

OXIDATIVE DEGRADATION OF CERTAIN DIOXANYLPHTHALIDES
OF THE TOLUIC ACIDS.

OXIDATIVE DEGRADATION OF CERTAIN DIOXANYLPHTHALIDES OF
THE TOLUIC ACIDS

by

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TABLE OF CONTENTS

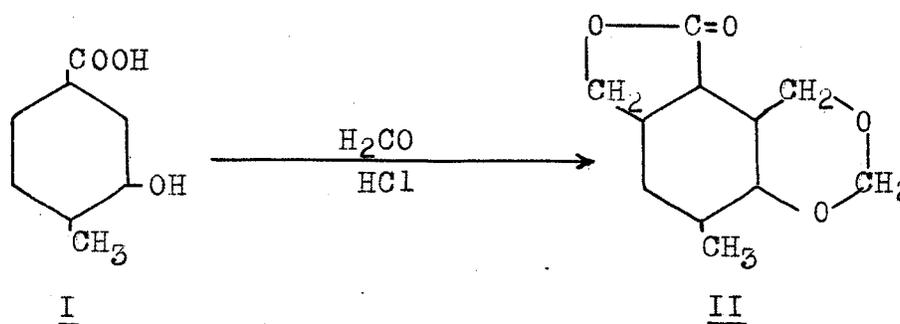
	<u>Pages</u>
<u>INTRODUCTION</u>	1
<u>LITERATURE SURVEY</u>	3
<u>DISCUSSION OF RESULTS</u>	24
Structure of 6-hydroxymethyl-1,3-benzodioxane-8-methyl- 5-carboxylic acid lactone.....	24
Synthesis of 4-methoxybenzene-1,2,3,5-tetracarboxylic acid.....	29
Other condensations.....	30
 <u>EXPERIMENTAL</u>	
I. Chromium Trioxide Oxidation of 6-Hydroxymethyl-1,3-Benzodioxane- 8-Methyl-5-Carboxylic Acid.....	32
(a) Preparation of p-toluic acid from p-tolunitrile.....	32
(b) Sulphonation of p-toluic acid.....	32
(c) Preparation of 3-hydroxy-p-toluic acid.....	33
(d) Preparation of the lactone of 6-hydroxy- methyl-1,3-benzodioxane-8-methyl-5-carboxylic acid.....	33
(e) Preparation of the 6-hydroxymethyl-8-methyl-1,3- benzodioxane-4-one-5-carboxylic acid.....	34
(f) Preparation of 4-methyl-5-hydroxy-1,2-phthalide-6- carboxylic acid.....	35
(g) Preparation of 4-methyl-5-hydroxy-1,2-phthalide.....	35
II. Synthesis of 4-Methyl-5-Hydroxy-1,2-Phthalide.....	36
(a) Preparation of 3-methoxy-p-toluic acid.....	36

(b) Preparation of 4-methyl-5-methoxy-1,2-phthalide.....	36
(c) Preparation of 4-methyl-5-hydroxy-1,2-phthalide.....	37
III. Synthesis of 4-Methoxybenzene-1,2,3,5-Tetracarboxylic Acid.....	37
(a) Preparation of bromobenzene.....	37
(b) Preparation of isodurene.....	38
(c) Preparation of isodurene sulphonic acid.....	40
(d) The oxidation of isodurene sulphonic acid.....	40
(e) Preparation of 4-hydroxybenzene-1,2,3,5-tetracarboxylic acid..	41
(f) Preparation of 4-methoxybenzene-1,2,3,5-tetracarboxylic acid..	42
(g) Preparation of the phenacyl ester of 4-methoxy- benzene-1,2,3,5-tetracarboxylic acid.....	43
IV. Other Condensations.....	44
1(a) Preparation of o-toluic acid.....	44
(b) Preparation of 3,5-disulphonic-p-toluic acid.....	44
(c) Preparation of 3,5-dihydroxy-o-toluic acid.....	45
(d) The condensation of 3,5-dihydroxy-o-toluic acid with formaldehyde and hydrochloric acid.....	45
2 The condensation of 5-hydroxy-m-toluic acid with formaldehyde and hydrochloric acid.....	46
<u>SUMMARY</u>	47
<u>BIBLIOGRAPHY</u>	48

INTRODUCTION

It has been found by Yan (27), Anderson (1) and Radych (19) that on condensation of hydroxy-substituted toluic acids with formaldehyde and concentrated hydrochloric acid, products containing a 1,3-dioxane ring as well as the expected phthalide ring were obtained.

Recently, Thompson (25) and Dudley (13) carried out this condensation with 3-hydroxy-p-toluic acid and 5-hydroxy-o-toluic acid, respectively.



However, the structures of the condensation products were not completely elucidated. The object of this research was to establish firmly, the structures of these substances.

The first part of the work deals with the breaking of the dioxane ring of the 6-hydroxymethyl-8-methyl-1,3-benzodioxane-7-carboxylic acid lactone (II) by oxidation with chromium trioxide in the presence of glacial acetic acid and the subsequent hydrolysis of the methylene ether-ester compound. The end-product of the above oxidative degradation, 5-hydroxy-3-methyl-phthalide was synthesized and a comparison of the two products proved their identity.

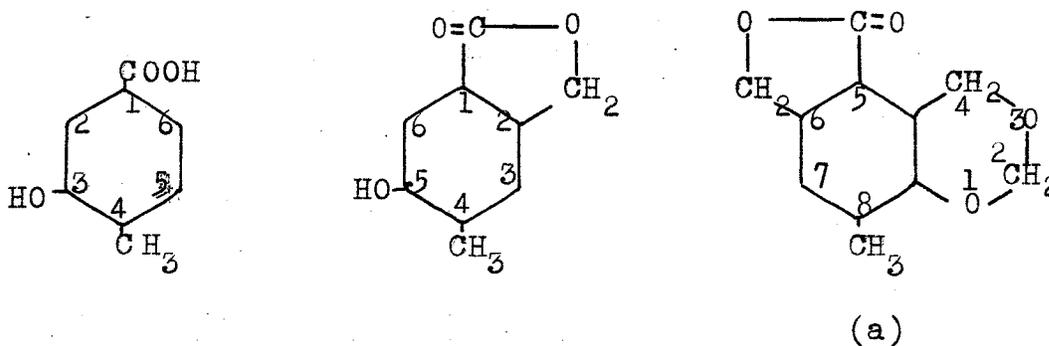
The second phase of the work consists of the synthesis of 4-methoxybenzene-1,2,3,5-tetracarboxylic acid, which is the end-product of the degradative work carried out by Dudley (13) on the condensation product of 5-hydroxy-*o*-toluic acid with formaldehyde and concentrated hydrochloric acid.

Lastly, the condensations of 3, 5-dihydroxy-*o*-toluic acid and 5-hydroxy-*m*-toluic acid with formaldehyde and concentrated hydrochloric acid were attempted.

LITERATURE SURVEY

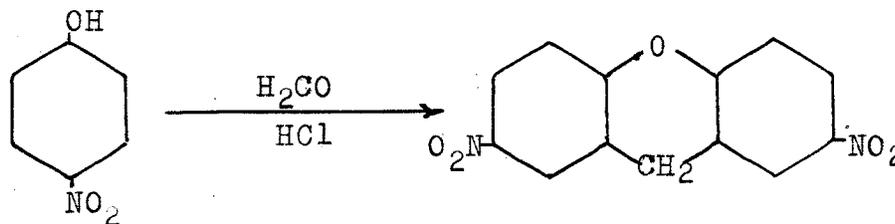
As the literature on the phthalide rings has been reviewed by Anderson (1) and Radych (18), only the relevant parts of these surveys will be considered in any detail.

The numbering systems used throughout this thesis are based on those of Patterson's Ring Index.

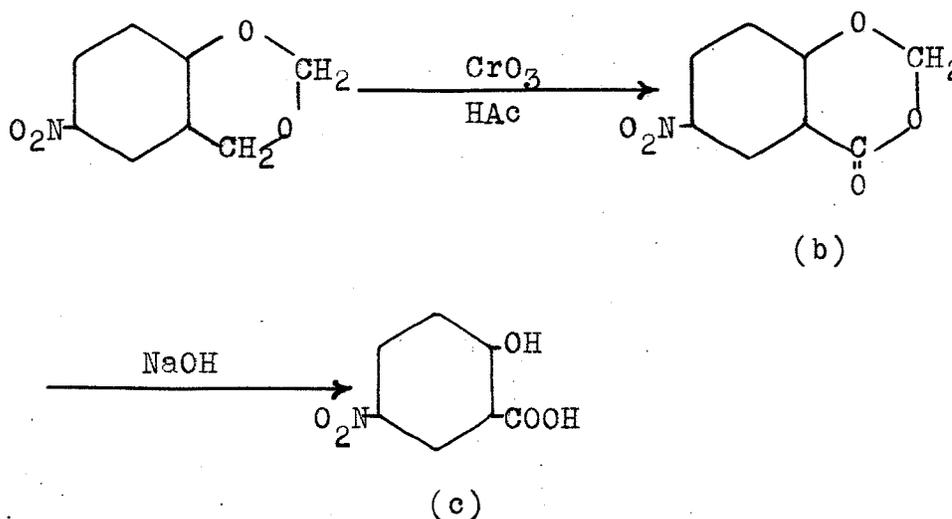


For example, the dioxanylphthalide (a) would be 6-hydroxymethyl-8-methyl-1,3-benzodioxane-5-carboxylic acid lactone.

Borsche and Berkhout (4) were the first to report the synthesis of a compound containing the benzodioxane ring. These authors re-investigated the product obtained by Borsche (3) from the condensation of p-nitrophenol with formaldehyde and hydrochloric acid and which Borsche originally claimed had a xanthene structure, as shown below.



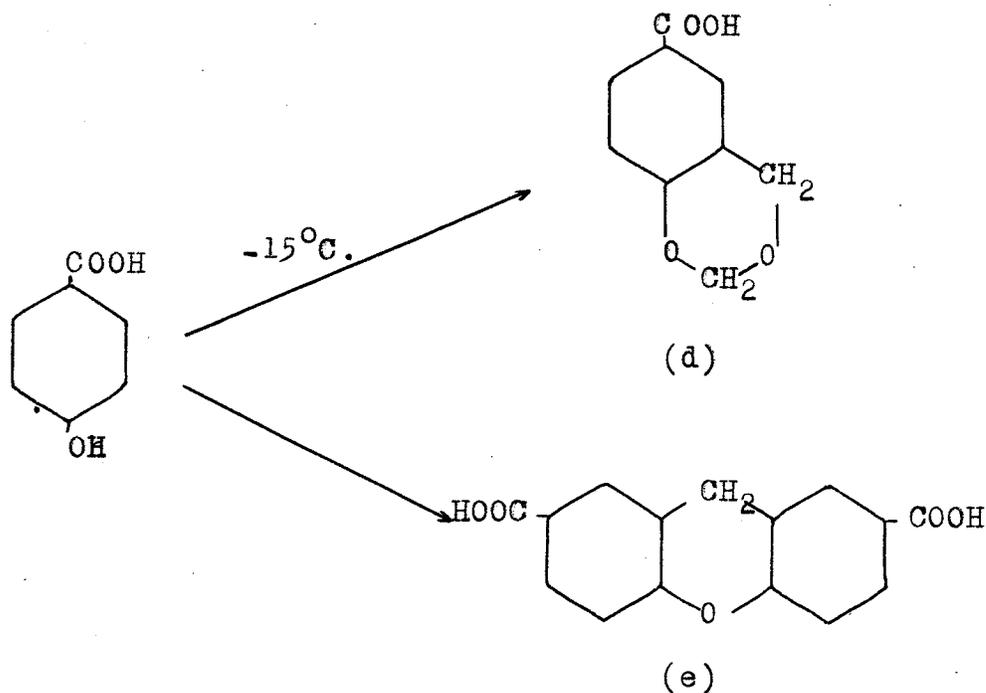
The above authors found that the condensation product did not have a xanthene structure but rather a benzodioxane structure. By oxidizing the condensation product with chromium trioxide in glacial acetic acid, they isolated a non-acidic material (b), which on hydrolysis with sodium hydroxide lost formaldehyde to give 5-nitrosalicylic acid (c).



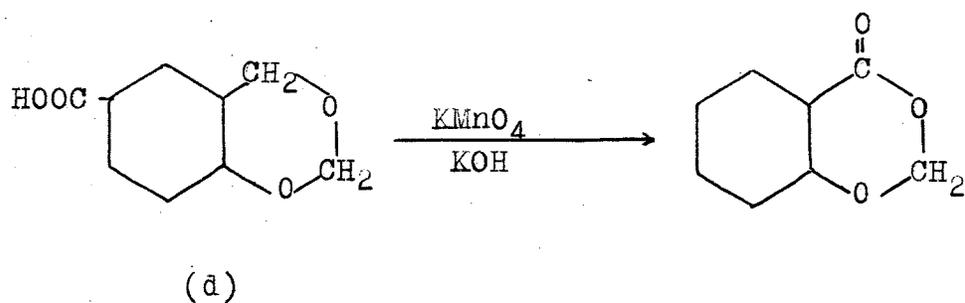
Borsche and Berkhout (4) also obtained dioxane rings by condensing 5-nitrocresol, 6-nitrocresol, *o*-nitronaphthol and *p*-nitrophenol with formaldehyde and concentrated hydrochloric acid. In each case, the dioxane ring was oxidized and hydrolyzed to a nitro-substituted *o*-hydroxy-carboxylic acid.

The next workers in this field were Mejuto and Calvet (17). They condensed *p*-hydroxybenzoic acid with formaldehyde and concentrated sulphuric acid at different temperatures and obtained two different

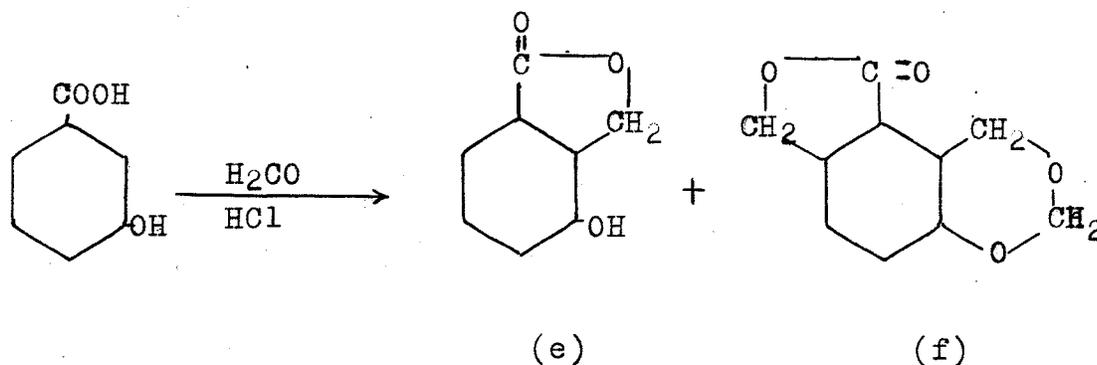
products. At -15°C , they obtained 6-carboxylic acid-1,3-benzodioxane (d), and at a higher temperature they obtained a compound having a xanthene structure (e).



