

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

**A Study of the Action of Formaldehyde
In the Presence of Concentrated Hydrochloric Acid
On Certain Aromatic Acids**

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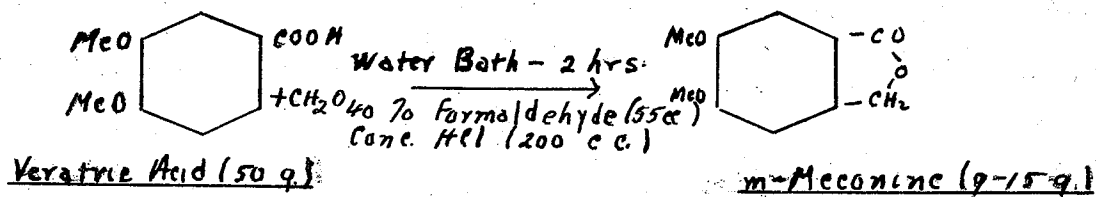
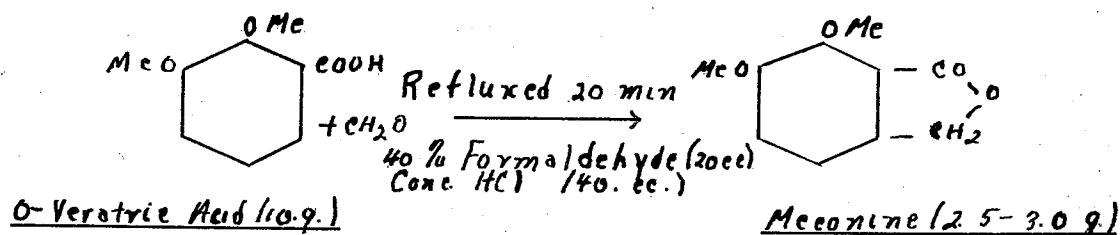
Introduction and Discussion of Previous Researches

The action of formaldehyde on aromatic compounds has been studied by a number of investigators under varying experimental conditions and with varying results. It has been observed that aromatic 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), 80, 225). On the other hand, phenols, phenolic ethers as well as the aromatic hydrocarbons and the halogen derivatives of these substances react with formaldehyde in acid solution to yield the corresponding chloromethylene derivatives.

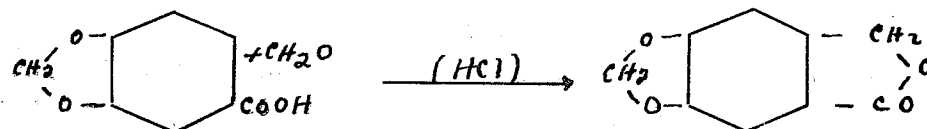
The action of formaldehyde in acid solution on aromatic acids, however, has received little investigation. The reactions of several acids have been studied, some in connection with researches on other types of reaction and some as the result of direct investigation. The acids thus studied were of the more complex type and the results obtained were often indefinite and, in some cases, the products isolated were not the substances normally desired from the reaction. It was therefore suggested that an investigation into the action of formaldehyde in acid solution on acids of less complex structure would be of interest, in an attempt to establish some general course of reaction for these substances and to determine the nature of the products obtained and the conditions under which these were formed.

The first paper written on this subject may be said to be that of Perkin, Edwards and Stoye (J.C.S., 1925, 127, 195). These authors pointed out that the introduction of the chloromethyl group into the benzene nucleus had been accomplished in a variety of ways and they mentioned the fact that benzyl chloride had been prepared from benzene

and *s*-dichloromethyl ether in the presence of zinc chloride (Stephen, Gladding and Short, J.C.S., 1920, 117, 520). The former authors found in their experiments that the veratric acids do not condense at all on being treated with *s*-dichloromethyl ether or with cold aqueous formaldehyde, but that on boiling with an excess of formaldehyde and concentrated hydrochloric acid, the corresponding meconine is formed. Since this synthesis of meconine was the first successful application of the method to the preparation of a phthalide, the description of the course of the reaction is of interest and is summarized below.



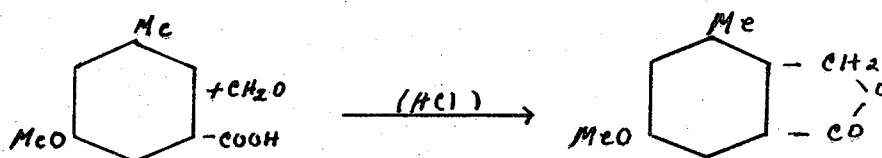
The authors also mentioned that an unsuccessful attempt had been made to prepare the methylene ether of 4:5-dihydroxyphthalide by the action of formaldehyde on piperonylic acid according to the following reaction.



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

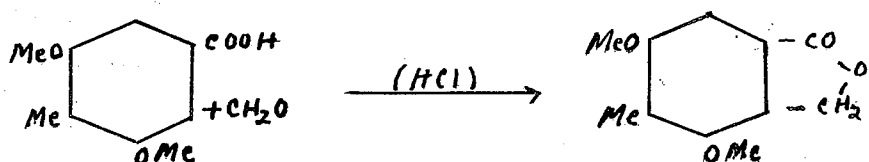
It is to be noted that in the cases described above where the reaction occurred, the corresponding phthalides were obtained from the acid employed. This type of reaction, in which formaldehyde and hydrochloric acid are used to convert an aromatic acid to the corresponding phthalide, will be referred to henceforth, simply as the normal reaction. This designation is merely for convenience and it is not intended to have any theoretical significance. It may therefore be stated that the above are examples of the normal reaction.

In the course of an investigation involving the synthesis of helminthosporin (4:5:6-trihydroxy-2-methylanthraquinone), Haistrick, Robinson and Todd (J.C.S., 1933, 121, 433) found it necessary to prepare a sample of 3-methoxy-2-methylphthalide from the corresponding 3-methoxy-*m*-toluic acid and they attempted to accomplish this by the method of Perkin, Edwards and Stoye (loc. cit.). This method did not yield the expected phthalide and the authors isolated an unidentified chloroproduct (private communication) which was not referred to in their paper and did not appear to be the trichlorophthalide. It therefore appeared that the following reaction did not occur under the conditions specified.



The attempt was therefore abandoned and the required phthalide was obtained by the Fritsch reaction with chloral hydrate.

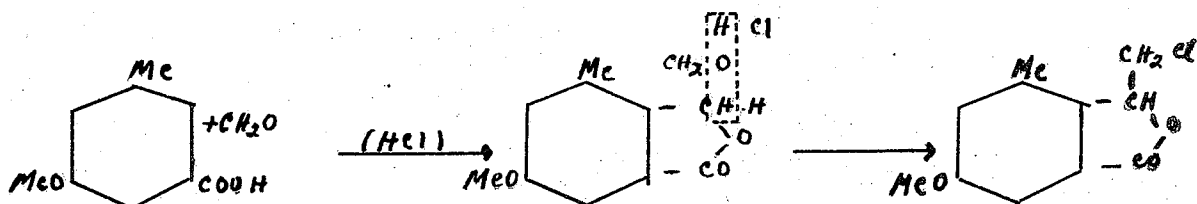
Charlesworth and Robinson (J.C.S., 1934, 1513) while working on the preparation of a dimethoxyphthalic acid, attempted to use the method of Perkin, Edwards and Stoye (loc. cit.) in the preparation of 4-methyl-3:5-dimethoxyphthalide from 4-methyl-3:5-dimethoxybenzoic acid according to the following reaction.



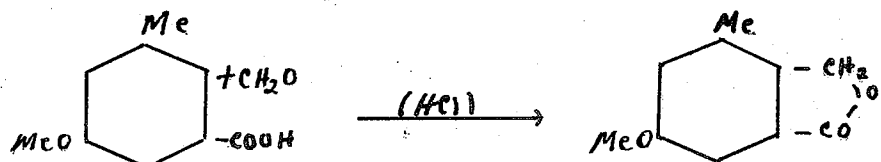
Here, as in the case of Paistrick, Robinson and Todd (*loc. cit.*) the phthalide was not produced but similarly an unidentified chloroproduct (M.P. 131°) was obtained.

Also G. Cameron (M.Sc. Thesis, Manitoba, 1939), in a further study of the reaction of formaldehyde in the presence of concentrated hydrochloric acid on 5-methoxy-*m*-toluic acid and of *s*-dichloromethyl ether on 3,5-dimethoxy-*p*-toluic acid, obtained chloroproducts which were definitely not the corresponding trichlorophthalides.

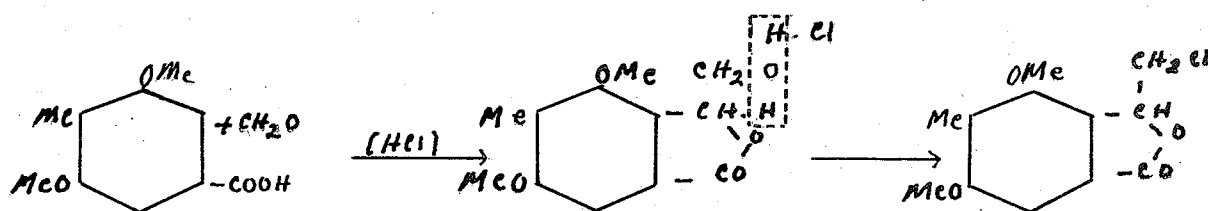
In the case of the 5-methoxy-*m*-toluic acid, a product containing chlorine was isolated by the following series of reactions, which was probably 5-methoxy-3-methylchloromethylphthalide.



Besides the chlorophthalide shown above, the corresponding α -phthalide was probably isolated in the reaction.



From the 3,5-dimethoxy-*p*-toluic acid this author probably obtained the corresponding 3,5-dimethoxy-3-methylchloromethylphthalide by the following reaction.



It is to be noted here that this production of chloroproducts constitutes exception to the normal reaction, i.e. production of the phthalide and the facts just presented are of interest here because of the present investigation to determine whether similar chloroproducts might be obtained from less complex acids.

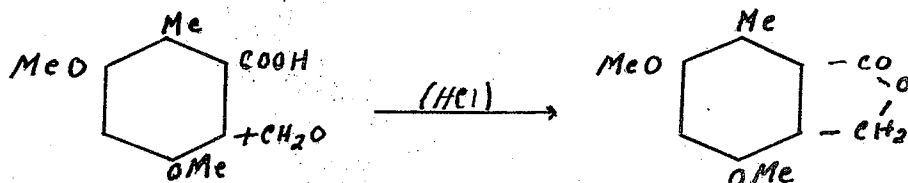
In drawing conclusions as to the results obtained, this author pointed out that, up to that time, only five different acids had been treated with formaldehyde and hydrochloric acid. These included the derivatives of benzoic acid (piperonylic acid, *o*-veratric acid and veratric acid) and the two toluic acids (3-methoxy-*m*-toluic acid and 3,5-dimethoxy-*o*-toluic acid). A third acid, creoscellenic acid (3,5-dimethoxy-*o*-toluic acid) had been reported as giving the normal phthalide, but since no details of the procedure had been recorded in this case, it was not known whether the experimental conditions were uniform with those in the other cases. This fact is of interest since the production of the normal phthalide from creoscellenic acid was confirmed in the present work.

Disregarding creoscellenic acid, the author drew certain conclusions from the information then available and this is of interest in comparison with the information supplied by the present work. In the first place it was noted that, up to that time, only the toluic acids had yielded chloroproducts, suggesting that the nuclear substituted methyl group might be essential to the reaction in some way. On the other hand, it was stated that 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 the occupation of the two ortho positions would prevent phthalide formation. In considering this fact it was noted, that with the two toluic acids mentioned, both the meta positions were occupied, while in none of the benzoic acids was this the case. Also it was noted that creoscellenic acid, like the benzoic acids mentioned, did not fulfil these conditions. It was also stated that although the conditions outlined above might be essential to the formation of chloroproducts, no generalizations could be made until information was available on many other simpler aromatic acids. From the results obtained, then, it was suggested that any aromatic acid of the type referred to, having methyl ~~or~~ ~~methoxy~~ or methoxyl groups substituted in the 3:5- or the 3:4:5- positions, other positions being free, would yield chloroproducts on treatment with formaldehyde and hydrochloric acid. Thus the trimethyl ether of gallic acid, 3:5-dimethoxybenzoic acid (α -resorcinic acid) would form chloroproducts while benzoic acid would not. These are of interest in the light of the present work.

Following the paper by Perkin, Edwards and Stoye (*loc. cit.*), Mitter, Sen and Paul (*J. Ind. Chem. Soc.*, 1927, 4, 535) claimed to have used the method of condensation with formaldehyde in the presence of hydrochloric acid in the preparation of 2-methyl-3:5-dimethoxyphthalide from 3:5-dimethoxy-*o*-toluic acid as mentioned previously. They stated that Fritsch (*Ann.*, 1897, 296, 344) had found that the methyl esters of 3-methoxybenzoic acid and 2:3-dimethoxybenzoic acid condensed readily with chloral hydrate in the presence of concentrated hydrochloric acid to give trichlorophthalides from which the corresponding phthalides and phthalic acid could be obtained. They also stated that the reaction had been successfully applied by Meldrum (*J.C.S.*, 1911, 99, 1712; 1920, 117, 964; 1921, 119, 201) for converting the oxybenzoic acids to the corresponding phthalic acids. These papers are discussed later in this section.

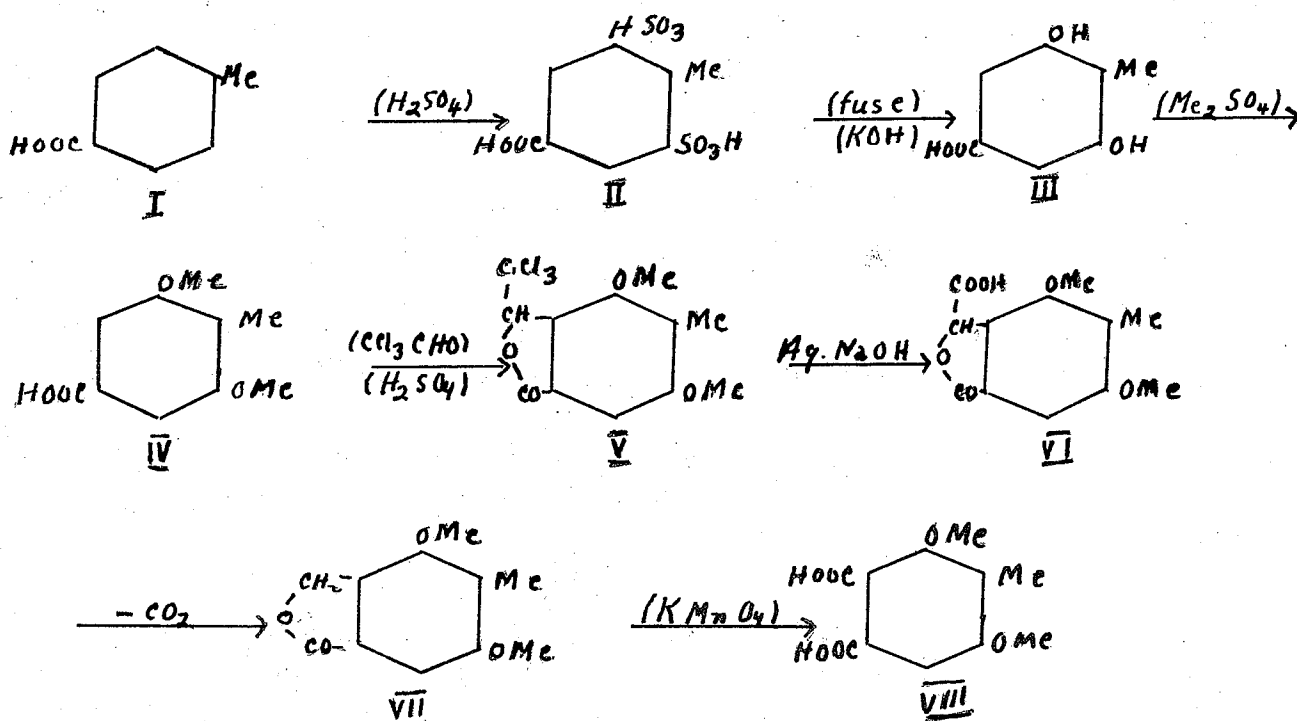
These authors attempted to apply the Fritsch reaction to 2-methyl-3:5-dimethoxybenzoic acid with the view of preparing the corresponding phthalic acid. They found that the reaction proceeded as far as the phthalide stage and they stated that the same phthalide could be prepared from the phenolic ether acid directly by condensation with formaldehyde in the presence of concentrated hydrochloric acid by the following reaction.



They stated that this method had been employed by them in preparing large quantities of the phthalide from creoscellenic acid for the attempted oxidation experiments to the phthalic acid. However, they failed to give any experimental details and it was for this reason that a confirmation of this work by the method of Perkin, Edwards and Stoylo (*loc. cit.*) was deemed advisable in the present research. It is of interest to note here that these authors stated that they had found it impossible to oxidize the 2-methyl-3:5-dimethoxyphthalide to the corresponding phthalic acid but as before they failed to mention the methods attempted. In the present work an attempted oxidation of the same phthalide was undertaken and these attempts were likewise unsuccessful.

In the paper of Charlesworth and Robinson (*loc. cit.*) the authors, on failing to produce the required phthalide by condensation with formaldehyde in the presence of concentrated hydrochloric acid, obtained the substance by the standard Fritsch reaction. The starting material employed was *p*-toluic acid which was converted to the 4-methyl-3:5-dimethoxyphthalic acid by the usual series of reactions and it is of interest because a similar series was carried out in the present work. Therefore a summary of the stages involved is given below and the practical advantage of securing a shorter method for

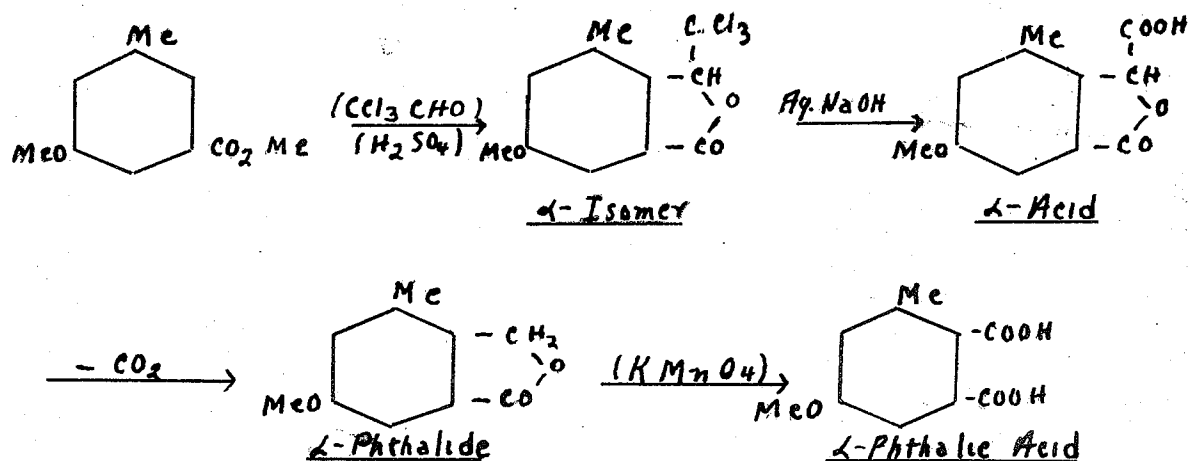
the preparation of the phthalides and the corresponding phthalic acids can readily be seen.



