

OXIDATIVE DEGRADATION OF CERTAIN DIOXANYLPHTHALIDES
OF THE TOLUIC ACIDS.

OXIDATIVE DEGRADATION OF CERTAIN DIOXANYLPHTHALIDES OF
THE TOLUIC ACIDS

by

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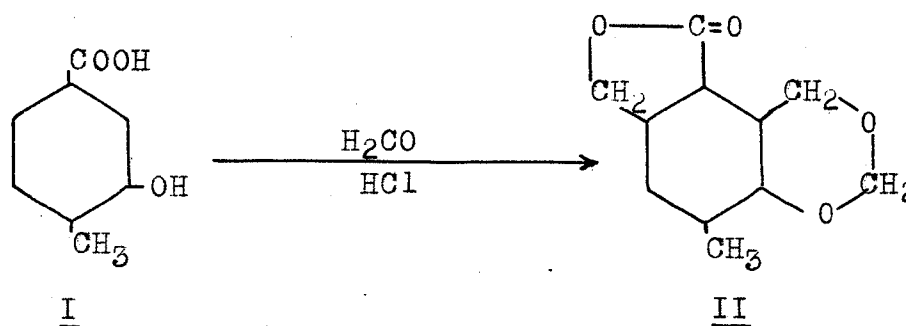
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INTRODUCTION

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.

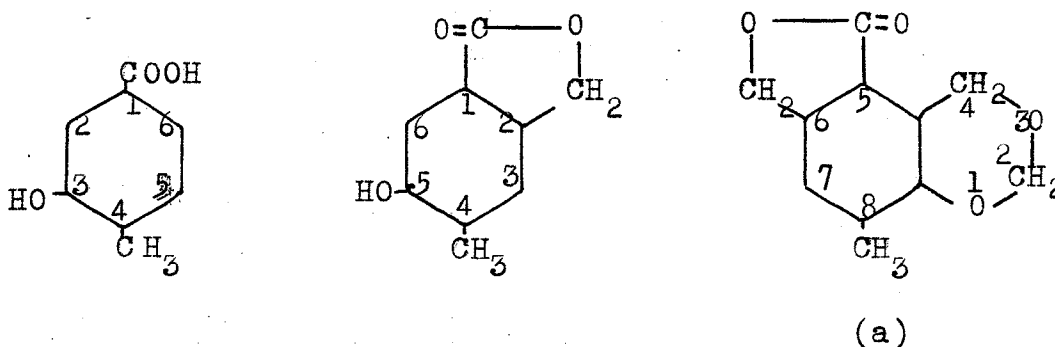
The second phase of the work consists of the synthesis of 4-methoxybenzene-1,2,3,5-tetracarboxylic acid, which is the end-product of the degradative work carried out by Dudley (13) on the condensation product of 5-hydroxy-o-toluic acid with formaldehyde and concentrated hydrochloric acid.

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

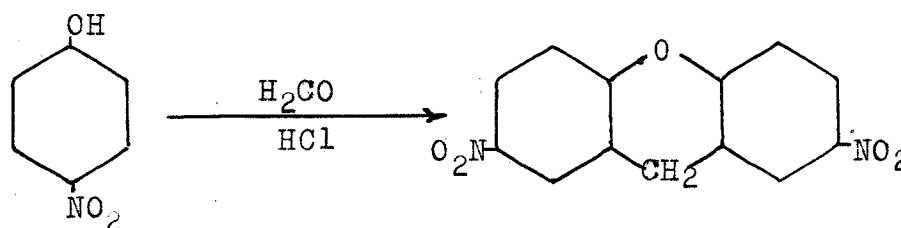
As the literature on the phthalide rings has been reviewed by Anderson (1) and Radych (18), only the relevant parts of these surveys will be considered in any detail.

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

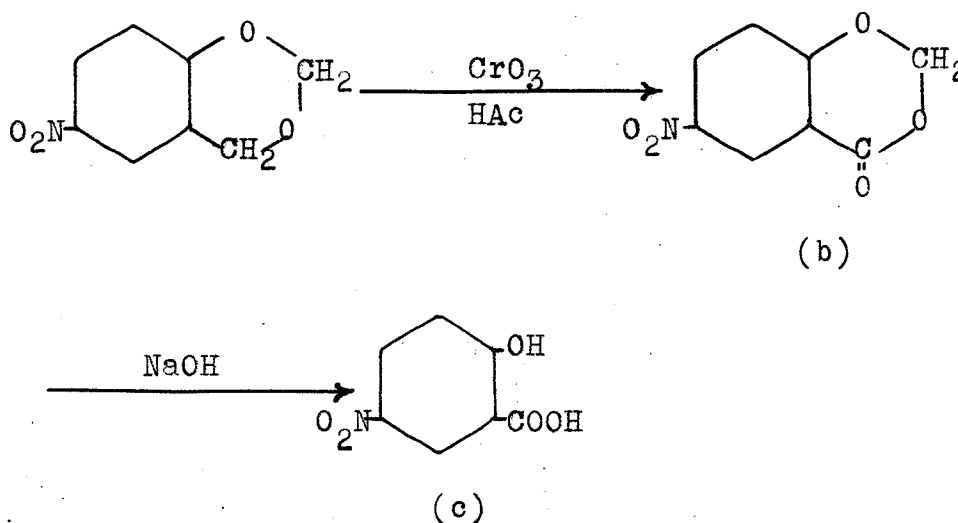


For example, the dioxanylphthalide (a) would be 6-hydroxymethyl-8-methyl-1,3-benzodioxane-5-carboxylic acid lactone.

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.



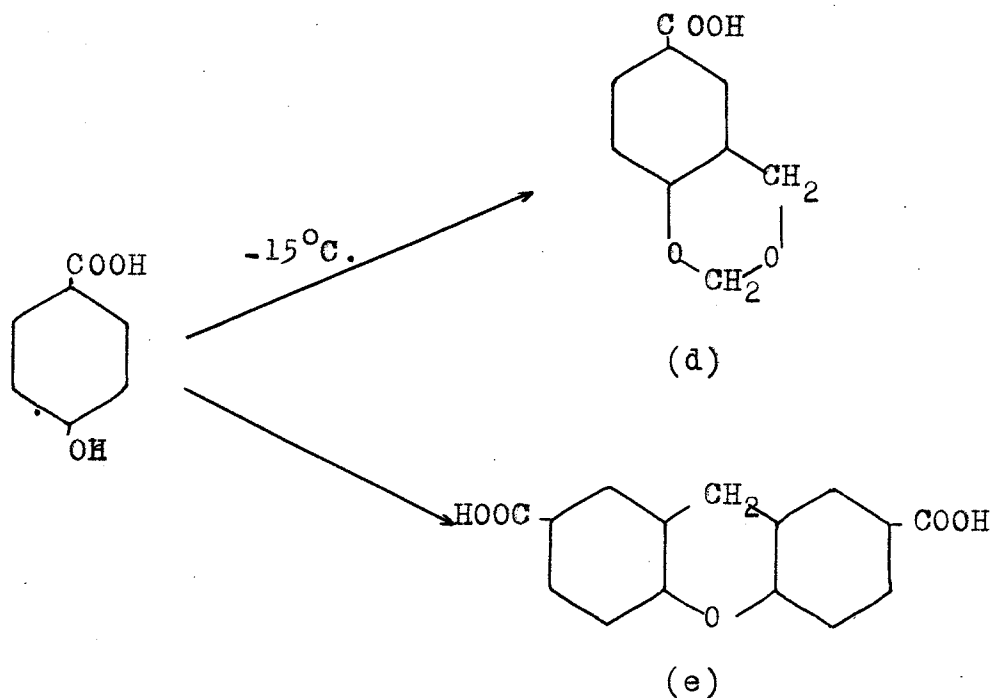
The above authors found that the condensation product did not have a xanthene structure but rather a benzodioxane structure. By oxidizing the condensation product with chromium trioxide in glacial acetic acid, they isolated a non-acidic material (b), which on hydrolysis with sodium hydroxide lost formaldehyde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