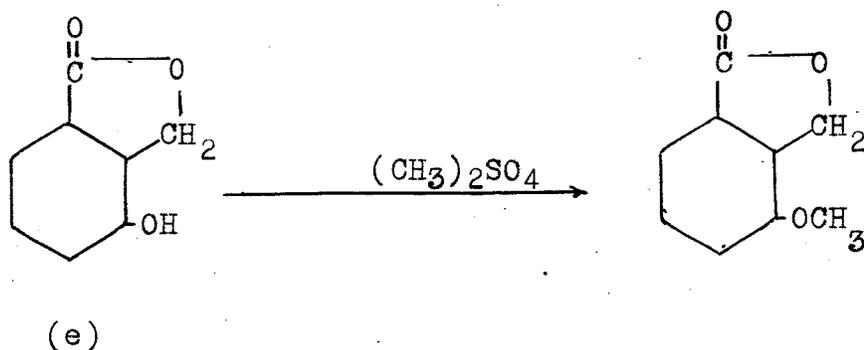
Oxidation of (d) with alkaline permanganate formed 4-keto-1,3-benzodioxane, with the evolution of carbon dioxide.

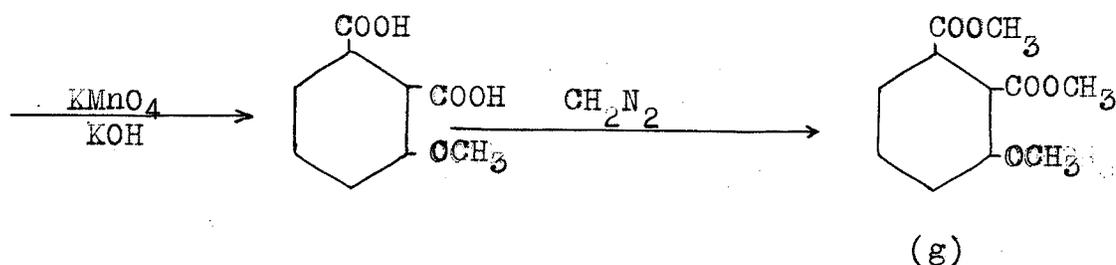


Finally, the most important advances in the study of 1,3-benzodioxane structures were accomplished by Buehler and his coworkers (5-9). Buehler, Powers and Michels (7) condensed 3-hydroxybenzoic acid with formaldehyde and hydrochloric acid and obtained two products of melting point 254°C and 175°C .

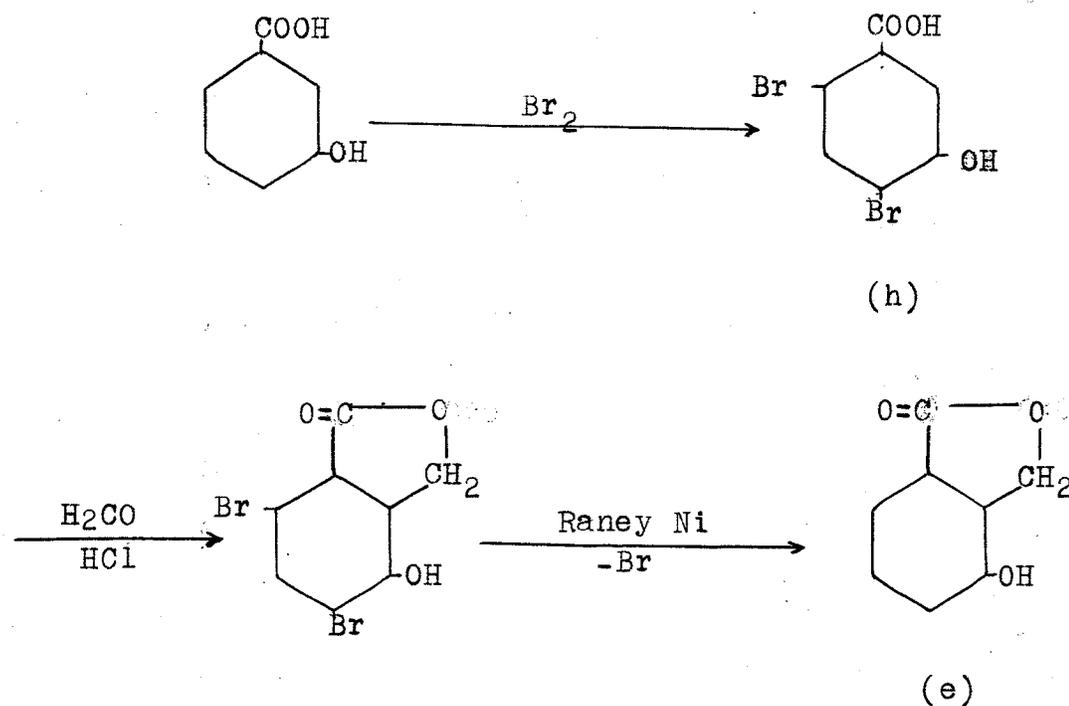


The compound with the higher melting point was found to be a simple phthalide in the following manner. The hydroxyphthalide (e) was methylated. This product was oxidized with alkaline permanganate to give a methoxyphthalic acid which when treated with diazomethane produced the known dimethyl ester of 3-methoxyphthalic acid (g).

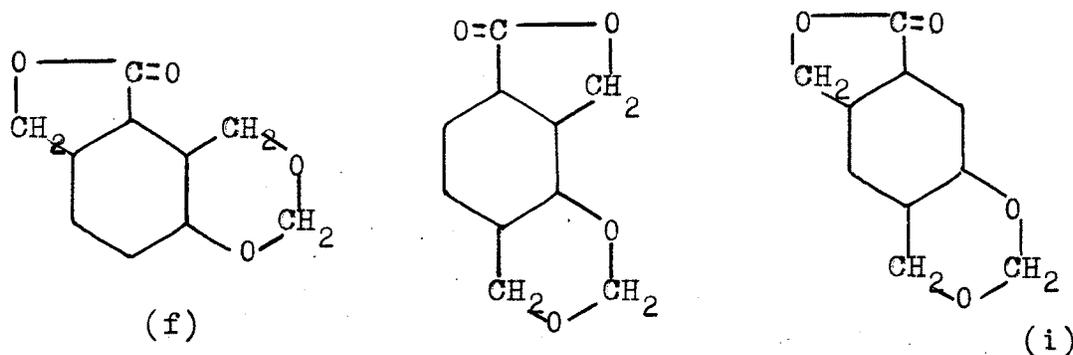




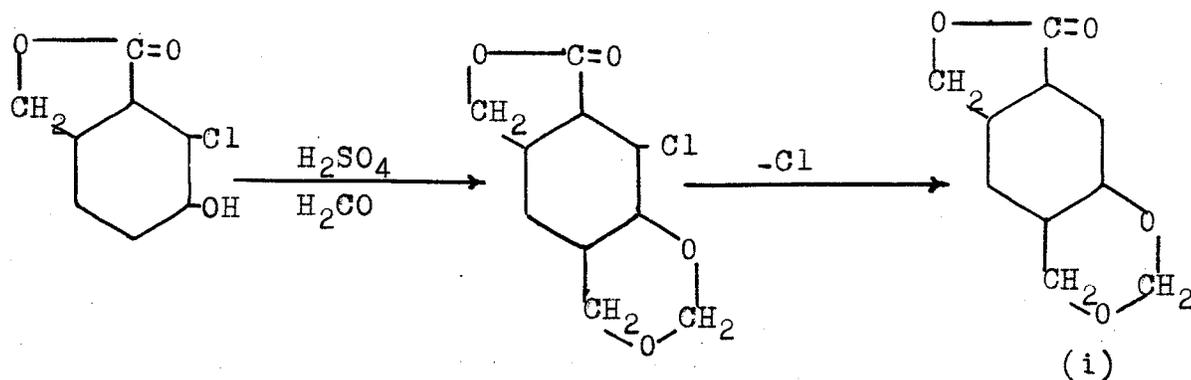
Further proof was presented by the synthesis of the 3-hydroxyphthalide (e). *m*-Hydroxybenzoic acid was brominated to give the known dibromo acid (h) which was then condensed with formaldehyde and hydrochloric acid. Due to the orientation of the dibromo acid (h), only one possible phthalide could result from the condensation. The dibromo phthalide was dehalogenated with Raney nickel under pressure to yield the 3-hydroxyphthalide (e).



Buehler, Harris, Schacklett and Block (6) carried out the investigation of the other condensation product. They found that this product could have three possible isomeric structures, namely;

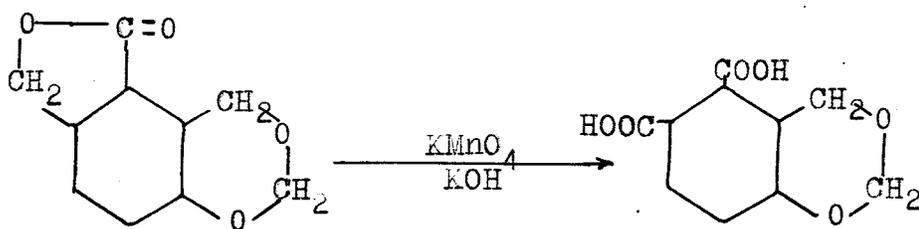


Compound (i) was synthesized by condensing 5-hydroxy-*o*-chlorophthalide with paraformaldehyde and sulphuric acid. This compound was shown to be different from the condensation product.

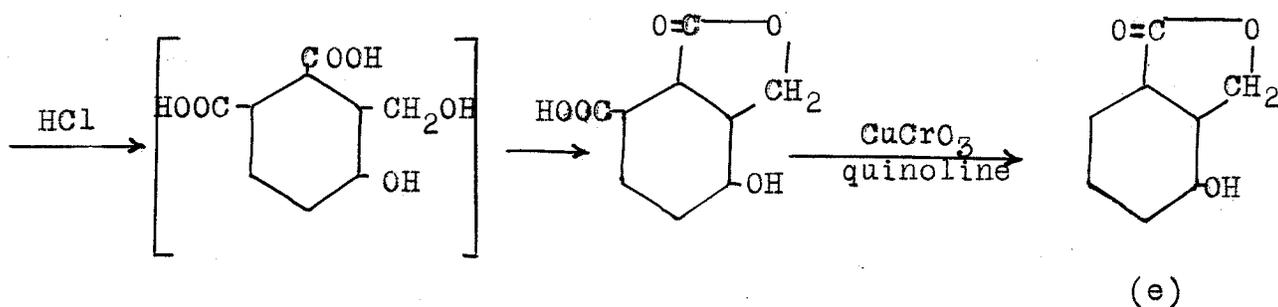


Oxidative degradation was then carried out on the condensation product and ^{it was thought} proved to have the structure (f). This dioxanylphthalide was oxidized in an alkaline medium to give a phthalic acid, which was converted into the monocarboxylic acid with a loss of formaldehyde by refluxing with hydrochloric acid. The intermediate product was not isolated but merely postulated by Buehler. The monocarboxylic acid was

then decarboxylated to give the known 3-hydroxyphthalide (e)



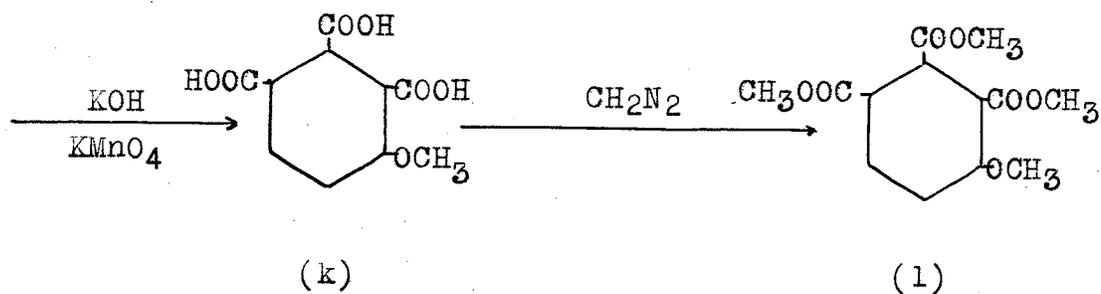
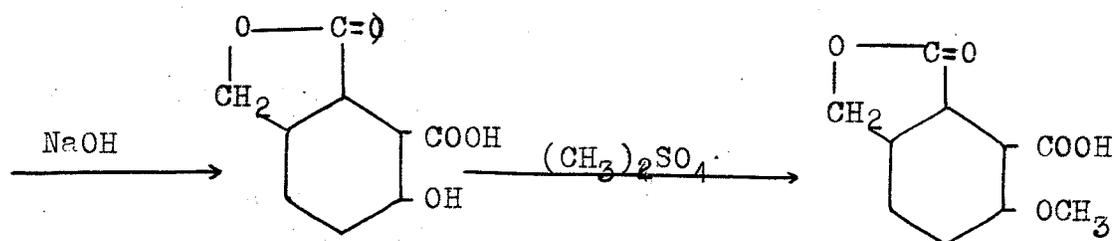
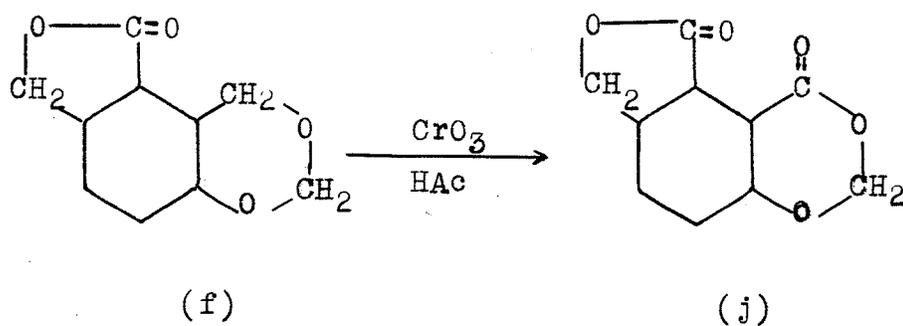
(f)



(e)

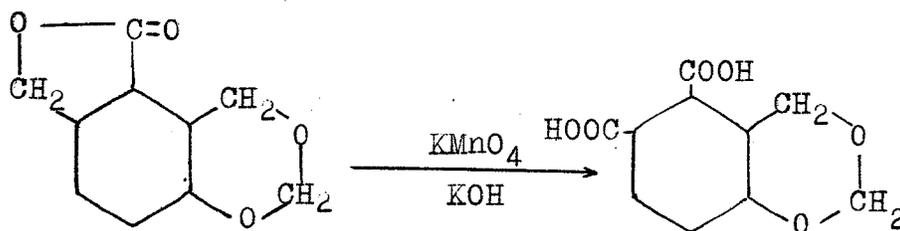
However, this proof was not conclusive and further work was done by Buehler, Slack, Shirley, Sanguinetti and Frey (8). They accomplished two series of oxidative degradation^s and in both cases the end-product was 4-methoxybenzene-1,2,3-tricarboxylic acid (l) which was synthesized by Buehler, Spees and Sanguinetti (9), as shown on pages 12 and 13.

