

PHTHALIDE STUDIES

The Degradative Proof of Structure of the Condensation
Product of 5-Hydroxy-c-Toluic Acid With
Formaldehyde and Concentrated Hydrochloric Acid

and

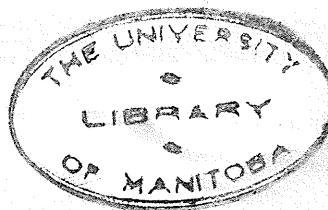
A Survey of Methods of Synthesis of Δ^3 -Dihydropyran

by

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A Thesis presented to the
Faculty of Graduate Studies and Research
of the University of Manitoba
in partial fulfillment of the requirements for
the degree of Master of Science.

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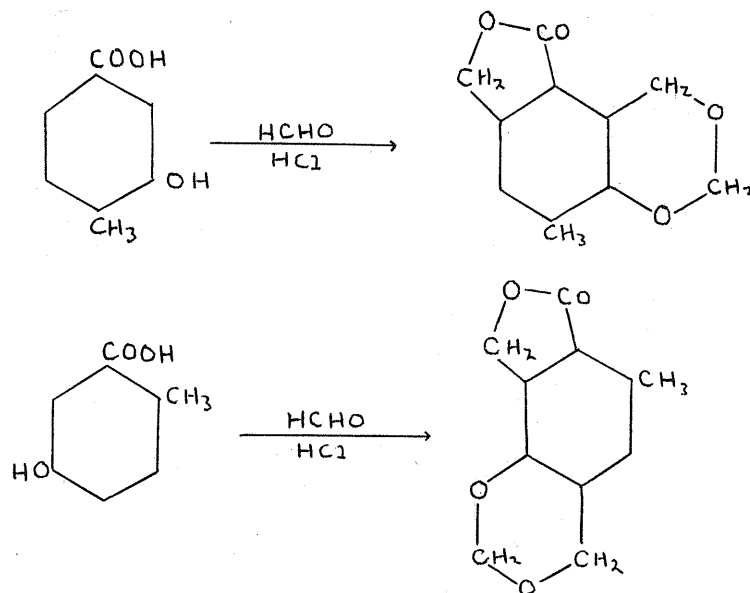
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PART I

THE DEGRADATIVE PROOF OF STRUCTURE OF THE CONDENSATION
PRODUCT OF 5-HYDROXY-*o*-TOLUIC ACID WITH
FORMALDEHYDE AND CONCENTRATED HYDROCHLORIC ACID

INTRODUCTION

Recently in these laboratories, Yan (22), Anderson (1), and Radych (15) have found that the condensation of hydroxy substituted toluic acids with formaldehyde and hydrochloric acid results in compounds containing a fused 1,3-dioxane ring as well as the expected phthalide ring:



The structure of the dioxanylphthalide resulting from the condensation of 3-hydroxy-*p*-toluic acid has been proven by Thompson (20), while the structure assigned to the condensation product of 5-hydroxy-*o*-toluic acid was based only on analytical results and colour tests indicating the presence of the dioxane and phthalide rings.

Thus it is the purpose of the first part of this Thesis to describe an attempt to elucidate and prove as completely as possible the structure of the condensation product of 5-hydroxy-*o*-toluic acid with formaldehyde and

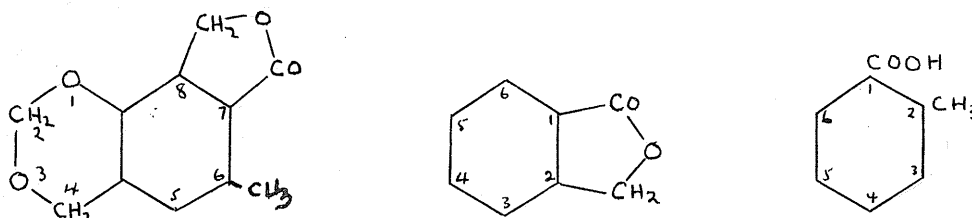
hydrochloric acid.

Two related pieces of work are included, the first of these being the synthesis of 4-methoxybenzene-1,2,3,5-tetracarboxylic acid tetramethyl ester. This is the end-product of the degradative work carried out on the condensation product. The second is the synthesis of 3-methoxy-4-methylphthalic acid, the end-product of the oxidative degradation of the condensation product of 3-hydroxy-p-toluic acid, as carried out by Thompson (20).

LITERATURE SURVEY

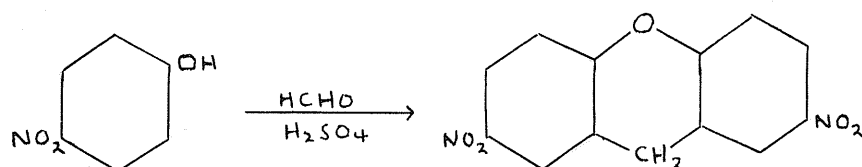
Inasmuch as the general literature of the simple phthalides has been adequately reviewed by Anderson (1) and Radych (15), this survey will cover only that literature dealing with the synthesis of benzodioxane and dioxanyl-phthalide compounds and proof of their structures.

The numbering system used is based on that of Patterson's Ring Index, and is illustrated here:

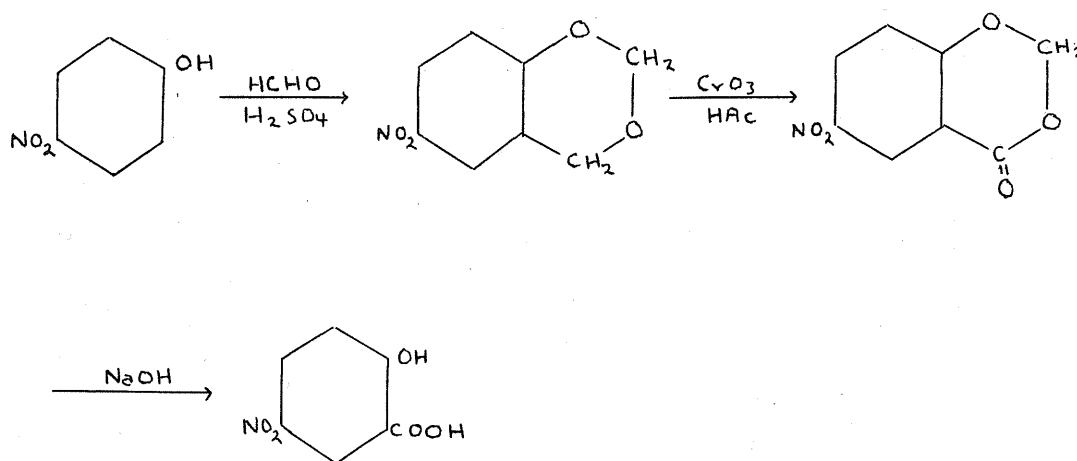


The systematic nomenclature of the dioxanylphthalides will follow that of Buehler and co-workers (3-9). As an example of its use, the systematic name of the dioxanyl-phthalide illustrated above will be 8-hydroxymethyl-6-methyl-1,3-benzodioxan-7-carboxylic acid lactone.

Borsche and Berkout (3) are the first to have reported the synthesis of a compound containing the benzodioxane ring system. This structure resulted from the condensation of p-nitrophenol with formaldehyde in the presence of sulphuric acid as previously carried out by Borsche (2), who had supposed the reaction product to be a xanthene derivative:



The paper of Borsche and Berkout describes the method whereby they were able to prove the condensation product to have the benzodioxane structure rather than the xanthene structure.

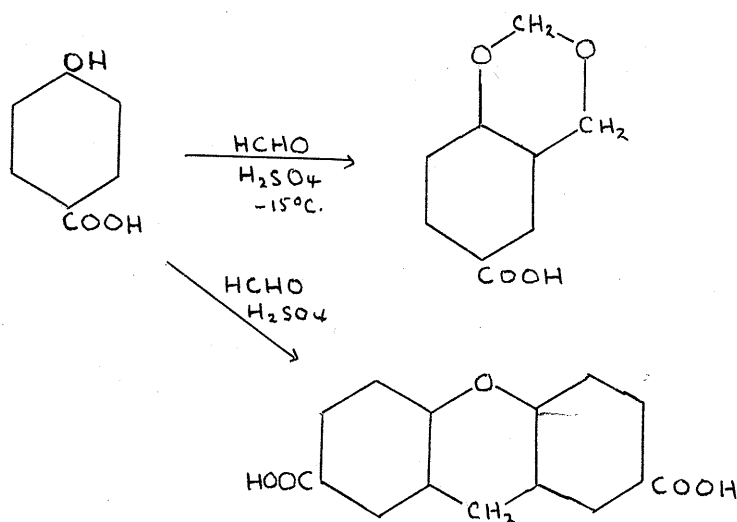


By oxidation of the condensation product with chromium trioxide in glacial acetic acid, a non-acidic material was obtained, which on hydrolysis with sodium hydroxide solution was converted to 5-nitrosalicylic acid with loss of formaldehyde.