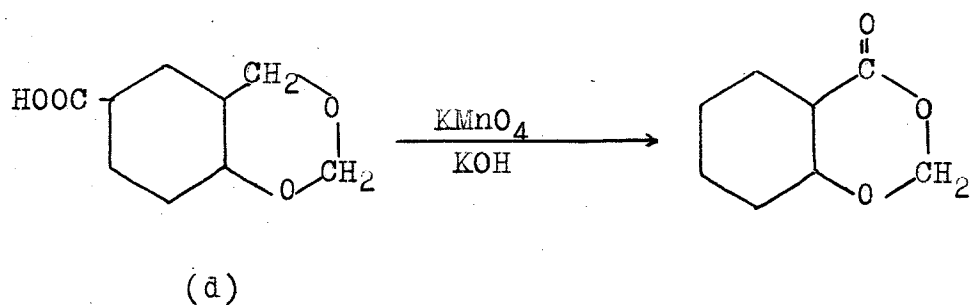
Borsche and Berkhout (4) also obtained dioxane rings by condensing 5-nitrocresol, 6-nitrocresol, *o*-nitronaphthol and *p*-nitrophenol with formaldehyde and concentrated hydrochloric acid. In each case, the dioxane ring was oxidized and hydrolyzed to a nitro-substituted *o*-hydroxy-carboxylic acid.

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

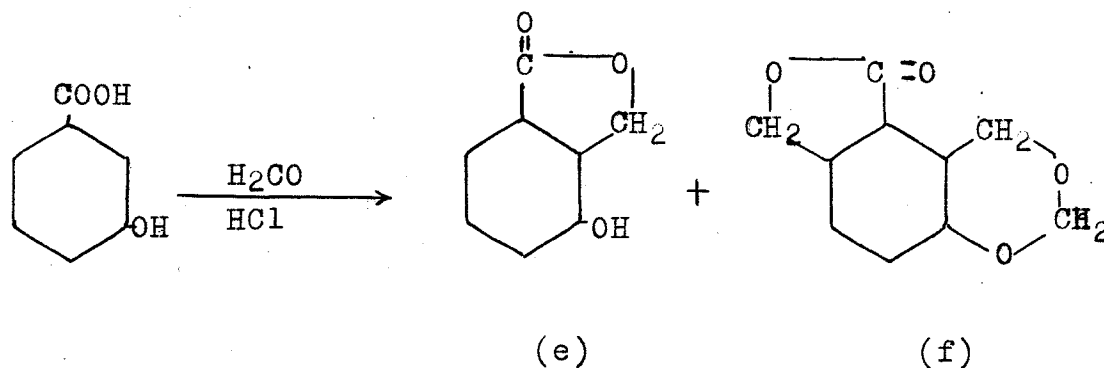
products. At -15°C , they obtained 6-carboxylic acid-1,3-benzodioxane (d), and at a higher temperature they obtained a compound having a xanthene structure (e).



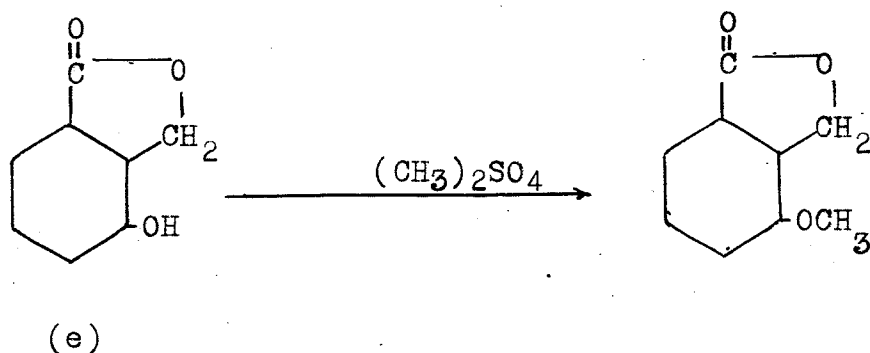
Oxidation of (d) with alkaline permanganate formed 4-keto-1,3-benzodioxane, with the evolution of carbon dioxide.

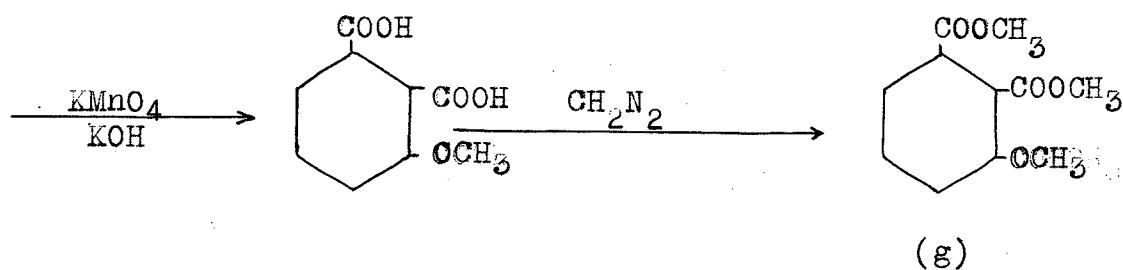


Finally, the most important advances in the study of 1,3-benzodioxane structures were accomplished by Buehler and his coworkers (5-9). Buehler, Powers and Michels (7) condensed 3-hydroxybenzoic acid with formaldehyde and hydrochloric acid and obtained two products of melting point 254°C and 175°C .