In the first degradative series, the dioxane ring was opened before breaking the phthalide ring. The dioxanylphthalide (f) was oxidized with chromium trioxide in glacial acetic acid to give the methylene ether-ester compound (j). Saponification of this product with sodium hydroxide gave the o-hydroxy carboxylic acid, which was methylated to produce the methyl ether. This compound was then oxidized with alkaline permanganate to give the known methoxy tricarboxylic acid (k). This acid was further identified by methylating with diazomethane to its methyl ester.

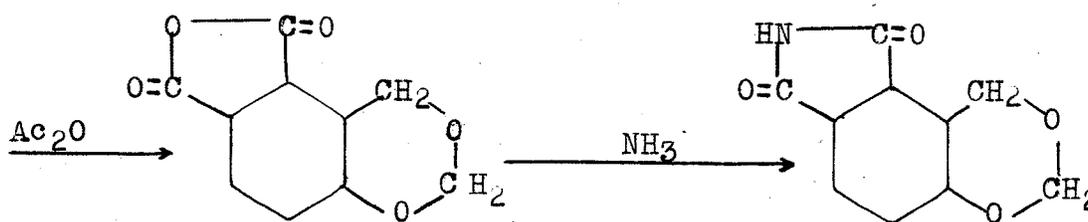


In the second series, the dioxanyl phthalide (f) was oxidized with alkaline permanganate. This broke the phthalide ring to give the dicarboxylic acid. Treatment of this acid with acetic anhydride gave the phthalic anhydride (m). Further treatment with ammonia gave the imide (n),

which was then oxidized with chromium trioxide in glacial acetic acid. Hydrolysis with aqueous sodium hydroxide opened both the methylene ether-ester ring and the phthalimide ring to give the hydroxy-substituted hemimellitic acid which was simultaneously esterified and etherified with diazo-methane to give the methyl ester of 4-methoxybenzene -1, 2, 3- tri-carboxylic acid (1).

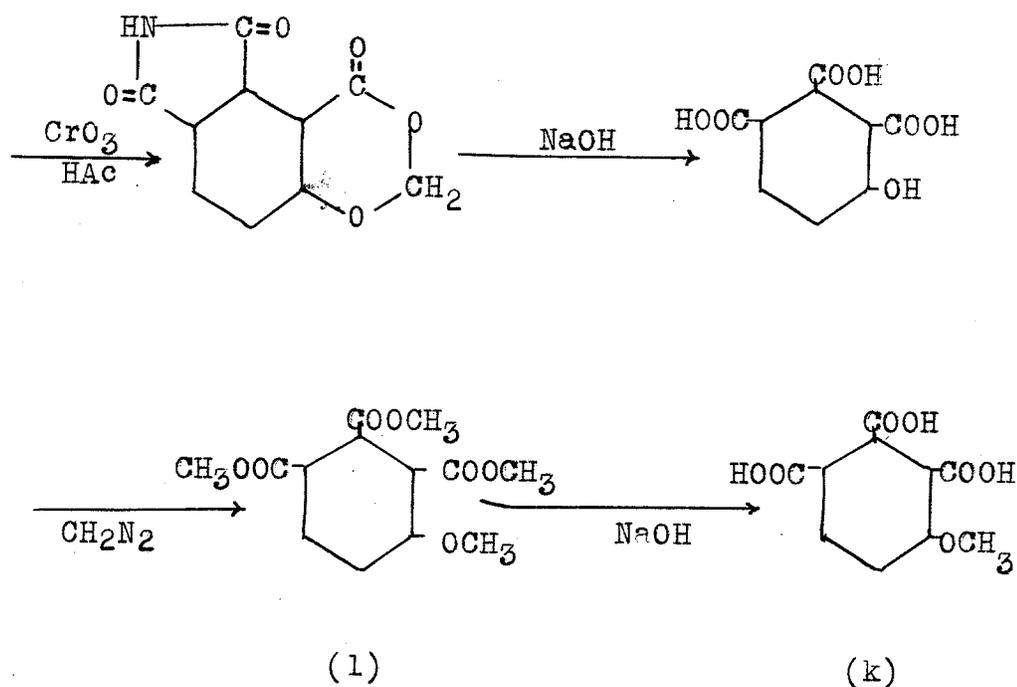


(f)

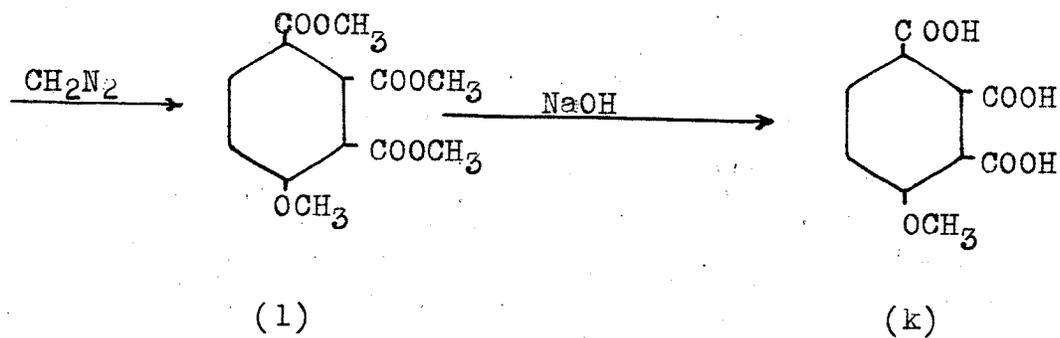
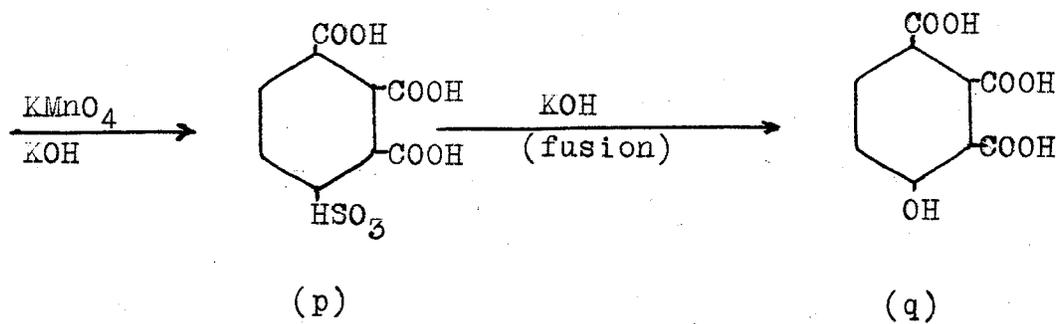
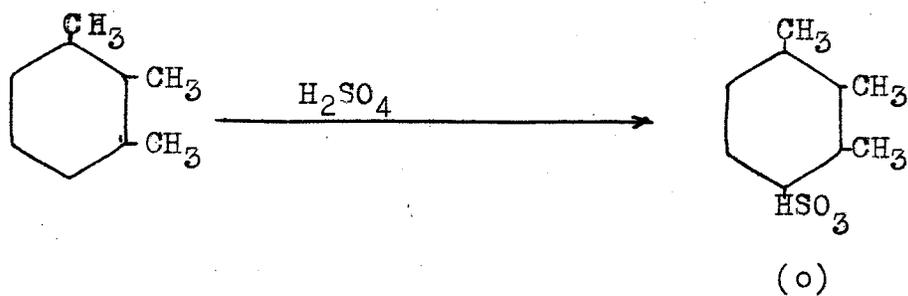


(m)

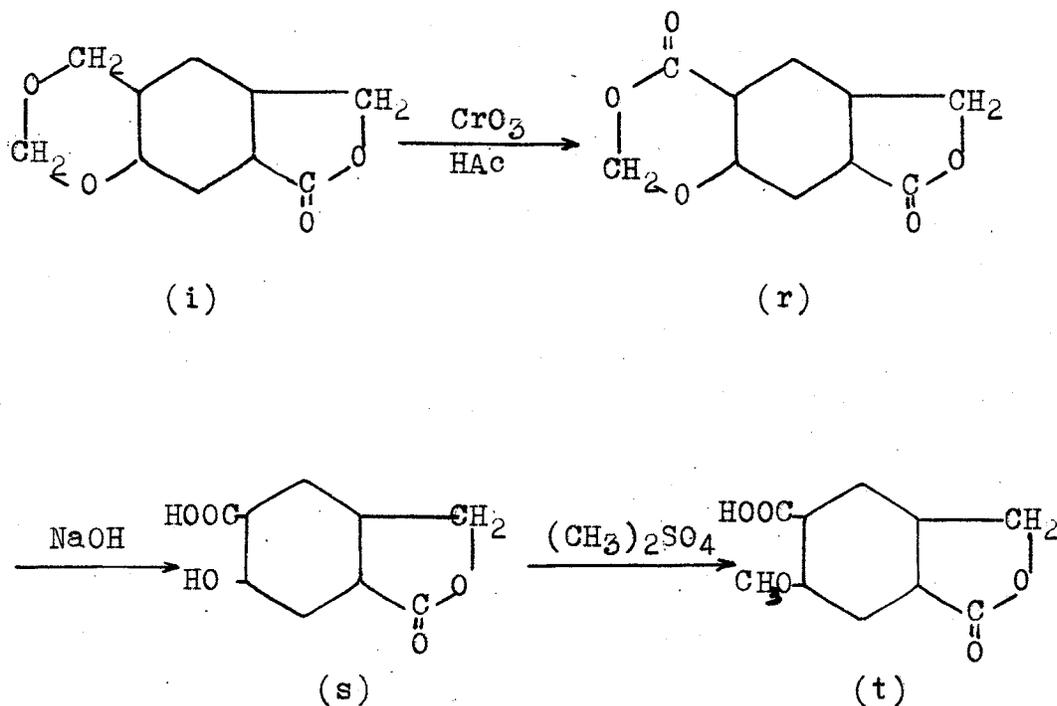
(n)



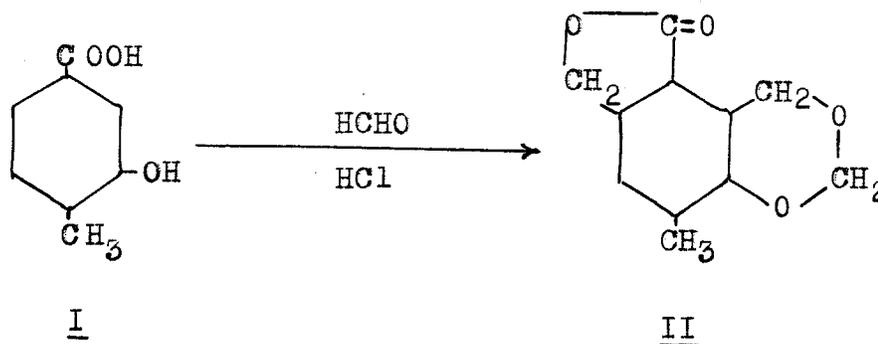
The end-product of the above oxidative degradation, 4-methoxy-1,2,3-tricarboxylic acid (k) was synthesized by Buehler, Spees and Sanguinetti (9) from hemimellitene in the following manner. The aromatic hydrocarbon, hemimellitene was treated with sulphuric acid to give the sulphonic acid (o). Oxidation of this substance with alkaline permanganate gave the acid (p). This new acid was fused with potassium hydroxide to replace the sulphonic acid group with a hydroxy group. The resulting acid (q) was treated with diazomethane to give the methoxy trimethylester of the acid (1). Saponification of this product gave the required 4-methoxy-1,2,3-tricarboxylic acid (k).



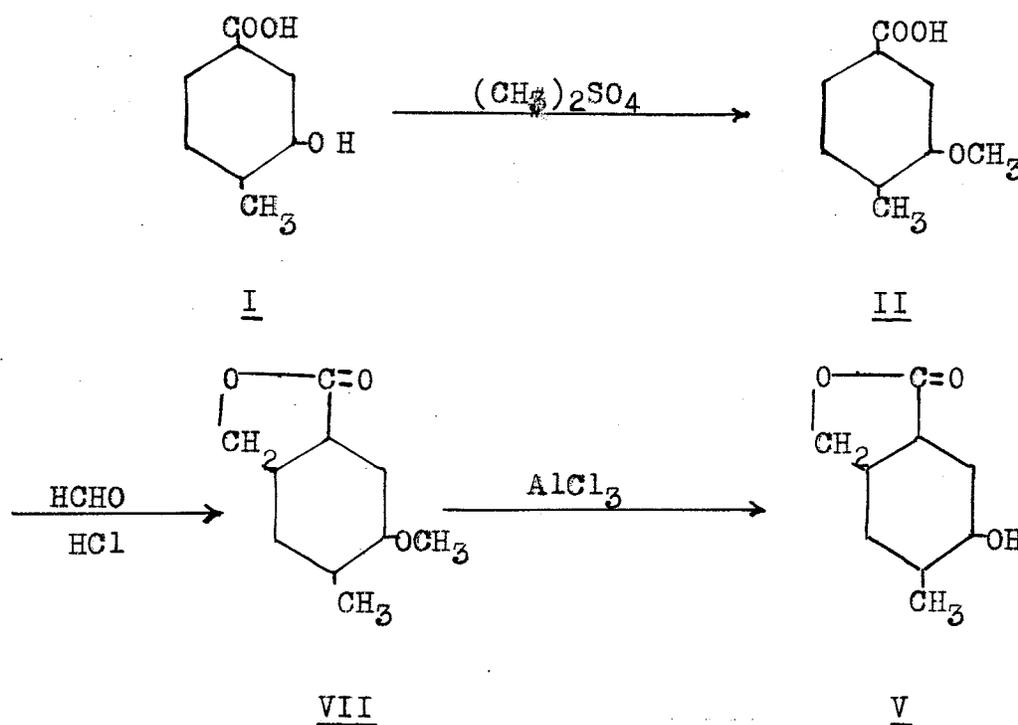
The final piece of work was done by Buehler and Block (5). They oxidized the 6-hydroxymethyl-1,3-benzodioxane-7-carboxylic acid lactone (i) with chromium trioxide to give a methylene ether-ester compound (r), which was hydrolyzed to produce an acidic material (s). This acid was methylated to show the presence of the phenolic group and the methyl ether (t) was isolated.