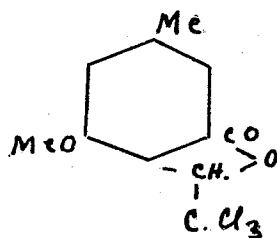
The reaction of formaldehyde in the presence of concentrated hydrochloric acid is therefore an attempt to pass from stage IV to stage VII.

The Fritsch reaction, or the chloral hydrate condensation as it is sometimes termed, has been applied to a large number of syntheses.

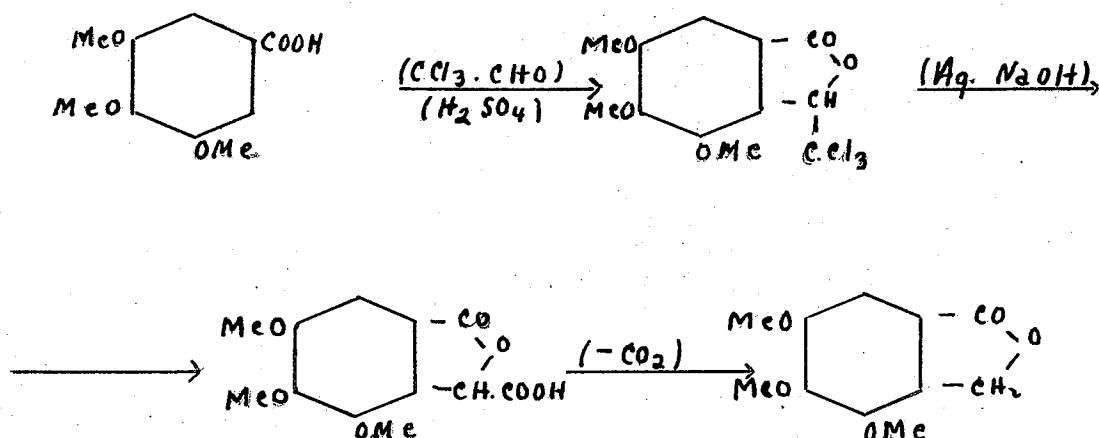
Meldrum (loc. cit.) carried out the synthesis of the isomeric trichlorophthalides of *m*-toluic acid, obtaining actually a mixture of the two and was unable to secure a separation. The work of Meldrum is outlined below.



Since two acids were obtained on hydrolysis of the trichlorophthalide, the possibility of the existence of the two trichlorophthalides became evident. The probable β -trichlorophthalide is indicated below.



The paper of Alimchandani and Meldrum (J.C.S., 1920, 117, 968) is of interest as an example of the Fritsch reaction in which they attempted to prepare 3:4:5-trimethoxyphthalide from gallic acid by the following series of changes.



It was found, however, that the reaction did not proceed in this way, but that if an excess of chloral hydrate and sulphuric acid was used, the result was apparent de-methylation in the 4-position, as it was found that the same trichlorophthalide was produced as that formed by the action of syringic acid (4-hydroxy-3:5-dimethoxybenzoic acid). In the synthesis of 3:4:5-trimethoxyphthalide it was necessary, therefore, to prepare the phthalide of syringic acid and subsequent re-methylation produced the required phthalide. Even when the methyl ester of 3:4:5-trimethoxybenzoic acid was used, as suggested by Fritsch (Ann, 1897, 296, 358; 1899, 301, 360), the same behavior was observed.

In a later paper (J.C.S., 119, 203) the authors succeeded in preparing the trichlorophthalide of gallic acid directly by the action of chloral hydrate and sulphuric acid, when an excess of gallic acid was introduced, but it was found impossible to carry the reaction beyond this stage. The trichlorophthalide of gallic acid had previously been prepared by Bargallina and Molina (Atti. R. Accad. Lincei., 1912, (v), 21, (11), 145). The preparation of the 3:4:5-trimethoxyphthalide is of interest in connection with the present work, for it had been hoped to obtain this phthalide by the action of formaldehyde in the presence of concentrated hydrochloric acid on 3:4:5-trimethoxybenzoic acid. However, the phthalide was not obtained in this case, the product isolated being methyl ester of the trimethoxybenzoic acid of melting point 81° while the 3:4:5-trimethoxyphthalide was recorded by Alimchandani and Meldrum as well as Bargallina and Molina as having a melting point of 135-136°.

Chattaway (J.C.S., 1926, 2720) and Chattaway and Frate (J.C.S., 1927, 625) have made detailed studies of the rather complicated reactions occurring between phenols, including nitrophenols and phenolic acids and chloral hydrate. While these reactions have no particular connection with those under discussion, they are mentioned here merely as important examples of the chloral hydrate condensation.

The study of the introduction of the chloromethyl group into the aromatic nucleus has been carried on by several workers. Among these investigations, the work of Stephen, Gladding and Short (loc. cit.), which was referred to briefly in connection with the paper of Perkin, Edwards and Stoyke (loc. cit.), is the most important in connection with the present investigation.

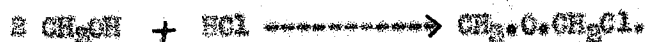
In this paper it was pointed out that no systematic attempt had been made, up till that time, to substitute the chloro- or bromo-methyl group into the aromatic nucleus, as a method of preparing such compounds as benzyl chloride or benzyl bromide. Grassi-Cristofaldi and Maselli (Gazzetta, 1898, 28,

(ii), 477) had obtained a product from the reaction between paraformaldehyde and hydrogen chloride which they termed chloromethyl alcohol. This product, they found, reacted with benzene in the presence of aluminium chloride, to give benzyl chloride and diphenyl methane, the latter being the main product obtained. From this it was concluded that, in the presence of a dehydrating agent, aromatic compounds like benzene react with a product formed by the action of hydrogen chloride either on paraformaldehyde or concentrated aqueous formaldehyde to yield such products as benzyl chloride along with corresponding derivatives of these.

A product from the formaldehyde-hydrogen chloride reaction had been identified as s-dichloromethyl ether, $(CH_2Cl)_2O$, (Tischaschenko, J. Russ. Phys. Chem. Soc., 1887, 19, 464; Loschmann, Chem. Zeit., 1890, 14, 1408; Littirscheld, Ann., 1904, 354, 1571; Littirscheld and Thimma, Ann., 1904, 354, 1).

The formation of a mono-chlorodimethyl ether, as well as the above product, is accounted for by the fact that commercial aqueous formaldehyde (40%) may contain some methyl alcohol, (Henry, Ber., 1893, 26, 938). This latter fact is of interest because in the present investigation the esterification of 3:4:5-trimethoxybenzoic acid on heating with formaldehyde and hydrochloric acid was considered as being due to the presence of methyl alcohol in the commercial formaldehyde solution employed.

The formation of the s-dichloromethyl ether and the mono-chloro-dimethyl ether apparently involves the reactions:



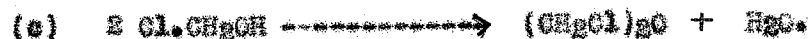
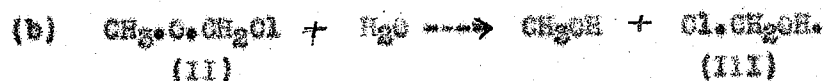
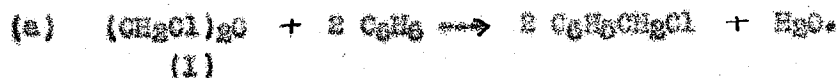
These substances were prepared by passing gaseous hydrogen chloride into a tower packed with glass beads, while the 40% formaldehyde was allowed to percolate down from the top of the tower. Stephen, Gladding and Short

re-isolated the chloro-derivatives referred to above and reported the following data.

s-Dichloromethyl ether $(\text{CH}_2\text{Cl})_2\text{O}$ (I). B.P. 105-106°

Monochlorodimethyl ether $(\text{CH}_3\text{O}\cdot\text{CH}_2\text{Cl})$ (II). B.P. 53-51°

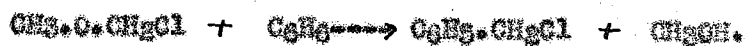
In the formation of benzyl chloride by the action of these products using zinc chloride, they found that (II) reacted more slowly than (I) and that when zinc chloride monohydrate was substituted for the anhydrous zinc chloride, the reaction was accelerated. This is of interest because the latter substance was introduced as a dehydrating agent in the present investigation. In view of these facts, the authors suggested an explanation based on the following reactions.



It was argued on the basis of these reactions that the anhydrous zinc chloride would facilitate (a) by removal of the water formed and the hydrous salt would facilitate (b) by providing water for the hydrolysis.

Other evidence has been pointed out in support of the theory just outlined and there seems to be little doubt that these reactions actually occur, with the possible exception of (b), when the isolated methyl ethers are employed. Thus that the regeneration of (I) by the hydrolysis of (II) actually occurs has been proven, since this occurred on shaking (II) with zinc chloride monohydrate at 27° yielding product (I). Moreover they pointed out that the monohydrate readily gives up its water at 27° forming the anhydrous salt.

Apparently the fact that (II) was found to react slowly with benzene in the presence of anhydrous zinc chloride to give benzyl chloride could be explained by assuming, in the first place, that gradual absorption of water from the air brought about reaction (b) and (c), the regenerated compound (I) then acting on the benzene, while the zinc chloride retained the water produced in the reaction (c), thus preventing the hydrolysis of compound (I) or, in the second place, that (II) reacted directly with benzene eliminating methyl alcohol in the following process:



Possibly the authors preferred to consider that both these changes or only one can occur under the circumstances but they did not state this specifically and the two possibilities are merely pointed out here. Apparently the above reaction does not proceed to any extent in the absence of anhydrous zinc chloride since the authors found it necessary to use this dehydrating agent and then only a slow reaction occurred. This fact seems to agree with the first suggested reaction, since there is no apparent reason why the presence of the salt should assist the second reaction suggested, in which methyl alcohol and not water is produced.

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



and this was found to occur to a greater extent in the presence of sulphuric acid, metal oxides and traces of iron, zinc or other metals.

A summary of the work of these authors is of interest in connection with the present investigation, in that the reaction of *s*-dichloromethyl ether on certain aromatic acids was studied and the results obtained explained on the basis of the work just described.

It is to be noted that among the substances investigated by these authors, no acids are to be found. However it is of interest to mention those that were studied and the products obtained and these results are therefore listed in the following table.

Table 1.

(Stephen, Gladding and Short)

<u>Compound Investigated</u>	<u>Compound Prepared</u>
Benzene	Benzyl chloride w:w-Dichloro-p-xylene Benzyl bromide
Toluene	w-Chloro-p-toluene w-Bromo-p-toluene
Xylene (isomeric)	w(1)-Chloro- α -cumene
Benzyl chloride	w:w-Dichloro-p-xylene
Chlorobenzene	p-Chlorobenzyl chloride p-Bromobenzyl chloride
Bromobenzene	p-Bromobenzyl chloride p-Bromobenzyl bromide
o-Chlorotoluene	2-w(4)-Dichloro-p-xylene
Nitrobenzene	m-Nitrobenzyl chloride
o-Nitrotoluene	(4)-Chloro-2-nitro-p-xylene
p-nitrotoluene	(2)-Chloro-4-nitro-o-xylene
Diphenyl	Indefinite reaction
Naphthalene	No reaction

(Table 1 continued)

<u>Compound Investigated</u>	<u>Compound Prepared</u>
Anthracene	No reaction
m-Dinitrobenzene	No reaction
2,4,6-Trinitrotoluene	No reaction
Phenol	Bakelite compound
Anisole	p,p'-Dimethoxydiphenylmethane
Aniline	Anhydro bases
o-, m-, p-Toluidines	Anhydro bases
Dimethylaniline	Tetramethyldiaminodiphenylmethane
Diethylaniline	Tetraethyldiaminodiphenylmethane
o- and p-Chloronitrobenzene	No reaction
p-Dichlorobenzene	No reaction
p-Chlorobenzene	No reaction

As regards to the orientation effects of the various substituent groups, the authors stated that the introduction of a chloro- or bromomethyl group into mono-substituted benzenoid compounds such as toluene or chlorobenzene appeared to take place exclusively in the para position. There was no evidence found for any of the corresponding ortho compound in the products. Benzyl chloride similarly gave only w,w'-dichloro-p-xylene. They also stated that the presence of the nitro group directed a chloromethyl group into the meta position.

The papers which have been discussed are those which are directly related to the problem undertaken in the present investigation. However, there are a number of other authors who have studied the action of formaldehyde in the presence of hydrochloric acid on other types of aromatic compounds. While these papers have no direct relationship to the problem under discussion, the results obtained by these authors serve to show the directing influence of other substituent groups on the

introduction of the chloromethyl group into the aromatic nucleus.

One of the earliest of these papers was that of Stoermer and Behn (Ber., 1931, 52, 2445) who studied the synthesis of the aromatic alcohols by means of formaldehyde. These authors stated that they had found that the presence of a negative group, such as $-\text{CHO}$, $-\text{NO}_2$, $-\text{COOH}$ and $-\text{Cl}$, in the ortho position relative to the hydroxyl of phenols, caused the latter to condense with formaldehyde in the presence of hydrochloric acid to form hydroxy benzyl alcohols containing the methanol group in the para position with respect to the hydroxyl radical. It was also stated that the introduction of the chloromethyl group was probably the first stage in the reaction, with the subsequent formation of the alcohol. It is to be noted, however, that the number of examples of reactions showing the orienting effects of the groups mentioned above are few and that the statement regarding the effect of the carboxyl group was apparently based on expected orienting influence, similar to the other meta-directing groups, rather than on experimental evidence, since no substance containing the substituent carboxyl group was investigated. The fact that in the present investigation definite evidence of an inhibiting effect of the carboxyl group on the introduction of the chloromethyl group into the aromatic nucleus was obtained, tends to support this view. The following table shows the substances investigated by the authors and the results obtained.

Table II
(Stoermer and Behn)

<u>Substance Investigated</u>	<u>Compound Prepared</u>
Salicylaldehyde	p-methylsalicylaldehyde
o-Hydroxytolylaldehyde	Compound of formula $\text{C}_9\text{H}_{10}\text{O}_3$
O-Nitrophenol	4-Hydroxy-3-nitrobenzyl alcohol
o-chloronitrobenzene	3-Chloro-4-nitrobenzyl alcohol

Bayer (Abs. J.C.S., 1901, 727) have investigated the halogen methyl derivatives of the aromatic aldehydes. These authors found that the radical (CH_2X) , where (X) is a halogen, was obtained by the interaction of these aromatic aldehydes with chloro- or bromomethyl alcohol more readily in the presence of a condensing agent such as zinc chloride, phosphorous oxychloride and phosphorous pentoxide. Table III shows the compounds investigated and the products obtained.

Table III

(Bayer)

<u>Substance Investigated</u>	<u>Compound Prepared</u>
Salicylaldehyde	p-Bromomethyl salicylaldehyde
Vanillin	Chloromethyl vanillin
Vanillin	Iodomethyl vanillin

R. Guetl has carried out extensive investigations in this field, i.e., on the introduction of the chloromethyl group into the aromatic nucleus. This author has investigated the action of formaldehyde in the presence of concentrated hydrochloric acid on various types of aromatic compounds. It is of interest to note here, however, that he failed to investigate the action of these reagents on any of the aromatic acids. In connection with his researches the author has published a large number of papers and while it is beyond the scope of the present work to discuss these in detail, it is of value to note the results obtained, particularly in connection with the effect of the various substituent groups on the introduction of the chloromethyl group. For this reason, therefore, a brief discussion of the results obtained is given below and a table showing the substances investigated and the products obtained.

In general the author has found that a variety of condensing agents are available for the reaction. Such substances as anhydrous zinc chloride, zinc chloride monohydrate and petroleum ether were used. These agents were employed in certain cases in the present investigation. In connection with a paper dealing with the preparation of the nitroanisoles (Compt. rend., 1933, 196, 1411) it was stated that the chloromethyl group was introduced in every case in the ortho and para positions in proportion to the function of the phenolic oxide as far away as possible from the nitro group. It was stated that it was thus the methoxyl group that introduced the ionization of the nucleus while the nitro group interfered by diminishing the mobility of the hydrogen that could be substituted.