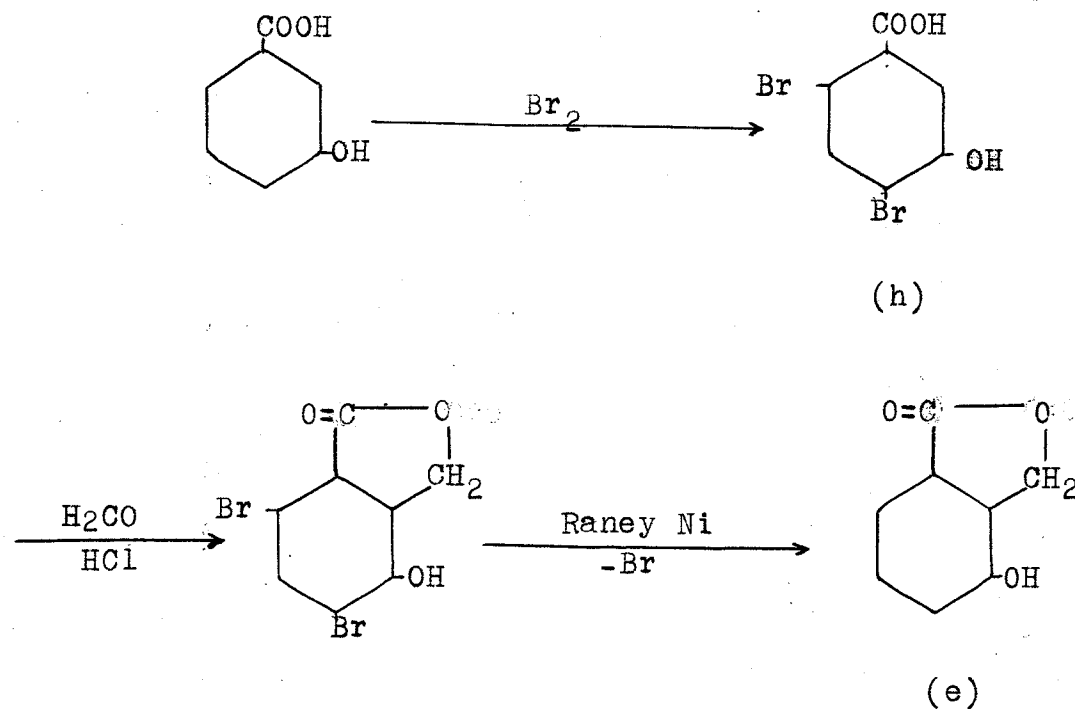


The compound with the higher melting point was found to be a simple phthalide in the following manner. The hydroxyphthalide (e) was methylated. This product was oxidized with alkaline permanganate to give a methoxyphthalic acid which when treated with diazomethane produced the known dimethyl ester of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

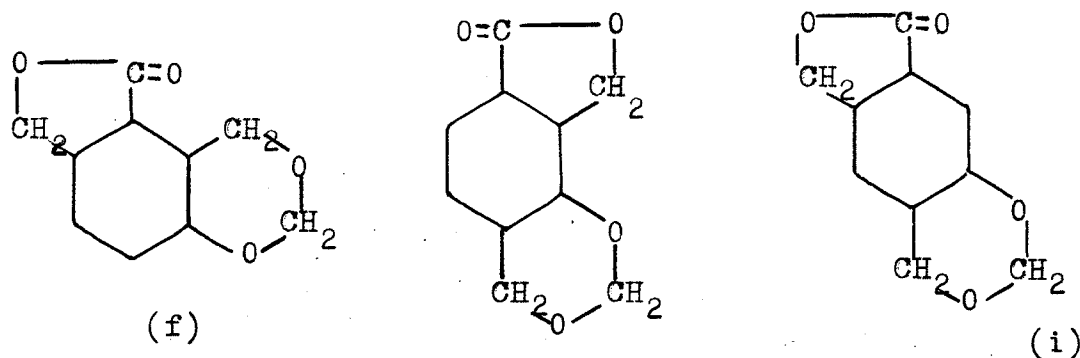




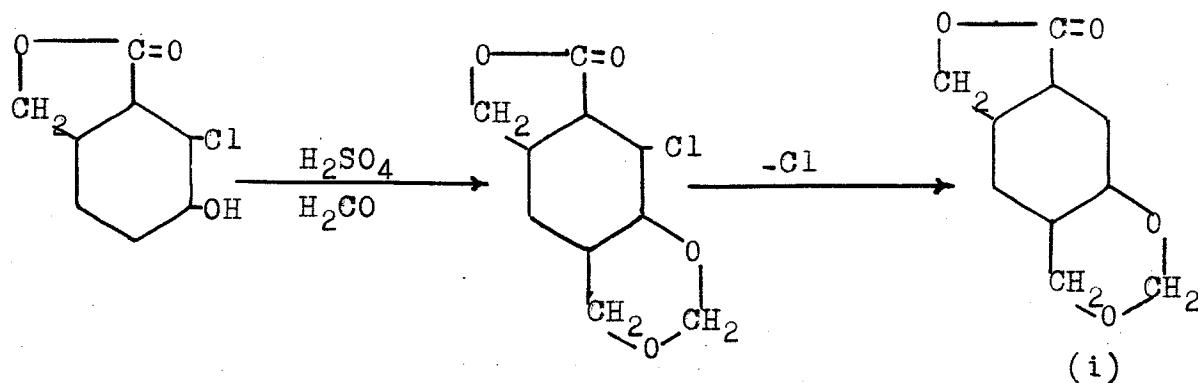
Further proof was presented by the synthesis of the 3-hydroxyphthalide (e). m-Hydroxybenzoic acid was brominated to give the known dibromo acid (h) which was then condensed with formaldehyde and hydrochloric acid. Due to the orientation of the dibromo acid (h), only one possible phthalide could result 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;

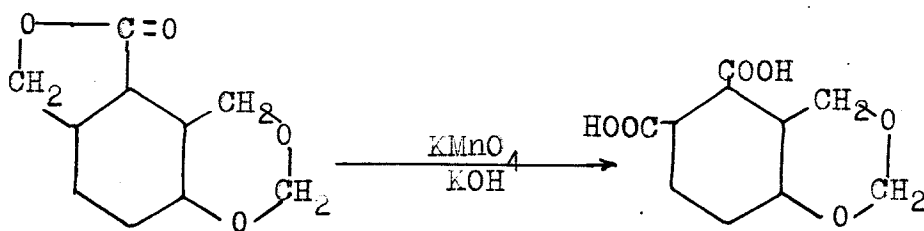


Compound (i) was synthesized by condensing 5-hydroxy-*o*-chlorophthalide with paraformaldehyde and sulphuric acid. This compound was shown to be different from the condensation product.

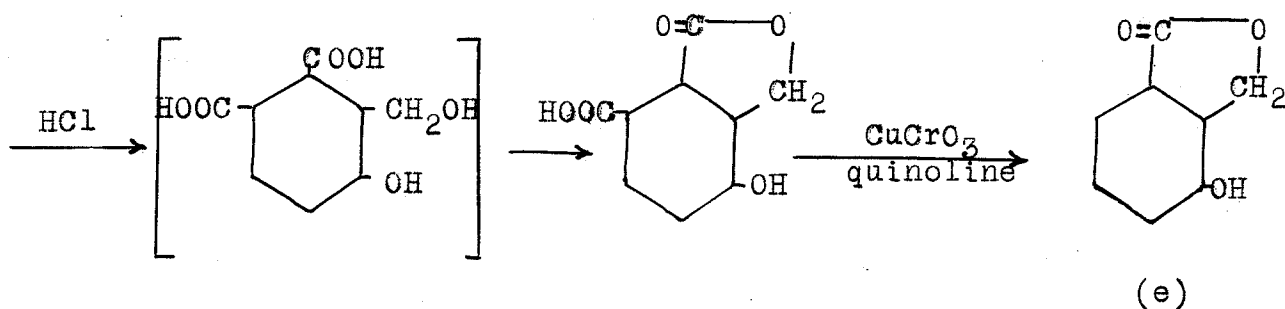


Oxidative degradation was then carried out on the condensation product and ^{it was thought} proved to have the structure (f). This dioxanylphthalide was oxidized in an alkaline medium to give a phthalic acid, which was converted into the monocarboxylic acid with a loss of formaldehyde by refluxing with 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)



