thrown down, and a greenish, gummy substance, which floated on the surface, was formed. This appeared to be the same substance as the white precipitate, but in a more impure form, since it showed practically identical properties. After recrystallizing twice from hot water, the white, non-chlorinated product was obtained in feather-like crystals (IV, m. p., 94-96°).

Yields obtained.

In a typical run, 2 grams of 5-methoxy-m-toluic acid produced 2.37 grams of crude product. From this material, 0.46 gram of product I was obtained, the remainder yielding small amounts of products II and III, respectively. The concentrated alcoholic mother-liquors obtained from these preparations, when combined (250 cc.), yielded a relatively large amount of product IV, in a rather crude form, as described.

Remarks.

The presence or absence of chlorine in each of the products obtained was determined both by ignition on copper wire and by sodium fusion.

The respective solubilities of products I and II in different solvents were investigated, in the hope of effecting a cleaner and more efficient separation of these from the crude material. The only other solvent suitable for this purpose, however, seemed to be carbon tetrachloride, but this was not employed since it contained chlorine, and might have contaminated the small amounts of pure product present. Any such contamination would introduce an additional source of error, in analysis of the purified product I for chlorine. The alcohol method of separation was therefore retained, and certain refinements of technique were introduced in view of the small quantities of material being handled.

In extracting product I from the crude material obtained, it was found that, for each gram of the latter, about 4-5 cc. of 95% alcohol were required, in each successive extraction. These extracts were examined separately, and fractional crystallization of each was employed, resulting in the isolation of I and II as described

A further quantity of a chloroproduct, obtained by the same method as already described in connection with I, was made available to the writer through the courtesy of Dr. Charlesworth. This material, after 3 crystallizations from alcohol, gave a melting-point of 175° , was found to contain chlorine, and a mixed melting-point determination

with a sample of product I gave the value 174-176°, showing the two substances to be identical.

THE NATURE OF PRODUCTS I, II, III AND IV.

Outline of Experiments.

A series of test was made on products I, II, III and IV, to determine their approximate relative solubilities in different solvents, and the presence or absence of acidic or phenolic properties. The results of these tests have already been indicated and discussed (for product I, see page 14; products II, III, page 56; product IV, page 63).

Quantitative analysis of product I for chlorine, and of product II for carbon and hydrogen have been carried out, and the results are indicated below. Analysis of products I, III and IV for carbon and hydrogen, and determination of molecular weight for some of the products obtained, were attempted, but in the circumstances, the results were of no significance. These circumstances included:

(a) shortage of time and material, which did not permit of conclusive analysis of products III and IV, and which prevented the introduction of certain necessary refinements in technique, such as those required in the microcrescopic determination of molecular weight (Ber., 1922, 55, 1050.);

(b) the fact that a silver gauze, required for carbon and hydrogen estimation of the chloroproducts, was not available:

(c) the fact that it was considered advisable to utilize the small amounts of material available, for repeated determinations of chlorine in the case of the chloroproducts, and for several determinations of carbon and hydrogen in the non-chlorinated products, in cases where sufficient material was obtained.

In order to obtain evidence as to the molecular structure of product I, a sample was treated with alcoholic sodium hydroxide, by a method to be described in detail.

A small amount of *s*-dichloromethyl ether was prepared from paraformaldehyde, strong sulphuric acid and sodium chloride (Stephen, Gladding and Short, *J. C. S.*, 1920, 117, 520.), and its action on 5-methoxy-*m*-toluic acid was investigated, with a view to obtaining further evidence regarding the nature of the reaction under discussion.

ANALYSIS OF PRODUCT I.

Estimation of Chlorine.

The percentage of chlorine present in product I was estimated in several samples, using the method of Stepanow (Thorpe and Whiteley, "Organic Chemical Analysis," page 52), in which the chlorine is removed in the form of sodium chloride. This method involves reduction in a mixture of metallic sodium and absolute alcohol, the sodium chloride thus obtained being estimated in this case by the indirect method of Volhard, in which a known volume of standard silver nitrate solution, more than sufficient to precipitate all the chlorine, is added to the solution. The excess silver nitrate is then estimated by titration with ammonium thiocyanate, using ferric alum as the indicator. The results obtained from two determinations are reported below.

Normality of AgNO_3 - - - - - 0.1000

Normality of NH_4CNS - - - - - 0.0990

1 cc. NH_4CNS is equivalent to .99 cc. AgNO_3 .

1 cc. AgNO_3 is equivalent to .00355 gram Cl.

DETERMINATION I.

DETERMINATION II.

Wt. of glass + sample = 6.3749 gms. - - - - 6.3747 gms.