Table IV

(sheet)

<u>References</u>	<u>Compounds Investigated</u>	<u>Compound Prepared</u>
Bull. Soc. Chem., 1927, 41, 329 C.A., 21, 2466	Bromobenzene	p-Bromochlorotoluene (70%) o-Bromochlorotoluene (30%)
Compt. rend., 1932, 195, 155 C.A., 26, 5552	p-Bromoisole	2-Methoxy-5-bromo-4-chlorotoluene 2;2'-Dimethoxy-5;5'-dibromo- diphenylmethane (residue)
Compt. rend., 1933, 196, 1411 C.A., 27, 3921.	o-Nitroisole	4-Methoxy-2-nitro-4-chloro- toluene (80%) 3;3'-Dinitrodiphenylmethane
	p-Nitroisole	2-Methoxy-5-nitro-4-chloro- toluene
	m-Nitroisole	2-Methoxy-4-nitro-4-chloro- toluene (poor yield)
Bull. Soc. Chem., 1933, 25, 222 C.A., 27, 3703	Benzyl chloride	p-Xylene dichloride (also some ortho isomer)
Compt. rend., 1934, 198, 102 C.A., 28, 2687	Anisole	4-Methoxy-4-chlorotoluene 4;4'-Dimethoxydiphenylmethane

	Ethyl phenate (phenetole)	4-Ethoxy- α -chlorotoluene (poor yield)
	o-Methoxytoluene	3-Methyl-4-methoxy- α -chloro- toluene (stable)
	m-Methoxytoluene	2-Methyl-4-methoxy- α -chloro- toluene (fairly stable)
	p-Methoxytoluene	5-Methyl-4-methoxy- α -chloro- toluene (unstable)
	3:4-Methoxyisopropyl- toluene	2-Methyl-4-methoxy-5-isopropyl- α - chlorotoluene. (fairly stable).
Bull. Soc. Chem., 1934, <u>1</u> , 537, C.A., <u>28</u> , 2687	p-Bromoanisole	As in Compt. rend., 1933, <u>195</u> , 329. Yield improved.
	o-Nitroanisole	As in Compt. rend., 1933, <u>195</u> , 1411. Yields improved.
	p-Nitroanisole	
	m-Nitroanisole	
Compt. rend., 1934, <u>198</u> , 2107 C.A., <u>28</u> , 5417	p-Bromoanisole	2-Methoxy-5-bromo- α -chlorotoluene (80%) yield.
Compt. rend., 1934, <u>197</u> , 150. C.A., <u>24</u> , 6125	Anisole	4-Methoxy- α -chlorotoluene
	Anisole	4-Methoxy- α -chloromethyltoluene (condensed with paraldehyde)
Compt. rend., 1935, <u>199</u> , 483 C.A., 1935, 142	Anisole	4-Methoxy- α -chloromethyltoluene (acetic acid added)
	4-Methoxytoluene	3-Methyl-5-methoxy- α -chloromethyl- toluene (acetic acid added).
Compt. rend., 1936, <u>203</u> , 242 C.A., 1936, 7103	Anisole	p-Methoxy- α -chlorotoluene (90%) o-Methoxy- α -chlorotoluene (10%)
	p-Methoxy- α -chlorotoluene (from above)	1:2:4-Methoxyxylene-dichloride
	1:2:4-Methoxyxylene- dichloride (from above)	1:2:4-MeO(ACOOCH ₂) ₂ .C ₆ H ₃ (with sodium acetate and acetic acid). Above with KOH gives:- CMe.(CH ₂ OH) ₂ .C ₆ H ₃ .

<u>References</u>	<u>Compound Investigated</u>	<u>Compound Prepared</u>
Compt. rend., 1936, 202, 965 C.A., 1936, 4159	Anisole	(with paraldehyde and heated with pyridine) gives:- $\text{OMe} \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2\text{CH}_3$ (vinyl anisole) and $\text{OMe} \cdot \text{C}_6\text{H}_4 \cdot \text{CH}(\text{CH}_3) \cdot \text{C}_6\text{H}_4\text{OMe}$
	Acetaldehyde	(condensing agent H_2PO_4^- heated with pyridine) $\text{OMe} \cdot \text{C}_6\text{H}_4 \cdot \text{CH}_2\text{CH} \cdot \text{CH}_3$ (anethole)
Compt. rend., 1936, 202, 1442 C.A., 1936, 4857.	o-Nitroanisole	4-Methoxy-3-nitro- α -chloro- toluene
Bull. Soc. Chem., 1937, (5), 4, 1092 C.A., 1937, 8520	o-Methoxytoluene	3-Methyl-4-methoxy- α -chloro- toluene.
	m-Methoxytoluene	2-Methyl-4-methoxy-chloro- toluene (unstable) (on hydrolysis gives) 2-Methyl-4-methoxybenzyl alcohol.
	p-Methoxytoluene	5-Methyl-2-methoxy- α -chloro- toluene.
	Methyl thymate	2-Methyl-4-methoxy-5-iso- propyl- α -chlorotoluene
	o-Nitroanisole	4-Methoxy-5-nitro- α -chloro- toluene (unstable) and the final product. 4-Methoxy-5-nitrobenzyl alcohol.
Compt. rend., 1937, 205, 258 C.A., 1937, 7412	Anisaldehyde	2-Methoxy-3-methyl- α -chloro- toluene. With potassium carbonate gives:- 2-Methoxy-3-methylbenzyl alcohol.
Compt. rend., 1937, 205, 146 C.A., 1937, 7412.	p-Bromoanisole	2-Methoxy-5-bromo- α -chlorotoluene (with aqueous potassium carbonate gives):- 2-Methoxy-5-bromobenzyl alcohol (with CuNO_3 , H_2O and acetic acid gives):- 2-Methoxy-5-bromoacetic acid.

<u>References</u>	<u>Compound Investigated</u>	<u>Compound Prepared</u>
Compt. rend., 1937, <u>204</u> , 130	<i>o</i> -Methoxytoluene	4-Methyl-4-methoxy- α -chloro- toluene. (with acetic acid and acetic anhydride gives):- 3-Methyl-4-methoxybenzyl alcohol (on permanganate oxidation gives):- 4-Methoxy- <i>m</i> -toluic acid.
	<i>m</i> -Methoxytoluene	Final product is:- 2-Methyl-4-methoxybenzyl alcohol (by similar procedure)
	Methyl thymol	2-Methyl-4-methoxy-5-iso- propylbenzyl alcohol.
Bull. Soc. Chem., Anisole 1937, (5), <u>3</u> , 1794. C.A., 1937, 99.		<i>p</i> -Methoxy- α -chlorotoluene <i>p</i> : <i>p'</i> -Dimethoxydiphenylmethane with acetic acid and sodium acetate gave anisyl acetate which on hydrolysis gave:- <i>p</i> -Methoxybenzyl alcohol.
Bull. Soc. Chem., <i>p</i> -Methoxybenzyl alcohol		(acetic anhydride added gave):- <i>p</i> -Methoxychlorotoluene. With acetic anhydride and conc. HCl, or conc. HCl and conc. H ₂ SO ₄ gave anisyl ether.
Compt. rend., 1938, <u>209</u> , 1109. C.A., 1939, 2117.	chloroacetal	<i>p</i> -Methoxy- α -chlorostyrene 4:4'-Dimethoxystilbene (small yield)
Compt. rend., 1939, <u>208</u> , 1817. C.A., 1939, 5822.	4-Methoxypropyl-benzene	2-Methoxy-6-propylbenzyl chloride Bis(2-methoxy-5-propylphenyl- methane) (small yield). With sodium acetate and hydrolysis. 2-Methoxy-5-propylbenzyl alcohol. With hexamethylene tetramine gives 2-Methoxy-5- propylbenzaldehyde. Oxidation gives (Me, C ₆ H ₃ (COOH) ₂ .
	4-Methoxypropylbenzene	2-Methoxy-5-propylisobenzyl chloride (with paraldehyde).

Finally it is of interest to mention the work of Blanc, (Bull. Soc. Chem., 1923, 33, 313) on the preparation of aromatic chloromethylene derivatives. In many respects this work is similar to that of Stephen, Gladding and Short (loc. cit.) as regards to the substances investigated. This author used

methods similar to those employed by Quelet (loc. cit.) and introduced the use of various condensing agents such as sulphuric acid and antimony trichloride but found that zinc chloride was the most effective. The author described experiments showing the action of hydrochloric acid in the presence of trioxymethylene or formaldehyde and powdered zinc chloride. Table V shows the substances investigated and the products obtained.

Table V

(Plane)

<u>Compound Investigated</u>	<u>Compound Prepared</u>
Benzene	Benzyl chloride p-Xylene dichloride
Toluene	p-Methylxylene dichloride (probably two isomers) (1:3:4- and 1:2:4-)
m-Xylene	Chloromethylxylene Dichloromethylxylene
Ethyl benzene	p-Ethylbenzyl chloride
Propyl benzene	p-Propylbenzyl chloride
Chlorobenzene	p-Chlorobenzylchloride
Cymene	p-Methylisopropylbenzyl chloride

Discussion of Experimental Results

Before entering upon a discussion of the experimental results obtained in the present investigation, it is necessary to present a brief summary of the various reactions studied.

Table VI

<u>Substance Investigated</u>	<u>Reagents</u>	<u>Product Obtained</u>
(1) Benzoic acid	$\text{CH}_2\text{O} + \text{HCl}$	No reaction
	$(\text{CH}_2\text{Cl})_2\text{O} + \text{ZnCl}_2$	No reaction

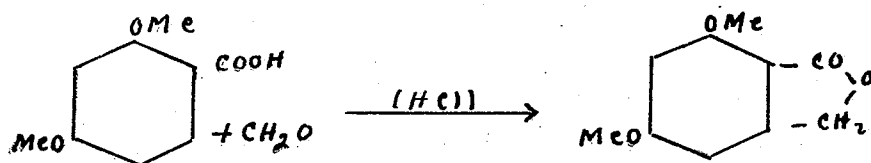
<u>Substances Investigated</u>	<u>Reagents</u>	<u>Product obtained</u>
(2) o-Methoxybenzoic	$\text{CH}_2\text{O} + \text{HCl}$	No reaction
	$(\text{CH}_2\text{Cl})_2\text{O} + \text{ZnCl}_2$	No Reaction
(3) p-Toluic acid	$\text{CH}_2\text{O} + \text{HCl}$	No reaction
	$(\text{CH}_2\text{Cl})_2\text{O} + \text{ZnCl}_2$	No reaction
(4) 2:4-Dimethoxybenzoic acid	$\text{CH}_2\text{O} + \text{HCl}$	2:4-Dimethoxyphthalide (I)
	$(\text{CH}_2\text{Cl})_2\text{O} + \text{ZnCl}_2$	2:4-Dimethoxyphthalide (II)
(5) 3:4:5-Trimethoxybenzoic acid	$\text{CH}_2\text{O} + \text{HCl}$	3:4:5-Trimethoxybenzoic acid (methyl ester) (III)
	$(\text{CH}_2\text{Cl})_2\text{O} + \text{ZnCl}_2$	3:4:5-Trimethoxybenzoic acid (methyl ester) (IV)
(6) Anisic acid (p-Methoxybenzoic acid)	$\text{CH}_2\text{O} + \text{HCl} + \text{ZnCl}_2 \cdot \text{H}_2\text{O}$	No reaction
(7) m-Toluic acid	$\text{CH}_2\text{O} + \text{HCl} + \text{ZnCl}_2$ petroleum ether	No reaction
(8) 3:5-Dimethoxy-o-toluic acid	$\text{CH}_2\text{O} + \text{HCl}$	3:5-Dimethoxy-2-methyl-phthalide (V)
(9) 5-Methoxy-o-toluic acid	$\text{CH}_2\text{O} + \text{HCl}$	5-Methoxy-2-methyl-phthalide (VI)

The products mentioned above are only those that were obtained in the reactions attempted with formaldehyde in the presence of concentrated hydrochloric acid and with *s*-dichloromethyl ether respectively. However, in the course of the investigation into the determination of the identity of these products by other types of reaction, several substances were isolated whose preparation had not previously been reported. These products are discussed later in this section.

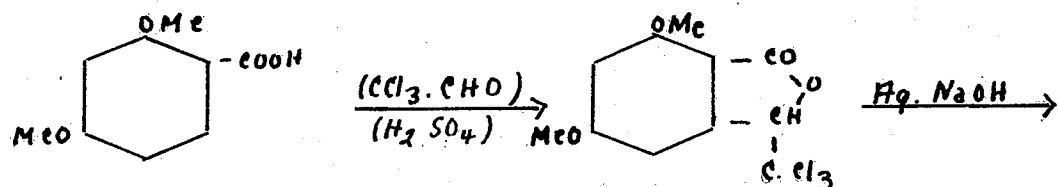
In order to avoid confusion it is necessary to mention the system of nomenclature employed in the introduction and in the present discussion. In naming the acid derivatives the nuclear substituted groups are numbered in a counter-clockwise direction beginning with the acid carboxyl group, in the usual way. In naming the phthalides corresponding to these acids, the original numbering of the groups is retained. In cases where the methyl group is present in the compound, the symbol "Me" is used for convenience in place of "CH₃" and "OMe" in place of "OCH₃".

The substances benzoic acid, o-methoxybenzoic acid and p-toluic acid showed no tendency to react either with formaldehyde and hydrochloric acid or with m-dichloromethyl ether even after long periods of heating at the temperature of the water bath followed by boiling over the free flame. In each case practically all of the material employed at the commencement of the period of heating was recovered unchanged from the reaction mixture. Likewise, in the case of anisic acid (p-methoxybenzoic acid) which was treated with formaldehyde and hydrochloric acid in the presence of zinc chloride monohydrate, suggested by Stephen, Gladding and Short (*loc. cit.*) as being a very effective condensing agent, the acid failed to show evidence of entering into the reaction. Similarly in the case of m-toluic acid, which was treated with formaldehyde and hydrochloric acid in the presence of zinc chloride and petroleum ether, a method employed by Quast (*loc. cit.*), the reaction failed to occur.

Such resistant behavior was not found, however, in the case of 2:4-dimethoxybenzoic acid. This substance on treatment with formaldehyde in the presence of concentrated hydrochloric acid readily yielded the corresponding 2:4-dimethoxyphthalide (product 1) in comparatively good yield by the following reaction.

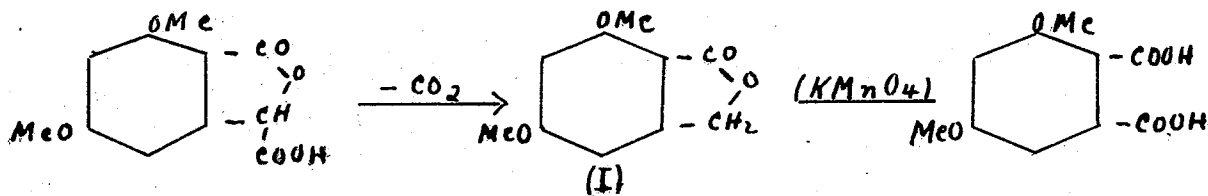


The identity of this phthalide was definitely established by its synthesis by the Fritsch reaction from 2:4-dimethoxybenzoic acid. During the course of this synthesis three substances, whose preparation had not previously been reported, were isolated. These were the corresponding 2:4-dimethoxy- α -trichloromethylphthalide and 2:4-dimethoxy-phthalide- α -carboxylic acid. Potassium permanganate oxidation yielded 2:4-dimethoxy-phthalic acid, whose preparation was likewise recorded for the first time. A summary of the stages involved in this synthesis and the substances obtained is given below.



2:4-Dimethoxybenzoic Acid

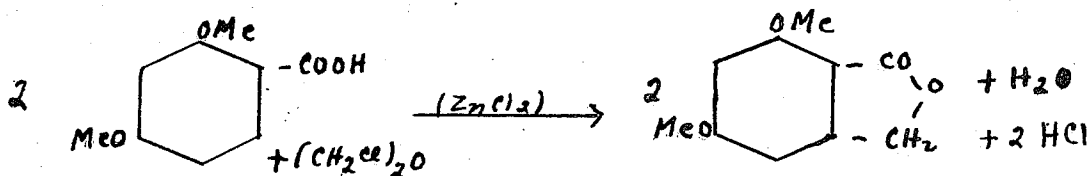
2:4-Dimethoxy- α -Trichloromethylphthalide



2:4-Dimethoxyphthalide- α -Carboxylic Acid

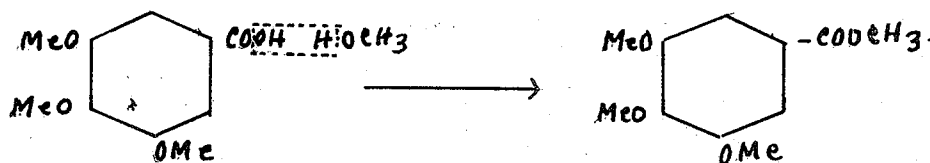
2:4-Dimethoxyphthalic Acid

The action of α -dichloromethyl ether in the presence of zinc chloride on 2:4-dimethoxybenzoic acid similarly gave rise to 2:4-dimethoxy-phthalide by the following reaction.



The course of the reaction described above is in agreement with the explanation of the action of *s*-dichloromethyl ether in the presence of zinc chloride on such substances as benzene, as stated by Stephen, Gladding and Short (*loc. cit.*), the *s*-dichloromethyl ether causing the introduction of the chloromethyl group into the nucleus with the liberation of water. Subsequent removal of hydrogen chloride from the intermediate chloromethyl derivative thus formed would produce the phthalide.

The treatment of 3:4:6-trimethoxybenzoic acid with formaldehyde in the presence of concentrated hydrochloric acid did not produce the corresponding 3:4:6-trimethoxyphthalide as prepared by Meldrum, (*loc. cit.*). The fact that the methyl ester of this acid (product III) was obtained in small yield, suggested that the reaction was probably due to the presence in the commercial aqueous formaldehyde employed, of small quantities of methyl alcohol, as mentioned by Stephen, Gladding and Short (*loc. cit.*) and Henry (*Ber.*, 1893, 26, 333). This view was also supported by the fact that a considerable quantity of unchanged trimethoxybenzoic acid was recovered from the reaction mixture, suggesting that the condensation between the acid and the formaldehyde and hydrochloric acid did not occur and that the production of the methyl ester was due, as stated previously, to the presence of methyl alcohol in the formaldehyde employed. The reaction forming the methyl ester of 3:4:6-trimethoxybenzoic acid may be represented as follows;



The identity of product III was definitely established by the synthesis of the ester by the method of Böger and Isham (J. Am. Chem. Soc., 36, 518) and also by the alkaline hydrolysis of product III with potassium hydroxide, which procedure yielded the original 3:4:5-trimethoxybenzoic acid.

It is interesting to note in this connection that in the case of benzoic acid, o-methoxybenzoic acid, anisic acid and meta and para-toluic acids which failed to condense with formaldehyde and hydrochloric acid, likewise failed to form the corresponding esters. It would therefore seem that the particular configuration of the substituent methoxyl groups in the trimethoxybenzoic acid allowed some activation of the carboxyl group, making it subject to esterification. This evidence is further supported by the fact that the 3:4:5-trimethoxybenzoic acid also reacted with s-dichloromethyl ether to produce a small yield of the methyl ester of the acid (IV); the largest portion of the original acid being likewise re-isolated from the reaction mixture. This reaction may be explained on the basis of the work of Stephen, Gladding and Short (loc. cit.). Thus in the preparation of the s-dichloromethyl ether employed in the reaction, the small amount of methyl alcohol present in the commercial formaldehyde may react with the hydrogen chloride to form a monochlorodimethyl ether by the following reaction.