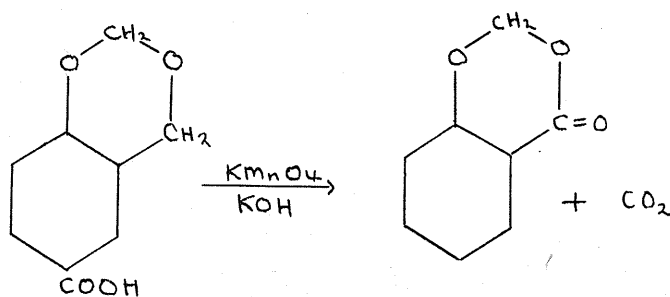
Borsche and Berkout obtained analogous condensation products with 5-nitrocresol, 6-nitrocresol, and α -nitronaphthol which could all be oxidized and hydrolysed in a similar

manner to nitro substituted o-hydroxy carboxylic acids.

The next new contributions to the field were those of Mejuto and Calvet (13). These workers were able to obtain two products from the condensation of p-hydroxybenzoic acid with formaldehyde in the presence of sulphuric acid, the direction of the reaction depending on the temperature. If the reaction were carried out at $-15^{\circ}\text{C}.$, a substituted benzodioxane resulted, and at higher temperatures a substituted xanthene was produced:

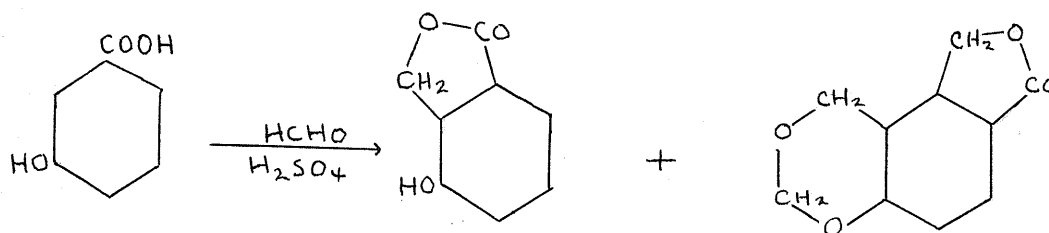


Alkaline permanganate oxidation of the substituted benzodioxane gave 1,3-benzodioxanone-4 with concomittant loss of carbon dioxide:

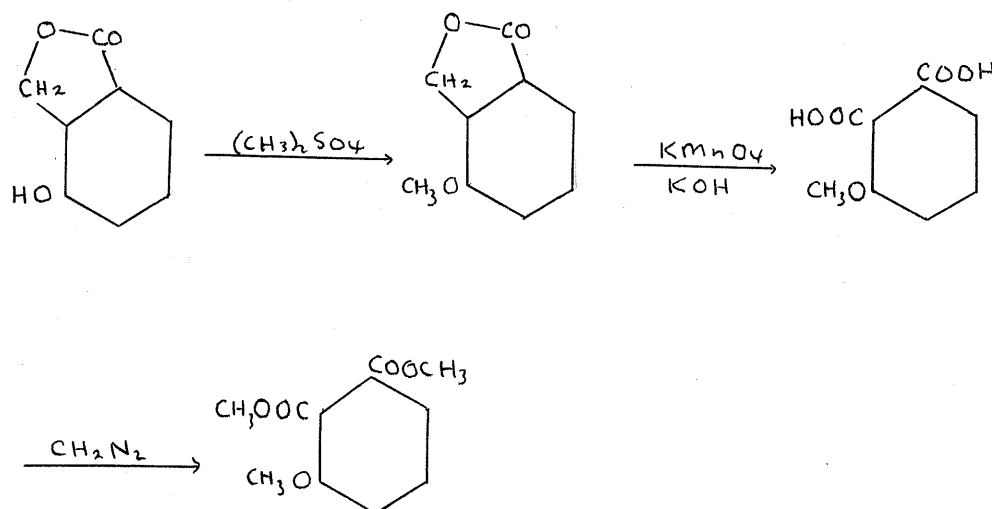


Presumably, this compound could be hydrolysed to salicylic acid.

The most important contributions to this field, in both synthetic and degradative work, are those of Buehler and his coworkers. The condensation of *m*-hydroxybenzoic acid with formaldehyde and hydrochloric acid was carried out by Buehler, Powers and Michels (7), resulting in two products of melting points 254°C. and 175°C.



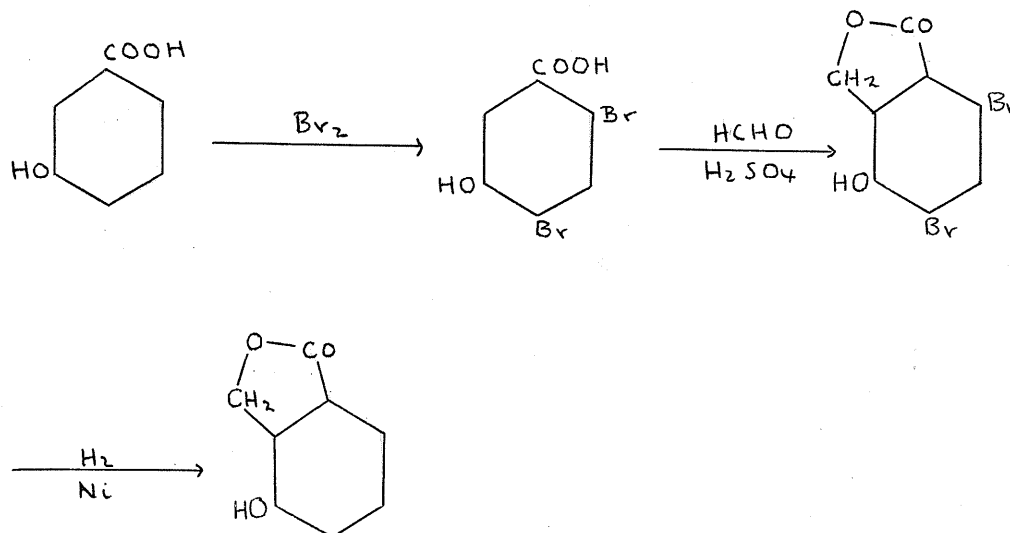
The higher melting compound was shown to be the simple phthalide by the oxidative degradation pictured below:



The hydroxyphthalide was converted to the methoxy derivative, and this oxidized with alkaline permanganate to 3-methoxyphthalic acid. This acid was esterified with

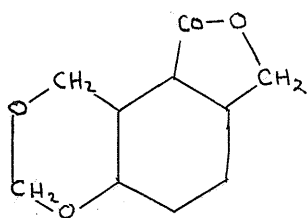
diazomethane to give the known dimethyl 3-methoxyphthalate.

The proof of structure of this compound was completed by the following synthesis:

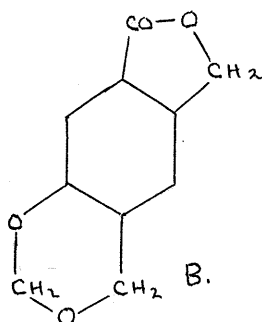


m-Hydroxybenzoic acid was brominated to the known dibromo acid, which was then condensed with formaldehyde. Because of the orientation of the dibromo acid, ^{only} ~~with~~ one possible phthalide could result from the condensation. This dibromo phthalide was dehalogenated with hydrogen and nickel to the 3-hydroxyphthalide.

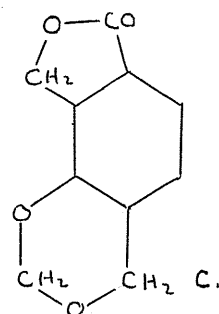
An investigation of the second condensation product was carried out by Buehler, Harris, Shacklett, and Block (6). These workers were of the opinion that this substance was a dioxanylphthalide. Since the condensation could give rise theoretically to any of three isomeric reaction products, further work was necessary to show which of the indicated structures was that of the isolated compound.



A.

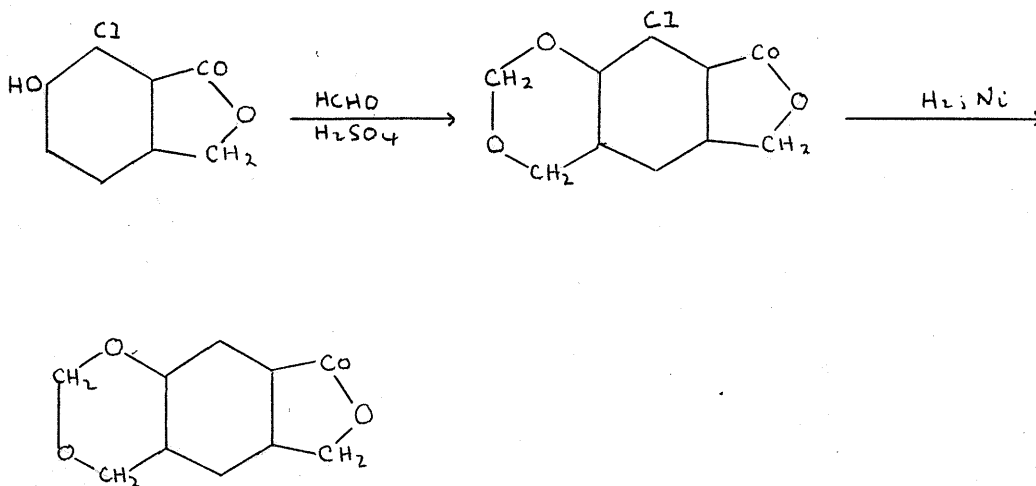


B.