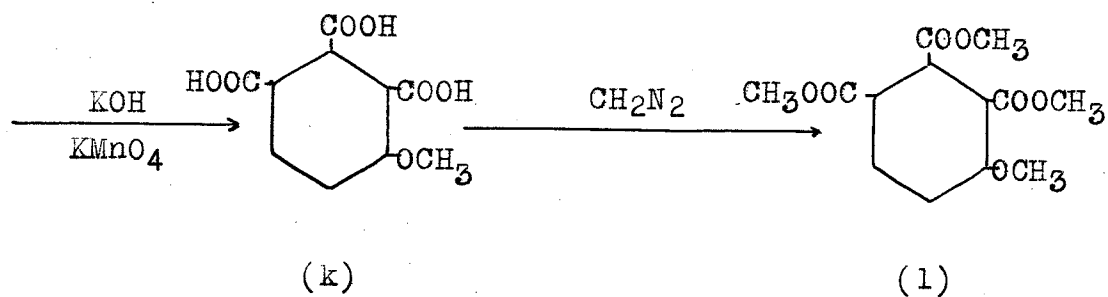
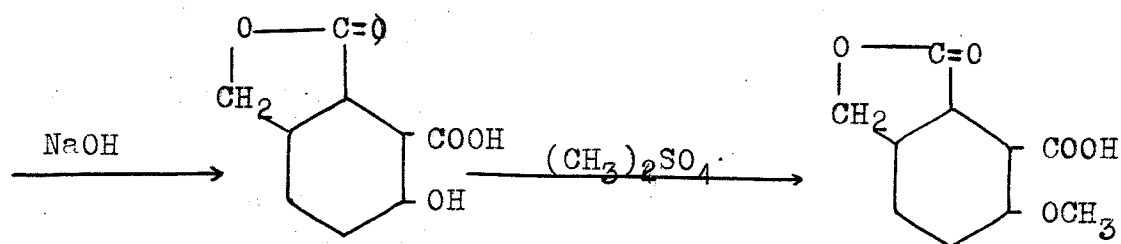
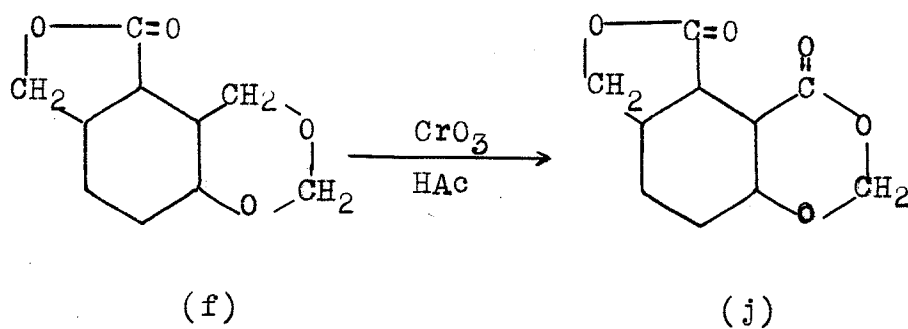
(f)



(e)

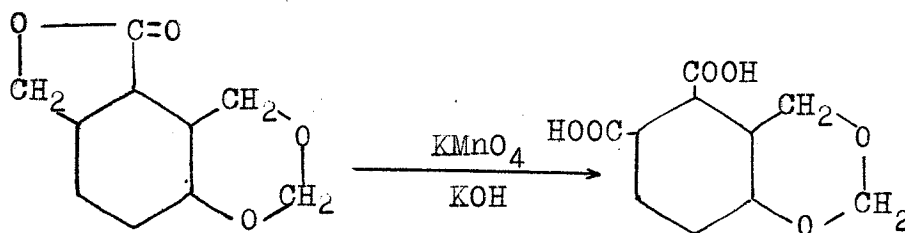
However, this proof was not conclusive and further work was done by Buehler, Slack, Shirley, Sanguinetti and Frey (8). They accomplished two series of oxidative degradation^s and in both cases the end-product was 4-methoxybenzene-1,2,3-tricarboxylic acid (l) which was synthesized by Buehler, Spees and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

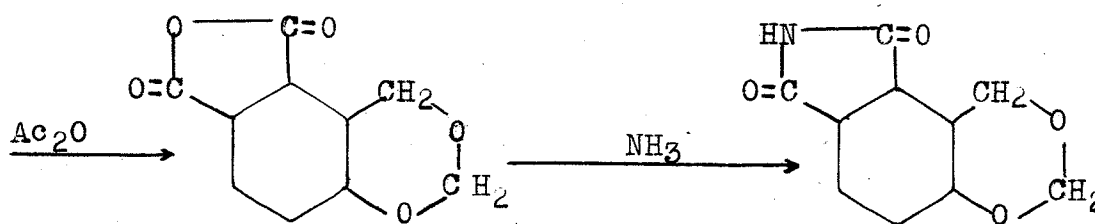


In the second series, the dioxanyl phthalide (f) was oxidized with alkaline permanganate. This broke the phthalide ring to give the dicarboxylic acid. Treatment of this acid with acetic anhydride gave the phthalic anhydride (m). Further treatment with ammonia gave the imide (n),

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).

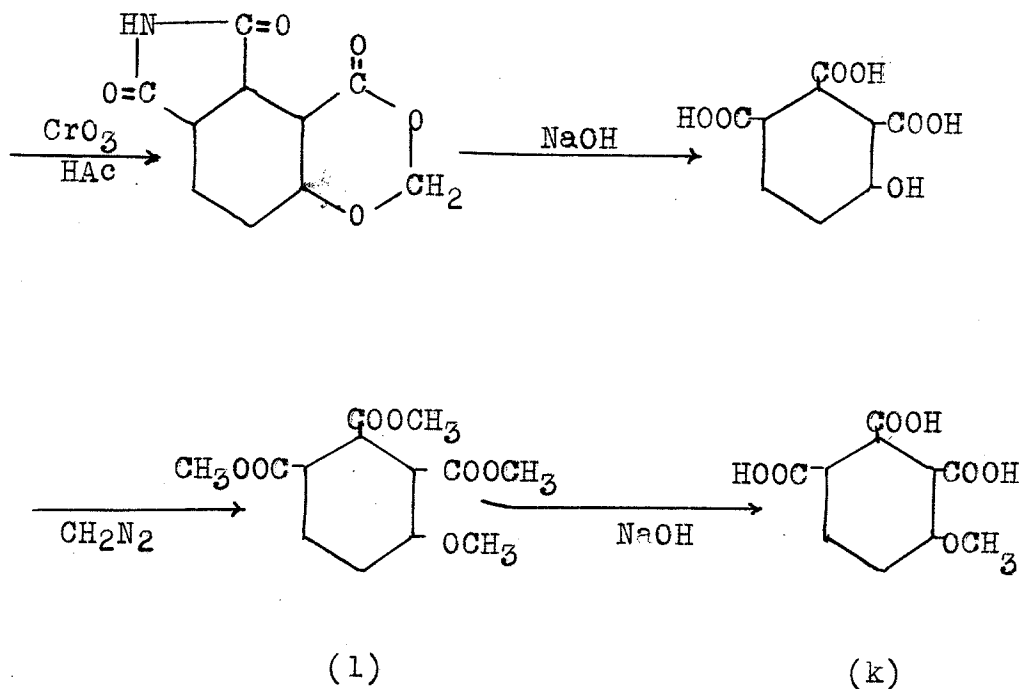


(f)