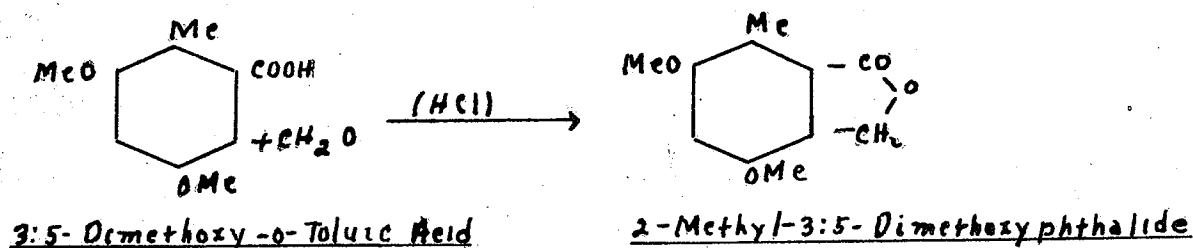


That this substance is actually present in the s-dichloromethyl ether prepared by the action of formaldehyde on hydrochloric acid has been shown to be the case by the above authors. It was also stated by them that under certain conditions, in the presence of traces of moisture or by absorption of moisture from the air, the decomposition of the monochlorodimethyl ether might occur, yielding methyl alcohol and chloromethyl alcohol.



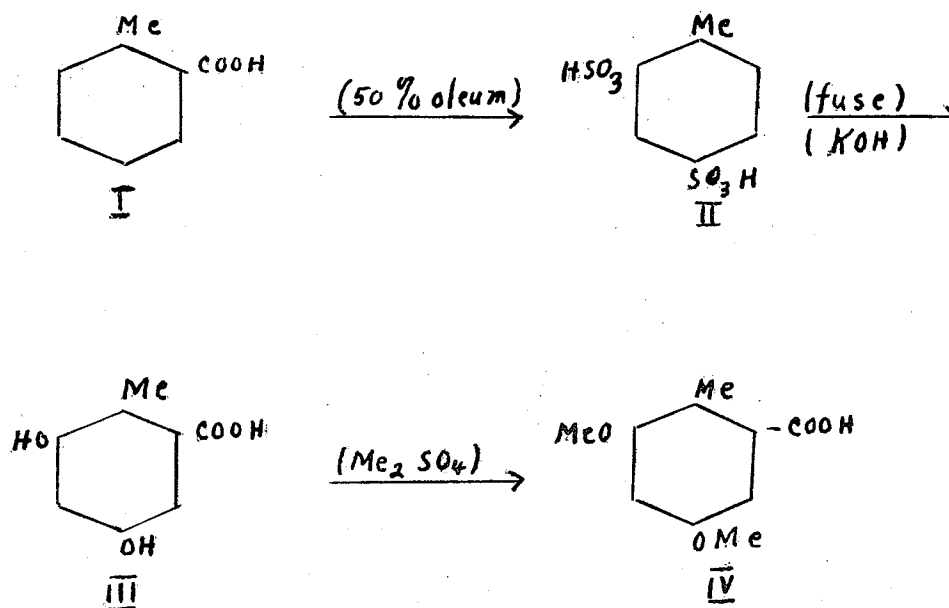
since the crude *o*-dichloromethyl ether was employed in the present investigation, it is reasonable to assume the occurrence of the above reaction and thus the subsequent formation of the ester. The fact that only small yields of the ester were produced in this case supports this view, since it is unlikely that the amount of methyl alcohol produced in this way would be very great. It can therefore be stated that condensation with formaldehyde in the presence of concentrated hydrochloric acid or with *o*-dichloromethyl ether respectively with 3:4:5-trimethoxybenzoic acid did not occur and that the reaction forming the ester of this acid was due to a secondary reaction involving impurities in the reagents employed.

The preparation of 2-methyl-3:5-dimethoxyphthalide (product V) from 3:5-dimethoxy-*o*-toluic acid (creosollic acid) is of interest because it represents a confirmation of the work of Mitter, Sen and Paul (*loc. cit.*) whose paper has previously been discussed. It was therefore found in the present investigation that the method of Parkin, Edwards and Stoyke, (*loc. cit.*) was applicable to this preparation and that the following reaction did occur under the conditions specified.

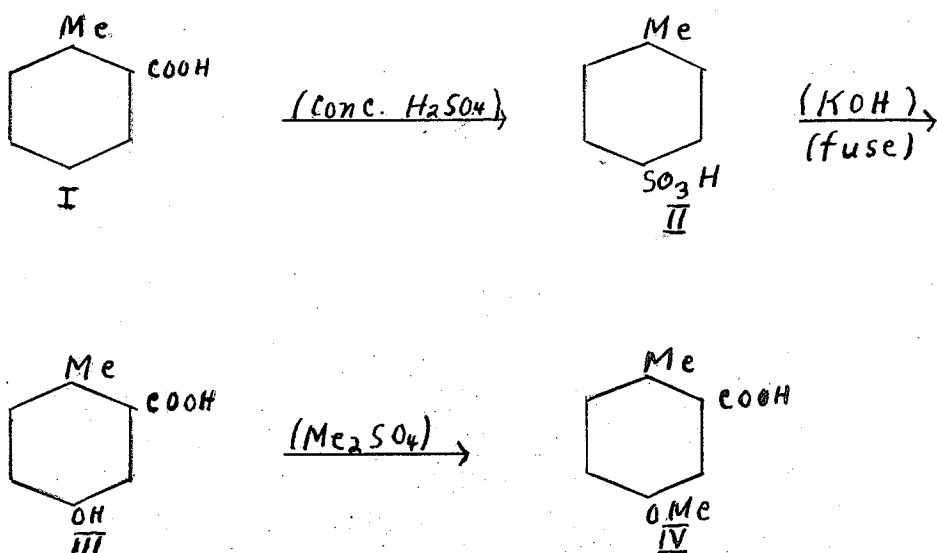


The reaction proceeded easily, the phthalide being obtained in good yield and was identical in all respects with that described by Mitter, Sen and Paul. It is of interest to note here that the authors found it impossible

to oxidize the phthalide to the corresponding phthalic acid. Similar attempted oxidations in the present investigation likewise failed. It may also be noted that the preparation of creorealleic acid was carried out by a series of reactions employed by the above authors and similar to a series used by Charlesworth and Robinson (*loc. cit.*) in the preparation of 3:5-dimethoxy-p-toluic acid.

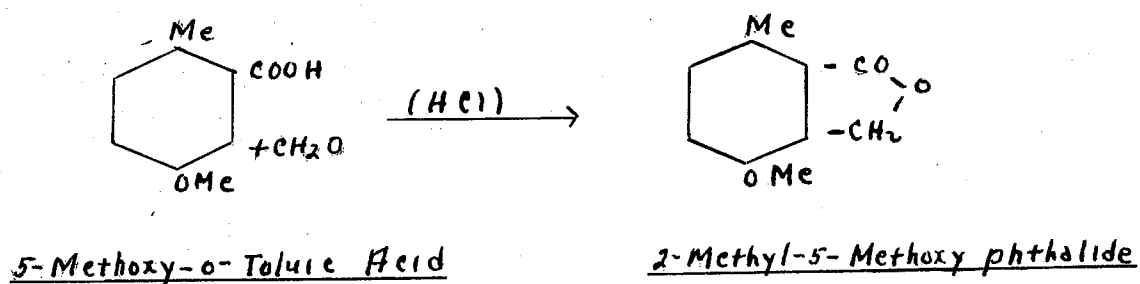


The production of 2-methyl-3:5-dimethoxyphthalide from creorealleic acid suggested an investigation into the action of formaldehyde and hydrochloric acid on 3-methoxy-o-toluic acid, which exhibits the presence of only one substituent methoxyl group. The starting material for the reaction involved was 3-methoxy-o-toluic acid which was prepared by a series of reactions similar to those employed in the preparation of the 3:5-dimethoxy-o-toluic acid of Mitter, Sen and Paul.



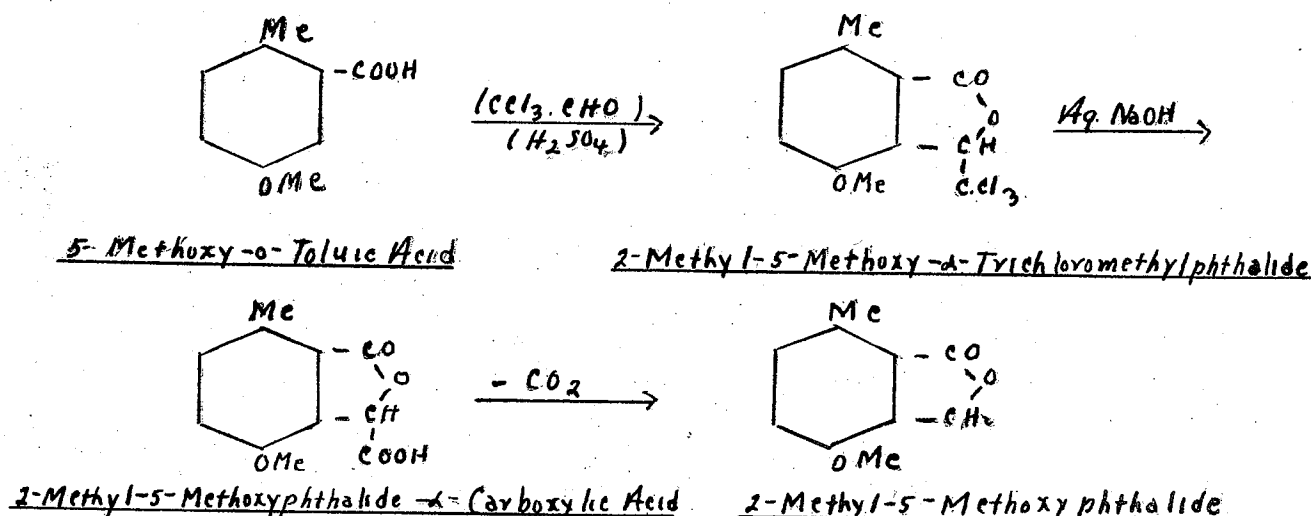
It may be noted here that the preparation of 5-methoxy-o-toluic acid had not previously been reported although the corresponding 5-hydroxy-o-toluic acid, from which the former acid is derived, had been prepared prior to the present investigation.

The reaction to produce 2-methyl-5-methoxyphthalide (product VI) proceeded with ease in the following manner.



The identity of this phthalide was fully established, as in the case of the 2,4-dimethoxyphthalide, by synthesis from the corresponding 5-methoxy-o-toluic acid, mentioned above, by the Fritsch reaction, the stages of which

are summarized below.



During the course of this synthesis two substances were prepared for the first time. These were 2-methyl-5-methoxy-2-trichloromethylphthalide and 2-methyl-5-methoxyphthalide-2-carboxylic acid as shown above. It is of interest to note that, as in the case of the 2-methyl-3,5-dimethoxyphthalide of Kitter, Sen and Paul, it was found impossible, at least by the experimental methods attempted, to oxidize the 2-methyl-5-methoxyphthalide to the corresponding phthalic acid. At present no explanation can be offered for this apparent resistance to oxidation in these two cases.

In conclusion it is of interest to discuss the results of the present investigation in the light of earlier researches, particularly with regard to the effect of nuclear substituent groups on condensations with formaldehyde in the presence of concentrated hydrochloric acid.

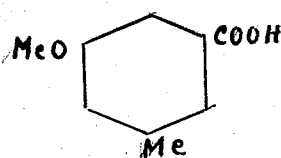
It is obvious that the presence of one substituent methoxyl group or one substituent methyl group is insufficient to cause the introduction of the chloromethyl group into the nucleus of an aromatic acid, as shown on the one hand by the failure of benzoic acid, o-methoxybenzoic acid and anisic acid (p-methoxybenzoic acid) to condense with formaldehyde even in

the presence of strong condensing agents; and on the other by the failure of the meta and p-toluic acids to condense under similar conditions, assuming that o-toluic acid would exhibit the same resistant behavior to condensation. It is of interest to note here that during the course of the present investigation, a repetition of the work of Quelet (Compt. rend. 1937, 205, 235) was undertaken in order to determine whether the same experimental conditions were being attained as those attained by the above author. The work consisted in the preparation of the chloromethyl derivative of anisaldehyde (2-methoxy-5-methyl-4-chlorotoluene) by the action of formaldehyde and hydrochloric acid. The substance mentioned above was isolated without difficulty and in good yield. The work of Quelet and others has shown that the introduction of the chloromethyl group into the nucleus of such compounds as the phenols, phenolic ethers, aromatic aldehydes and hydrocarbons and the halogen derivatives of these compounds, proceeds without difficulty and because of this fact it must be concluded that the presence of the acid carboxyl group hinders the introduction of the chloromethyl group into the aromatic nucleus. This statement must be regarded as a direct contradiction of the statement of Stoerner and Behn (loc. cit.) to the effect that the presence of the substituent carboxyl group ortho to the hydroxyl of phenols directed the chloromethyl group into the para position with respect to the hydroxyl radical. However, as it has been previously pointed out, the authors apparently based their statement on expected orienting influence rather than on experimental evidence.

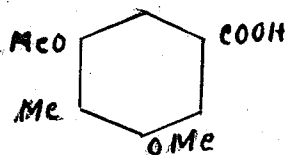
It is to be noted, however, that the acids mentioned above are those exhibiting the presence of only one nuclear substituent group. However, it has been found that in the case of the aromatic acids possessing more than

one nuclear substituent group, e.g. the veratric acids and the methoxy toluic acids, that such resistant behavior to condensation with formaldehyde is not so evident. However, as mentioned previously two types of product have been obtained from reactions involving these acids; one in which the preparation of an abnormal chloroproduct was found and the other in which the normal phthalide was the product of the reaction. It is of interest, then, to note the conditions under which each type of product is produced.

Up till the present time two acids have yielded the first type of product, i.e., the chloroproducts, whose identity have not yet been definitely established but which are probably the corresponding chloromethylphthalides. These two acids are represented below.

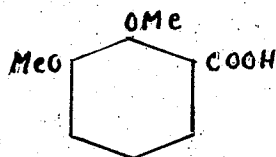


3-Methoxy-m-Toluic Acid

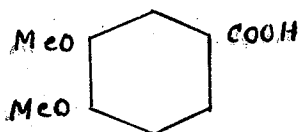


3:5-Dimethoxy-p-Toluic Acid

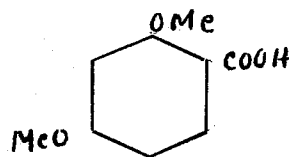
Similarly five acids have yielded the corresponding normal phthalide by the action of formaldehyde and hydrochloric acid.



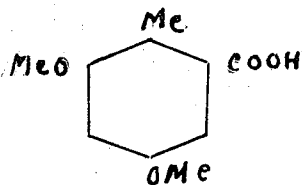
6-Veratric Acid



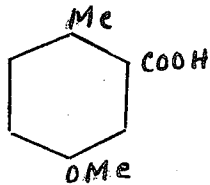
Veratric Acid



2:4-Dimethoxybenzoic Acid



Creoscellenic Acid



5-Methoxy-o-Toluic Acid

In dealing with the conditions which were essential to the formation of the chloroproducts, G. Cameron, (loc. cit.) on the basis of the evidence then available, suggested that the nuclear substituted methyl group might be essential to the reaction and that the occupation of both meta positions, as exhibited by the two acids forming chloroproducts, might also be a required condition. On the basis of this latter fact it was suggested that such substances as the dimethyl ether of α -resorcylic acid (3:5-dimethoxybenzoic acid) and 3:4:5-trimethoxybenzoic acid would form chloroproducts. On the basis of the present investigation it is evident that the substituent methyl group is probably essential to the formation of these chloroproducts and that this methyl group must occupy either the meta or the para position with respect to the carboxyl group, since in the case of creoscellenic acid and 5-methoxy-o-toluic acid where the nuclear substituted methyl group occupies the ortho position, the normal phthalide was obtained. Further support is also given to the suggestion by the same author that the occupation of both meta positions is essential to the occurrence of the reaction. However, this second condition must exist in conjunction with the first, i.e. that while both meta positions must be occupied the methyl group must be found in the meta or para position, since in the case of creoscellenic acid both meta positions are occupied but the methyl group is in the ortho position.

While it is possible to draw the above conclusions from the evidence available at the present time, these conditions must be regarded as merely tentative, since the nature of the chloroproducts or the course of the reaction by which they are formed are not definitely known.

It is to be noted that the acids yielding the normal phthalide do not conform to the conditions outlined above. Thus on the basis of this suggestion the dimethyl ether of α -resorcylic acid would be expected to give

rise to the normal phthalide as would 3:4:5-trimethoxybenzoic acid.

However since this latter acid has been shown not to give the reaction, further investigation is necessary to determine the cause of this apparent exception to normal behavior.

Experimental

Section One

The Action of Formaldehyde in the Presence of Concentrated Hydrochloric Acid and of s-Dichloromethyl Ether Respectively on Benzoic Acid and the Hydroxybenzoic Acids.

Preliminary Preparations

o-Methoxybenzoic Acid

The method of Graebe (Annalen, 340, 210) was employed in this preparation and in all subsequent methylations carried out in this research, the method being modified in certain cases to meet the conditions at hand. A solution of salicylic acid (50 grams) and sodium hydroxide (21.6 grams) in water (150 grams) were shaken together for from 10 to 15 minutes with dimethyl sulphate (30 cc.), then warmed to boiling and sodium hydroxide (10 grams) was added and the solution refluxed over wire gauze for five hours or until all traces of ester formed during the course of the reaction had been hydrolysed, as noted by the disappearance of oil present on top of the liquid. The method was modified here, in that an excess of the dimethyl sulphate was added rather than the calculated quantity, in order to insure complete methylation of the acid, as it was found very difficult to remove unchanged acid at the end of the reaction. The excess of dimethyl sulphate was destroyed and any ester formed was hydrolysed, by the long boiling with an excess of alkali, more being added at intervals during the refluxing period. In all cases it was found that a much purer product was obtained in this way.

After the required time of heating had been completed, the solution was cooled, acidified with concentrated hydrochloric acid and the o-methoxybenzoic acid thus precipitated, removed. It was purified by washing several times with water at a temperature a little below the melting point of the acid. Yield 30 grams or 90% of the theoretical. M.P. 95-96°. A sample on recrystallisation melted at 100-101°.