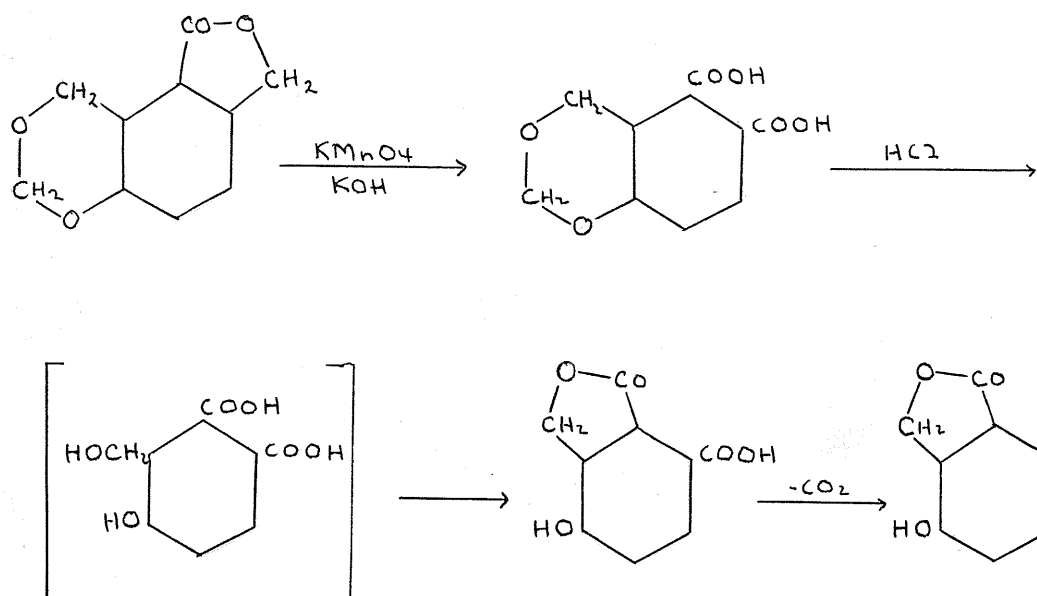
C.

Structure B was eliminated as a possibility by condensing 5-chloro-6-hydroxyphthalide with paraformaldehyde and sulphuric acid, and dechlorinating the resultant chlorodioxanylphthalide to produce a dioxanylphthalide of structure B.



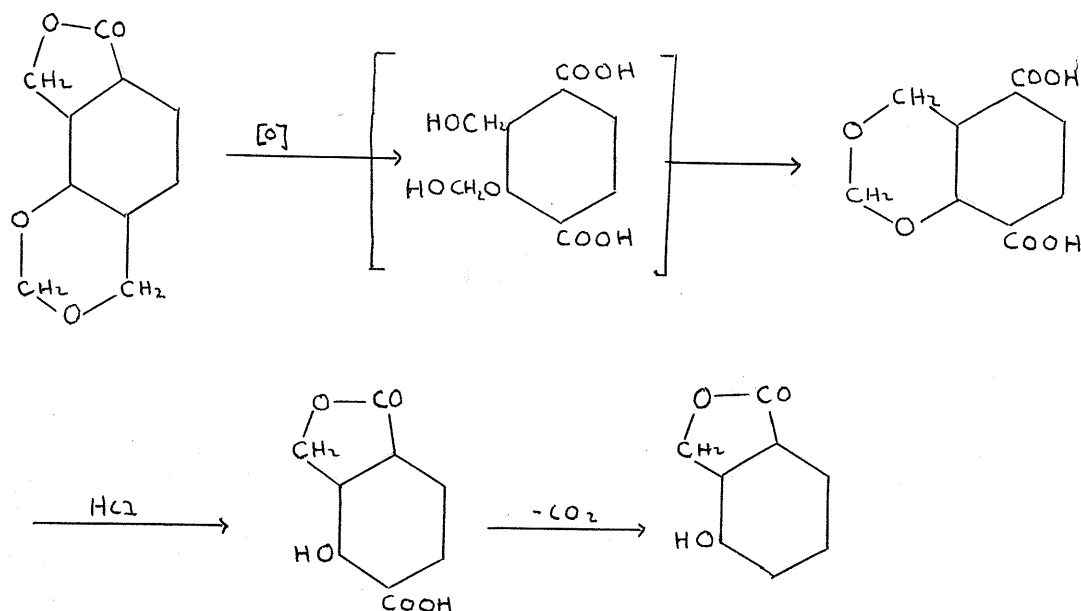
A mixed melting point indicated that B was not the structure of the compound isolated.

A series of degradative reactions was then carried out on the isolated dioxanylphthalide supposedly proving it to have structure A.

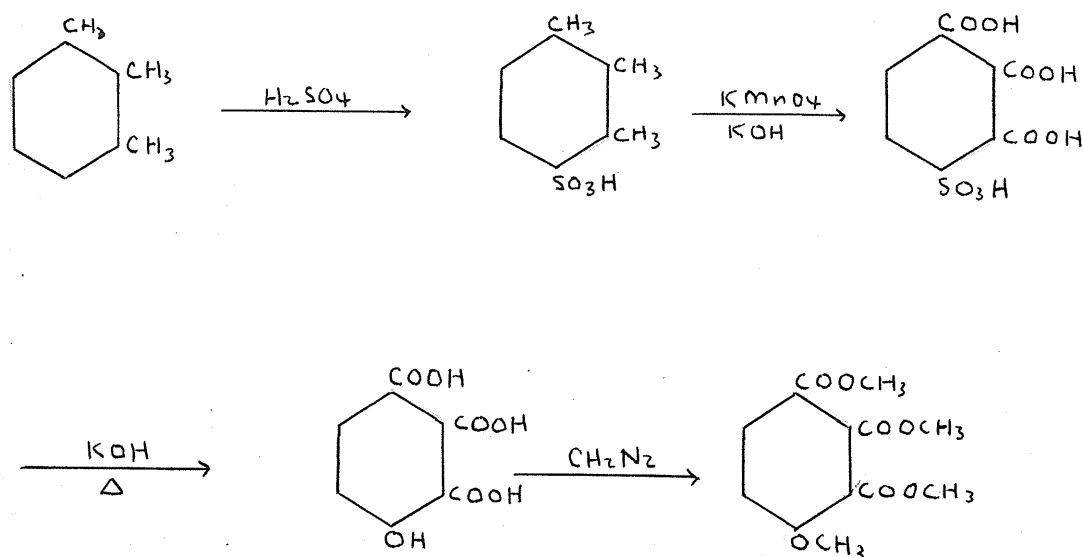


The dioxanylpthalide was subjected to an alkaline permanganate oxidation which converted it to a dicarboxylic acid. Upon further refluxing in an acidic medium the dioxane ring was opened. The intermediate hydroxymethyl compound immediately lost water with one of the carboxyl groups in the formation of a new phthalide ring. The remaining carboxyl group was removed to give rise to the known 3-hydroxyphthalide.

Thompson (20) has argued that this degradative evidence is inconclusive, however. The dicarboxylic acid was not proven to be an *o*-phthalic acid, and a similar degradation carried out on compound C would give a dioxanyl-*p*-phthalic acid which on decarboxylation would also give rise to 3-hydroxyphthalide.