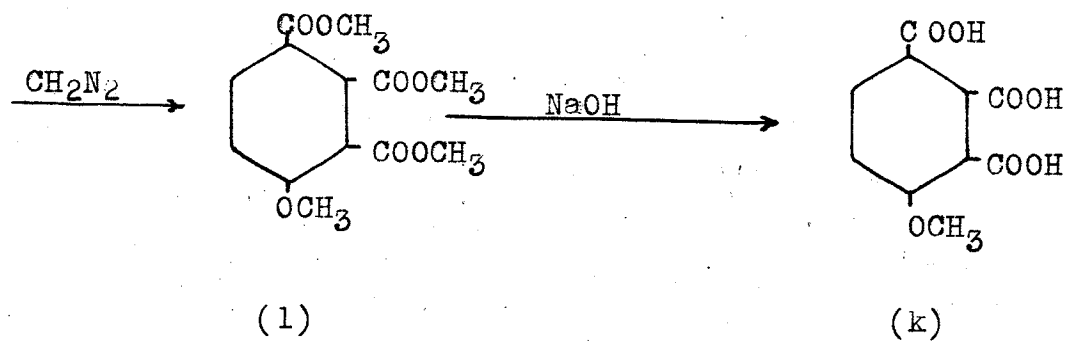
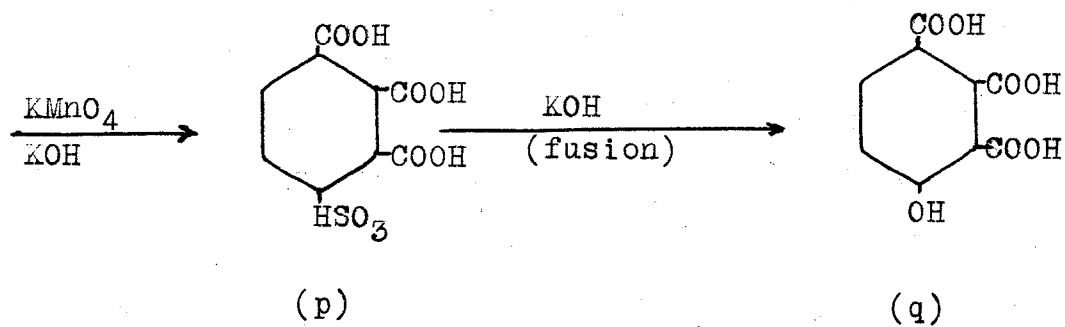
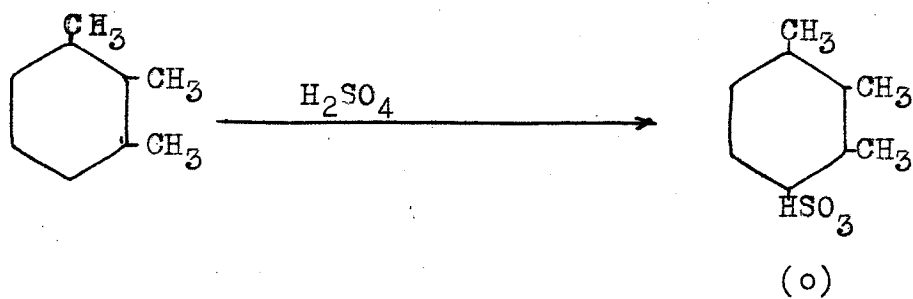


(m)

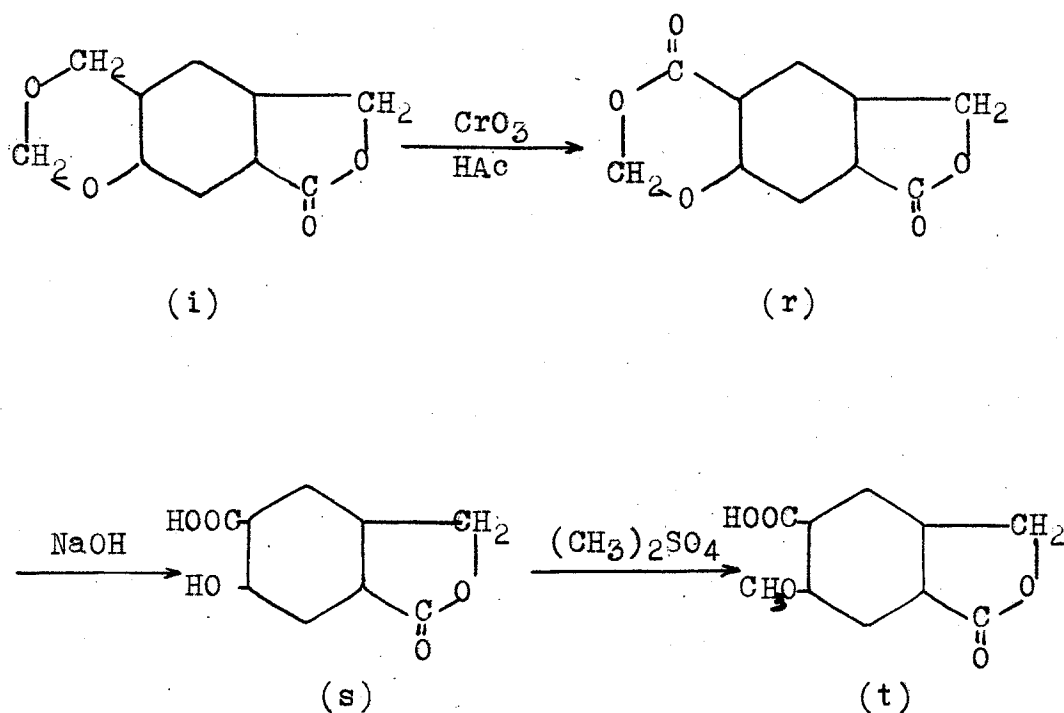
(n)



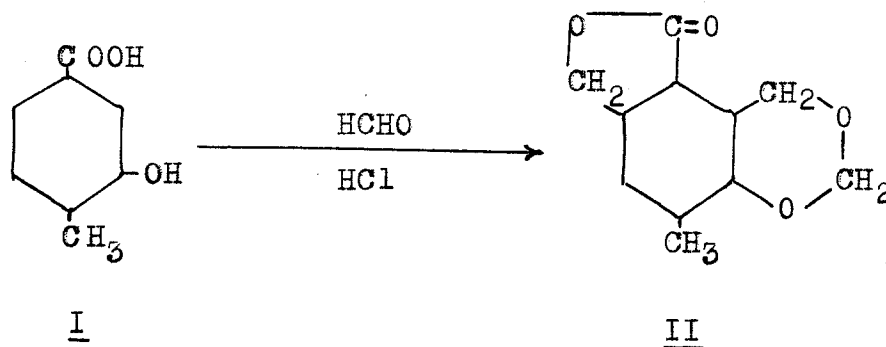
The end-product of the above oxidative degradation, 4-methoxy-1,2,3-tricarboxylic acid (k) was synthesized by Buehler, Spees and Sanguinetti (9) from hemimellitene in the following manner. The aromatic hydrocarbon, hemimellitene was treated with sulphuric acid to give the sulphonic acid (o). Oxidation 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).