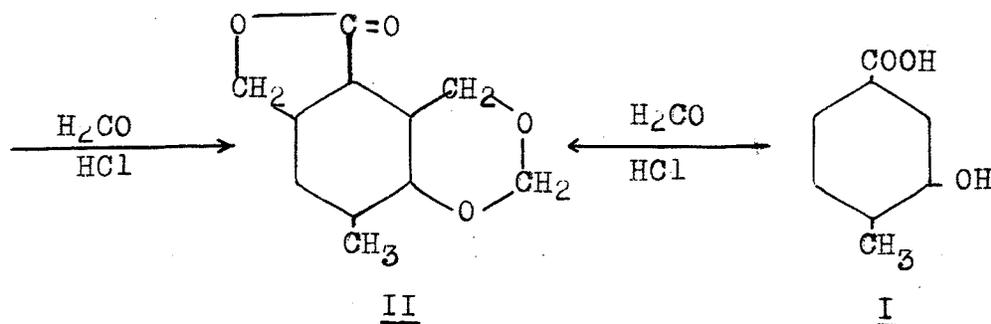


The condensation of 3-hydroxy-p-toluic acid (I) with formaldehyde and hydrochloric acid was first attempted by Yan (27). He isolated a chlorine-free, non-acidic material of melting point 165°C. This work was repeated by Winestock (24), and by various tests and analytical results it was shown that the compound obtained from the condensation was a dioxanylphthalide.

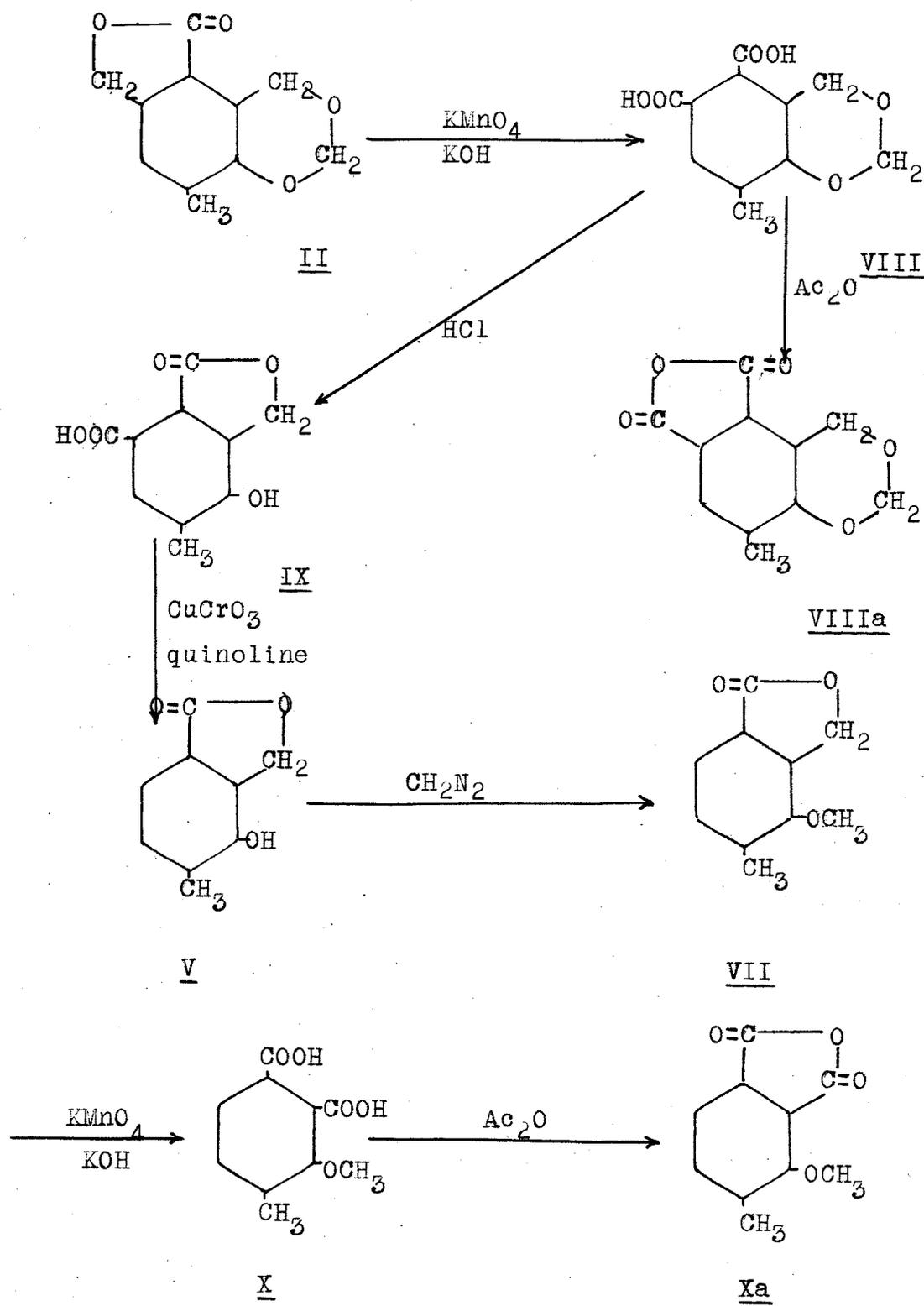


Anderson (1) synthesized the above mentioned dioxanylphthalide directly and indirectly. The indirect synthesis was carried out by treating 3-hydroxy-p-toluic acid (I) with methyl sulphate to obtain methoxy-p-toluic acid (VI). This compound was condensed with formaldehyde and hydrochloric acid to give the known 5-methoxy-4-methylphthalide (VII) which was then demethylated with aluminum chloride to the hydroxyphthalide (V). The hydroxyphthalide was condensed with formaldehyde and hydrochloric acid to obtain the final dioxanylphthalide (II) which was prepared directly from 3-hydroxy-p-toluic acid by condensing it with formaldehyde and hydrochloric acid.

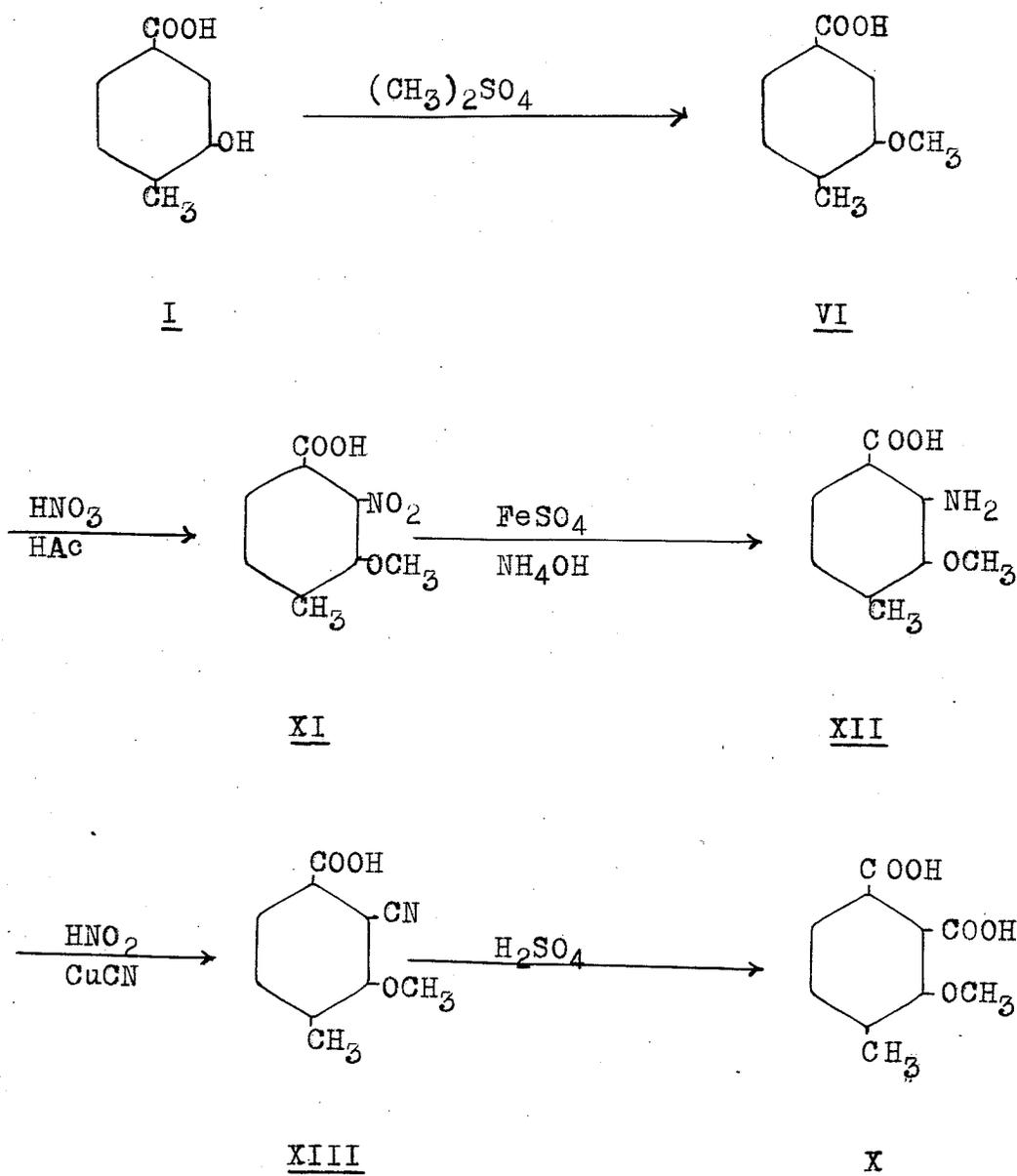




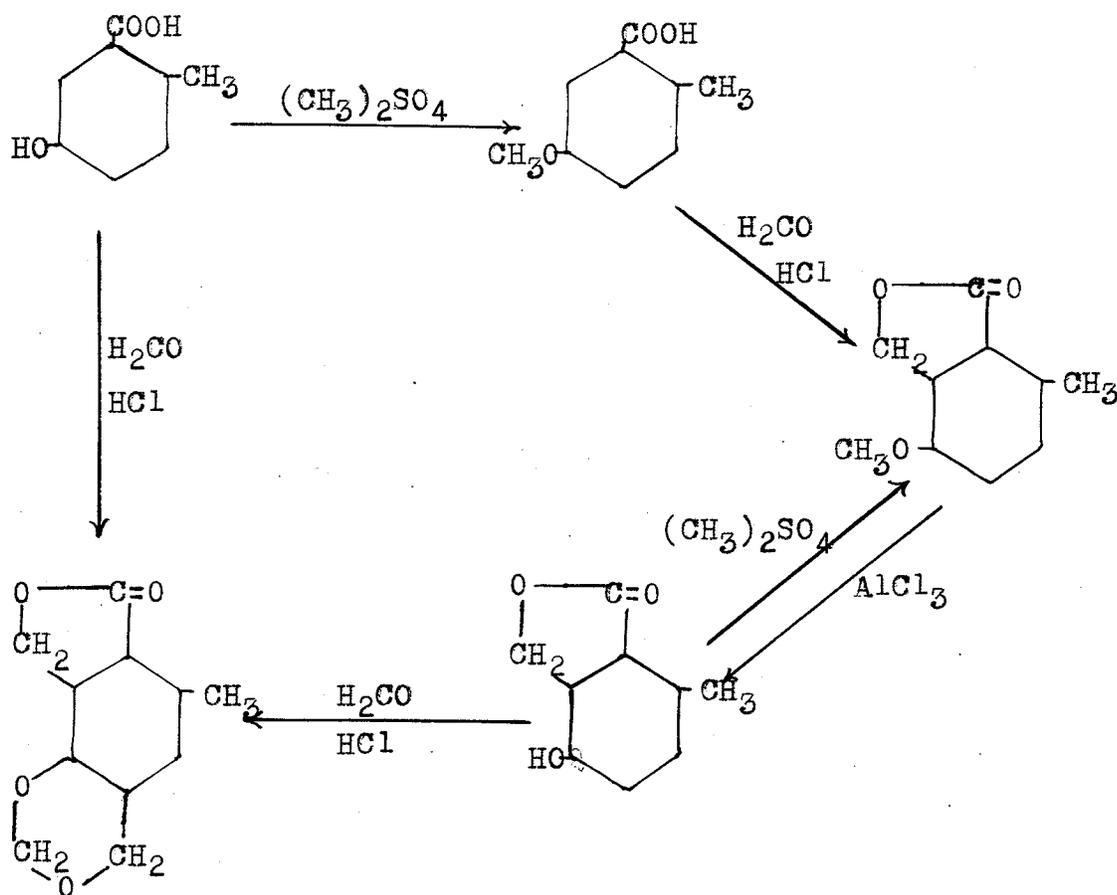
Charlesworth, Anderson and Thompson (10) partially proved the structure of this dioxanylphthalide by a series of degradative oxidations. The phthalide ring was opened by oxidizing the dioxanylphthalide (II) in cold alkaline permanganate. The dicarboxylic acid (VIII) which was obtained, was shown to be an *o*-phthalic acid by treating it with acetic anhydride to give the phthalic anhydride (VIIIa). The phthalic acid was hydrolyzed with hydrochloric acid to give a monocarboxylic acid (IX). The remaining carboxylic group was then removed by heating it with copper chromite and quinoline to produce 3-hydroxy-4-methylphthalide (V). Finally, after methylation of the hydroxy group, the phthalide ring was opened with alkaline permanganate to give the end-product, 3-methoxy-4-methyl-*o*-phthalic acid (X), which was synthesized by Simonsen and Rau (21), as given below. This product had a melting point of 172-173° C. The anhydride of the above phthalic acid (Xa) was also prepared. This substance melted at 132-133° C. which is in agreement with Simonsen and Rau's value of 135° C.



The synthesis of 3-methoxy-4-methylphthalide was accomplished by Simonsen and Rau (21) and repeated by Dudley (13). 3-Hydroxy-p-toluic acid was treated with methyl sulphate to give the ether (VI), which was nitrated to give (XI). The nitro acid was reduced with ferrous sulphate to the amino acid (XII). The amino acid was then converted through the Sandmeyer reaction to the cyano acid (XIII), which was hydrolyzed with dilute sulphuric acid to give the desired phthalic acid (X).