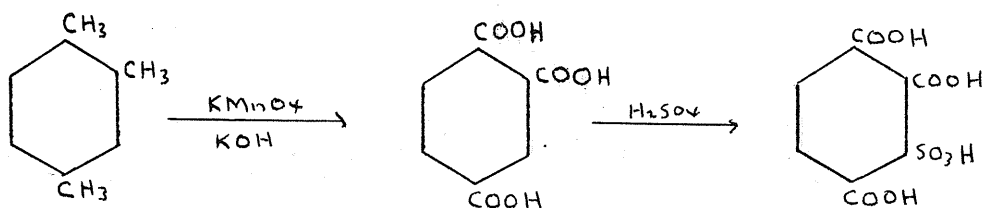


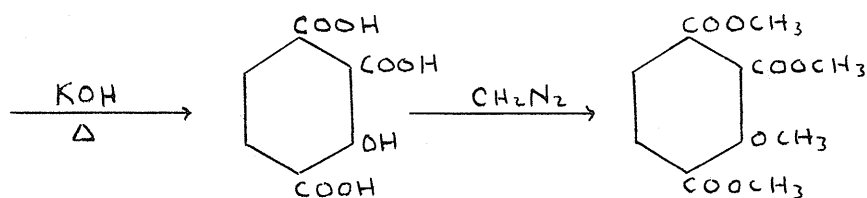
To obtain conclusive proof of the identity of structure A with that of the dioxanylphthalide resulting from the condensation of *m*-hydroxybenzoic acid with formaldehyde and hydrochloric acid, Buehler, Spees, and Sanguinetti (9) synthesized the trimethyl ester of 4-methoxybenzene-1,2,3-tricarboxylic acid and the trimethyl ester of 3-methoxybenzene-1,2,4-tricarboxylic acid from hemimellitene and pseudocumene respectively. These were to be compared with the esterified end-product resulting from the proposed complete oxidation of the dioxanylphthalide. By this scheme structure A would give the trimethyl ester of 4-methoxybenzene-1,2,3-tricarboxylic acid, while structure C would give the trimethyl ester of 3-methoxybenzene-1,2,4-tricarboxylic acid. The synthesis of the first of these is shown below:



Hemimellitene was sulphonated to produce the monosulphonic acid. This was oxidized with alkaline permanganate to the tricarboxylic acid - sulphonic acid. The crude product was subjected to a potassium hydroxide fusion to replace the sulphonic acid group by a hydroxyl group. The resulting hydroxy acid was simultaneously esterified and etherified with diazomethane.

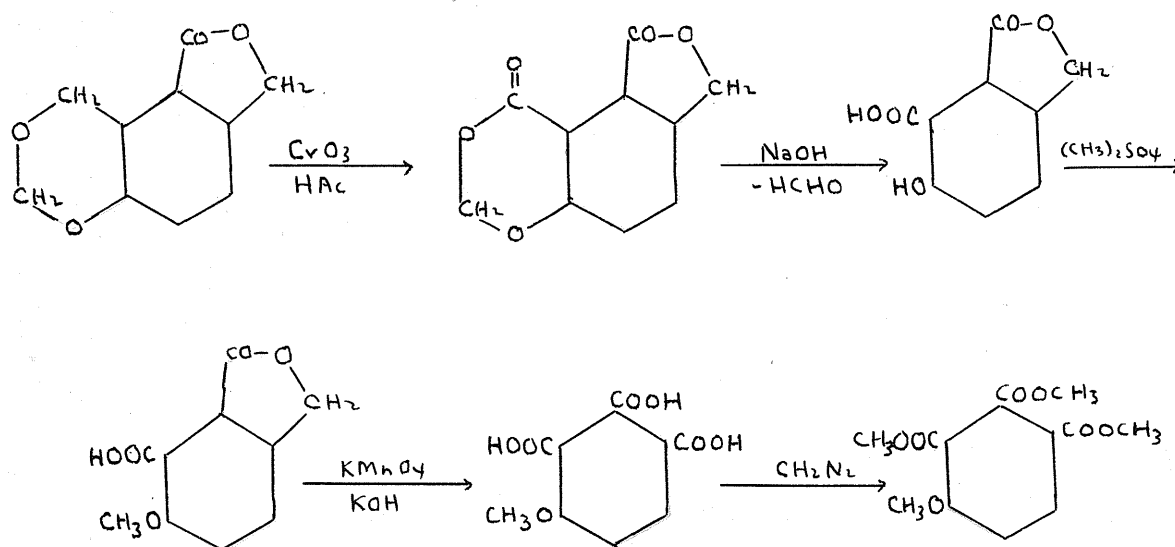
The trimethyl ester of 3-methoxybenzene-1,2,4-tricarboxylic acid was prepared in the same manner, except that the oxidation step was carried out prior to the sulphonation:





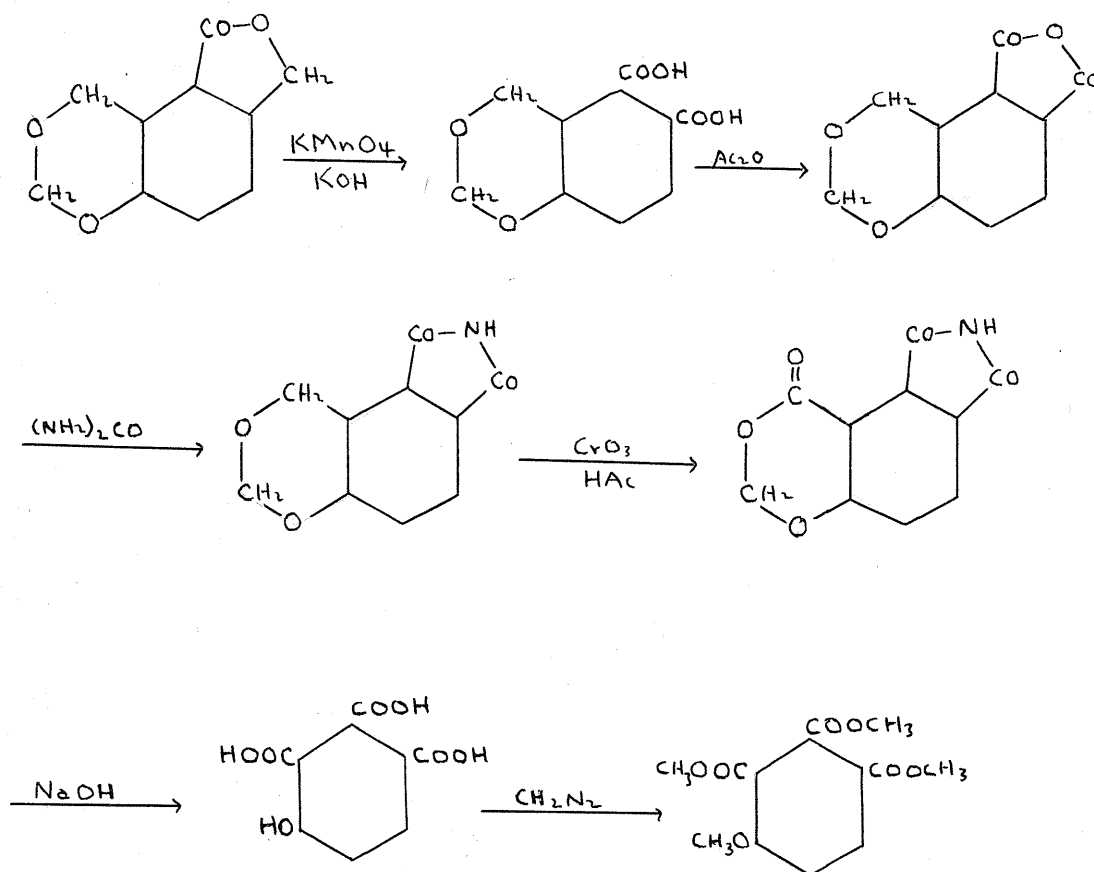
The next paper published by Buehler and his coworkers (8) described two series of oxidative degradations, the end-product of each being the trimethyl ester of 4-methoxybenzene-1,2,3-tricarboxylic acid. Thus this paper proves that the structure of the dioxanylphthalide from *m*-hydroxybenzoic acid with formaldehyde and acid is structure A. In the first of these series the dioxane ring was opened before breaking the phthalide ring, and in the second series, the reverse procedure was carried out.

The first degradative series was carried out in the following steps:



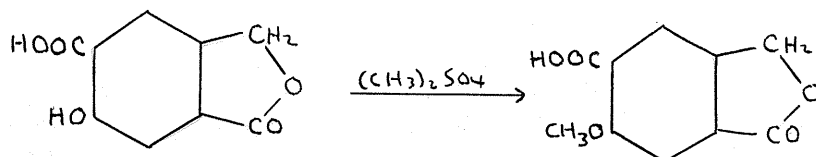
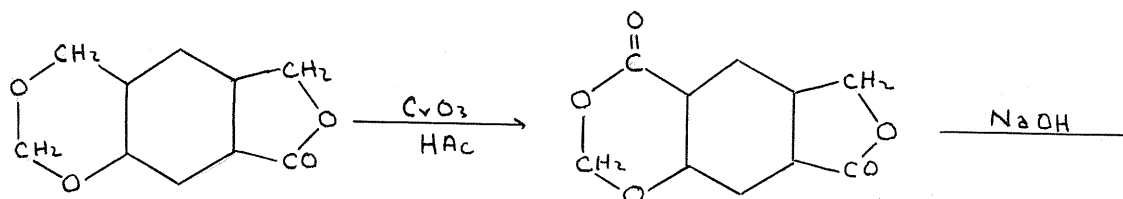
The dioxanylphthalide was converted to the dioxanone-phthalide by oxidation with chromium trioxide in glacial acetic acid. The dioxanone ring of this compound was opened by saponification with aqueous sodium hydroxide. After methylation of the hydroxyl group so produced, the phthalide ring was opened oxidatively to produce the methoxy substituted hemimellitic acid. The three carboxy groups were then esterified with diazomethane to yield trimethyl 4-methoxybenzene-1,2,3,-tricarboxylate, which was found to be identical with the synthetic product.