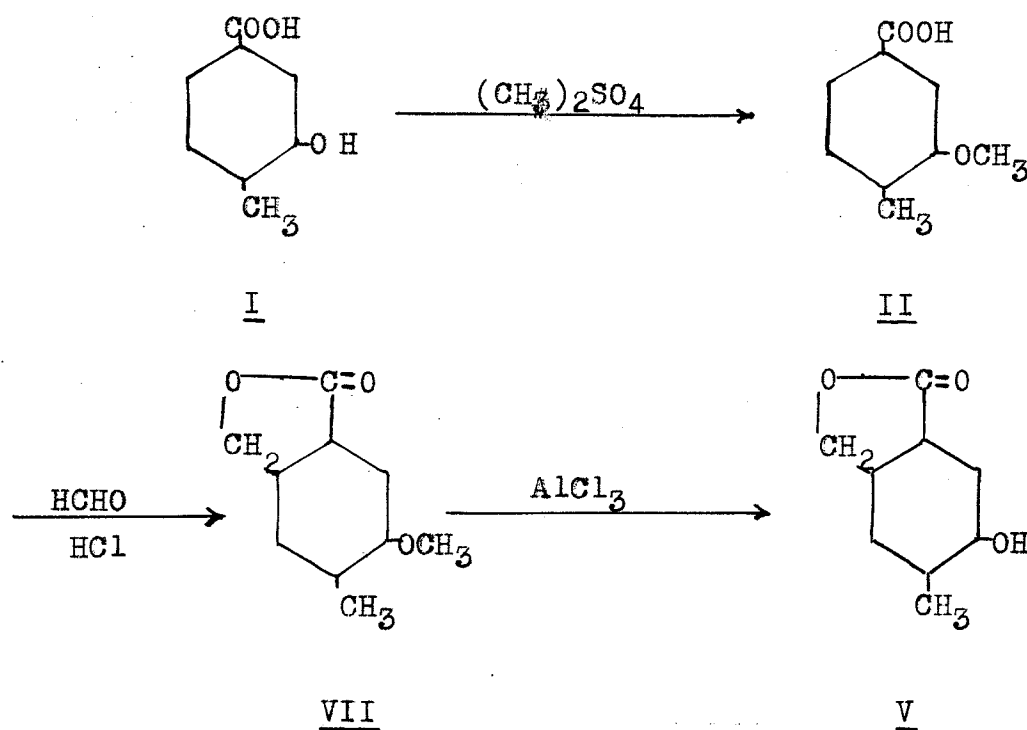
The final piece of work was done by Buehler and Block (5). They oxidized the 6-hydroxymethyl-1,3-benzodioxane-7-carboxylic acid lactone (i) with chromium trioxide to give a methylene ether-ester compound (r), which was hydrolyzed to produce an acidic material (s). This acid was methylated to show the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

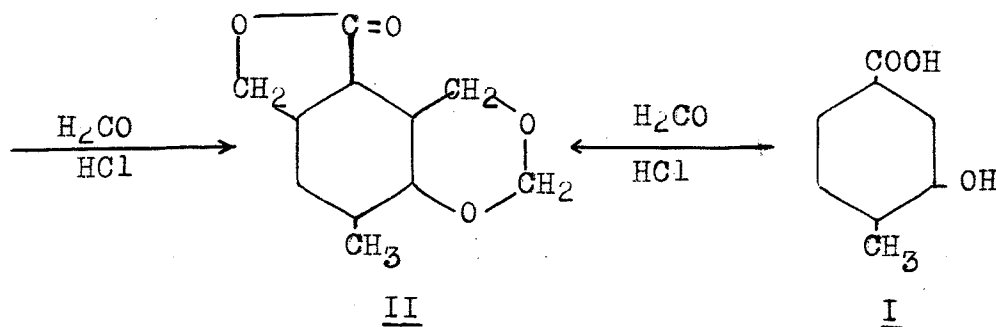


The condensation of 3-hydroxy-p-toluic acid (I) with formaldehyde and hydrochloric acid was first attempted by Yan (27). He isolated a chlorine-free, non-acidic material of melting point 165°C . This work was repeated by Winestock (24), and by various tests and analytical results it was shown that the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