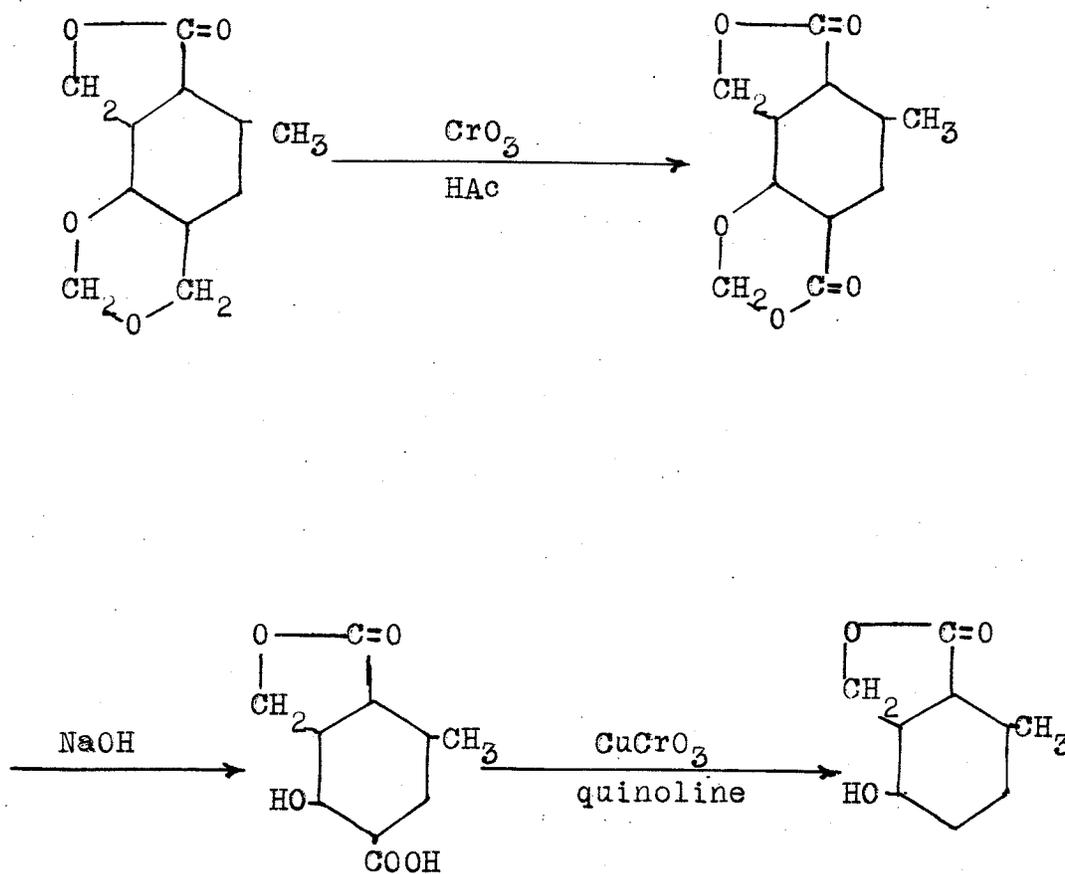


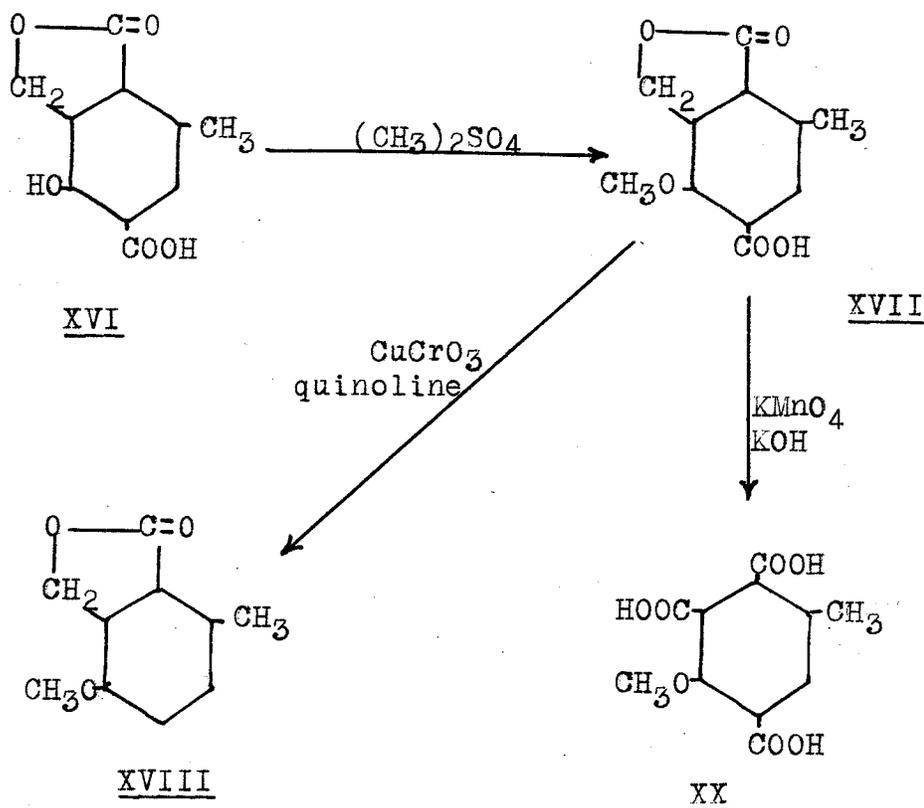
Radych (19) condensed 5-hydroxy-*o*-toluic acid with formaldehyde and hydrochloric acid to obtain the corresponding dioxanylphthalide, and also carried out the indirect synthesis as was described on pages 15 and 16.



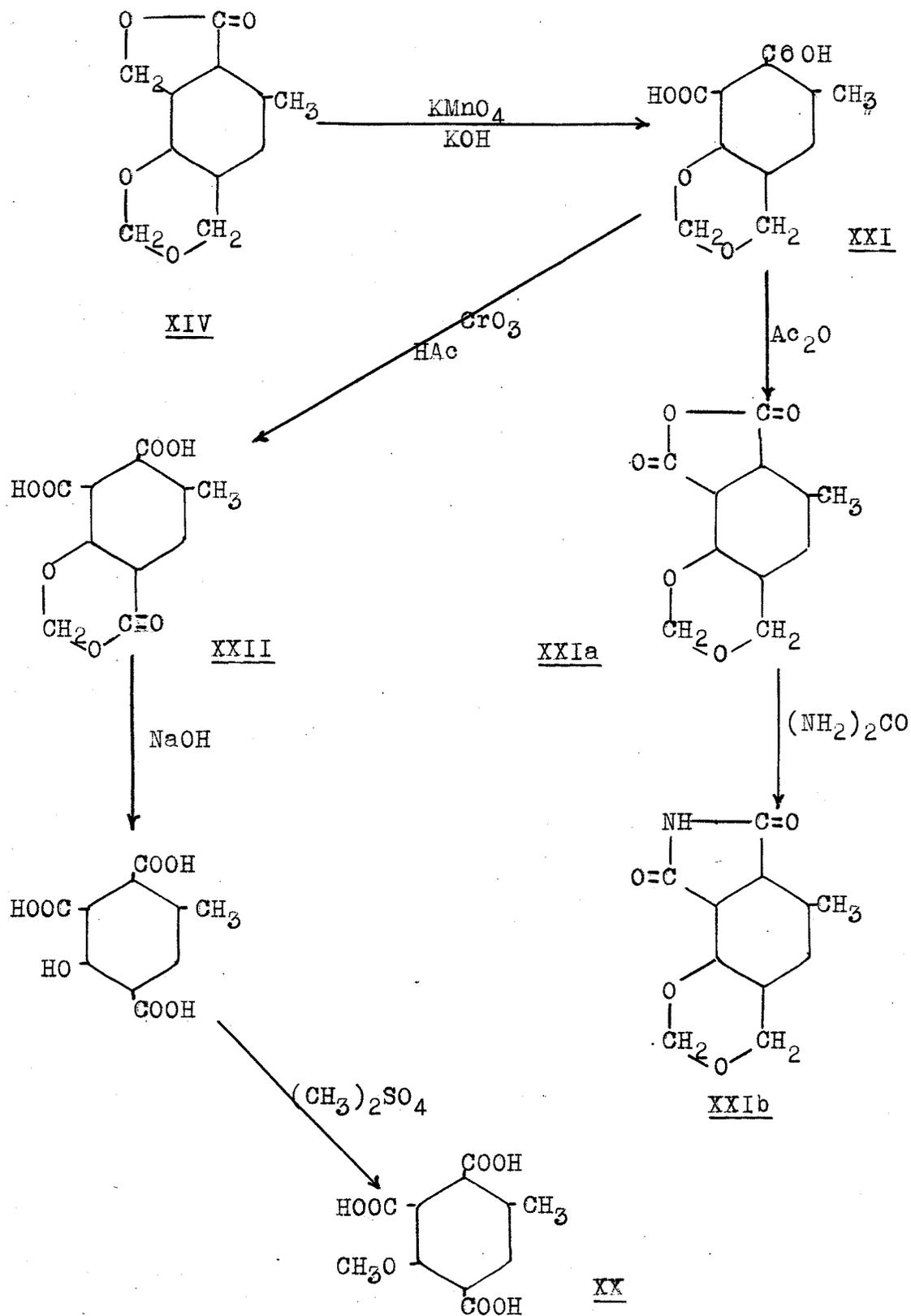
The structure of the resulting dioxanylphthalide was proved by Dudley (13) in two series of degradative oxidations. In the first series, the dioxane ring of the dioxanylphthalide (XIV) was oxidized with chromium trioxide in glacial acetic acid to give an ester (XV). Saponification of this material resulted in a monocarboxylic acid (XVI) which was treated with methyl sulphate to give a methoxy derivative (XVII).

The carboxyl groups of both the monocarboxylic acid and its methyl derivative were removed by heating in quinoline in the presence of copper chromite. The resultant decarboxylated compounds were found to be identical with samples of 3-hydroxy-6-methylphthalide (XVIII) and 3-methoxy-6-methylphthalide (XIX), respectively, which had been synthesized by Radych (19). The phthalide ring of the compound (XVII) was then opened by oxidizing it in an alkaline permanganate solution to give 3-methoxy-6-methyl-1,2,4-tricarboxylic acid (XX).

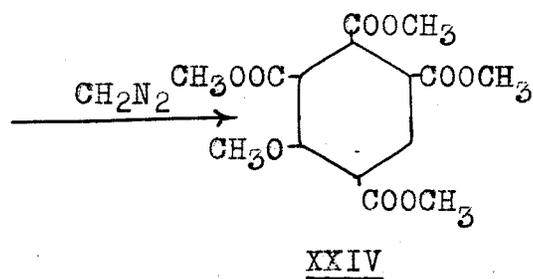
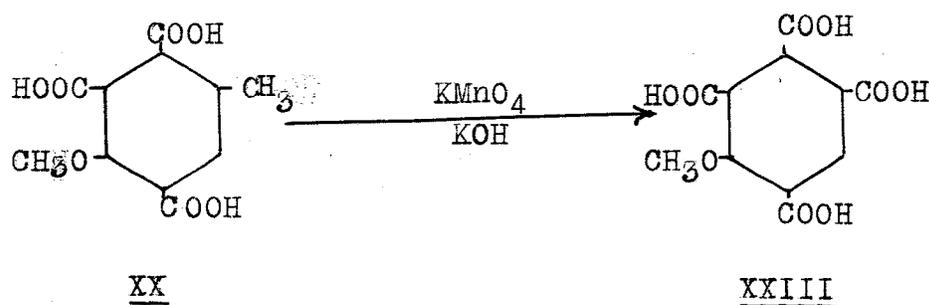




In the second series the phthalide ring of the dioxanylphthalide (XIV) was broken by treating it with alkaline permanganate to give a phthalic acid (XXI). The ortho position of the two carboxylic acid groups was shown by its ability to form an anhydride (XXIa), and its imide derivative (XXIb). The dicarboxylic acid (XXI) was then treated with chromium trioxide and glacial acetic acid to give the dioxanonephthalic acid (XXII). Hydrolysis and subsequent methylation of the phenolic group of this acid yielded the 3-methoxy-6-methyl-1,2,4-tricarboxylic acid (XX), which was shown to be identical with the end-product isolated from the first degradative series.



The tricarboxylic acid (XX) was oxidized to a tetracarboxylic acid (XXIII). Dudley (13) attempted to prepare the methyl ester derivative (XXIV) of this acid but obtained a tarry material which was not suitable for identification purposes.



DISCUSSION OF RESULTS

The work will be discussed in three sections: firstly, the series of oxidative degradations of the dioxanylphthalide of p-toluic acid, secondly, the synthesis of the end-product of Dudley's (13) degradative work, and lastly, the various other condensations.

For convenience, a schematic flow sheet of the degradative and synthetic work has been placed at the end of this thesis for reference purposes. Each compound has been tagged with a Roman numeral which will be used throughout the thesis. A simple derivative of a compound will have a Roman numeral corresponding to its parent substance, and a suffixed letter to differentiate it from other derivatives.

Structure of 6-Hydroxymethyl-1,3-Benzodioxane-8-Methyl-5-Carboxylic Acid Lactone (II).

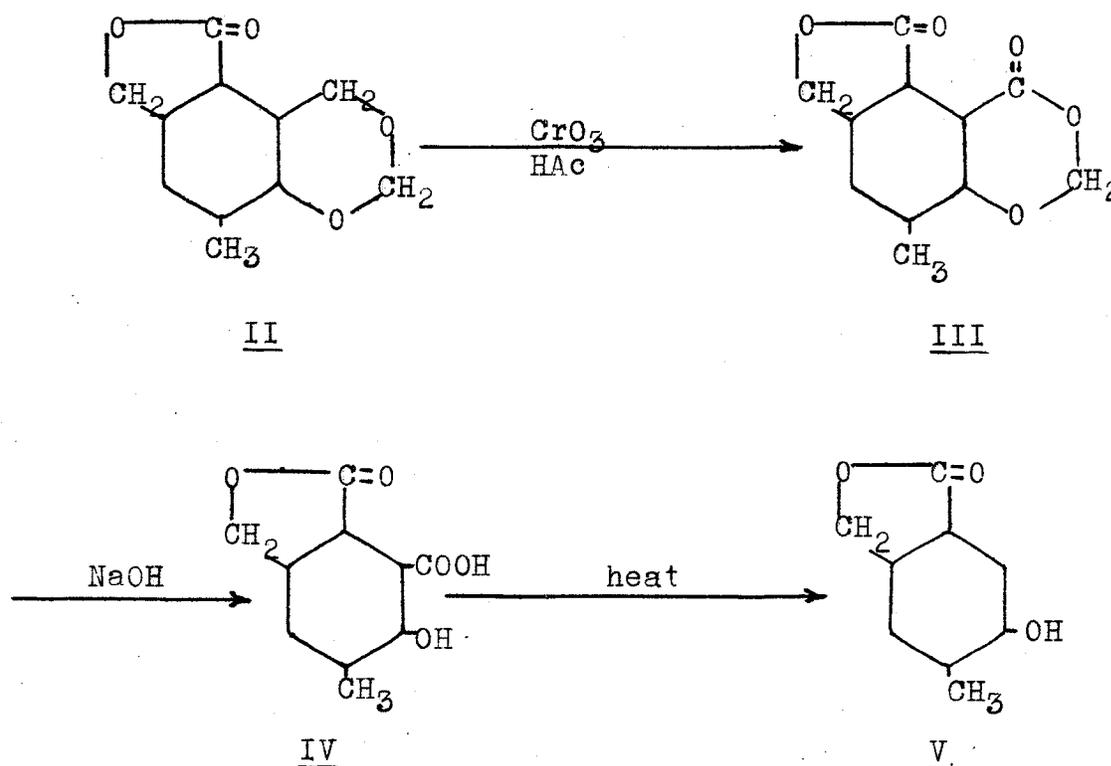
It has been shown by several workers (3), (5) and (8), that it is possible to oxidize a 1,3-benzodioxane ring with chromium trioxide in glacial acetic acid. A non-acidic methylene ether-ester type of molecule is obtained.