The second degradative series was then carried out as pictured below:

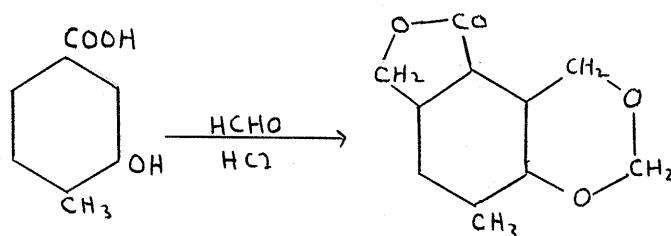


The initial step of this series consisted of the oxidative cleavage of the phthalide ring with alkaline permanganate, resulting in the production of a dioxanylphthalic acid. This production of a phthalic acid was demonstrated by subsequent conversion to a phthalic anhydride by heating with acetic anhydride, converted in turn to a phthalimide by heating the anhydride with urea. The dioxanylphthalimide was oxidized with chromium trioxide in glacial acetic acid to the dioxanonephthalimide. Then the dioxanone and phthalimide rings were both opened by saponification with aqueous sodium hydroxide. The resulting hydroxy substituted hemimellitic acid was simultaneously esterified and etherified with diazomethane to yield again trimethyl 4-methoxybenzene-1,2,3-tricarboxylate.

The last piece of work of Buehler and coworkers to be described here is that of Buehler and Block (4), concerning the oxidation of the lactone of 6-hydroxymethyl-1,3-benzodioxane-7-carboxylic acid. Presumably this material was synthesized as described on page 8. This dioxanylphthalide was oxidized with chromium trioxide to the dioxanonephthalide, which on hydrolysis yielded the corresponding 5-hydroxymethyl-salicylic acid-4-carboxylic acid lactone. This could then be methylated to prove the presence of a hydroxyl group.

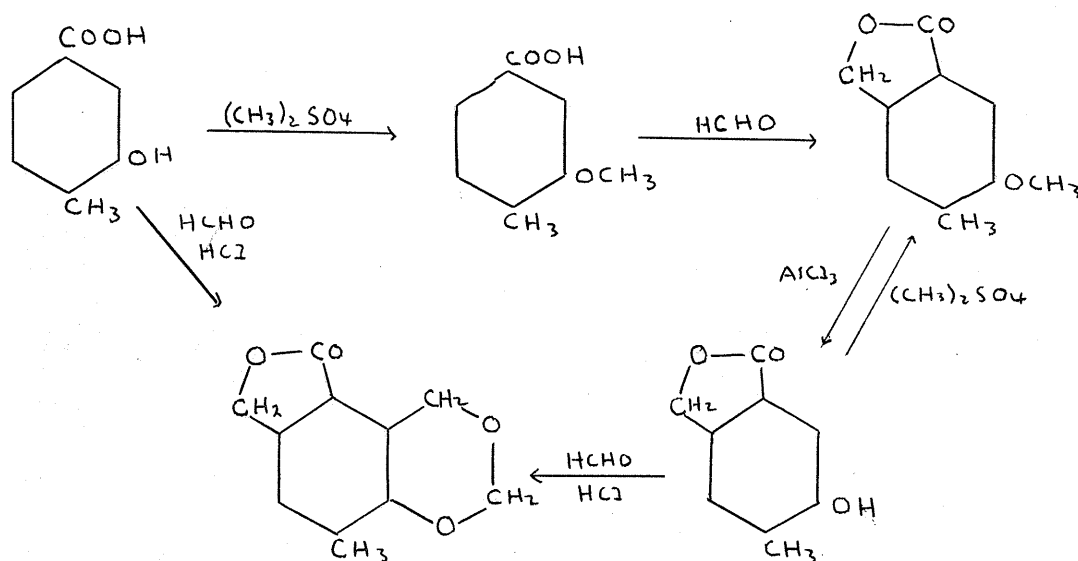


Considerable work has been done by this Department with the condensation of hydroxy substituted toluic acid with formaldehyde and hydrochloric acid. From the condensation of 3-hydroxy-p-toluic acid with formaldehyde and hydrochloric acid Yan (22) isolated a chlorine-free, non-acidic material melting at 165°C , Winestock (21) repeated this work, and on the basis of analytical results and colour tests concluded that the compound was a dioxanyolphthalide:



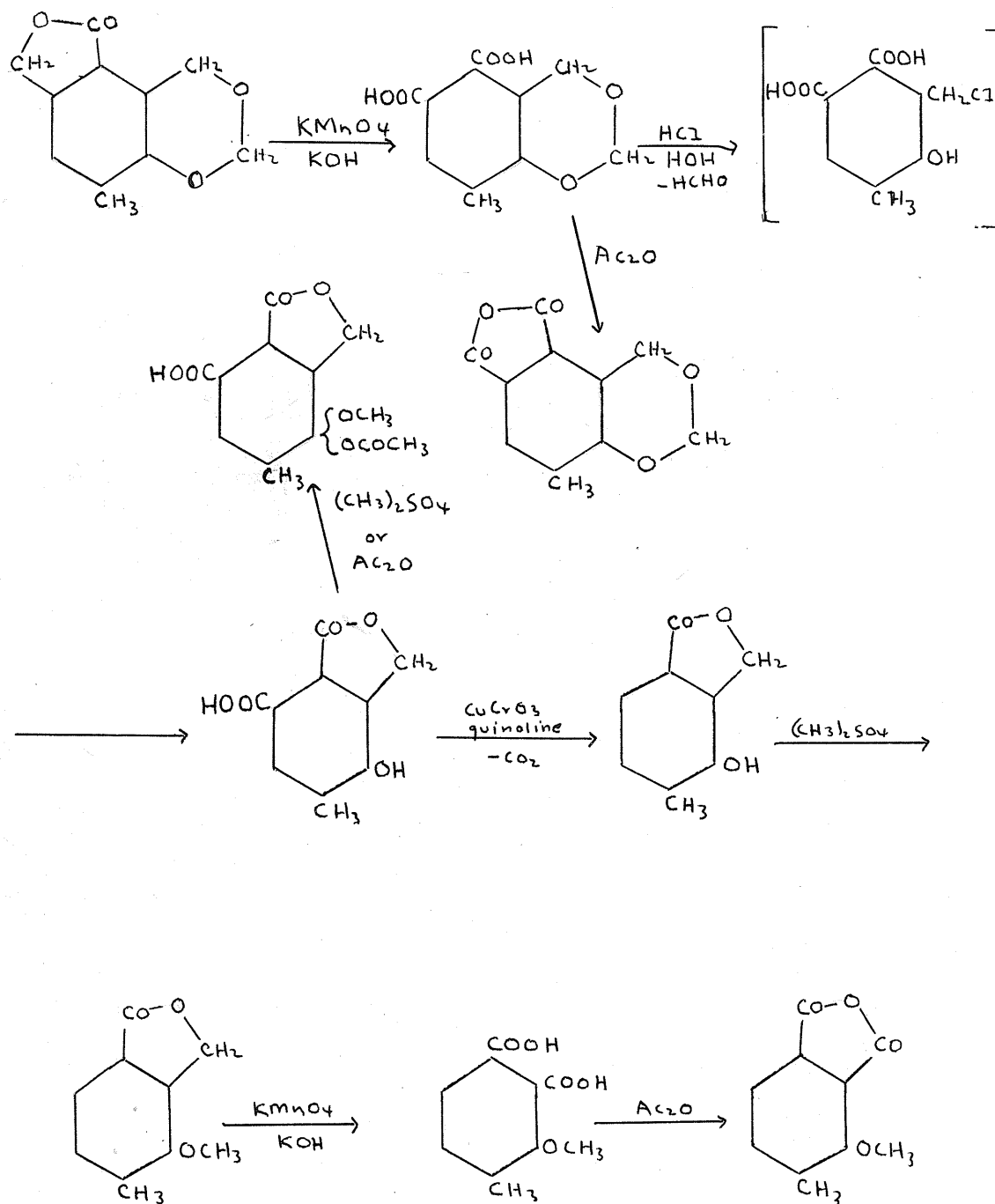
Another reason for this conclusion was that an attempted methylation indicated that the hydroxyl group was no longer unsubstituted.