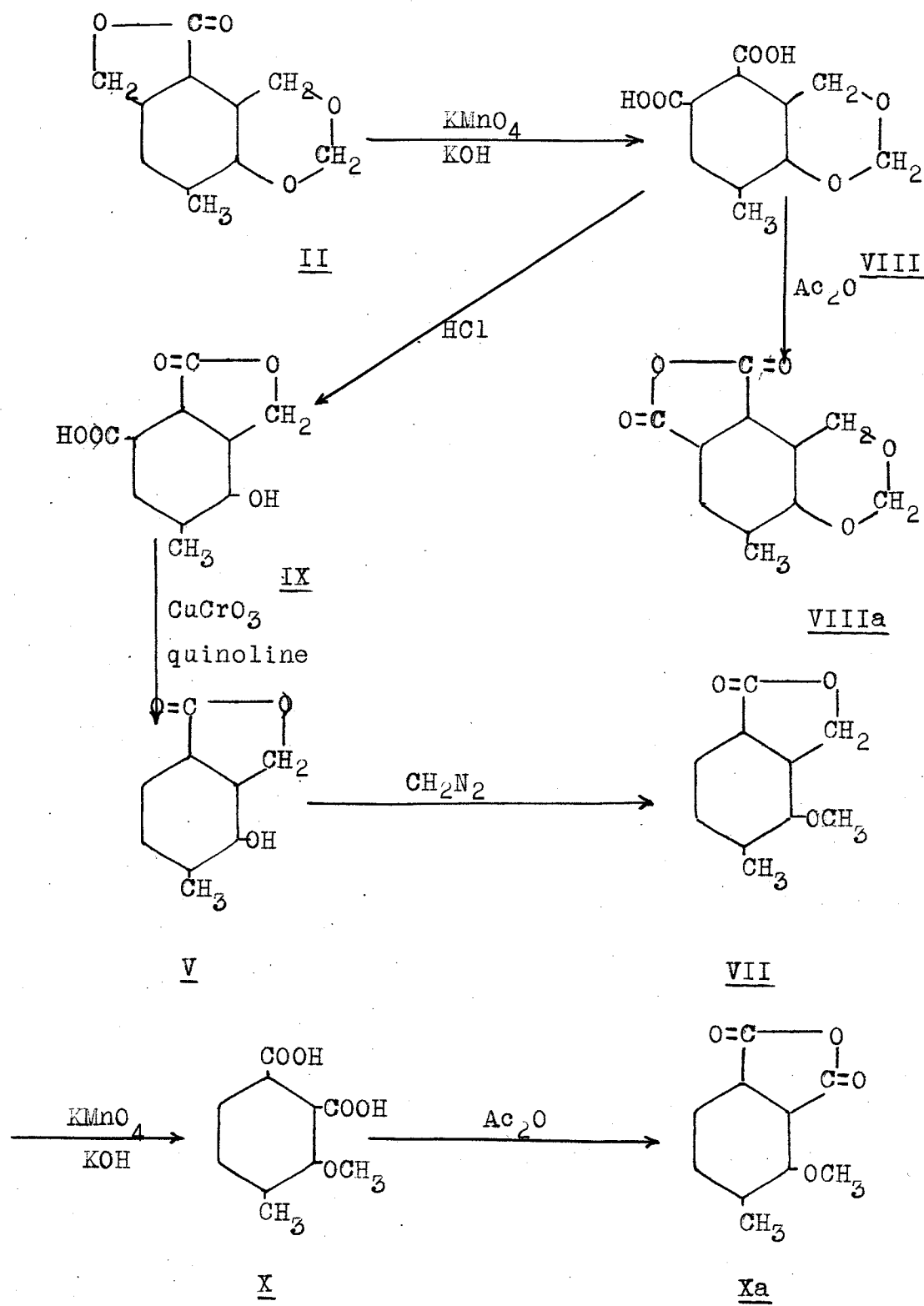


Anderson (1) synthesized the above mentioned dioxanylphthalide directly and indirectly. The indirect synthesis was carried out by treating 3-hydroxy-p-toluic acid (I) with methyl sulphate to obtain methoxy-p-toluic acid (VI). This compound was condensed with formaldehyde and hydrochloric acid to give 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.

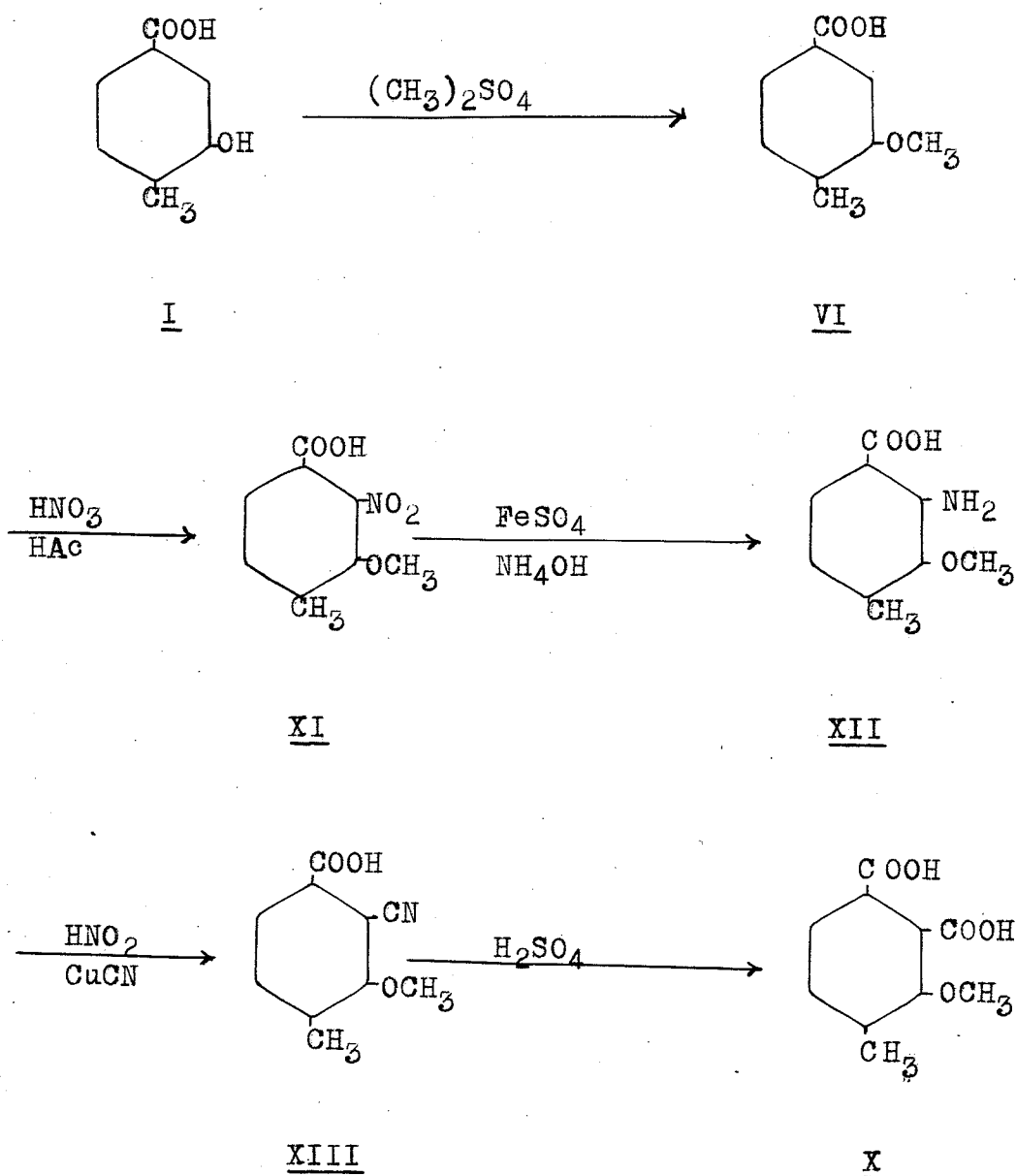




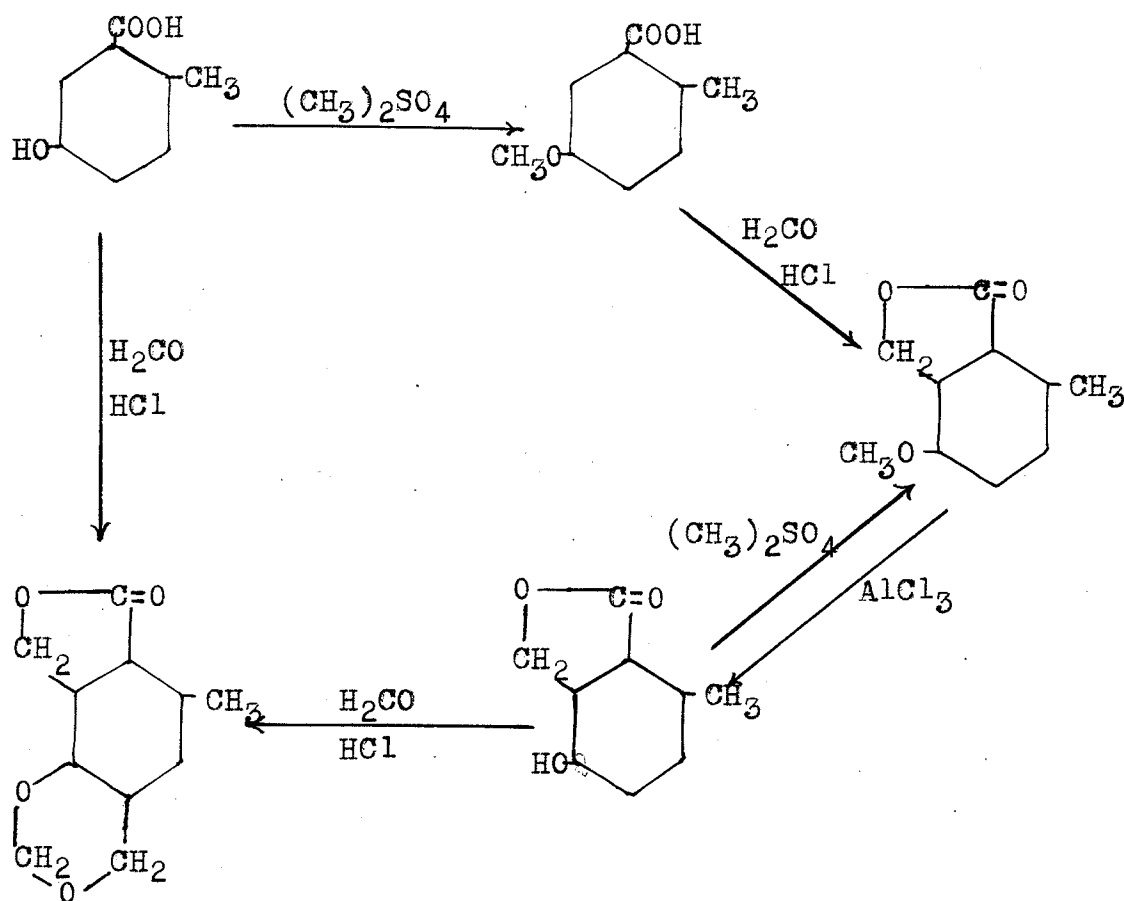
Charlesworth, Anderson and Thompson (10) partially proved the structure of this dioxanylphthalide by a series of degradative oxidations. The phthalide ring was opened by oxidizing the dioxanylphthalide (II) in cold alkaline permanganate. The dicarboxylic acid (VIII) which was obtained, was shown to be 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).