β -Resorcylic Acid (2:4-Dihydroxybenzoic Acid)

The method of Bistrzski and Kostanecki (ber., 1935, 19, 1935) was employed. Dry resorcinol (50 grams), sodium bicarbonate (250 grams) and water (800 grams) were mixed in a large round bottom flask and the mixture was heated under reflux for $1\frac{1}{2}$ to 2 hours in a continuous stream of carbon dioxide, supplied from a Kipp's generator. The solution, which was a pale amber color, was acidified with concentrated hydrochloric acid and extracted again with ether. The etherial solution was now extracted with a solution of sodium bicarbonate, acidified with concentrated hydrochloric acid and extracted again with ether. The ether was removed by distillation and the β -resorcylic acid remained as a pale amber material in a nearly pure condition. Yield 33 grams or 48% of the theoretical, m.p. 213°. Subsequent preparations gave proportional yields. A sample on recrystallisation melted at 214°.

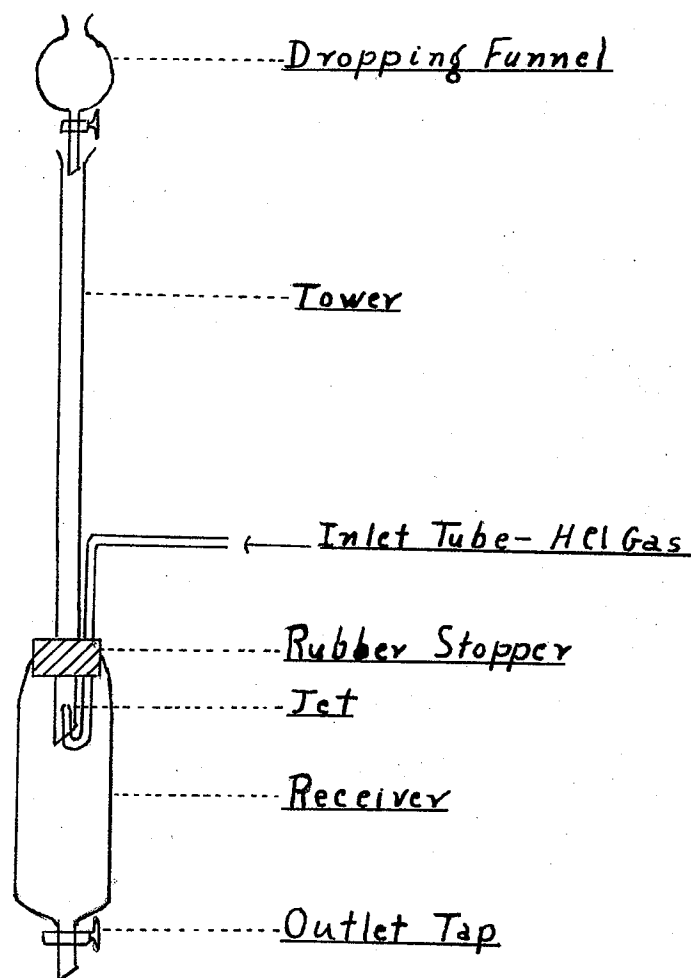
2:4-Dimethoxybenzoic Acid

The same procedure was employed as in the methylation of o-hydroxybenzoic acid, but in this case an atmosphere of coal gas was introduced. A three holed flask was fitted with a tap funnel, stirrer and inlet and outlet tubes to the gas supply and during the time of the addition of the dimethyl sulphate, which was added through the tap funnel, a stream of coal gas was introduced into the flask. The acid was obtained in a nearly pure condition.

Yield from β -resoroylic acid (30 grams) was 32.5 grams or 86% of the theoretical m.p. 98-100°. A sample on recrystallization melted at 100-102°.

Preparation of the *o*-Dichloromethyl Ether by the Tower Method

This procedure was the standard method described by Stephen, Gladding and Short (loc.cit.). The apparatus employed was essentially the same as that of the authors with some minor modifications.



Apparatus

An air condenser packed with glass beads was used instead of a tower packed with pumice and a separating funnel for a receiver in place of a

Woulf's bottle, which was not available. The hydrogen chloride was introduced by a tube passing through the cork in the mouth of the funnel and bent upwards into the bottom of the condenser. The condensing arrangement at the top of the tower was omitted. Formaldehyde (40%) was allowed to percolate slowly down the tower from a tap funnel suspended at the top and at the same time, a rapid stream of hydrogen chloride gas from the generator, was passed upward through the jet. The reaction soon became evident from the fact that the tower became quite warm after the first two or three minutes. As the liquid collected in the receiver, the formation of oil was observed almost at once and as the quantity of liquid increased, the oil was seen floating on the acid layer. The oil sank only after saturation with hydrogen chloride. When the formaldehyde had all passed down the tower, the oil was separated and the formaldehyde solution passed down the tower a second time. More oil was formed and this was again separated. This process was repeated again twice, after which no more oil was formed. However the formaldehyde solution, on standing several hours, separated more of the crude oil. In all approximately 70-80 grams of oil were obtained from 200 grams of 40% formaldehyde, or the yield was 50% of the theoretical. A portion of the crude oil was purified by shaking with potassium carbonate to remove the excess hydrochloric acid and it was then distilled, B.P. 103-104°. For subsequent use in the condensations, the oil was employed in the original "crude" form.

An attempt was also made to prepare the *n*-dichloromethyl ether by the action of hydrochloric acid on hexamethylene tetramine, by the method of Stephen, Cladding and Short (J.C.S., 1920, 117, 510), the hexamethylene tetramine being prepared by the method described in Catterman's "Organic

Chemistry" (p. 161). However the writer was unable to obtain the *s*-dichloromethyl ether by this method.

A similar attempt was made to prepare the "crude oil" by the action of sodium chloride on paraformaldehyde, this being the rapid method described by Stephen, Gladding and Short (*loc. cit.*) for the preparation of small quantities of the oil. A very small amount of the *s*-dichloromethyl ether (2.5 grams) was prepared in this manner but was impure and the method was abandoned due to the small yields obtained.

Attempted Condensation of Benzoic Acid with Formaldehyde in the Presence of Concentrated Hydrochloric Acid

The method followed was that used by Perkin, Edwards and Stoyke (J.C.S., 1926, 127, 195) in the preparation of the *m*-mesonines, and this method was adopted in all the condensations attempted, with certain modifications, as required, in the method of separation of the reaction products. Thus a description of the method here serves as a general outline of the procedure used in subsequent condensations.

Benzoic acid (15 grams) was mixed with 40% formaldehyde (50 cc's) and concentrated hydrochloric acid (50 cc's) and the mixture was heated under reflux on the water bath for 3 hours and then over wire gauze for $\frac{1}{2}$ hour. Partial solution occurred after about 10 minutes, the contents of the flask assuming a milky appearance. Finally separation into two layers was observed, and this condition existed until the end of the period of heating. On cooling a white crystalline mass separated which was removed, washed well with water and dried. M.P. 117-118°. On recrystallization from water the melting point rose to 120-121°. Yield 10.5 grams. Sodium fusion and the copper wire test gave no

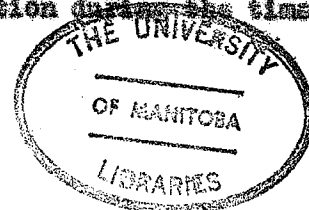
evidence of the presence of halogen. On addition of water to the formaldehyde-hydrochloric acid of mother liquor, a little more material, similar to the above was precipitated. Mixed melting point determinations and the properties and appearance definitely identified the substance as benzoic acid and it was concluded that no reaction had occurred. In all about 13.7 grams of the original benzoic acid were recovered.

Attempted Condensation of Benzoic Acid with s-Dichloromethyl Ether

As in the case of the formaldehyde-hydrochloric acid condensations, a description of the method employed is of general application to all subsequent reactions with s-dichloromethyl ether. The method was that of Stephen, Gladding and Short (loc.cit). Benzoic acid (10 grams) was mixed with s-dichloromethyl ether (20 grams) and the mixture heated on the water bath for 3 hours and then over wire gauze for $\frac{1}{2}$ hour. After about 10 minutes solution was complete and the liquid remained colorless and homogenous throughout the period of heating. On cooling a white crystalline solid separated. This was removed on the filter and washed well with water. M.P. 116-117°. The material was crystallized from water. M.P. 120°. Sodium fusion and the copper wire test gave no evidence of the presence of halogen and since mixed melting point determinations and the properties and appearance of the material showed the substance to be identical with the original benzoic acid, it was concluded that no reaction had occurred. About 9 grams of the original acid were recovered.

Attempted Condensation of o-Methoxybenzoic Acid with Formaldehyde in the Presence of Concentrated Hydrochloric Acid.

The same procedure as described for benzoic acid was employed. In this case no solution occurred, the substance melting and settling to the bottom of the flask as a thick oil and remaining in this condition during the time



of heating. On the removal of the hydrochloric acid and formaldehyde solution and the addition of water, crystallization of the oil occurred. M.P. 92-93°. Tests for halogen were negative and practically all of the 13 grams of the original o-methoxybenzoic acid were recovered.

Attempted Condensation of o-Methoxybenzoic Acid with s-Dichloromethyl Ether in the Presence of Zinc Chloride

The same procedure as used in the case of benzoic acid was followed, but here a little zinc chloride was introduced as dehydrating agent. After about five minutes solution of the acid in the s-dichloromethyl ether was complete, the liquid assuming a colorless appearance, and it remained in this condition throughout the period of heating. On cooling a heavy colorless oil separated to the bottom of the flask. The supernatant liquid was removed, a little water added to remove any zinc chloride present, and the contents of the flask warmed, and on cooling the mass crystallized. M.P. 92-93°. Tests for halogen were negative and the material was shown to be identical with the original o-methoxybenzoic acid by mixed melting point determinations. About 6.2 grams of the 10 grams of the acid introduced were recovered. From the original mother liquor a small amount of tarry material separated but all attempts to crystallize this failed. It was therefore concluded that no reaction had occurred.

Attempted Condensation of p-Toluic acid with Formaldehyde in the Presence of Concentrated Hydrochloric Acid

With the use of the same procedure as that employed with benzoic acid, practically all of the toluic acid introduced at the commencement of the period of heating was recovered.

Attempted Condensation of p-Toluic Acid with s-Dichloromethyl Ether in the presence of Zinc Chloride

In this case as with the attempted condensation of p-toluic acid with

formaldehyde in the presence of concentrated hydrochloric acid, nearly all of the original acid was recovered in an unchanged condition. It was therefore concluded from this attempt and from the previous trial, that p-toluic acid does not react with either formaldehyde and hydrochloric acid or with s-dichloromethyl ether in the presence of anhydrous zinc chloride.

Preparation of 2:4 - Dimethoxy phthalide By The Action of Formaldehyde in

Presence of Concentrated Hydrochloric Acid in 2:4 - Dimethoxybenzoic Acid.

Pure 2:4-dimethoxybenzoic Acid (10 grams) and 40% formaldehyde (50cc.) and concentrated hydrochloric acid (50cc.) were heated on the water bath for 3 hours and then over wire gauze for $\frac{1}{2}$ hour. At first intense frothing was noted, the solid remaining on top of the liquid and the solution beneath both becoming dark purple in color, turning to dark red toward the end of the reaction. The solid on top gradually changed to an oil which separated to the bottom of the flask. It is of interest to note here that this sequence of changes was observed in the condensations in which definite reactions were obtained and a similar sequence of changes was noted by Cameron (loc.cit.) in the reaction of 5-methoxy-m-toluic with formaldehyde in the presence of concentrated hydrochloric acid. After the required time of heating, the contents of the flask were allowed to cool and the new solid and crystalline, dark red mass at the bottom of the flask was separated. Yield 8.0 grams. An accident caused the loss of about one third of this material. The remaining substance was dissolved in absolute alcohol and boiled repeatedly with animal charcoal and finally allowed to crystallize, the material separating as a greenish yellow crystalline solid. No definite melting point was obtained, the substance appearing to decompose at 140-145° and becoming dark red in the melting point tube.

It was crystallized again several times from absolute alcohol and was now a light amber color and appeared to be as pure as could be obtained. The

substance darkened at 140-145° and the temperature of apparent decomposition was 180-185°. (I). It was at first thought that product I, might be the methyl ester of 2:4-dimethoxybenzoic acid, this being suggested by the fact that esterification had occurred in the case of the trimethyl ether of gallic acid in its reaction with formaldehyde in the presence of concentrated hydrochloric acid. But the methyl ester of 2:4-dimethoxybenzoic acid was found to be a liquid of boiling point 294-295° or 160-165° (13mm.) and therefore not identical with product I. It was therefore suspected that product I. was the phthalide of 2:4-dimethoxybenzoic acid.

An attempt was made to obtain another product by the addition of water to the alcoholic mother liquors from the re-crystallizations but this resulted in the precipitating of a little more of product (I). The total yield of recrystallized material was 4.7 grams. The copper wire test and sodium fusion showed no evidence of the presence of halogen.

A similar attempt was made to obtain some product from the original formaldehyde-hydrochloric acid mother liquor from the condensation, by the addition of water, but no precipitation occurred. Subsequent concentration of this aqueous solution failed to produce any such material.

Nature of Product (I).

Appearance-----Amber colored crystals (alcohol)

Melting Point-----Decomposition 180-185°

Solubility

Water-----Insoluble

Ether-----Soluble

Acetone-----Insoluble

Glacial Acetic Acid-----Soluble Hot

Ethyl Acetate-----Slightly Soluble

(Nature of product (1) . continued:-)

Benzene-----Soluble
 Petroleum Ether -----Soluble
 Chloroform -----Soluble
 Carbon Tetrachloride -----Insoluble
 Carbon Disulphide -----Insoluble
 Reaction to Litmus -----Neutral
 Aqueous NaHCO_3 -----No reaction
 Aqueous NaOH -----Insoluble, no reaction
 Aqueous or alcoholic FeCl_3 ---No colour
 Conc. H_2SO_4 -----Soluble without decomposition

Analysis of Product (1):-

Determination

<u>Material</u>	<u>I</u>	<u>II</u>
	<u>Weight in Grams</u>	<u>Weight in Grams</u>
Boat + Sample -----	5.1504	5.1756
Boat -----	4.8874	4.9485
Sample -----	0.2180	0.2297
KOH bulbs after combustion -----	69.7510	69.7510
KOH bulbs before combustion -----	69.2518	69.2550
CO_2 absorbed -----	00.4892	00.5140
CaCl_2 tube after combustion -----	44.7024	44.8100
CaCl_2 tube before combustion -----	44.6000	44.7024
H_2O absorbed -----	00.1024	00.1076

Analysis of Product (1). Continued.

$$\text{Percentage Carbon} \quad \frac{12 \times 0.4892 \times 100}{44 \times 0.2180} = \frac{12 \times 0.5104 \times 100}{44 \times 0.2297} =$$

61.19%

61.15%

$$\text{Percentage Hydrogen} \quad \frac{2 \times 0.1084 \times 100}{18 \times 0.2180} = \frac{2 \times 0.1076 \times 100}{18 \times 0.2297}$$

5.20%

5.21%

Mean Results

Carbon 61.18%

Hydrogen 5.20%

$\text{C}_{10}\text{H}_{10}\text{O}_4$ requires

Carbon 61.80%

Hydrogen 5.16%

Condensation of 2:4-Dimethoxybenzoic Acid with s-Dichloromethyl Ether

In the Presence of Zinc Chloride

The 2:4-dimethoxybenzoic acid (10 grams) and s-dichloromethyl ether (20 grams) and anhydrous zinc chloride (5 grams) were mixed in a round flask. No reaction occurred in the cold and the mixture was then heated under reflux on the water bath for about $\frac{1}{2}$ hour. On slight warming a vigorous reaction occurred, accompanied by a great deal of frothing, the mixture assuming a deep red color. Considerable quantities of hydrochloric acid gas were evolved. After $\frac{1}{2}$ hour the reaction had subsided and the mixture was then allowed to cool. A little water was added to dissolve out the zinc chloride and the gummy mass remaining was dissolved in absolute alcohol. After repeated boiling with charcoal, the solution was allowed to cool and a dark brown amorphous solid separated, apparently in a very impure form (II.) No definite melting point was obtained, the material decomposing above 180° .

This substance was now recrystallized several times from absolute alcohol with the addition of charcoal until it finally separated as a light brown material

and was apparently as pure as could be obtained. The yield of the pure product was about 0.2-0.5 grams, the low yield being caused by the great difficulty encountered in the purification of the substance.

The material decomposed at 178-181° and in all respects appeared to be identical with product (I).

Analysis of (II):-

<u>Material</u>	<u>Weight in Grams</u>
Boat + sample	4.9720
Boat	4.8573
Sample	0.1047
KOH bulbs after combustion	67.3690
KOH bulbs before combustion	67.1350
CO ₂ absorbed	00.2360
CaCl ₂ tube after combustion	44.4701
CaCl ₂ tube before combustion	44.4206
H ₂ O absorbed	00.0495

$$\text{Percentage Carbon} = \frac{12 \times 0.2360 \times 100}{44 \times 0.1047} =$$

$$\frac{61.49\%}{2 \times 0.0495 \times 100} = \frac{18 \times 0.1047}{}$$

$$5.27\%$$

$$\text{C}_{10}\text{H}_{10}\text{O}_4 \text{ required} \quad \text{Carbon } 61.80\% \quad \text{Hydrogen } 5.15\%$$

Preparation of 2:4-Dimethoxyphthalide by the Chloral Hydrate Condensation

Since products I and II were suspected of being 2:4-dimethoxyphthalide, it was decided to prepare the above substance by the standard Fritsch reaction and in this way attempt to establish definitely the nature of these products. The

starting material for the series of reactions involved was 2:4-dimethoxybenzoic acid and this substance was prepared from resorcinol as described previously in this section.

2:4-Dimethoxy-/-Trichloromethylphthalide

2:4-Dimethoxybenzoic acid (37.5 grams) was mixed in a stoppered flask with powdered chloral hydrate (46.8 grams) and sulphuric acid (206cc. with 10cc. water) added. After 24 hours the reaction mixture was poured on ice and the separated solid was washed with water and 10% aqueous alcohol and crystallised from 30% acetic acid. The trichloromethylphthalide was a fine white crystalline material, m.p. 210-211° and decomposed at 224-225°. The substance was soluble in most of the common organic solvents and only slightly soluble in dilute acetic acid.