Anderson synthesized this dioxanylphthalide indirectly from 5-hydroxy-4-methylphthalide as well as directly from 3-hydroxy-p-toluic acid. These synthetic routes are shown below:



3-Hydroxy-p-toluic acid was methylated, and the resulting 3-methoxy-p-toluic acid was condensed with formaldehyde and hydrochloric acid to give 5-methoxy-4-methylphthalide. This phthalide was demethylated with aluminum chloride to 5-hydroxy-4-methylphthalide. This hydroxy group could, of course, be remethylated with methyl sulphate. The hydroxyphthalide was then condensed with formaldehyde and hydrochloric acid to give a dioxanylphthalide identical with that prepared directly from 3-hydroxy-p-toluic acid.

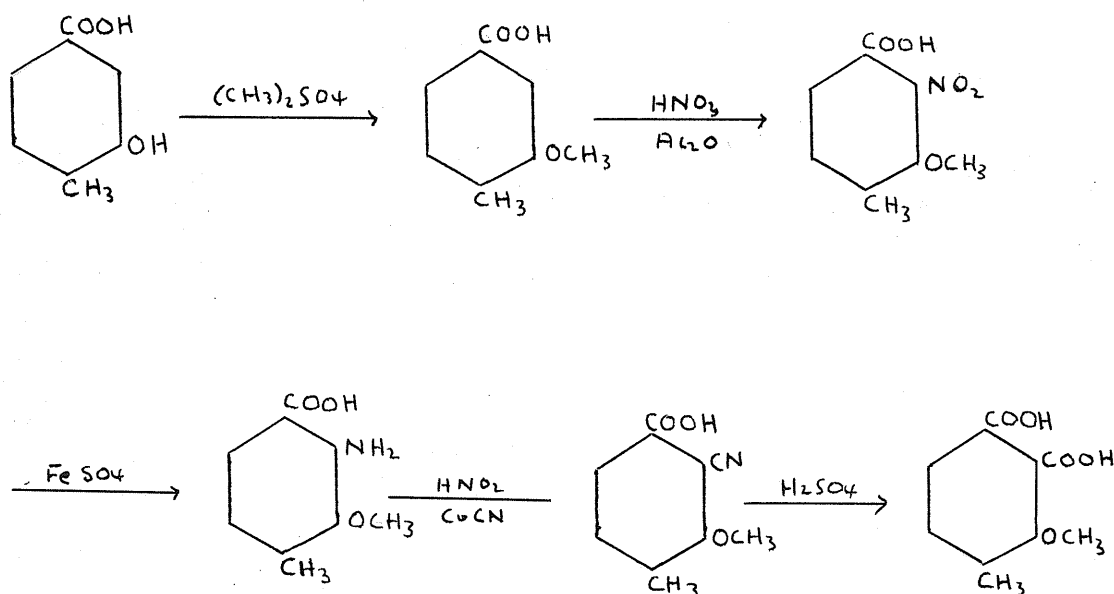
The structure of this dioxanylphthalide was proved in a series of degradative oxidations carried out by Thompson (20). The degradative series is pictured on the next page:



The phthalide ring of the dioxanylphthalide was split oxidatively with cold basic permanganate. The resulting dioxanylphthalic acid was refluxed with hydrochloric acid when a rearrangement took place, the dioxane ring opening and the resulting chloromethyl side chain

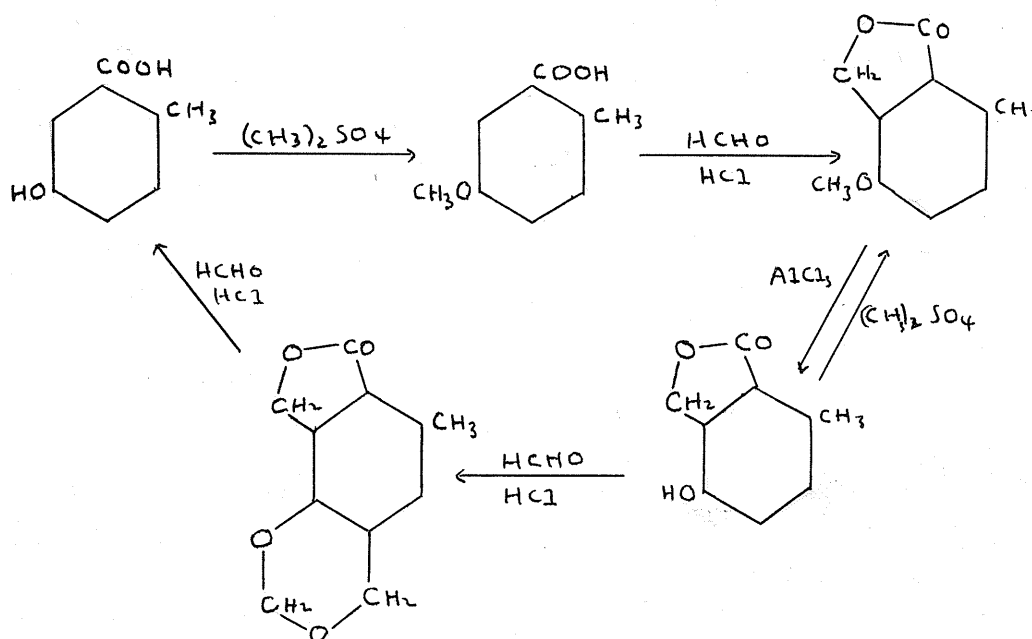
condensing with the vicinal carboxyl group to lose HCl and form a new phthalide ring. The remaining carboxyl group was then removed by heating with copper chromite in quinoline to produce 3-methoxy-4-methylphthalide. Finally, after methylation of the hydroxyl group with methyl sulphate, the new phthalide ring was oxidized with alkaline permanganate, the end-product being 3-methoxy-4-methylphthalic acid. The hydroxyl group was also acetylated, and the phthalic acids of both the first and last steps could be made to form anhydrides. The end-product melted at $173-174^{\circ}\text{C}.$, which is in good agreement with the value of $175^{\circ}\text{C}.$ published by Simonsen and Rau (16) for their synthetic product.

The Simonsen and Rau synthesis of 3-methoxy-4-methylphthalic acid was carried out as follows:



3-hydroxy-p-toluic acid was methylated with methyl sulphate and the methylated product nitrated in the cold with fuming nitric acid in acetic anhydride. The nitro acid was reduced with ferrous sulphate to the amino acid. The amino acid was converted to the cyano acid via the Sandmeyer method, and this cyano acid hydrolysed with dilute sulphuric acid to the desired phthalic acid. This synthesis was repeated as described later in this Thesis, and a mixed melting point of Thompson's end-product and the synthetic 3-methoxy-4-methylphthalic acid showed the two to be identical.

Radych (15) condensed 5-hydroxy-o-toluic acid with formaldehyde and hydrochloric acid to produce the corresponding dioxanylphthalide, and also carried out the indirect synthesis as was described under Anderson's work on page 16. These are shown below:



DISCUSSION OF RESULTS

The work will be described and discussed in four sections: the two series of oxidative degradations, the synthesis of the end-product of Thompson's (20) degradative work, and the attempted synthesis of the end-product of the present degradative work.

A flow sheet of the two degradative series opens out at the end of the first part of this Thesis for reference purposes. Each compound thereon has been assigned an identifying Roman numeral which will be used throughout the discussion and experimental section.

First Degradative Series

In this degradative work the plan of Buehler and coworkers (8) of degrading a dioxanyolphthalide via two routes was adopted. In the first series of degradative reactions, the dioxane ring is opened before the phthalide ring, while in the second series the reverse procedure is carried out.

The oxidation of the dioxane ring of the dioxanyolphthalide to a dioxanone ring comprises the first step of this series. The dioxanyolphthalide (I) was dissolved in glacial acetic acid, and chromium trioxide was added. Upon working up the reaction mixture, the resultant dioxanophthalide (II) was obtained in rather poor yield. Although several modifications of the procedure were tried, the yield

could not be raised above 20% of the theoretical.

The dioxanone ring of (II) was opened with loss of formaldehyde by saponification with aqueous sodium hydroxide. Acidification of the reaction mixture gave the expected o-hydroxy carboxylic acid substituted phthalide (III) in almost quantitative yield. The presence of the hydroxyl group was indicated by the dark violet colour given with 1% ferric chloride solution, and the carboxyl group by formation of a p-nitrobenzyl derivative.

The hydroxyl group of compound (III) was methylated with methyl sulphate. The resulting methoxy derivative (IV), after two recrystallizations from water, gave no ferric chloride test.

The carboxyl groups of both compounds (III) and (IV) could be removed by heating their quinoline solution with a catalytic amount of copper chromite. The resultant decarboxylated compounds (XV) and (XIV) were found by the method of mixed melting points to be identical with specimens of 3-hydroxy-6-methylphthalide and 3-methoxy-6-methylphthalide respectively. These compounds were synthesized according to Radych (15).

The phthalide ring of compound (IV) was opened oxidatively with warm weak alkaline permanganate solution. The resultant toluene tricarboxylic acid (V) was isolated in good yield.