Wt. of glass - - - - 6.2649 gms. - - - - 6.2649 gms.

Wt. of sample - - - - 0.1100 gm. - - - - 0.1098 gm.

Vol. AgNO₃ added - - 10.00 cc. - - - - 15.00 cc.

Vol. NH₄CNS required - 5.20 cc. - - - - 9.85 cc.

$$\text{Chlorine, } \left[10 - (5.2 \times .99) \right] \times \frac{.355}{.11}; \quad \left[15 - (9.85 \times .99) \right] \times \frac{.355}{.1098}$$

$$= \underline{15.66\%}$$

$$= \underline{16.97\%}$$

From determination I, Cl = 15.66%.

From determination II, Cl = 16.97%.

Mean, Cl = 16.32%.

(C₁₁H₁₁O₃Cl requires Cl, 15.67%).

See probable structures (a), (b), (c) suggested for product I, page 17; also discussion of the degree of accuracy of this method for estimating chlorine, page 17.

ANALYSIS OF PRODUCT II.

Estimation of Carbon and Hydrogen.

Three combustions were carried out, in the analysis of product II for carbon and hydrogen. The following are the results obtained from two combustions.

<u>MATERIAL WEIGHED..</u>	<u>DETERMINATION I.</u>	<u>DETERMINATION II.</u>
Boat + sample - - -	5.0447 gms.	5.0446 gms.
Boat - - -	4.9645 ..	4.9644 ..
Sample - - -	0.0802 ..	0.0802 ..
KOH bulbs after combustion	44.0221 ..	43.3302 ..
KOH bulbs before combustion	43.8142 ..	43.1217 ..
CO ₂ absorbed - - -	00.2079 ..	00.2085 ..
CaCl ₂ tube after combustion	35.4903 ..	35.4116 ..
CaCl ₂ tube before combustion	35.4508 ..	35.3715 ..
H ₂ O absorbed - - -	00.0395 ..	00.0401 ..
<u>Percentage Carbon,</u>	$\frac{12 \times .2079 \times 100}{44 \times .0802}$	$\frac{12 \times .2085 \times 100}{44 \times .0802}$
	= <u>70.7%</u>	= <u>70.9%</u>
<u>Percentage Hydrogen,</u>	$\frac{2 \times .0395 \times 100}{16 \times .0802}$	$\frac{2 \times .0401 \times 100}{16 \times .0802}$
	= <u>5.5%</u>	= <u>5.6%</u>

From determination I, Carbon = 70.7%; Hydrogen = 5.5%.

From determination II, Carbon = 70.9%; Hydrogen = 5.6%.

Mean, Carbon = 70.80%; Hydrogen = 5.55%.

By difference, Oxygen = 23.65%.

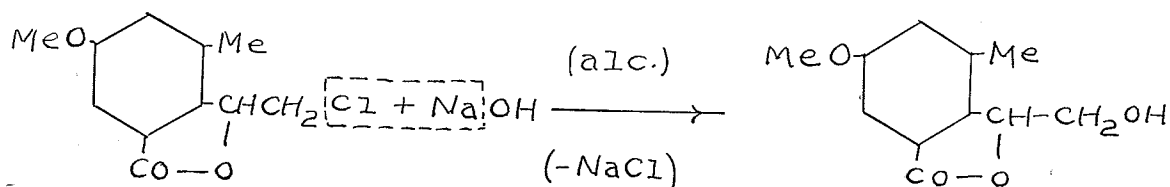
These results would indicate the simplest formula possible for product I to be C_4H_4O . However, this composition does not agree with that represented by the theoretical structure ($C_{20}H_{20}O_6$: simplest ratio, $C_{10}H_{10}O_3$) already suggested (page 58). This discrepancy may be due to impurities present in the sample analyzed.¹ On the other hand, there is very little theoretical evidence available as yet (see discussion, pages 54 - 61, inclusive).

¹ Improbable explanation, since the third combustion, not reported, gave similar results (C, 70.1%; H, 5.7%).

THE REACTION OF PRODUCT I WITH
ALCOHOLIC SODIUM HYDROXIDE.

Introduction.

Assuming the structure already indicated for product I, an attempt was made to obtain the corresponding primary alcohol by treatment with hot alcoholic sodium hydroxide. Such a reaction would be conveniently formulated as indicated below:



Procedure.

A modification of the method employed by Meldrum (J. C. S., 1911, 29, 1916) in degrading the corresponding trichloromethylphthalide was used. A sample of product I (.15 gram) was dissolved in boiling 95% alcohol (3 cc.) and the hot solution was poured into hot 50% aqueous sodium hydroxide (2 cc.). The resulting solution was heated on a boiling water-bath for one hour, under reflux, a little more alcohol being added during the heating. Finally the excess alcohol was driven off and the cold solution was acidified.

a white precipitate being thrown down. This substance was crystallized twice from hot water, and was finally obtained in minute flakes (IX, m. p., 135-145°).