Analysis:-

It was impossible to undertake the determination of the carbon and hydrogen present in the compound prepared above by the combustion method, as a silver gauze was not available for the retention of the chlorine. Therefore analysis of the compound for chlorine was undertaken in order to prove the identity of the substance.

During the course of this investigation, an apparatus for semi-micro determination of halogen became available in the department. The method which had previously been used was Bacon's modification of Stepanoff's method, which gave fairly satisfactory results. It was therefore thought that an account of the various methods of chlorine determination would be of interest and particularly a comparison of the results obtained by the two methods employed in the present work, namely, the Stepanoff method and the semi-micro method.

Probably the oldest method of chlorine analysis is that of Carius (Ann., 1860, 116, 1). The method consists in heating the substance under examination

in a small sealed tube with fuming nitric acid and an excess of finely powdered silver nitrate and the silver halide thus formed, determined by weight. The method gives good results and the only chlorine and bromine compounds that fail to give good results by this method are the highly halogenated aromatic derivatives such as hexachlorobenzene. Iodine compounds often give unreliable results, since the silver iodide is appreciably soluble in nitric acid solution of silver nitrate and, moreover, free iodine is formed in some instances. Therefore this method is not particularly desirable, for not only is it not generally applicable, but requires considerable time and is unpleasant to carry out for working with sealed tubes is somewhat dangerous.

The fusion method of Pira and Schiff is applicable to all substances which are not highly volatile. The method consists of fusion of the chlorine-containing substance with sodium carbonate and calcium oxide and subsequent precipitation of silver halide with silver nitrate. However the method is not of general applicability and the results with iodine are unreliable.

The method of Robertson (J.C.S., 1915, 197, 902), has been employed for the estimation of halogen. The halogen compound is heated with sulphuric and chromic acids and a slow current of dry air is bubbled through the solution. The halogen and the halogen acid evolved are absorbed in alkaline hydrogen peroxide. After the reaction is complete, the alkaline solution is heated to boiling, cooled, acidified with nitric acid and the halogen estimated by the Volhard method.

The Stepanoff method (Bacon's modification) (J.F. Thorpe and M.A. Whitely A Students Manual of Organic Chemical Analysis - p.52) was employed, as stated previously, in the present work. The method is applicable to all types of organic halogen compounds, including those of the aromatic series, although failures have been reported with compounds containing the nitro group. It

depends on the reducing action of sodium in absolute alcohol and upon the action of sodium ethoxide on organically combined halogen. However, as stated above, the method is not completely applicable and it is suggested that, in some cases the halogen is not completely reduced and that the subsequent use of the Volhard method in the determination of the chloride, may also introduce considerable additional error.

A weighed sample of the substance (about 0.5 grams) was dissolved in absolute alcohol (20-24cc.) in a flask fitted with a reflux condenser. To the boiling solution was gradually added metallic sodium (cut in clean strips) amounting to 25 to 50 times the quantity calculated from the equation:



and based upon the anticipated halogen content of the substance. When all had been added the mixture was heated with a free flame until all the sodium had reacted and for some time (15 minutes) following this. The mixture was then allowed to cool, diluted with water, filtered when necessary, acidified with dilute nitric acid and titrated by the Volhard method. This method consists in adding a large excess of standard silver nitrate solution to the reaction products of the above, removal of the precipitated silver halide by filtration and the determination of the excess of silver nitrate present by titration with standard ammonium thiocyanate solution using ferric-alum indicator.

Experimental Results for Determination of Chlorine in 2:4-Dimethoxy-1-Trichloromethylphthalide by the Stepanoff Method

	<u>Determination</u>		
	<u>I</u>	<u>II</u>	<u>III</u>
Watch Glass Sample ---	6.8022 g.		
		6.7672 g.	6.7702 g.
Watch glass -----	6.6636 g.	6.6636 g.	6.6636 g.
Sample -----	0.1382 g.	0.1036 g.	0.1066 g.

Sodium required -----	3.8000 g.	1.9500 g.	2.0000 g.
Alcohol required -----	25.0 cc.	15.0 cc.	15.0 cc.
NH ₄ OH required -----	11.15 cc.	14.61 cc.	14.25 cc.
<u>Percentage Chlorine -----</u>	<u>32.71%</u>	<u>32.56%</u>	<u>32.74%</u>

Mean --- 32.67%

$C_{11}H_9O_4.Cl_3$ requires -- 34.18%

The semi-micro method employed was that of B. Bobranski (Z. anal. Chem., 1931, 84, 225) (Cf. Suchardá and Bobranski Semimicro-methods for the Elementary Analysis of Organic Compounds - p.29) for the determination of the halogens. This author stated that any method, which was to be perfectly applicable, must be founded on reactions whose course was not in the least ambiguous, and in the procedure which he established, attention was directed to three processes, namely, destruction of the organic part of the molecule so that the halogen was liberated in the free condition, quantitative absorption of the halogen and estimation of the halogen in the ionic form. In formulating a procedure the author considered only those methods in which the substance was completely oxidised, preferably in the dry state. Thus the substance could be burnt in oxygen with or without a catalyst, but in the latter case very high temperatures were required thus making the cost of the apparatus very high and the method inconvenient and therefore in this procedure platinum was employed as the catalyst.

The author also stated that the main object of elementary analysis was to establish the empirical formula of the compound under examination and that the accurate determination of one element was often sufficient for this purpose.

Thus the importance of the development of a simple, accurate method in this case.

Because of the fact that in a semi-micro method one deals only with the analysis of a few mg. of material, the titration of the halide-ion must therefore be carried out with correspondingly greater accuracy than in macro-analysis.

In this case therefore a weight method of standardization was introduced, since the weight of a standard solution can be determined with far greater accuracy than its volume. For this purpose a tapless weight-burette was employed, the apparatus consisting of a bulb with one end drawn out to a capillary of such a bore that liquid would not flow until pressure was applied at the other end, which was open and to which could be attached a rubber mouthpiece. Both ends of the apparatus were provided with ground glass caps which were in place during the time of weighing.

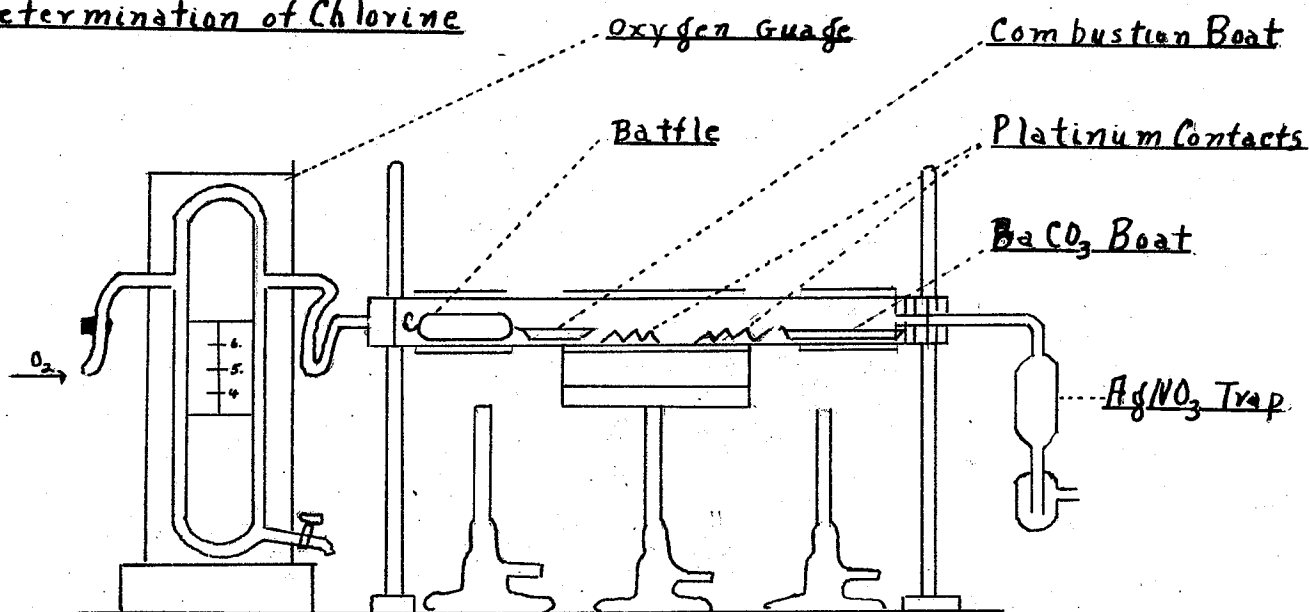
In the present method the absorption indicators fluorescein and eosin were used, the former for the estimation of chlorine and the latter for the estimation of bromine and iodine. The author stated that in this method was found the first application of these absorption indicators to micro-analysis, as previously they had only been applied to macro determinations. These indicators give a sharp end point and it was found that the addition of a few cc. of 1 percent starch solution considerably increased the sharpness of the end point. The starch acts as a protective colloid and effectively retards coagulation of the colloidal silver halide first formed even in the presence of strong electrolytes, while the intensity of the color of the absorbed dye is also considerably augmented on account of the large surface of the colloidal particles.

Thus the silver nitrate solution employed was standardized by the weight method. Sodium chloride (5 to 6 mg.) was accurately weighed out, the chloride having been previously dried at 300°. Approximately 20 cc. of the silver nitrate solution (8.5 grams per litre) were drawn into the weight-burette, the apparatus weighed, the sodium chloride dissolved in a little water and 2 drops of

I : 1000 fluorescein solution and 5 cc. of 1 percent starch solution added. The titration was made and the weight of silver nitrate solution corresponding to the weight of sodium chloride employed was found and the results calculated in weight of chlorine corresponding to 1 gram of the silver nitrate solution.

In the present method absorption of the halogens, bromine and chlorine, was accomplished with barium carbonate heated to a dull red condition in the combustion tube. In the case of chlorine, no further treatment of the barium carbonate was necessary if the solution prepared for titration was exactly neutral, but this was not the case with bromine using eosin as the indicator. Here it was necessary to acidify with dilute nitric acid before titration. About 0.5 grams of barium carbonate were used in the determination. The carbonate does not interfere with the chloride titration unless it is present in far too great excess, when the reddish salt of barium fluorescein is formed on the surface of the precipitate and obscures the true end point. Unfortunately on account of the low reactivity of iodine, absorption by barium carbonate is impracticable. In this case, therefore, absorption is carried out in 40% sodium sulphite solution in a special apparatus.

Determination of Chlorine



Since the writer employed the method for chlorine, an account of this procedure only is described below. In carrying out the actual determination about 2 to 5 g. of material was weighed out and placed in the combustion tube and behind the boat carrying the material under investigation was placed a glass baffle to prevent back distillation. Over the combustion tube at the position of the baffle was placed a brass guard to protect the tube when heating. In front of the boat and over the tube burner (9 cm.) were placed the platinum contacts and this part of the tube was likewise protected by a brass guard. Toward the outlet end of the tube was placed the boat carrying the barium carbonate and the outlet of the tube was closed with a trap containing a few drops of silver nitrate acidified with nitric acid. The portion of the tube under the barium carbonate was protected by a guard as before. Before the determination, the platinum contacts were activated by treatment with aqua regia and subsequent ignition. The oxygen was supplied from a gas holder and passed through a special gauge constructed to read the amount of delivery in cc.

Oxygen was passed in at the rate of about 5 cc. per minute and the combustion tube under the barium carbonate and the platinum contacts heated to a dull red condition. The portion of the tube under the baffle was heated and the flame and the brass guard gradually moved forward toward the boat containing the substance under examination, until the combustion was complete (10 - 20 minutes). Oxygen was passed for three minutes following the extinguishing of the burners. The barium carbonate was then washed into a porcelain basin (50 cc.) after cooling, a little water added and the titration made. From the value obtained, the percentage of chlorine present in the compound was calculated.

Experimental Results for Determination of Chlorine in

2:4-Dimethoxy-4-Trichloromethylphthalide by the Semi-micro Method

Standardisation:

1 gram of AgNO_3 solution was equivalent to 0.001752 grams Cl.

Determination

	<u>I</u>	<u>II</u>
Boat Sample -----	1.0792 g.	1.0778 g.
Boat -----	1.0552 g.	1.0552 g.
Sample -----	0.0240 g.	0.0226 g.
Burette before combustion -----	55.0674 g.	57.9758 g.
Burette after combustion -----	56.4474 g.	55.6227 g.
Weight of AgNO_3 solution used -	4.6200 g.	4.3481 g.
Percentage Chlorine -----	35.72 %	35.71 %

Mean --- 35.715 %

$\text{C}_{11}\text{H}_9\text{O}_4\cdot\text{Cl}_3$ requires - 34.18 %.

From a comparison of the results obtained by the Stepanoff method and the Dobranski semi-micro method it was observed that the latter procedure possessed many advantages. The results obtained showed that a much higher order of accuracy could be obtained and the time required to complete the analyses was found to be comparatively short as compared with the Stepanoff method. Moreover the apparatus was found to be extremely convenient to operate and since the amounts of material required were so small and the applicability of the method perfectly general, the method seemed to be an excellent one in every respect.

2:4 - Dimethoxyphthalide- λ -Carboxylic acid

2:4-Dimethoxy- λ -trichloromethylphthalide (45 grams) and 20% aqueous sodium hydroxide (210 cc.) were mixed in a large beaker and heated on the steam bath for an hour. The dark solution was filtered and acidified with concentrated hydrochloric acid and the precipitated acid separated at the pump and dried. The material was crystallized once from 50% acetic acid. Yield 21.7 grams or 61% of the theoretical. A small sample was crystallized from acetic acid (50%) and had a m.p. of 156° with decomposition at $210-215^\circ$. The acid was light brown in

appearance and was soluble in most of the common organic solvents.

Analysis:

	<u>Determination</u>	
	<u>I</u>	<u>II</u>
	<u>Weight in Grams</u>	<u>Weight in Grams</u>
Boat + Sample -----	5.0248	5.1751
Boat -----	4.8682	4.9488
Sample -----	0.1566	0.1373
KOH bulbs after combustion -----	70.0216	70.2980
KOH bulbs before combustion -----	69.7048	70.0216
CO ₂ absorbed -----	00.3168	00.2773
CaCl ₂ tube after combustion -----	45.8987	45.9507
CaCl ₂ tube before combustion -----	45.8382	45.8987
H ₂ O absorbed -----	00.0596	00.0520
Percentage Carbon -----	$\frac{12 \times 0.3168 \times 100}{44 \times 0.1566}$	$\frac{12 \times 0.2773 \times 100}{44 \times 0.1373}$
	= 55.17 %	= 55.22 %
Percentage Hydrogen -----	$\frac{2 \times 0.0596 \times 100}{18 \times 0.1566}$	$\frac{2 \times 0.0520 \times 100}{18 \times 0.1373}$
	= 4.23 %	= 4.21 %
<u>Mean</u> -----	<u>Carbon</u> = 55.20 %	<u>Hydrogen</u> = 4.22 %
C ₁₁ H ₁₀ O ₆ requires -	<u>Carbon</u> = 55.46 %	<u>Hydrogen</u> = 4.20 %

2:4-Dimethoxyphthalide

The 2:4-dimethoxyphthalide- α -carboxylic acid was converted by two methods to the corresponding 2:4-dimethoxyphthalide.

In the first trial the method employed by Alimohandani and Meldrum (J.C.S., 1920, 117, 964) was used. The acid (5 grams) was mixed with naphthalene (15 grams) in a round flask and heated on the oil bath at 200-210° until all the carbon dioxide had been evolved. As the phthalide was insoluble in water, the naphthalene was removed by washing several times with boiling water and decanting off the melted naphthalene in the form of oil from the top of the liquid. The phthalide was crystallized several times from absolute alcohol with the addition of a little charcoal. Yield 2.7 grams or 55% of the theoretical. The substance decomposed at 180°-185°.

In the second trial the method used by Charlesworth and Robinson (J.C.S., Oct. 1934, 1513) was employed. The method required the use of copper chromite as the catalyst and as a sufficient quantity of this material was not available, it was necessary to prepare a sample of the substance. The method used was that of S. G. Briggs (Mellor - Inorganic Chemistry) (p. 560). In a vessel fitted with a reflux condenser, a mixture of copper carbonate (12 grams) and chromium trioxide (21 grams) and water (15 cc.) were heated on the oil bath. The product was removed and washed with water and dried. This product was copper chromate. The chromate was converted to the chromite by heating the former in an open crucible at 400° when it became a black powder. Yield 5 grams.

2:4-Dimethoxyphthalide- α -carboxylic acid (5 grams) was mixed with copper chromite (0.5 grams) and quinoline (15 cc.) and the mixture was heated on the oil bath at 200-210° until all the carbon dioxide had been evolved. The quinoline solution was decanted from the catalyst into dilute hydrochloric acid, and the greenish precipitate crystallized from absolute alcohol with the addition of a little charcoal. The phthalide was a pale amber material decomposing at 180-182°. Yield 3.0 grams. By the use of the second method it was found that

a slightly purer product was obtained with less difficulty in purification.

Analysis:

	<u>Weight in Grams</u>
Boat + Sample -----	5.0623
Boat -----	4.9488
Sample -----	0.1135
KOH bulbs after combustion -----	67.7950
KOH bulbs before combustion -----	67.5379
CO ₂ absorbed -----	00.2571
CaCl ₂ tube after combustion -----	46.0489
CaCl ₂ tube before combustion -----	45.9962
H ₂ O absorbed -----	00.0526

$$\text{Percentage Carbon } \frac{12 \times 0.2571 \times 100}{44 \times 0.1135} = 61.61 \%$$

$$\text{Percentage Hydrogen } \frac{2 \times 0.0527 \times 100 \times 100}{18 \times 0.1135} = 5.17 \%$$

C₁₀H₁₀O₄ requires Carbon = 61.65% Hydrogen 5.13%

The synthesis of 2:4-dimethoxyphthalide by the Fritsch reaction definitely established the nature of the products I and II, obtained by the action of formaldehyde in the presence of concentrated hydrochloric acid and of s-dichloromethyl ether respectively on 2:4-dimethoxybenzoic acid, as identical with the first named substance. Their identity was shown analysis and mixed melting point determinations.

2:4-Dimethoxyphthalic Acid

Since it had been found that the preparation of 2:4-dimethoxyphthalic acid had not, up to the present time, been attempted, it was thought to be of interest to prepare this substance from the 2:4-dimethoxyphthalide obtained in the previous section and to record its properties.