An oxidation of this nature should be carried out on the dioxanylphthalide (II) if it is to be proven conclusively that a 1,3-dioxane ring is present in the molecule. In addition, the position of the 1,3-dioxane ring can be shown.

Such an oxidation was first attempted by Anderson (1) and modified

by Thompson (25). This oxidation was repeated by the present author and the compound obtained was found to be identical with the substance isolated by Thompson.

This oxidation product (III) has been referred to as a methylene ether-ester. Examination of the molecules will show the reason for this.



The term was first applied to this type of molecule by Borsche and Berkhout (4). The name of the compound by modern conventional nomenclature is the lactone of 6-hydroxymethyl-8-methyl-1,3-benzodioxan-4-one-5-carboxylic acid.

It was found that the dioxanyl phthalide (II) was much more reactive than the dioxanylphthalide oxidized by Buehler and Block (5). This was noticeable in the chromium trioxide oxidation where the temperature of the oxidation had to be kept below the temperatures reported by Buehler.

The methylene ether-ester type of compound (III) was hydrolyzed with sodium hydroxide to give the expected *o*-hydroxy-carboxylic acid substituted phthalide (IV), with a loss of formaldehyde. The presence of the hydroxy group was indicated by the dark violet colour given with 1% solution of ferric chloride, and the carboxyl group was identified by the evolution of carbon dioxide with sodium bicarbonate.

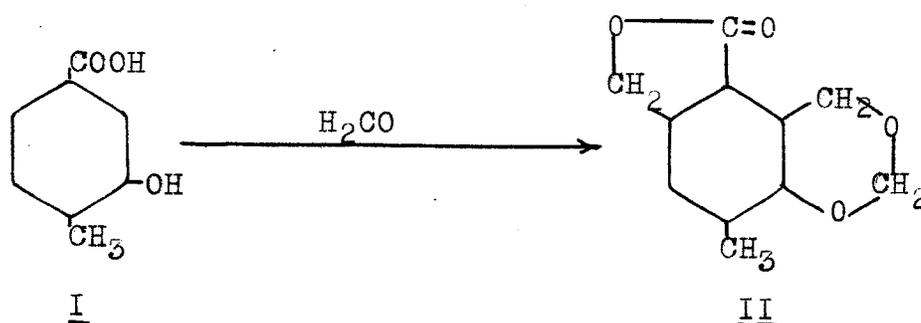
The 5-hydroxy-4-methyl-6-carboxylic acid phthalide (IV) was decarboxylated in a quinoline solution in the presence of a small quantity of copper chromite at 185-190°C. The solution, after acidification, was extracted with an acetone-ether mixture. The solvent was evaporated and recrystallized from water. This product which melted at 202°C was identical with 5-hydroxy-4-methylphthalide, which was synthesized as outlined below.

The 5-methoxy-4-methylphthalide was prepared according to the method outlined by Yan (26). 3-Hydroxy-*p*-toluic acid was treated with methyl sulphate and the resulting compound (VI) was condensed with formaldehyde and concentrated hydrochloric acid to yield the 5-methoxy-4-methylphthalide (VII). This compound was then demethylated with aluminum chloride to give the required 5-hydroxy-4-methylphthalide (V).

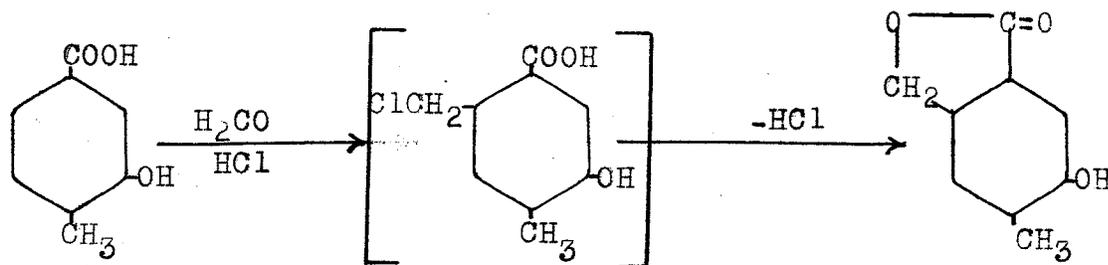
From the previous work done by Charlesworth, Anderson and Thompson (10) and the present work, the presence and position of both the 1,3-dioxane and the phthalide ring is firmly established.

At this point of the discussion, it would be appropriate to show how the structure of the condensation product of 3-hydroxy-4-methylbenzoic

acid is that of formula II, i.e., 6-hydroxymethyl-1,3-benzodioxane-8-methyl-5-carboxylic acid lactone. The most important requirement is the proof of formation of both the dioxane and phthalide rings during the condensation. Granting the formation of both of these rings (to be proven later), it is obvious that only one dioxanylphthalide could be formed because of the orientation of the 3-hydroxy-4-methylbenzoic acid (I).

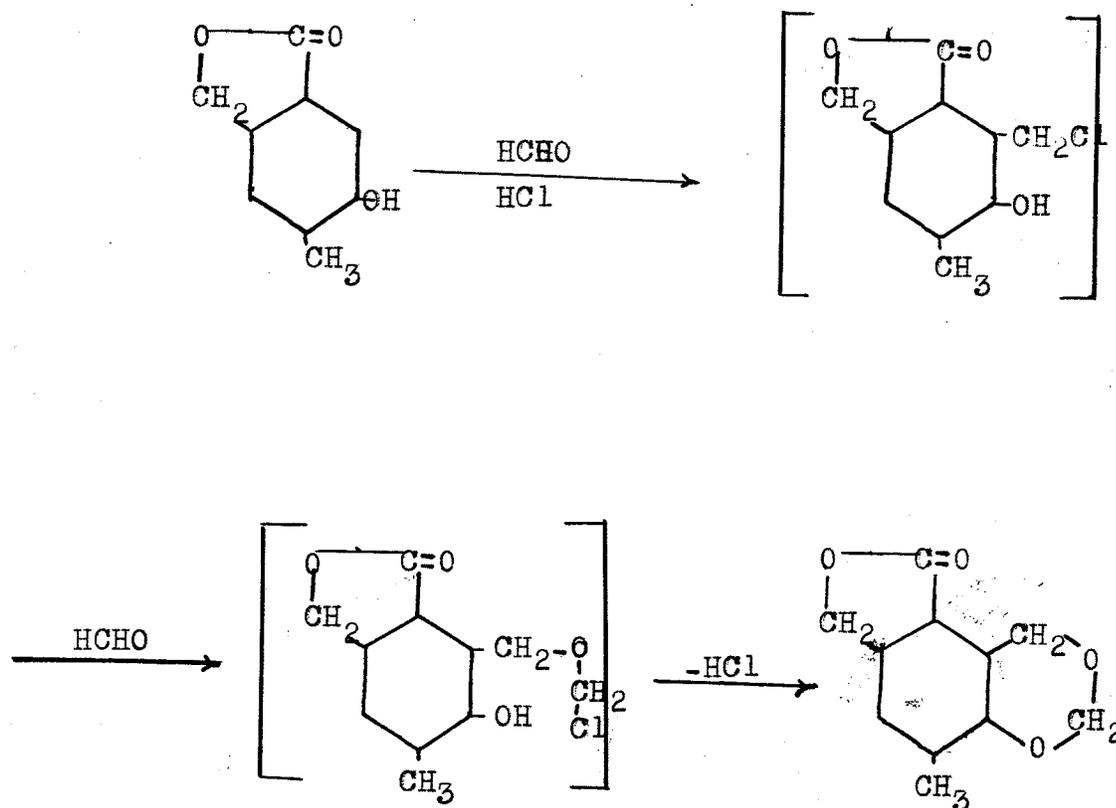


The chloromethyl group, from which the phthalide ring is formed by a loss of hydrogen chloride, can enter into two positions; i.e., in position 2 or 6. Since the dioxane ring as well as the phthalide ring is formed in the condensation, it must mean that the chloromethyl group enters into position 6, as illustrated below:



This argument, of course, is based on the supposition that the phthalide ring is formed prior to the dioxane ring in the condensation.

When the dioxane ring is formed at the hydroxyl group in the second step of the condensation, one of ortho positions is blocked, the 5 position being occupied by the methyl group. Thus the entering chloromethyl group must attach itself to the 2-position:



The degradative work offers two proofs for the formation of both the phthalide and the dioxane rings.

The oxidation with alkaline permanganate carried out by Charlesworth, Anderson and Thompson (10) offers one proof for the formation of each ring. The dioxanylphthalide was oxidized to a substituted phthalic acid (VIII) with alkaline potassium permanganate. The formation of an *o*-phthalic acid was substantiated by; 1. the loss of water with the formation of a phthalic anhydride (VIIIa) and 2. the analytical results showed a gain of two oxygen atoms in the reaction, as would be expected in the conversion of a phthalide to a phthalic acid.

The formation of the dioxane ring was also proven by this oxidation. The phthalic acid (VIII) was hydrolyzed with concentrated hydrochloric acid to give the phthalide (IX). This compound was decarboxylated with pure quinoline and methylated to give the methyl derivative (VII). Oxidation with alkaline permanganate gave the phthalic acid (X), which on heating gave the known 3-methoxy-4-methylphthalic anhydride (Xa).

The second proof for the formation of the two rings was obtained from the degradative oxidation with chromium trioxide and glacial acetic acid. The discussion of this work is given on pages 25 and 26.

Synthesis of 4-Methoxybenzene-1,2,3,5-Tetracarboxylic Acid (XXIII).

The synthesis of this compound was modeled along the preparation of 4-methoxybenzene-1,2,3-tricarboxylic acid by Buehler and his coworkers (9).

Mesitylene was brominated in cold carbon tetrachloride solution according to the directions of Smith (22). The bromomesitylene was then

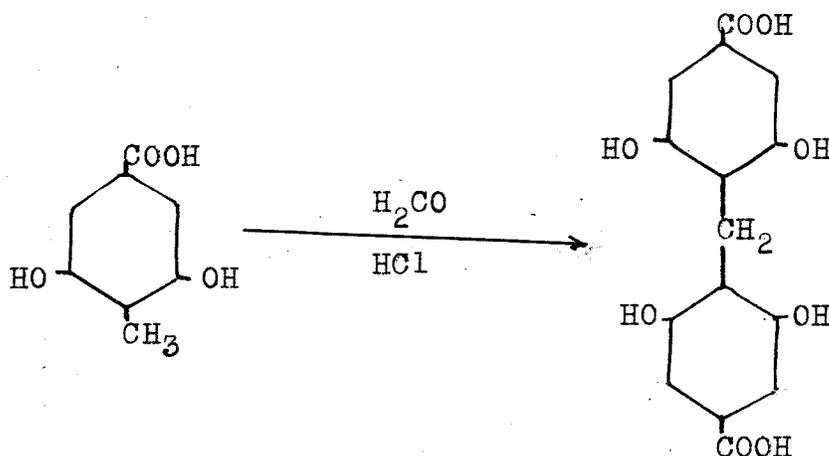
subjected to a Grignard reaction with methyl sulphate, which gave isodurene (XXVII), following the method of Smith (23). Isodurene was sulphonated according to the procedure of Smith and Cass (24), which gave the sulphonic acid (XXVIII) in quantitative yield. The isodurene sulphonic acid was oxidized to the corresponding tetracarboxylic acid (XXIX). Analytical results of this material agreed with the empirical formula $C_{10}H_6O_9$. The tetracarboxylic acid (XXX) was then methylated to give the 3-methoxy-1,2,3,5-tetracarboxylic acid (XXIII). A determination of mixed melting point with the end-product of Dudley's (13) degradative work showed it to be the same substance. A phenacyl ester (XXXI) of this acid was prepared according to Shriner and Fuson (20). The product obtained was purified by treatment with sodium bicarbonate to remove any unreacted acid and then recrystallized from alcohol.

Other Condensations:

Two other condensations of hydroxy-*o*-toluic acids with formaldehyde and hydrochloric acid were attempted, but unfortunately, products of high melting, semi-crystalline ~~or~~ amorphous nature were obtained. This, according to Charlesworth, Anderson and Thompson (10) seems to indicate the formation of compounds having a diphenylmethane or Bakelite structure.

The first one of these reactions was the condensation of 3,5-dihydroxy-*o*-toluic acid with formaldehyde and hydrochloric acid. The 3,5-dihydroxy-*o*-toluic acid was prepared from *o*-toluic acid according to the method of Asahino and Asano (2), and of Charlesworth and Robinson (11).

Condensation of this acid yielded an orange compound of very high melting point and another compound of melting point 245-250°C. These compounds were thought to be substances having a diphenylmethane or Bakelite structure, as indicated below:



These structures may be arrived at by considering first, the formation of chloromethylphthalide, according to King and King (17), which then loses hydrogen chloride between two molecules to give the diphenylmethane structure, or in the case of a very reactive hydroxy-substituted acids, a Bakelite structure, i.e. a polymerization with the loss of hydrogen chloride.

When 5-hydroxy-*m*-toluic acid was condensed with formaldehyde and concentrated hydrochloric acid, no dioxanylphthalide was isolated. The product obtained had a melting point of over 290°C. and therefore showed that this compound was likely to be a substance having a diphenylmethane or Bakelite structure.

EXPERIMENTAL

Chromium Trioxide Oxidation of 6-Hydroxymethyl-1,3-Benzodioxane-8-Methyl-5-Carboxylic Acid (II).

a. The preparation of p-toluic acid from p-tolunitrile.

The p-tolunitrile (14) was hydrolyzed to p-toluic acid according to the method of Clarke and Taylor (12).