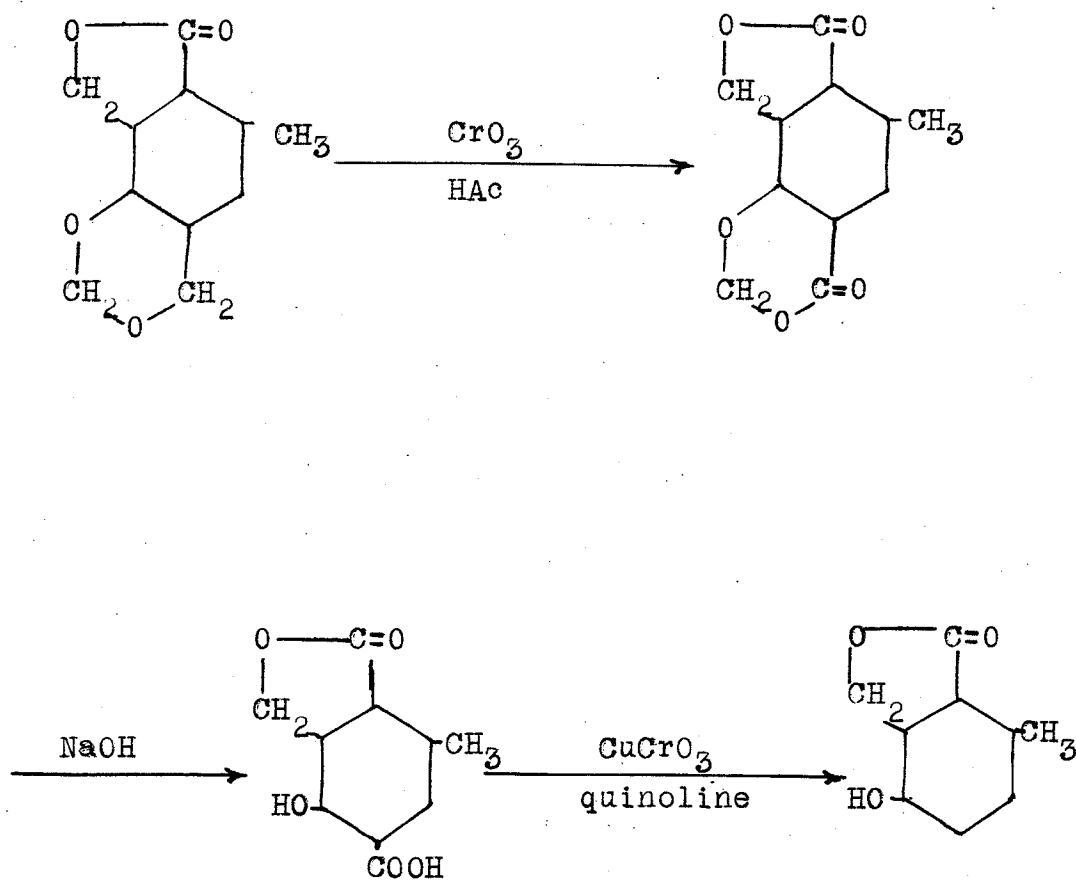


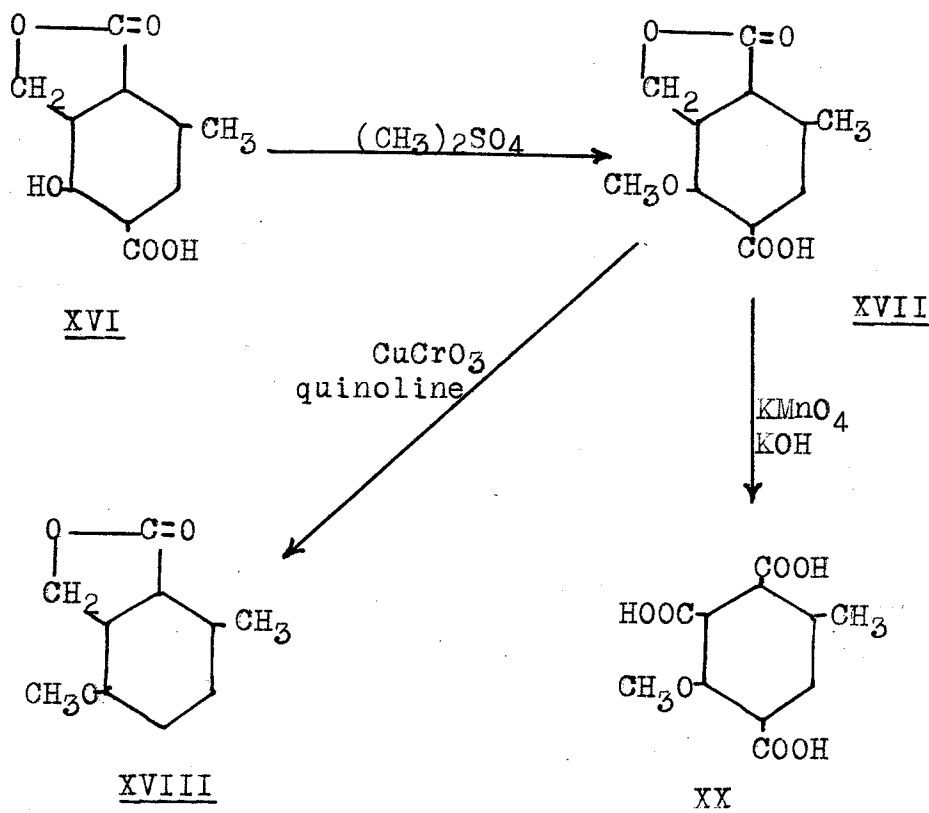
Radych (19) condensed 5-hydroxy-*o*-toluic acid with formaldehyde and hydrochloric acid to obtain the corresponding dioxanylphthalide, and also carried out the indirect synthesis as was described on pages 15 and 16.



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.