The 2:4-dimethoxyphthalide (4.5 grams) was dissolved in aqueous potassium hydroxide (100 cc. of 5%) and potassium permanganate (6.2 grams) in water (100 cc.) added at room temperature. After about 24 hours the liquid was filtered and some remaining permanganate reduced by sulphur dioxide. The solution was then concentrated to a small volume and acidified with hydrochloric acid. The crude acid which separated was crystallized from acetic acid (30%). Yield 2.4 grams or 42% of the theoretical M.P. 97-98°. The material was light brown in color and soluble in most of the common organic solvents.

Analysis:

	<u>Determination</u>	
	I	II
	<u>Weight in Grams</u>	<u>Weight in Grams</u>
Boat + Sample -----	4.9684	5.0605
Boat -----	4.8661	4.9483
Sample -----	0.1023	0.1117
KOH bulbs after combustion -----	70.0957	70.3125
KOH bulbs before combustion -----	69.9021	70.0957
CO ₂ absorbed -----	00.1945	00.2168
CaCl ₂ tube after combustion -----	40.3870	40.4324
CaCl ₂ tube before combustion -----	40.3464	40.3870
H ₂ O absorbed -----	00.0406	00.0454

(analysis continued)

$$\text{Percentage Carbon} \text{ ----- } \frac{12 \times 0.1945 \times 100}{44 \times 0.1003} \quad \frac{12 \times 0.2168 \times 100}{44 \times 0.1117}$$

$$= 52.89\%$$

$$= 54.92\%$$

$$\text{Percentage Hydrogen} \text{ ----- } \frac{2 \times 0.0406 \times 100}{18 \times 0.1003} \quad \frac{2 \times 0.0454 \times 100}{18 \times 0.1117}$$

$$= 4.50 \%$$

$$= 4.50 \%$$

Attempted Condensation of 3:4:5-Trimethoxybenzoic Acid with Formaldehyde

In the Presence of Concentrated Hydrochloric Acid

The pure substance 3:4:5-trimethoxybenzoic acid (15 grams) and 40% formaldehyde (50cc.) and concentrated hydrochloric acid (50cc.) were mixed in a round flask and heated on the steam bath for 3 hours and then over wire gauze for $\frac{1}{2}$ hour. At first partial solution seemed to occur, but most of the acid remained floating on top of the formaldehyde-hydrochloric acid mixture. After about $\frac{1}{2}$ hour the solid on top turned to a dark brown oil and settled to the bottom of the flask, where it remained in this condition until the completion of the time of heating. On cooling the oil solidified to a hard resinous mass and was separated by decanting off the formaldehyde-hydrochloric acid liquid above. Yield 8.2 grams. The substance appeared to be in a very impure state. It was crystallized once from absolute alcohol with the addition of a little charcoal. M.P. 78-80° (III) After several more crystallizations from absolute alcohol and the melting point was 80-81°. In all 1.5-2.0 grams of the pure material was obtained, a great deal being lost in the re-crystallizations, these being extremely difficult, the substance tending to separate as an oil. The copper wire test and sodium fusion gave no evidence of the presence of halogen. A second run gave a slightly increased yield.

The formaldehyde-hydrochloric acid mother liquor from the reaction mixture

which had been saved for further examination; on standing several days separated a small amount of white crystalline material, m.p. 78-80°, and this apparently was a little more of (III). On addition of water to the mother liquor a light brownish material was separated and was recrystallized from water. M.P. 163-165°. Yield 2.0-4.0 grams. Sodium fusion and the copper wire test gave no evidence of the presence of halogen and this material was determined to be a portion of the original 3:4:5-trimethoxybenzoic acid by mixed melting point determination with the latter substance.

Product III, separated in white needles from alcohol, was insoluble in water and soluble in most of the common organic solvents except carbon tetrachloride and petroleum ether. It was neutral to litmus and aqueous sodium bicarbonate, insoluble in aqueous sodium hydroxide and soluble with decomposition in concentrated sulfuric acid.

Analysis of Product (III.)

Determination	I	II
Material	Weight in Grams	Weight in Grams
Boat / Sample -----	4.5724	3.0612
Boat -----	4.5623	4.9432
Sample -----	0.1024	0.1133
KOH bulbs after combustion -----	63.0350	62.3373
KOH bulbs before combustion -----	63.5721	62.0250
CO ₂ absorbed -----	00.2229	00.3423
CaCl ₂ tube after combustion -----	45.7755	45.6233
CaCl ₂ tube before combustion -----	45.7173	45.7754
H ₂ O absorbed -----	00.0522	00.0634

Analysis continued

Percentage Carbon	$\frac{12 \times 0.2229 \times 100}{44 \times 0.1042}$	$\frac{12 \times 0.2423 \times 100}{44 \times 0.1133}$	=
	<u>58.37%</u>	58.34%	
Percentage Hydrogen	$\frac{2 \times 0.0582 \times 100}{18 \times 0.1042}$	$\frac{2 \times 0.0634 \times 100}{18 \times 0.1133}$	
	<u>5.51%</u>	6.23%	

It was at first thought that product III, might be the phthalide of 3:4:5-trimethoxybenzoic acid, but this phthalide had been prepared previously by several authors among whom were Alimchandani and Meldrum (J.C.S., 1920, 117, 964) and its melting point determined to be 135-136°. Hence this substance was not identical with III. It was therefore suspected that Product III, was the methyl ester of 3:4:5-trimethoxybenzoic acid, and it was proved to be the ester by the synthesis in the following section.

Preparation of the Methyl Ester of 3:4:5-Trimethoxybenzoic Acid

The method employed in this preparation was that of Bogert and Isham (J. Am. Chem. Soc., 36, 518).

Pure 3:4:5-trimethoxybenzoic acid (5 grams) was suspended in methyl alcohol (30 cc.) and dry hydrochloric acid gas was passed in until solution of the 3:4:5-trimethoxybenzoic acid was complete, and until the alcohol was saturated. On cooling the ester separated almost completely in glistening colorless plates, which were filtered and washed with dilute methyl alcohol and dried. The ester was then recrystallized from 50% methyl alcohol. Yield 5.2 grams, or nearly theoretical. Mixed melting point determinations of this substance with products (III), and (IV) showed the three substances to be identical.

Mean Results

Carbon 58.35%.

Hydrogen 6.22%

C₁₁H₁₄O₅ requires

Carbon 58.4%

Hydrogen 6.1%

Attempted Condensation of 3:4:5-Trimethoxybenzoic Acid with o-Dichloromethyl
Ether in the Presence of Zinc Chloride

The substance 3:4:5-trimethoxybenzoic acid (10 grams) was mixed with o-dichloromethyl ether (20 grams) and anhydrous zinc chloride (5 grams) in a round flask. No reaction occurred in the cold but on gentle warming, a reaction appeared to take place, the liquid becoming dark brown in color. Considerable quantities of hydrochloric acid gas were evolved. The reaction subsided quickly and the mixture was then heated on the water bath for $\frac{1}{2}$ hour and following this it was allowed to cool. A little water was added to dissolve out the zinc chloride. The small amount of dark gummy residue, which remained after the removal of the water, was dissolved in absolute alcohol (75cc.). The alcoholic solution was boiled twice with charcoal, concentrated and allowed to cool and stand for some time. A small amount of light brown substance (IV), m.p. 40-45° separated, the alcoholic mother liquor remaining dark brown in color. This product was crystallized twice from absolute alcohol and the melting point now was 70-80°. On addition of water to the alcoholic mother liquors from the re-crystallizations, a small amount of substance, identical to (IV) separated. The total amount of the substance obtained in a pure form was about 1-1.2 grams, the yields being greatly reduced by the difficulty of the crystallizations, the substance tending to separate as an oil. The material obtained resembled in every way product (III.), the pure substance separating in needles from the alcohol. Mixed melting point determinations with (III.) showed the two substances to be identical. Sodium fusion and the copper wire test gave no evidence of the presence of halogen.

The water solution from the extraction of the zinc chloride, which had been saved for further examination, on standing separated a considerable quantity of a light brown material (3.6 grams) which was separated and dried. M.P. 162-164°. The sodium fusion and the copper wire test gave no evidence of the presence of

halogen and this substance was concluded to be unchanged 3:4:5-trimethoxybenzoic acid by mixed melting point determinations with the latter substance.

Analysis of (IV):-

<u>Material</u>	<u>Weight in Grams</u>
Boat + Sample -----	5.0848
Boat -----	4.9488
Sample -----	0.1360
KOH bulbs after combustion -----	70.4895
KOH bulbs before combustion -----	70.1980
CO ₂ absorbed -----	00.1360
CaCl ₂ tube after combustion -----	44.5413
CaCl ₂ tube before combustion -----	44.7408
H ₂ O absorbed -----	00.0705

$$\text{Percentage Carbon } \frac{12 \times 0.2915 \times 100}{44 \times 0.1360} =$$

58.47 %

$$\text{Percentage Hydrogen } \frac{2 \times 0.705 \times 100}{18 \times 0.1360} =$$

5.77 %.

C₁₁H₁₄O requires Carbon 58.4 % Hydrogen 6.1 %.

Alkaline Degradation of Product III.

Product III. [.4-.5 grams] was mixed with 50% potassium hydroxide solution (20 cc.) in a small round flask and heated over wire gauze for about $\frac{1}{2}$ hour. After this period, solution was complete, the liquid having assumed a light brown color. Acidification of this solution precipitated a light amber colored precipitate which was separated, and dried. Yield 0.1-0.2 grams. M.P. 150-152°. This material was recrystallized from water. Mixed melting point determinations

with 3:4:5-trimethoxybenzoic acid showed the two substances to be identical.

The above procedure and the mixed melting point determinations of products III and IV with the methyl ester of 3:4:5-trimethoxybenzoic acid definitely establish the identity of the above products with the latter substance.

Attempted Condensation of Anisic Acid with Formaldehyde in the Presence of Concentrated Hydrochloric Acid and Zinc Chloride Monohydrate

In the course of the experimental work undertaken in connection with a study on the introduction of the chloromethyl group into the aromatic nucleus, Stephen, Gladding and Short (*loc.cit.*), employed the monohydrate of Zinc Chloride in place of the anhydrous reagent as condensing agent. This substance was observed to be considerably more effective than the anhydrous form, greatly increasing the yields in the reactions in which it was employed. It was for this reason that the attempted reaction with anisic acid was undertaken, in order to determine whether or not condensation would occur in the presence of this substance.

As a supply of this reagent was not available, it was necessary to prepare a sample for use in the reaction. This was carried out by the method of R. Schindler (*Mag. Farm.*, 1830, 31, 187; *Keller's Inorganic Chemistry* - p.540). Concentrated hydrochloric acid was mixed with a syrupy solution of zinc chloride and the colorless hexagonal plates of the monohydrate which separated were filtered and put immediately into the reaction, as the transition temperature of the monohydrate to the anhydrous form is at 27° and the substance was therefore unstable at room temperature.

Anisic acid (10 grams), 40% formaldehyde (50cc.) concentrated Hydrochloric acid (50 cc.) and zinc chloride monohydrate (10 grams) were mixed in a round flask and the mixture heated on the steam bath for three hours and then over wire

gauge for $\frac{1}{2}$ hour. Partial solution seemed to occur, part of the solid settling to the bottom of the flask and the solution above becoming milky in appearance. At the conclusion of the period of heating the mixture was cooled and the solid was separated on the filter. The material was crystallized from dilute alcohol. M.P. 183-184°. Yield 9.4 grams. Mixed melting point determinations with the original anisic acid showed the two substances to be identical. It was therefore concluded that no reaction had occurred.

Attempted Condensation of m-Toluidic Acid with Formaldehyde in the Presence of Concentrated Hydrochloric Acid, Zinc Chloride and Petroleum Ether

R. Guet (Compt. rend., 1934, 198, 102), while investigating the action of formaldehyde and hydrochloric acid on anisole, employed the reagents zinc chloride and petroleum ether as condensing agents in the introduction of the ethyl remethyl group into the nucleus in the production of 4-methoxy- γ -chlorotoluene. The authors found that this combination of reagents was very effective in the reaction, the yield of the above product being 90% of the theoretical. It was therefore thought to be of interest to introduce these reagents in an attempt to obtain a condensation of m-toluidic acid with formaldehyde in the presence of concentrated hydrochloric acid. In undertaking this work two procedures were attempted.

In the first procedure the method employed by Guet (loc. cit.) was used. A rapid stream of hydrochloric acid gas from the generator was passed into a mixture of m-toluidic acid (10 grams), 40% formaldehyde (20 cc.) and petroleum ether (50 cc.) and zinc chloride (5 grams), the mixture being kept at a temperature of 0 - 5° during the addition of the hydrochloric acid. The toluidic acid gradually dissolved in the petroleum ether, the mixture in the flask forming two distinct layers. At the conclusion of the required time of saturation with hydrochloric acid, the mixture was poured on ice and transferred to a separating funnel and the two layers separated. The ethereal layer was washed several

times with cold water and the ether was then removed. The substance which was obtained was recrystallized from water and was shown to be the original *m*-toluic acid by mixed melting point determinations with the latter substance. Practically all the *m*-toluic acid employed at the beginning of the reaction was recovered in an unchanged condition.

In the second procedure the method of Perkins, Edwards and Stoyie (*loc. cit.*) was employed. Similar quantities of the same substances as employed in the first method were mixed in a round flask and heated under reflux on the water bath for 3 hours and then over wire gauze for $\frac{1}{2}$ hour. On cooling the two layers which formed were separated and the etherial layer washed with cold water. The ether was removed and the substance which separated was crystallized from water. Mixed melting point determinations identified the material as unchanged *m*-toluic acid and, as in the first procedure, practically all of the original acid employed was recovered.

It was therefore concluded that in each case no reaction had occurred between the *m*-toluic acid and the formaldehyde and hydrochloric acid in the presence of zinc chloride and petroleum ether.

Section II.

The Action of Formaldehyde in the Presence of Concentrated Hydrochloric Acid on 3:5-Dimethoxy-o-Toluic Acid.

Outline of Preliminary Preparations

In order to obtain the necessary 3:5-dimethoxy-o-toluic acid in sufficient quantities for experimental purposes, this material was synthesized from o-toluidine by converting the latter substance to the corresponding nitrile and toluic acid and subsequently through the disulpho and dihydroxytoluic acids to the dimethoxy-o-toluic acid.

The o-toluidine was first converted to the o-cyanotoluene by the Sandmeyer reaction, following the method described in Organic Syntheses (III., 33; IV., 96). This method was abandoned after the first run due to the low yield obtained and in subsequent preparations of this substance the original method of Sandmeyer, as described in Cohen's Practical Organic Chemistry (p.191) was used with more success.

Hydrolysis of the o-nitrile by means of 50% sulphuric acid yielded the o-toluic acid which was sulphonated by the method of Ashine and Asano (Ber. 1933, 66, 687). The 3:5-disulpho-toluic acid thus obtained was converted to the corresponding hydroxy acid by alkali fusion. Methylation of the product in the usual manner, employing dimethyl sulphate in alkaline solution gave the required 3:5-dimethoxy-o-toluic acid.

Preliminary Preparations

3:5-Disulpho-o-Toluic Acid

The method of Ashine and Asano (Ber., 1933, 66, 687) was employed in this preparation. A mixture of o-toluic acid (25 grams) and fuming sulphuric acid (75 cc. Approximately 50 % free SO_3) prepared by mixing sixty-five percent oleum (55 cc.) with 20% oleum (20cc.) was heated under reflux for eight hours

at 180° on the electric oil bath.

The product was cooled, poured into water (500 cc.) and heated to boiling, neutralized first with barium hydroxide and finally with barium carbonate until all effervescence had ceased and the solution was alkaline. The solution was now concentrated (200 cc.) and concentrated hydrochloric acid was added. Upon standing the barium salt separated and was filtered off at the pump. More was obtained from the mother liquor. The barium salt was now dissolved in water (600 cc.) it being dissolved with difficulty and the barium precipitated with potassium bicarbonate solution. The barium was filtered off and the solution evaporated to dryness. The potassium salt of 3:5-disulpho-o-toluic acid was not converted to the free acid. Yield 80 grams.

3:5-Dihydroxy-o-Toluic Acid

The 3:5-disulpho-o-toluic acid (potassium salt) (80 grams) was added to moist caustic potash (240 grams), fused in a nickel crucible, the mixture being stirred with a thermometer protected by a brass tube in the usual way. The salt was added at 210-220° and the temperature was gradually raised to 260-270° and held at this point for about 20 minutes. After the melt had cooled, the product was dissolved in water, neutralized with sulphuric acid almost to the neutral point, the potassium sulphate removed and the solution acidified with concentrated hydrochloric acid. The crude phenol was extracted with ether, the ethereal solution dehydrated over calcium chloride and the ether removed. Yield 6.5 grams. The melting point of the crude material was 220-225°. The crude product was recrystallized from water by the addition of a little charcoal, when a granular white crystalline substance was obtained, mp. 235-237°. The final yield of the pure material was 20% of the theoretical.

3:5-Dimethoxy-o-Toluic Acid

The pure 3:5-dihydroxy-o-toluic acid (6 grams), from the preceding preparation

was dissolved in 20% aqueous sodium hydroxide (3 grams in 15 cc. water) in a round flask. A three holed cork stopper, equipped with inlet and outlet tubes connected to the gas supply, and a tap funnel was inserted in the flask. Gas was passed in and dimethyl sulphate (10 cc.) was added slowly in three portions with continued shaking and cooling. The solution was now boiled over wire gauze for $1\frac{1}{2}$ hours. On acidifying with concentrated hydrochloric acid, the crude methyl ether was thrown down, m.p. $145-150^{\circ}$. Yield 4.5 grams. A small portion was recrystallized once from water. M.P. $159-160^{\circ}$.

Condensation of 3:5-Dimethoxy-o-Toluic Acid with Formaldehyde in the Presence
Of Concentrated Hydrochloric Acid

The 3:5-dimethoxy-o-toluic acid from the previous preparation was mixed with 40% formaldehyde (15 cc.) and concentrated hydrochloric acid (15 cc.) in a round flask and heated under reflux on the steam bath for 3 hours and then over wire gauze for $\frac{1}{2}$ hour. A considerable amount of frothing was observed at first, accompanied by partial solution. After about an hour the material floating on top of the mixture slowly settled to the bottom of the flask in crystalline flakes and remained in this condition until the completion of the time of heating. The crude solid was separated and dried. M.P. $210-220^{\circ}$. The formaldehyde-hydrochloric acid mother liquor was treated with a little water in order to determine the presence of any other material in this mixture, but none was precipitated from solution. The crude solid from the condensation was crystallized twice from 50% acetic acid. M.P. $248-249^{\circ}$. Yield 3 grams. Sodium fusion or the copper wire test gave no evidence of the presence of halogen.