A 75% sulphuric acid solution (300 gm.) was placed in an l-l. three-necked flask equipped with a stirrer, a reflux condenser and a dropping funnel. The solution was heated to 150°C. and the stirrer was started. p-Toluic acid (100 gm.) was added through the dropping funnel during the course of 1 hour, the temperature being maintained at 150-160°C. The mixture was stirred for 2 more hours after the addition of the nitrile was completed. The temperature was then raised to 190°C. and the stirring was continued for another hour. Some crystalline substance condensed on the flask. The mixture was poured into ice-water mixture and filtered. The crude material was dissolved in an excess of 10% sodium hydroxide, filtered hot, and acidified with dilute sulphuric acid. On cooling, white crystals precipitated, which were recrystallized from the minimum amount of alcohol. The yield of the acid, melting at 175-176°C. was 93 gm. (80% of the theoretical).

b. The sulphonation of p-toluic acid.

The sulphonation of p-toluic acid was carried out according to the directions of Thompson (25).

p-Toluic acid (100 gm.) was heated with 15% oleum (250 ml.) at a temperature of 145-155°C. for 12 hours. The solution

was cooled and cautiously poured into water (350 ml.). The mixture was heated to effect solution of the precipitate and cooled in a refrigerator. The precipitate, which appeared to be a solid mass was filtered through a sintered glass funnel and recrystallized from the minimum amount of hot water. The precipitate was then filtered and dissolved in a saturated solution of salt water. Immediately, the sodium salt of the sulphonic acid separated. This salt when filtered and dried weighed 130 gm. (74% of the theoretical).

c. The preparation of 3-hydroxy-p-toluic acid (I).

Potassium hydroxide (290 gm.) with a little water was heated to 210°C. in a nickel crucible. The sodium salt of 3-sulphonic-p-toluic acid (93 gm.) was added at this temperature and then heated to 260°C. After 30 minutes, the mixture was cooled and leached with 500 ml. of water. The aqueous solution was neutralized cautiously with concentrated sulphuric acid until slightly acid. The solution was then made alkaline with a few pellets of potassium hydroxide. After evaporating to 300 ml., the inorganic salt was filtered from the cooled solution. Acidification with concentrated hydrochloric acid gave an impure, yellow precipitate of 3-hydroxy-p-toluic acid. The acid was recrystallized from water to give 39 gm. (66% of the theoretical) of the acid melting at 205-206°C.

d. Preparation of the Lactone of 6-hydroxymethyl-1,3-benzodioxane-8-methyl-5-carboxylic acid (II).

3-Hydroxy-p-toluic acid (20 gm.) was heated for $\frac{1}{2}$ hour under reflux

with concentrated hydrochloric acid (100 ml.) and 40% formaldehyde (100 ml.). The resulting solution was poured into cold water (300 ml.) and allowed to stand. The precipitate was filtered and washed until the odour of formaldehyde was no longer detectable. The dried solid was dissolved in boiling alcohol and filtered to remove the insoluble material. The solid precipitating on cooling, was filtered and dried. A further quantity of dioxanylphthalide was recovered by evaporating $\frac{2}{3}$ of the alcohol. The yield was 13 grams (49% of the theoretical). This product melted at 160-162°C. and a mixed-melting-point determination with Thompson's (25) sample gave no depression.

e. The preparation of the 6-hydroxymethyl-8-methyl-1,3-benzodioxane-4-one-5-carboxylic acid (III).

Various methods were adopted in order to obtain a satisfactory yield of 6-hydroxy-8-methyl-1,3-benzodioxane-4-one-5-carboxylic acid. The method which gave the greatest yield is given below.

Dioxanylphthalide (2 gm.) was dissolved in glacial acetic acid (50 ml.) by heating gently. Finely powdered chromium trioxide (7 gm.) was added slowly to keep the temperature between 65-70°C. After the addition of chromium trioxide was completed, the mixture was kept at 65-70°C. for 1 hour. The solution was set aside for 12 hours at room temperature and then poured into water (250 ml.) and allowed to stand overnight. The mixture was refrigerated for 2 hours and the white precipitate was filtered. The methylene ether-ester compound was recrystallized from acetone to give 0.3 gm. (14% of the theoretical) of pure compound melting at 243-244°C.

Analysis:

Calculated for $C_{11}H_8O_5$: C, 60.00%; H, 3.64%

Found: C, 59.90%; H, 3.65%.

f. The preparation of 4-methyl-5-hydroxy-1,2-phthalide-6-carboxylic acid (IV).

The oxidation product (III) was hydrolyzed in the manner described by Buehler and Block (5). The methylene-ether-ester compound (2.0 gm.) was treated with a 20% solution of sodium hydroxide (10 ml.) and refluxed for 30 minutes. The solution was acidified and cooled. The precipitate was filtered and recrystallized from acetone. The white needles which separated, melted at 189-190°C. The yield was 1.5 gm. (74% of the theoretical).

Analysis:

Calculated for $C_{10}H_8O_5$: C, 57.69%; H, 3.87%.

Found: C, 57.64%; H, 3.95%.

g. The preparation of 4-methyl-5-hydroxy-1,2-phthalide (V).

The crude product melting at 185-188°C was decarboxylated by heating the acid (0.5 gm.) with pure quinoline and a little copper chromite in a sulphuric acid bath, which was kept at 180-190°C. The quinoline solution was filtered and cooled. The solution was acidified and extracted with ether-acetone mixture. The solvent was evaporated and the residue was taken up in hot water. It was decolorized with charcoal and the solution on cooling, precipitated 0.2 gm. of white crystals which melted at

201-202°C. The yield was 52% of the theoretical. Mixed-melting-point determination with the 4-methyl-5-hydroxy-1,2-phthalide which was synthesized as shown below, gave no depression.

Synthesis of 4-Methyl-5-Hydroxy-1,2-Phthalide (V).

a. The preparation of 3-methoxy-p-toluic acid (VI).

The methylation of 3-hydroxy-p-toluic acid was accomplished according to the method of Yan (27). 3-Hydroxy-p-toluic acid (5 gm.) was dissolved in 20% sodium hydroxide (35 ml.) in an eight inch test tube with a side arm. The solution was cooled in an ice-water bath and propane gas was passed through the mixture to create an inert atmosphere and also to stir the solution. The escaping gas was burnt by connecting a burner to the side arm. Methyl sulphate (10 gm.) was added slowly by means of a dropper and the solution was stirred for 1 hour. Sodium hydroxide (1.5 gm.) was added and the solution was refluxed for another hour. The solution was cooled and sodium sulphate was filtered off. On acidification with concentrated hydrochloric acid, a white precipitate formed which on recrystallization from an ethyl alcohol-water mixture gave 4.5 gm. (82% of the theoretical) of white compound of melting point 156°C.

b. 4-Methyl-5-methoxy-1,2-phthalide (VII).

5-Methoxy-p-toluic acid (4 gm.) was refluxed with concentrated hydrochloric acid (10 ml.) and 40% formaldehyde (10 ml.) for 1 hour. The precipitate which formed on cooling was filtered off and recrystallized from alcohol. It gave 2 gm. of white, shining needles which melted at

140-142°C. A mixed melting point determination with Yan's (26) sample of 5-methoxy-p-toluic acid showed that the two compounds were identical. The yield was 46% of the theoretical.

c. The preparation of 4-methyl-5-hydroxy-1,2-phthalide (V).

A mixture of 3-methoxy-4-methylphthalide (1.5 gm.) and aluminum chloride (3 gm.) in dry benzene (20 ml.) was refluxed for 10 hours on a water bath. At first, there was a violent evolution of gas and the solution turned orange. After the completion of the reaction, the benzene was evaporated to dryness. The residue was extracted with hot alcohol and decolorized with charcoal. On cooling, white crystals of 5-hydroxy-4-methyl-1,2-phthalide were precipitated. The yield was 0.8 gm. (66% of the theoretical).

Analysis:

Calculated for $C_9H_8O_3$; C, 65.85%; H, 4.89%.

Found: C, 65.69%; H, 5.00%.

Synthesis of 4-Methoxybenzene-1,2,3,5-Tetracarboxylic acid (XXIII).

a. The preparation of bromomesitylene (XXVI).

Bromomesitylene was prepared according to the method of Smith (21).

Mesitylene (106 gm.) in carbon tetrachloride (70 ml.) was placed in an 1-l. three-necked flask provided with a reflux condenser, a stirrer and a separatory funnel. The flask was cooled in an ice-salt bath until the temperature of the mixture had dropped below 10°C. A solution of bromine (150 gm.) in carbon tetrachloride (95 ml.) was then added to the well-

stirred solution. The hydrogen bromide which was evolved during the reaction was absorbed in a solution of sodium hydroxide. The temperature of the solution was maintained at 10-15°C. during the addition. The reaction mixture was then allowed to stand at room temperature for 1 hour.

The resultant solution was washed with water and then with two 100 ml. portions of 20% sodium hydroxide solution. The carbon tetrachloride was distilled through a fractionating column until the temperature of the vapor reached 120°C.

The residue was added to a solution of sodium (8.5 gm.) in absolute alcohol (200 ml.). The resultant solution was boiled under reflux for one hour and then allowed to stand overnight. The reaction mixture was diluted with 1 l. of water and the two layers were separated. The aqueous layer was extracted with three, 100 ml. portions of carbon tetrachloride, and the extract was added to the bromomesitylene. This solution was washed thoroughly with water and dried over calcium chloride. The carbon tetrachloride was distilled, and the residue was transferred to a Claisen flask and distilled under reduced pressure. The fraction boiling at 100-101°C. at 10 mm. was collected. The yield was 130 gm. (74% of the theoretical).

b. The preparation of isodurene (XXVII).

Isodurene was synthesized according to the directions of Smith (23). A 1-l. three-necked flask fitted with a reflux condenser, which was protected from the air by a calcium chloride tube, a separatory funnel, and a stirrer was mounted on a steam bath. Magnesium turnings (16 gm.),

anhydrous ether (50 ml.), bromomesitylene (30 ml.), and a crystal of iodine were placed in the flask. The reaction was started by an application of gentle heat. The remaining bromomesitylene (100 gm.) in dry ether (250 ml.) was added at such a rate that the ether refluxed gently. When the addition was completed, the mixture was heated on a water bath until all the magnesium had dissolved.

The Grignard mixture was cooled to 10°C. and pure methyl sulphate (200 gm.) in ether (100 ml.) was added. The addition required 3 hours. After standing for 24 hours, the mixture was decomposed by the addition of dilute hydrochloric acid through the separatory funnel. Stirring was started as soon as possible, and when all the magnesium salt had gone into solution, the ether layer was separated, and washed three times with water. The ether layer was evaporated, and the residue was added to a solution of sodium (10 gm.) in absolute methanol (125 ml.). This mixture was boiled for 30 minutes to decompose the excess methyl sulphate. To the cooled solution was added ether (60 ml.), and the alkali and alcohol was removed by washing with water. The ether solution was dried over calcium chloride, filtered, and the ether was distilled. The residue was heated on a steam bath with sodium cuttings (10 gm.) for 3 hours. The mixture was filtered, and the filtrate was fractionated under reduced pressure in a Claisen flask. A large amount of low boiling material was obtained, namely, impure mesitylene. The fraction boiling at 82-85°C at 15 mm. was collected. The yield was 35 gm. (40% of the theoretical).

c. The preparation of isodurene sulphonic acid (XXVIII).

This compound was prepared according to the method of Smith and Cass (24).

Equal volumes of isodurene and concentrated sulphuric acid were shaken together in a small flask for 10 minutes. During this time the isodurene gradually dissolved with the evolution of heat and the development of turkey-red colour. The reaction mixture was then poured into a 100 ml. beaker filled with crushed ice. Filtration gave the sulphonic acid which was recrystallized immediately. The sulphonic acid was dissolved in ice-water (50 ml.) and the solution was saturated with hydrogen chloride gas. The pure product having a melting point of 72°C separated out in quantitative yield. On standing, the crystals gradually turned green and then brown.

d. The oxidation of isodurene sulphonic acid.

This and the following steps are modifications of the methods outlined in French (15) and German (16) Patents for the oxidation and fusion of hemimellitene sulphonic acid.

Isodurene sulphonic acid (15 gm.) and a solution of potassium hydroxide (5.5 gm.) in water (250 ml.) were placed in a 1-l. three-necked flask equipped with a reflux condenser and a stirrer. The solution was heated to 90°C . with a heating mantle. While the solution was stirred vigorously, powdered potassium permanganate (62.8 gm.) was added at such a rate that the temperature did not rise above 95°C . After the addition was completed, the oxidation was continued for another 24 hours at this temperature. Excess potassium permanganate was decolorized with alcohol,

and the manganese dioxide was filtered and washed with two 150 ml. portions of boiling water. The resultant yellow solution was evaporated to dryness, and 15 gm. (41% of the theoretical) of pulverized residue was obtained. The bulk of the material was not purified but put into the next reaction. A small portion of the potassium salt was acidified and extracted with ethyl acetate. The solvent was evaporated and the residue was extracted with a small quantity of hot water. On cooling, an acid melting at 238°C was obtained.

e. The preparation of 4-hydroxybenzene-1,2,3,5-tetracarboxylic acid (XXX).

Crude potassium salt (14 gm.) of the sulphonic acid was mixed with potassium hydroxide (40 gm.) and water (5 ml.), and fused at 200-220°C. for 5 hours in a nickel crucible. The melt was cooled to a slush and mixed with water (60 ml.) and cautiously acidified with concentrated hydrochloric acid. After the addition of water (150 ml.), the mixture was heated to boiling and filtered. The filtrate was evaporated to dryness. The residue was re-crystallized from 60 ml. of hot 5% hydrochloric acid to give 6 gm. (60% of the theoretical) of white powder melting at 281-282°C.

Analysis:

Calculated for $C_{10}H_6O_9$: C, 44.03%; H, 2.26%.

Found: C, 44.44%; H, 2.35%.



f. The preparation of 4-methoxybenzene-1,2,3,5-tetracarboxylic acid (XXIII).

4-Hydroxybenzene-1,2,3,5-tetracarboxylic acid (4 gm.) was dissolved in 10% sodium hydroxide (25 ml.) in a 8-inch test tube. Propane gas was bubbled through the solution in order to maintain an inert atmosphere and also to stir the solution. The escaping gas was destroyed by attaching a burner to the outlet. Methyl sulphate (5 ml.) was added to the solution at such a rate that the temperature of the solution did not rise above 40°C. The methyl sulphate tended to decompose the base present in the solution, and in a short time, the solution became acid. Solid sodium hydroxide was added to keep the solution basic and the methylation was continued. When the methyl sulphate was used up, three more 5 ml. portions of methyl sulphate was added along with some solid sodium hydroxide. The basic solution was allowed to stand overnight in contact with methyl sulphate (1 ml.). The methyl sulphate was decomposed by warming the basic solution. The sodium sulphate that precipitated on cooling was filtered. The acidified solution was extracted with three 15 ml. portions of ethyl acetate, and the solvent was evaporated. Purification of this compound was very difficult. The crude material was dissolved in sodium bicarbonate solution to remove any insoluble material, and decolorized with charcoal. The solution was acidified and extracted with ethyl acetate and the solvent was evaporated. The product melted at 164-166°C. A mixed-melting-point determination with the end-product of Dudley's (13) oxidative degradation gave no depression. The yield was 1.3 gm. (31% of the theoretical).