The observed properties of product IX have already been indicated (page 29) and its probable nature has been considered (pages 30-31).

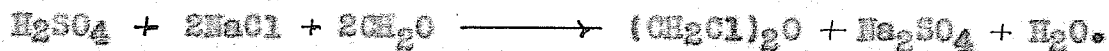
PREPARATION OF CRUDE *s*-DICHLOROMETHYL ETHER.

Introduction.

In order to study the reaction involving *s*-dichloromethyl ether and 5-methoxy-*m*-toluic acid, it was necessary to prepare a sample of the former. A rapid method described by Stephen, Gladding and Short (J. C. S., 1920, 117, 520.) was employed. However, the amount of crude product obtained by this method was small, and was only sufficient for one experiment.

Procedure.

Sodium chloride was added gradually to a suspension of paraformaldehyde in concentrated sulphuric acid, the proportions used being calculated from the reaction equation (see below). After a time, a layer of oil appeared on the surface of the acid mixture, and this was mechanically separated. The yield of crude *s*-dichloromethyl ether was low.



Remarks.

A sample of hexamethylenetetramine (7.2 grams) was prepared by the standard method (Fisher, "Laboratory Manual of Organic Chemistry," second edition, page 100.), with a view to using it in preparing the dichloromethyl ether by another method, described by Stephen et al. However, time did not permit of further experimenting in this connection.

THE REACTION OF *s*-DICHLOROMETHYL ETHER
WITH 5-METHOXY-*m*-TOLUIC ACID.

Procedure.

5-Methoxy-*m*-toluic acid (2.5 grams) was added to a mixture of the crude *s*-dichloromethyl ether, obtained as above (2.5 grams) with anhydrous zinc chloride (2.5 grams) in a small flask, the mixture being stirred frequently during the process, the flask being cooled in a stream of cold water. After the reaction had subsided, the mixture was warmed gently on the water-bath for half an hour, then allowed to cool. A little water was added to dissolve out the zinc chloride, the undissolved residue was removed, washed with

water and extracted with alcohol, as already described in the isolation of products I and II from the crude material obtained from the acid formaldehyde mixture.

Changes observed.

On mixing the reagents, a semi-solid, gummy mass was formed and considerable heat was evolved. The mass gradually swelled up, due to the formation of bubbles of gas, and copious fumes of hydrogen chloride were produced.

Products obtained.

The material obtained from the alcoholic extract was found to consist of at least two different products, one of which was isolated in a rather impure form (VII, m. p., 165-175°, amorphous from alcohol). The small amount of this product obtained gave a negative test for chlorine by the sodium fusion method, but this test could not be repeated due to lack of material. The other product, obtained in somewhat larger amount, contained no chlorine, as far as could be determined from several tests (VIII, m. p., +240°, microcrystalline from 75-80% acetic acid).

The observed properties of the two crude products obtained in this experiment are summarized in table III.

page 46, and their probable nature has also been considered (pages 45-46, 57-88).

THE PREPARATION AND ISOLATION
OF PRODUCTS V AND VI.

Preparation and Isolation.

The preparation of products V and VI was made possible through the courtesy of Dr. Charlesworth, who very kindly provided the writer with a sample of the required 3,5-dimethoxy-p-toluic acid, prepared from the corresponding 3,5-disalphe-p-toluic acid.

The preparation was carried out exactly as in the case of products I, II, etc., corresponding quantities of formaldehyde and hydrochloric acid being used.. The crude product obtained was treated with alcohol as before, and two products were finally isolated in a fairly pure condition: a lower-melting, relatively soluble product containing chlorine (V, m. p., 128-130°), and a higher-melting, less soluble, non-chlorinated substance (VI, m. p., 246-250°, after a final crystallization from 75-90% acetic acid).

In a typical run, 0.50 gram of 3,5-dimethoxy-p-toluic acid gave 0.53 gram of crude material. From this material 0.16 gram of product V was obtained, along with a small amount of product VI.

In extracting product V from the crude material obtained, it was found that, for each gram of crude material, about 20 -25 cc. of 95% alcohol were required, in each successive extraction. Fractional crystallization of each of these extracts finally yielded products V and VI, as described.

The presence or absence of chlorine in each case was determined as with products I, II, etc.

THE NATURE OF PRODUCTS V AND VI.

Outline of Experiments.