Analysis of Product V:-

<u>Material</u>	<u>Weight in Grams</u>
Boat + Sample -----	5.1288
Boat -----	4.9492
Sample -----	0.1796
KOH bulbs after combustion -----	59.9244
KOH bulbs before combustion -----	59.5078
CO ₂ absorbed -----	00.0940
CaCl ₂ tube after combustion -----	40.3388
CaCl ₂ tube before combustion -----	40.2449
H ₂ O absorbed -----	00.0240

$$\text{Percentage Carbon } \frac{12 \times 0.4166 \times 100}{44 \times 0.1796} =$$

$$63.28 \%$$

$$\text{Percentage Hydrogen } \frac{2 \times 0.0940 \times 100}{18 \times 0.1796} =$$

$$5.81 \%$$

$\text{C}_{11}\text{H}_{12}\text{O}_4$ requires Carbon 63.46% Hydrogen 5.81 %.

Since the analysis, melting point and properties of product V. were all consistent with those described by Mitter, Sen and Paul (loc.cit.) for 2-methyl-3:5-dimethoxyphthalide, it was concluded that product V. was identical with the above mentioned substance.

Attempted Oxidation of 2-Methyl-3:5-Dimethoxyphthalide

The following was an attempt by the writer to oxidize 2-methyl-3:5-dimethoxyphthalide to the corresponding phthalic acid.

As the phthalide was insoluble in acid and alkali, even on heating, acetone was introduced as the solvent. The acetone was purified by refluxing

commercial acetone over potassium permanganate until a sample distilled off produced no decolorization of a permanganate solution.

A small sample of the phthalide was dissolved in pure acetone (5 cc.) in a test tube and permanganate solution added. There was no apparent decolorization and no evidence of a reaction, even on heating.

Attempted Acid Permanganate Oxidation

The phthalide (1 gram) was dissolved in the pure acetone (10 cc.) and glacial acetic acid (10 cc.) added. The calculated quantity of permanganate (1.42 grams) was dissolved in water (10 cc.) and the solution was slowly added to the phthalide-acid solution with constant stirring. There was no apparent reaction in the cold. The mixture was allowed to stand for from 3 to 4 hours and was then heated for a short time, but this treatment failed to produce evidence of a reaction. The solution was then heated on the water bath until all the acetone was removed, whereby the original phthalide was precipitated from solution, as determined by the melting point, 248-249°.

Attempted Alkaline Permanganate Oxidation.

Exactly the same procedure as above was employed but in this case 5 Normal sodium hydroxide solution (10 cc.) was added in place of the acetic acid. On acidification of the alkaline solution following heating no precipitation resulted and upon removal of the acetone, the phthalide was recovered.

It was therefore concluded that, at least by the above methods, the 3-methyl-3:5-dimethoxy-phthalide can not be oxidized to the corresponding phthalic acid.

The results obtained above are in accordance with those of Witter, Sen and Paul (loc. cit.) who stated that they had found it impossible to oxidize the 3-methyl-3:5-dimethoxy-phthalide to the corresponding phthalic acid. However the above authors failed to mention the methods that had been attempted.

The Action of Formaldehyde in the Presence of Concentrated Hydrochloric Acid on 5-Methoxy-o-Toluic Acid.

Since the 2-methyl-3:5-dimethoxyphthalide of Mitter, Sen and Paul (loc.cit.) had been re-isolated by the action of formaldehyde in the presence of concentrated hydrochloric acid on 3:5-dimethoxy-o-toluic acid and the reaction thus shown to occur by the method of Perkin, Edwards and Stoyie (loc.cit.), it was thought to be of interest to investigate the action of formaldehyde and hydrochloric acid on 5-methoxy-o-toluic acid, in an attempt to obtain the corresponding 2-methyl-5-methoxyphthalide and thus to investigate the reaction of the o-toluic acid exhibiting the presence of one nuclear substituent methoxyl group.

As in the case of 3:5-dimethoxy-o-toluic acid, in order to obtain the necessary 5-methoxy-o-toluic acid in sufficient quantities for experimental purposes, this material was synthesized from o-toluic acid by converting the latter through the sulpho- and hydroxytoluic acids to the methoxytoluic acid.

Preliminary Preparations

5-Sulpho-o-Toluic Acid

The method of Meldrum and Perkin (J.C.S., 1909, 1899) was employed. A mixture of o-toluic acid (100 grams) and concentrated sulphuric acid (150 cc.) was heated under reflux on the paraffin bath for 8 hours. The product was then cooled, water (180 cc.) added and the dark colored solution allowed to stand for several hours. The crystals of sulphonic acid which separated were removed and crystallised from acetic acid (30%). M.P. 115-117°. Yield 125 grams or 72 % of the theoretical.

5-Hydroxy-o-Toluic Acid

The 5-hydroxy-o-toluic acid was prepared by the same procedure as employed in the preparation of 3:5-dihydroxy-o-toluic acid described previously. The

acid crystallized in needles from water. M.P. 183-185°. The yield from 120 grams of the sulphonie acid was 27 grams or 38% of the theoretical value.

5-Methoxy-o-Toluic Acid

The 5-Methoxy-o-toluic acid was prepared by methylation of the 5-hydroxy-o-toluic acid from the corresponding hydroxy acid. The product was crystallized twice from acetic acid (50%). M.P. 146-147°. The yield from 25 grams of the 5-hydroxy-o-toluic acid was 23.3 grams or 75% of the theoretical. Since it had been found that the preparation of this acid had not previously been reported, analysis of the material was undertaken.

Analysis:

	<u>Determination</u>	
	<u>I.</u>	<u>II.</u>
	<u>Weight in Grams</u>	<u>Weight in Grams</u>
Boat / Sample -----	4.8682	4.9488
Boat -----	5.0031	5.0905
Sample -----	0.1349	0.1417
KOH bulbs after combustion -----	65.9923	66.3297
KOH bulbs before combustion -----	65.6714	65.9923
CO ₂ absorbed -----	00.3209	00.5374
CaCl ₂ tube after combustion -----	44.8586	44.9361
CaCl ₂ tube before combustion -----	44.7245	44.8586
H ₂ O absorbed -----	00.0743	00.0775
Percentage Carbon -----	$\frac{12 \times 0.3209 \times 100}{44 \times 0.1349}$	$\frac{12 \times 0.5374 \times 100}{44 \times 0.1417}$
	= 64.87 %	= 64.94 %.

(analysis continued)

Percentage Hydrogen -----	$\frac{2 \times 0.0743 \times 100}{18 \times 0.1349}$	$\frac{2 \times 0.0775 \times 100}{18 \times 0.1417}$
	= 6.12 %	= 6.02 %
Mean -----Carbon = 64.90 %.	Hydrogen = 6.10 %	
$C_9H_{10}O_3$ requires-- Carbon = 65.05%	Hydrogen = 6.02 %	

Condensation of 5-Methoxy-o-Toluic Acid with Formaldehyde in the Presence of Concentrated Hydrochloric Acid

The 5-methoxy-o-toluic acid (10 grams) from the previous preparation was mixed with 40% formaldehyde (50 cc.) and concentrated hydrochloric acid (50 cc.) in a round flask and heated under reflux on the steam bath for 3 hours and then over wire gauze for $\frac{1}{2}$ hour. After completion of the time of heating, the crude solid was separated and dried. The substance crystallized in white needles from acetic acid (50%) (Product VI). M.P. 165-166°. Yield 7.2 grams or 71% of the theoretical. Sodium fusion or the copper wire test gave no evidence of the presence of halogen. The formaldehyde-hydrochloric acid mother liquor from the condensation was treated with a little water in order to determine the presence of any other material in this mixture, but none was precipitated from solution.

Analysis:

Determination

	<u>I.</u>	<u>II.</u>
	<u>Weight in Grams</u>	<u>Weight in Grams</u>
Boat + Sample -----	5.0057	5.0732
Boat -----	4.8682	5.0732
Sample -----	0.1375	0.1244

KOH bulbs after combustion -----	69.7135	69.0184
KOH bulbs before combustion -----	68.3719	68.7133
CO ₂ absorbed -----	00.3394	00.3071
CaCl ₂ tube after combustion -----	45.1876	45.2505
CaCl ₂ tube before combustion -----	45.1182	45.1876
H ₂ O absorbed -----	00.0696	00.0627

Percentage Carbon -----	$\frac{12 \times 0.3394 \times 100}{44 \times 0.1375}$	$\frac{12 \times 0.0627 \times 100}{44 \times 0.1244}$
-------------------------	--	--

= 67.32 %

= 67.32 %.

Percentage Hydrogen -----	$\frac{2 \times 0.0696 \times 100}{18 \times 0.1375}$
---------------------------	---

= 5.63 %.

$\frac{2 \times 0.0627 \times 100}{18 \times 0.1244}$

= 5.60 %.

Mean ----- Carbon = 67.32 % Hydrogen = 5.61 %.

C₁₀H₁₀O₃ requires ----- Carbon = 67.41% Hydrogen = 5.61 %.

Preparation of 2-Methyl-5-Methoxyphthalide by the Chloral Hydrate Condensation

As in the case of products (I) and (II) (2:4-dimethoxyphthalide) previously described, product (VI) was suspected of being the corresponding 2-methyl-5-methoxyphthalide. It was therefore decided to prepare the latter substance by the standard Fritsch reaction and in this way attempt to establish definitely the nature of this product. The starting material for the series of reactions involved was 2:4-dimethoxy-o-toluic acid whose preparation was described previously in this section.

2-Methyl-5-Methoxy-1-Trichloromethylphthalide

A similar procedure was employed in this case as in the preparation of 2:4-dimethoxy-1-trichloromethylphthalide from 2:4-dimethoxybenzoic acid.

5-Methoxy-o-toluic acid (10 grams) was mixed in a stoppered flask with powdered chloral hydrate (21.1 grams) and sulphuric acid (46 cc. with 3 cc. water) added. After 24 hours the reaction mixture was poured on ice and the separated solid was washed with water. The 2-methyl-5-methoxy- α -trichloromethylphthalide was crystallized from alcohol and separated as a fine white crystalline material. M.P. 134-135°. Yield 12.2 grams of 75% of the theoretical.

Analysis

Since it was impossible to undertake the analysis of this material for carbon and hydrogen content for reasons mentioned previously, the substance was analysed for chloride using the semi-micro method of B. Bobranski (loc. cit.).

Standardization:

1 gram of AgNO_3 solution was equivalent to 0.001752 grams Cl.

Determination

	<u>I</u>	<u>II</u>
Boat Sample -----	1.0866 g.	1.0852 g.
Boat -----	1.0852 g.	1.0852 g.
Sample -----	0.0314	0.0300 g.
Burette before combustion -----	61.9000	55.4865 g.
Burette after combustion -----	55.4865	49.3615 g.
Weight of AgNO_3 solution used -----	6.4201	6.1250 g.
Percentage Chlorine -----	45.82 %.	35.77 %.

Mean ----- 35.79%

$\text{C}_{11}\text{H}_9\text{O}_4 \cdot 0.01_3$ requires 35.04 %.

2-Methyl-5-Methoxy-4-Carboxylic Acid

The same procedure as employed in the preparation of 2:4-dimethoxyphthalide-4-carboxylic acid described previously was used in this case. - 2-Methyl-5-methoxy-4-trichloromethylphthalide (8 grams) and 20% aqueous sodium hydroxide (80 cc.) were mixed in a beaker and heated on the steam bath for 1 hour. The dark red solution was filtered and acidified with concentrated hydrochloric acid and the precipitate separated at the pump and dried. The 2-methyl-5-methoxyphthalide -4-carboxylic acid crystallized in pale yellow needles from water. M.P. 157 - 158°. Yield 5.5 grams or 88% of the theoretical.

Analysis:

	<u>Determination</u>	
	<u>I.</u>	<u>II.</u>
	<u>Weight in Grams</u>	<u>Weight in Grams</u>
Boat + Sample -----	4.9296	5.0761
Boat -----	4.8682	4.9488
Sample -----	0.1314	0.1273
KOH bulbs after combustion -----	65.0074	65.2848
KOH bulbs before combustion -----	64.7219	65.0074
CO ₂ absorbed -----	00.2855	00.2770
CaCl ₂ tube after combustion -----	44.9893	44.0414
CaCl ₂ tube before combustion -----	44.9383	44.9893
H ₂ O absorbed -----	00.0535	00.0521
Percentage Carbon -----	$\frac{12 \times 0.2855 \times 100}{44 \times 0.1314}$	$\frac{12 \times 0.2770 \times 100}{44 \times 0.1273}$
	= 59.25 %	= 59.34 %

Analysis Continued:

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$$\text{Percentage Hydrogen} = \frac{2 \pm 0.0535 \pm 100}{18 \pm 0.1343}$$

$$\frac{2 \pm 0.0521 \pm 100}{18 \pm 0.1275}$$

$$= 4.53 \%$$

$$= 4.55 \%$$

$$\text{Mean} \longrightarrow \text{Carbon} = 59.30 \%$$

$$\text{Hydrogen} = 4.54 \%$$

$$\text{C}_{11}\text{H}_{10}\text{O}_5 \text{ requires Carbon} = 59.45 \%$$

$$\text{Hydrogen} = 4.50 \%$$

2-Methyl-5-Methoxyphthalide

The method used by Charlesworth and Robinson (J.C.S., 1934, 1513) was employed. This method had previously been used in the preparation of 2:4-dimethoxyphthalide from 2:4-dimethoxyphthalide-1-carboxylic acid. - 2-Methyl-5-methoxyphthalide-1-carboxylic acid (4.5 grams) was mixed with copper chromite (0.4 grams) and quinoline (15 cc.) and the mixture heated on the oil bath at 170-180° until all the carbon dioxide had been evolved. The quinoline solution was decanted from the catalyst into dilute hydrochloric acid and the greenish precipitate crystallized from acetic acid with the addition of a little charcoal. The phthalide separated in fine white needles. M.P. 165-166°. Yield 2.8 grams or 80% of the theoretical.

Analysis

	<u>Weight in Grams</u>
Boat Sample	5.0195
Boat	4.8662
Sample	0.1514
KOH bulbs after combustion	67.3986
KOH bulbs before combustion	67.0143
CO ₂ absorbed	00.3743
CaCl ₂ tube after combustion	45.1183

Analysis Continues

CaCl₂ tube before combustion ----- 45.0412

H₂O absorbed ----- 60.0771

Percentage Carbon ----- $\frac{12 \times 0.3743 \times 100}{44 \times 0.1514}$

= 67.37 %

Percentage Hydrogen ----- $\frac{2 \times 0.0771 \times 100}{18 \times 0.1514}$

= 5.66 %.

$\text{C}_{10}\text{H}_{10}\text{O}_3$ requires Carbon = 67.41 % Hydrogen = 5.61 %

The synthesis of 2-methyl-5-methoxyphthalide by the Fritsch reaction definitely established the nature of product VI., obtained by the action of formaldehyde in the presence of concentrated hydrochloric acid on 5-methoxy- α -toluic acid, as identical with the first named substance. The identity of the two products was shown by analysis and mixed melting point determinations.

Attempted Oxidation of 2-Methyl-5-Methoxyphthalide

Since it had been found during the course of the present investigation that it was impossible, at least by the experimental methods attempted, to oxidize 2-methyl-3:5-dimethoxyphthalide (Mitter, Sen and Paul, loc. cit.), it was thought to be of interest to attempt an oxidation of the 2-methyl-5-methoxyphthalide prepared in the previous section, in order to determine whether this substance showed a similar resistance to oxidation and if possible to prepare the corresponding phthalic acid and record its properties.

In this case the same procedure as employed in the attempted oxidation of 3-methyl-3:5-dimethoxyphthalide was used, with the exception that the 2-methyl-5-methoxyphthalide was found to be soluble in the alkaline permanganate solution and therefore introduction of the purified acetone was not necessary.

Both alkaline and acid permanganate oxidations failed to produce the corresponding phthalic acid and in each case practically all of the original phthalide was regained. It may therefore be stated that it is impossible, at least by the experimental methods attempted, to oxidize 2-methyl-2-methoxyphthalide to the corresponding phthalic acid.

SUMMARY

1. An introductory discussion of previous researches on related reactions has been presented.
2. A theoretical discussion of the various reactions undertaken has been given.
3. The action of formaldehyde in the presence of concentrated hydrochloric acid and of *s*-dichloromethyl ether respectively on benzoic acid, *o*-methoxybenzoic acid, anisic acid and *m*- and *p*-toluic acids has been investigated and it has been found that these reagents give no reaction with the acids mentioned. Definite evidence has been presented to show that the presence of the carboxyl group inhibits the introduction of the chloromethyl group into the aromatic nucleus.
4. -3:4:5-Trimethoxybenzoic acid has been shown to give no condensation products with formaldehyde in the presence of concentrated hydrochloric acid or with *s*-dichloromethyl ether, but the formation of the methyl ester of the acid was observed which was probably due to impurities in the reagents employed.
5. -2:4-Dimethoxyphthalide has been prepared for the first time by the action of formaldehyde in the presence of concentrated hydrochloric acid and *s*-dichloromethyl ether respectively on 2:4-dimethoxybenzoic acid. The same phthalide has been prepared by the Fritsch reaction, in the course of which 2:4-dimethoxy- α -trichloromethylphthalide and 2:4-dimethoxyphthalide- α -carboxylic acid were prepared for the first time. Oxidation of the phthalide yielded 2:4-dimethoxyphthalic acid.
6. The work of Mitter, Sen and Paul (J. Ind. Chem. Soc., 1927, 4, 534) in regard to the preparation of 2-methyl-3:5-dimethoxyphthalide by the action of formaldehyde in the presence of concentrated hydrochloric acid on

creoscellenic acid, has been confirmed.

7. The preparation of 2-methyl-5-methoxyphthalide has been recorded for the first time by the action of formaldehyde in the presence of concentrated hydrochloric acid on 5-methoxy-o-toluic acid. Preparation of the same phthalide by the Fritsch reaction yielded 2-methyl-5-methoxy- - trichloromethylphthalide and 2-methyl-5-methoxyphthalide-4-carboxylic acid in their first recorded preparation. It was found impossible to oxidize this phthalide to the corresponding phthalic acid.

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