Analysis:

Calculated for $C_{11}H_8O_9$: C, 46.48%, H, 2.83%.

Found: C, 46.04%; H, 2.98%.

g. The preparation of the phenacyl ester of 4-methoxybenzene-1,2,3,5-tetracarboxylic acid (XXXI).

The phenacyl ester derivative of the acid was prepared according to the method of Shriner and Fuson (20). The acid (1.0 gm.) was added to water (5 ml.) in an eight-inch test tube and carefully neutralized with a 10% solution of sodium hydroxide. A few drops of acid were added to make the solution slightly acidic to litmus paper. Ethyl alcohol (10 ml.) and phenacyl bromide (1 gm.) were added to the solution and the mixture was heated under reflux for 4 hours. From time to time, more alcohol was added to keep the precipitate in solution. On cooling, the ester separated, which was dissolved in sodium bicarbonate and the impurities were filtered. The precipitate which formed on acidification was recrystallized from alcohol to give 0.9 gm. (19% of the theoretical) of the ester. The pure substance melted at 189-190°C. with previous softening and darkening.

Analysis:

Calculated for $C_{43}H_{32}O_{13}$: 68.25%; H, 4.23%.

Found: C, 67.99%; H, 4.27%.

Other Condensations:

la. The preparation of o-toluic acid.

This acid was prepared according to the method of Clarke and Taylor (12). An l-l. flask was equipped with a mechanical stirrer, a reflux condenser, and a separatory funnel. A 75% solution of sulphuric acid (150 gm.) was heated to 150°C., and the stirrer was started. o-Tolunitrile (50 gm.) was added over a period of one hour, the temperature being maintained at 150-160°C. The mixture was stirred for 2 more hours and then the temperature was raised to 190°C. The reaction mixture was poured into ice-water mixture and filtered. The crude material was dissolved in an excess of 10% sodium hydroxide solution, filtered hot, and the filtrate was acidified with dilute sulphuric acid. The product was filtered and dried. Recrystallization from benzene gave 46 gm. (80% of the theoretical) of the acid which had a melting point of 102-103°C.

lb. The preparation of 3,5-disulphonic-o-toluic acid.

The sulphonation of o-toluic acid was carried out according to the method of Asahino and Asano (2).

o-Toluic acid (14 gm.) was heated with fuming sulphuric acid (90 gm., 50% oleum) for 8 hours at 170-180°C. on an oil bath. The cooled solution was carefully poured into water (500 ml.) and boiled for a short time. The solution was neutralized with barium hydroxide until it was slightly acidic and then made alkaline with barium carbonate to prevent the violent evolution of carbon dioxide. Barium sulphate was filtered off and the solution was

evaporated to 100 ml. and concentrated hydrochloric acid was added to precipitate the barium salt. This salt was filtered off and dissolved in boiling water. Enough potassium carbonate was added to convert the barium salt into a potassium salt and the barium carbonate was filtered off. The solution was evaporated to dryness to yield 28 gm. of the potassium salt of 3,5-disulphonic acid (70% of the theoretical).

lc. The preparation of 3,5-dihydroxy-o-toluic acid.

The fusion of the disulphonate was carried out according to the methods of Asahino and Asano (2) and Charlesworth and Robinson (11). The potassium disulphonate (10 gm.) was heated with potassium hydroxide (50 gm.) and a little water for 20 minutes at 250°C., and then for 10 minutes at 270°C. The cooled mass was leached with water (100 ml.) and acidified with hydrochloric acid. The phenolic acid was extracted with ether and the solvent was evaporated. The black tarry material was dissolved in hot water and treated with charcoal. The water solution was concentrated and cooled in a refrigerator. White crystals melting at 233.5-234.5°C. was isolated. The yield was 5.2 gm. or 43% of the theoretical.

ld. The condensation of 3,5-dihydroxy-o-toluic acid with formaldehyde and concentrated hydrochloric acid.

3,5-Dihydroxy-o-toluic acid (1 gm.) was heated under reflux with concentrated hydrochloric acid (5 ml.) and 40% formaldehyde (5 ml.) for 30 minutes. A yellowish-brown mass began to separate after 5 minutes of heating. The mixture was poured into cold water and filtered. The dried sample

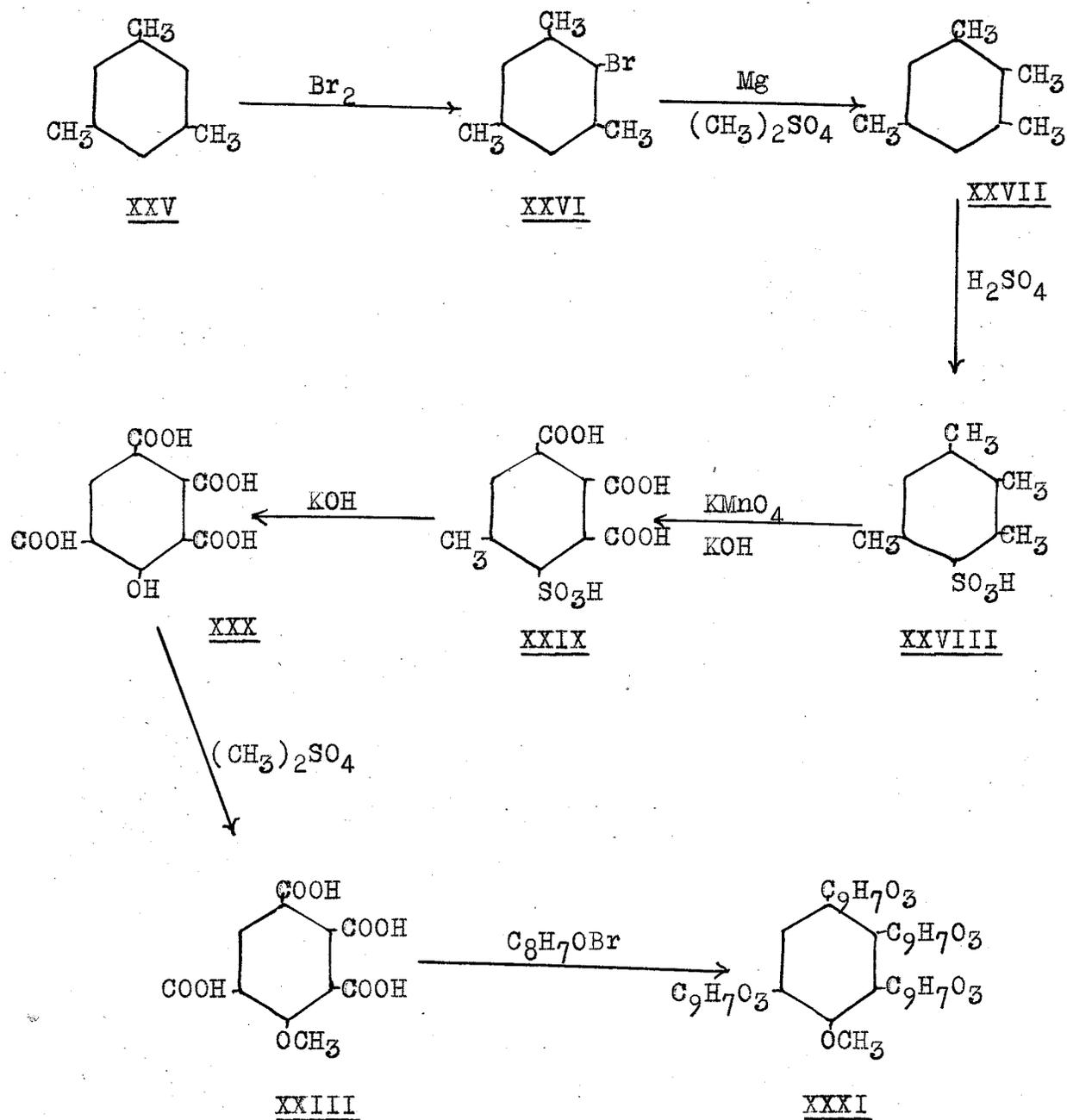
was dissolved in alcohol. The insoluble material was yellowish-orange in colour and had a very high melting point. On cooling the alcoholic solution, a precipitate appeared which was a white, semi-crystalline compound of melting point 247-249°C. This substance was thought to be a compound having a diphenyl methane type of structure.

2. Condensation of 5-hydroxy-m-toluic acid with formaldehyde and concentrated hydrochloric acid.

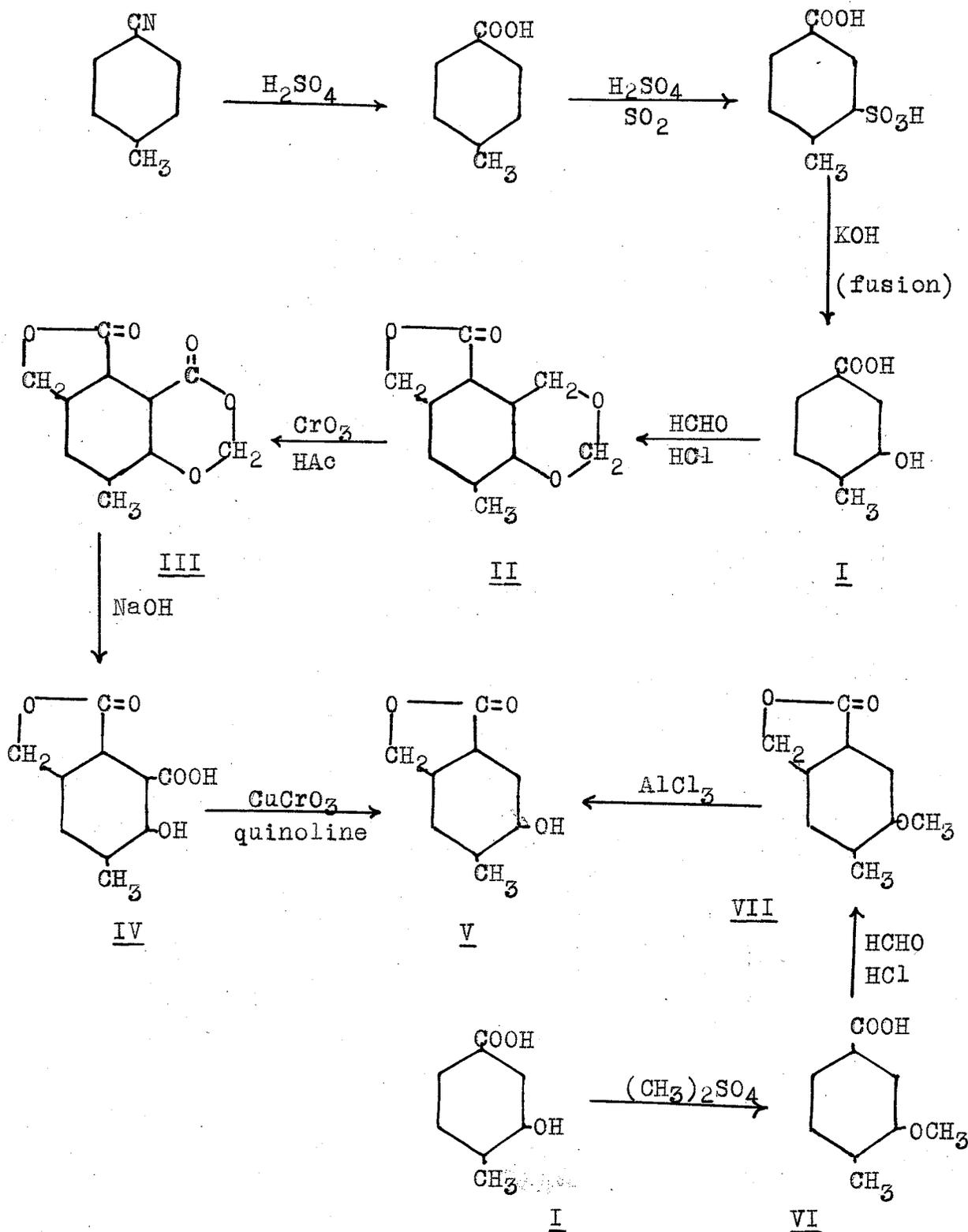
5-Hydroxy-m-toluic acid¹ (1 gm.) was refluxed with formaldehyde (5 ml.) and concentrated hydrochloric acid (5 ml.) for 5, 10, 15, and 30 minutes. The precipitate obtained in all 4 cases appeared to be the same. This product had a melting point well above 280°C.

¹ 5-Hydroxy-m-toluic acid was donated by Dr. E. H. Charlesworth for the purpose of this experiment.

THE PREPARATION OF
4-METHOXYBENZENE-1,2,3,5-TETRACARBOXYLIC ACID



THE CHROMIUM TRIOXIDE-GLACIAL ACETIC ACID OXIDATION
OF 6-HYDROXY-8-METHYL-1,3-BENZODIOXANE-5-CARBOXYLIC ACID LACTONE



SUMMARY

1. The structure of 6-hydroxymethyl-8-methyl-1,3-benzodioxan-5-carboxylic acid lactone (II), the dioxanylphthalide resulting from the condensation of 3-hydroxy-p-toluic (I) acid with formaldehyde and concentrated hydrochloric acid was confirmed by:
 - a. the chromium trioxide-acetic acid oxidation of the dioxanylphthalide to the methylene ether-ester compound and the subsequent hydrolysis and decarboxylation to the 5-hydroxy-4-methylphthalide (V).
 - b. the synthesis of 5-hydroxy-4-methylphthalide from 3-hydroxy-p-toluic acid.

2. 4-Methoxybenzene-1,2,3,5-tetracarboxylic acid (XXIII), the end-product of the oxidative degradation of 8-hydroxymethyl 6-methyl-1,3-benzodioxan-7-carboxylic acid lactone was synthesized from mesitylene. A phenacyl ester of the acid was prepared. Therefore, the structure of the dioxanylphthalide resulting from the condensation of 5-hydroxy-o-toluic acid was confirmed.

3. Attempts were made to obtain the dioxanylphthalides of;
 - a. 3,5-dihydroxy-o-toluic acid and
 - b. 5-hydroxy-m-toluic acidby condensing them with formaldehyde and concentrated hydrochloric acid. However, in both cases, high melting, semi-crystalline substances, having probably a diphenylmethane type of structure were isolated.

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