Second Degradative Series

As mentioned above, this series starts with the opening of the phthalide ring. Initial attempts at accomplishing the reaction followed the experimental procedure of Buehler and coworkers (8), in which warm alkaline permanganate is used. A substance of m.p. 159-160°C. was isolated from these oxidations which was not the desired phthalic acid (VIII), as shown by the inability of the compound to form either an acid anhydride or acid imide. Unfortunately, time did not permit an investigation into the nature of this oxidation product.

When the initial oxidation was run in the cold as according to Thomson (20) however, the desired material (VIII) could be isolated in the usual manner in very poor yield. If at any time the solution of the phthalic acid became distinctly acid, the only isolable material was a dark brown tar. This tar could be converted to the desired product by boiling with aqueous sodium hydroxide. On recrystallization, the dioxanyolphthalic acid (VIII) was obtained as a light yellow powder of m.p. 223-224°C. with effervescence.

The dioxanyolphthalic acid was converted to its anhydride (IX) by heating with acetic anhydride. Only small amounts could be reacted at one time, since the liberation of much acetic acid resulted again in the formation of a brown tar. Upon recrystallization, the anhydride was obtained as an unstable white powder, which reverted easily to the free acid.

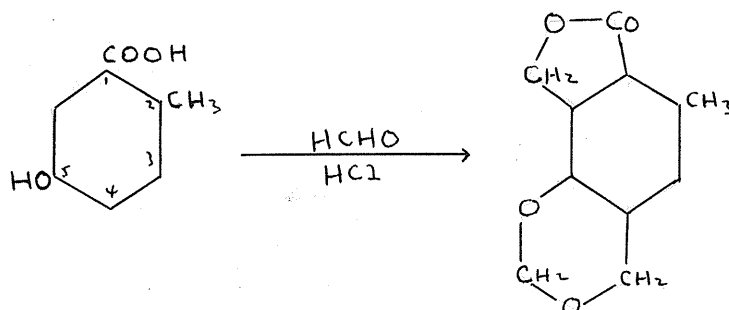
Conversion of the dioxanyolphthalic anhydride (IX) to the dioxanyolphthalimide (X) was effected by heating an intimate mixture of the anhydride and urea. The phthalimide could be isolated only in poor yield.

It was originally intended to continue the second degradative series on from the dioxanyolphthalimide, but the poor yield in the degradative steps leading to this compound forced a switch to the direct oxidation of the phthalic acid (VIII).

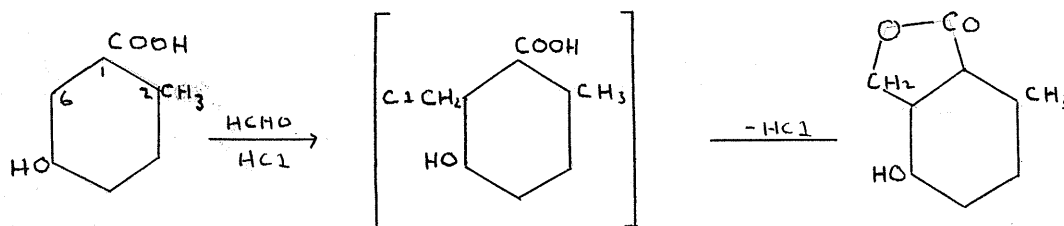
The dioxanyolphthalic acid (VIII) was oxidized to the dioxanonephthalic acid with chromium trioxide in glacial acetic acid. Due to the high acid concentration the resultant substituted phthalic acid (XI) was, as usual, isolable only as a brown tar. This could not be converted to a pure product by the usual method of boiling with aqueous sodium hydroxide, as the dioxanone ring was hydrolysed in the production of the hydroxytoluene tricarboxylic acid (XII). This compound was methylated with difficulty to give a small amount of an impure brown powder of m.p. 229°C . As there was only sufficient material for one recrystallization, the melting point could be raised only to 234°C . The melting point of (V) as produced in the first degradative series was 238°C ., but a mixed melting point showed the identity of the two compounds.

At this stage of the discussion, it would be appropriate to show how the above degradative work indicates the structure of the condensation product of 5-hydroxy-o-toluic acid to be (1), i.e., 8-hydroxymethyl-1,3-benzodioxan-6-methyl-7-

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 these rings (to be proven later), it is obvious that only one dioxanylphthalide could be formed because of the orientation of the 5-hydroxy-*o*-toluic acid:



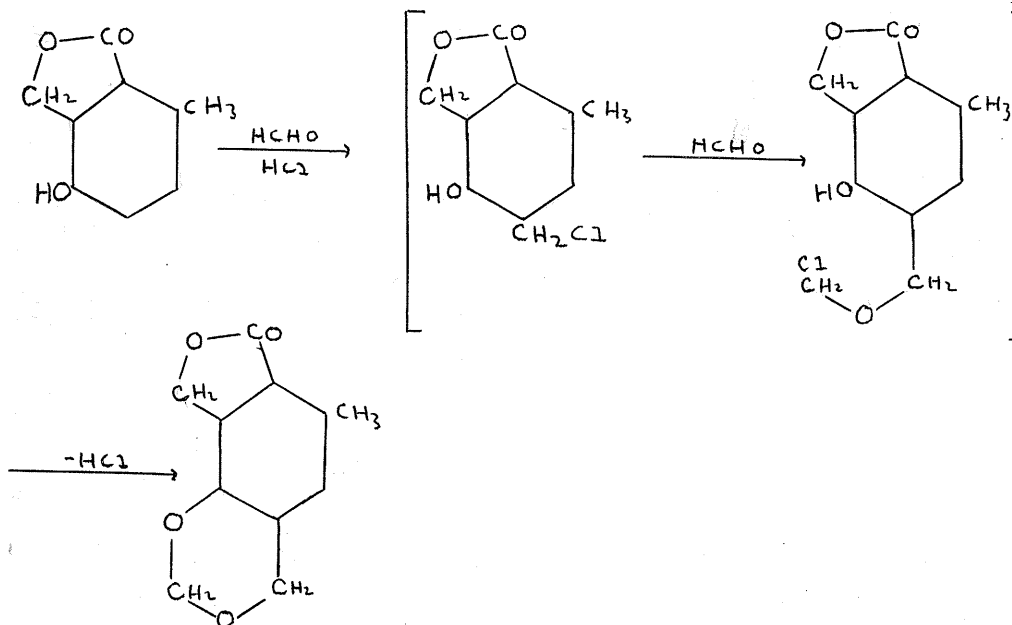
Since one of the two positions ortho to the carboxyl group - the 2-position, is blocked by the methyl group, the entering chloromethyl group (from which the phthalide ring is formed by loss of hydrogen chloride with the carboxyl group) can enter only in position 6 as illustrated:



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

When the dioxane ring is formed at the hydroxyl group in the second step of the condensation, one of the ortho positions is again blocked, the 6-position being

occupied by the methylene group of the phthalide ring. Thus the entering chloromethyl group must attach itself to the 4-position (the numbering system still being that of substituted toluic acids):



Concerning the formation of the phthalide ring, the degradative work described in the first and second series offers two proofs.

In the first series the dioxanylphthalide was oxidized to a dioxanonephthalide (II), which was then hydrolysed to an o-hydroxy carboxylic acid substituted phthalide (III). When this compound was decarboxylated, the product was found to be identical with the known 3-hydroxy-6-methylphthalide (XV). When the hydroxy compound (III) was methylated to produce the o-methoxy carboxylic acid substituted phthalide (IV), and this decarboxylated, the resultant product was found to be identical with the known 3-methoxy-6-methylphthalide. This then establishes the

formation, and incidentally the location, of the phthalide ring.

The second proof of formation of the phthalide ring is given by the oxidative formation of a phthalic acid, which reaction step occurs in both degradative series. In the second series, the dioxanylphthalide (I) was oxidized to a substituted phthalic acid (VIII). The formation of an o-phthalic acid was substantiated in three ways: firstly, loss of water could occur with the formation of a phthalic anhydride (IX); secondly, the phthalimide (X) could be formed; and lastly, combustion results showed the gain of two oxygen atoms in the reaction, as would be expected in the conversion of a phthalide to a phthalic acid. The same conversion occurs in the first degradative series where the o-methoxy carboxylic acid substituted phthalide (IV) is oxidized to a substituted phthalic acid (V). This conversion is again indicated by combustion results and anhydride formation.

The formation of the dioxane ring is also proven in both degradative series. The initial step of the first series consisted of the chromium trioxide-glacial acetic acid oxidation of the dioxanylphthalide (I). Combustion results indicate a loss of two hydrogen atoms and a gain of one oxygen atom. This is in agreement with the expected oxidation of a dioxane ring to a dioxanone ring, here as the dioxanonephthalide (II). When this compound was boiled with aqueous sodium hydroxide it gradually went into solution with loss of formaldehyde. Acidification of the reaction

mixture gave a product (III) which was demonstrated to contain both a hydroxyl and a carboxyl group. All this evidence is in complete agreement with the existence of a dioxane ring in compound (I), as can be seen by comparison with the work of Borsche and Berkout (3) and Mejuto and Calvet (13) as outlined in the Literature Survey.