A series of tests was made on each of products V and VI, as in the case of products I, II, etc., to determine their relative solubilities in different solvents, and their general chemical behaviour. The results of these tests have already been indicated and discussed (for product V, see page 14, also 23-24; for product VI, see page 56, also 55, 61).

Quantitative analysis of product V for chlorine has been carried out, and the results are shown below. No conclusive analytical data for the carbon and hydrogen content of products V or VI are available,¹ and their respective molecular weights could not be determined, for reasons already mentioned in connection with products I, III and IV (pages 73-74).

¹ Two combustions on product VI gave discordant results XXXXXXXXXX

ANALYSIS OF PRODUCT V.

Estimation of Chlorine.

The chlorine content of product V was determined by the method of Stepanow and Volhard, already described (page 75). There was only enough purified material for one determination, the results of which are given below.

Weight of glass + sample	-	-	-	-	8.4022	gms.
Weight of glass	-	-	-	-	8.4022	gms.
Weight of sample	-	-	-	-	0.0000	gm.

Normality of AgNO_3 - - - - 0.1000

Normality of NH_4CNS - - - - 0.0990

1 cc. NH_4CNS is equivalent to .99 cc. AgNO_3 .

1 cc. AgNO_3 is equivalent to .00355 gram Cl.

Volume AgNO_3 added - - - - 5.00 cc.

Volume NH_4CNS required - - - - 2.05 cc.

$$\begin{aligned} \text{Percentage Chlorine} &= [5 - (2.05 \times .99)] \times \frac{.355}{.03} \\ &= \underline{13.19\%}. \end{aligned}$$

($\text{C}_{12}\text{H}_{13}\text{O}_4\text{Cl}$ requires Cl, 13.84%).

See probable structure suggested for product V, page 24; also discussion regarding the nature of product I, which applies also to V (pages 13-23 inclusive).

LIST OF PRODUCTS OBTAINED.

For reference, the nine products which have been obtained in the course of this work are listed in table VI (page 87), along with their respective melting-points. The appearance of each product, any available analytical data, and the materials used in the preparation of each are also indicated. All these products are colourless solids.

TABLE VI

PRODUCT	M. P.	APPEARANCE	ANALYSIS	PREPARED FROM
I.	175-176°.	Needles from alc.	Cl, 16.32%.	5-Methoxy- m-toluic acid, 40% CH ₂ O, conc. HCl.
II.	247-248°.	Microcryst. from 75% acetic acid.	No Cl; C, 70.90%; H, 5.55%.	
III.	263-264°d.	Microcryst. from 75% acetic acid.	No Cl.	
IV.	94-96°.	Feathery crystals from water.	No Cl.	
V.	129-130°.	Needles from alc.	Cl, 13.16%.	3,5- Dimethoxy- p-toluic acid, 40% CH ₂ O, conc. HCl.
VI.	246-250°.	Microcryst. from 75% acetic acid.	No Cl.	
VII.	165-175°.	Amorph. from alc.	No Cl (?)	5-Methoxy- m-toluic acid, (CH ₂ Cl) ₂ O.
VIII.	+240°.	Microcryst. from 75% acetic acid.	No Cl.	
IX.	135-145°.	Flakes from water.	No Cl.	Product I, alc. NaOH.

SUMMARY.

An introductory discussion of previous researches on related reactions has been presented.

It has been shown that product I, obtained from 5-methoxy-m-toluic acid, formaldehyde and hydrochloric acid, is probably 3-methyl-5-methoxy-chloromethylphthalide; and that product V, obtained from 3,5-dimethoxy-p-toluic acid, formaldehyde and hydrochloric acid, is probably 3,5-dimethoxy-4-methyl-chloromethylphthalide.

The probability that structural isomers of product I may exist has been considered briefly.

The probable mechanism of formation of products I and V has been considered, and several theories in this connection have been suggested and critically discussed.

Three non-chlorinated products of unknown structure, II, III and IV, respectively, have been obtained from the reaction yielding product I, and the probable nature and mechanism of formation of each have been discussed.

One non-chlorinated product of unknown structure, VI, has been obtained from the reaction yielding product V, and its probable nature and manner of formation have been considered.

The action of dry s-dichloromethyl ether on 5-methoxy-m-toluic acid, and the action of alcoholic sodium hydroxide on product I, have been investigated, two unidentified products, VII and VIII, being obtained from the former, and one, product IX, from the latter reaction. The probable nature of each of these products has been considered.

ACKNOWLEDGMENT.

In conclusion, the writer wishes to express his gratitude to Dr. E. H. Charlesworth, who suggested and directed this investigation, for his deep interest in the work carried out, for many helpful suggestions offered, and particularly, for providing certain reagents, without which it would have been impossible to continue the work.