The same series of steps was carried out in the second series where the supposed dioxanyolphthalic acid (VIII) was oxidized to a dioxanonephthalic acid (XI), which was then hydrolysed to a compound (XII) which on methylation produced a substance identical with compound (V). Thus (XI) had lost formaldehyde to expose a hydroxyl group and a carboxyl group as indicated by methylation, and by the neutralization equivalent of the resultant compound.

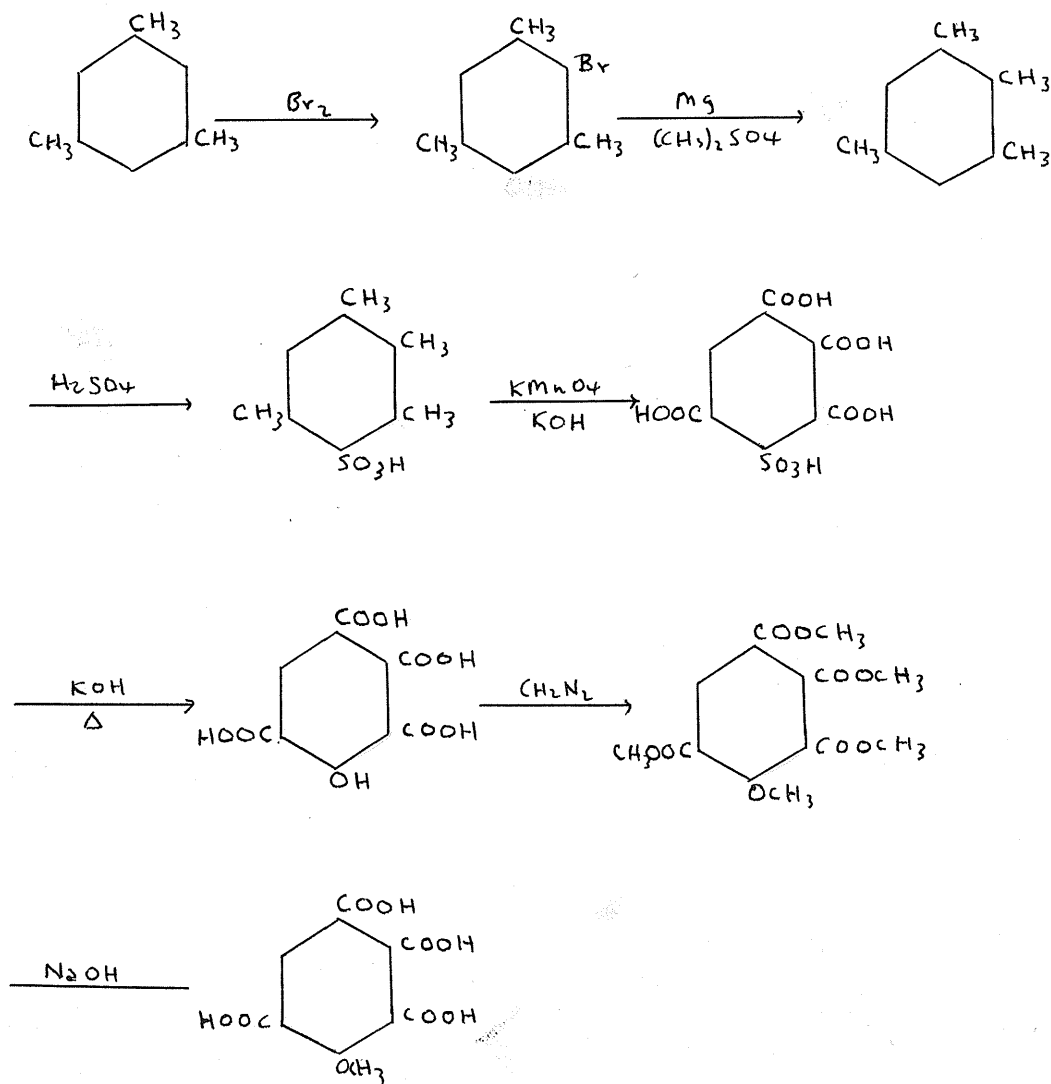
The final step of the degradative proof of structure was originally intended to be a comparison of the common end-product (V) of the two degradative series with a synthetic specimen of 4-methoxytoluene-2,3,5-tricarboxylic acid or its trimethyl ester. However, a search of the literature revealed that the compound has not been synthesized, and no method of synthesis presented itself. Thus it was found necessary to attempt oxidation of the methyl group of compound (V) and comparison of the reaction product with a synthetic specimen of 4-methoxybenzene-1,2,3,5-tetracarboxylic acid or its tetramethyl ester. Upon oxidation of (V) with hot concentrated basic permanganate to the tetracarboxylic acid (VI) and esterification of the resultant product, the ester (VII) was

isolated as a liquid. As this material was useless for purposes of identification, and it was necessary to use the free acid (VI) as the comparative end-product.

Synthesis of the Degradative End Products

a) Synthesis of 4-methoxybenzene-1,2,3,5-tetracarboxylic acid

The attempted synthesis of this compound was modeled along the synthesis of Buehler and coworkers (9) of 4-methoxybenzene-1,2,3-tricarboxylic acid and is outlined below:



Mesitylene was brominated in cold carbon tetrachloride solution according to the directions of Smith (17). The bromomesitylene was then subjected to a Grignard reaction with methyl sulphate to give isodurene, also according to Smith (18). Isodurene was sulphonated according to the directions of Smith and Cass (19) to give isodurene sulphonic acid in quantitative yield. The isodurene sulphonic acid was oxidized to the corresponding tetracarboxylic acid by a method outlined in French (10) and German (11) patents for the oxidation of hemimellitene sulphonic acid. The crude oxidation product was subjected to an alkaline fusion to produce impure 4-hydroxybenzene-1,2,3,5-tetracarboxylic acid. Combustion analyses on the fusion product indicated incomplete oxidation of one of the methyl groups. It is extremely unfortunate that time did not permit a conclusion of this line of work to provide a final tie-up of the degradative proof of structure.

b) Synthesis of 3-methoxy-4-methylphthalic Acid

The scheme of synthesis of this acid by Simonsen and Rau (16) has been outlined in the Literature Survey. Certain difficulties were encountered in the application of the published method, but small changes resulted in the successful synthesis of the desired material.

The starting material was 3-methoxy-p-toluic acid, synthesized according to Anderson (1). This compound was nitrated in the 2-position with fuming nitric acid in acetic anhydride in the cold. The resultant nitro compound was reduced with ammonium sulphide, since the use of ferrous

sulphate as described in Simonsen and Rau's paper gave a reaction mixture from which none of the desired product could be isolated. The amino acid could not be dissolved in the hydrochloric acid solution for diazotization. This was not surprising, since these authors state that the amino acid hydrochloride is only sparingly soluble in water. Thus it was necessary to carry out the diazotization by dissolving the amino acid and the sodium nitrite in a sodium hydroxide solution and adding this to the hydrochloric acid dropwise. When the diazonium chloride solution was added to a cuprous cyanide solution, 3-methoxy-2-cyano-p-toluic acid resulted. This was then hydrolysed with sulphuric acid to the desired 3-methoxy-4-methylphthalic acid.

EXPERIMENTAL

The Synthesis of the Lactone of 8-Hydroxymethyl-6-methyl-1,3-benzodioxan-7 carboxylic Acid (1)

a) The preparation of o-toluic acid

The greater part of the o-toluic acid necessary for this research was prepared by the oxidation of o-xylene as described by Zaugg and Rapala (23), with a few necessary modifications.

In a 1 liter round bottom interjoint flask were placed 320 ml. water, 160 ml. concentrated nitric acid, and 120 ml. (1.13 moles) o-xylene. The flask was then fitted with a long reflux condenser attached to a gas absorption trap. The mixture was refluxed vigorously on a heating mantle (an input of 90 volts) for 55 hours. The hot mixture was then poured onto 200g. of ice in a 1 liter beaker. When cold, the solid product was filtered off and dissolved in 400 ml. of 10% sodium hydroxide solution. After chilling the deep red solution, any unreacted xylene was removed by extraction with 50 ml. ether. The aqueous layer was heated gently with decolorizing carbon and filtered. The warm filtrate was added with stirring to a solution of 90 ml. concentrated hydrochloric acid in 110 ml. water. The product, after chilling, filtering and washing, appeared as a light tan powder. Although it is stated in the published method that this material is sufficiently pure for synthetic purposes, it was found that recrystallization from water (100 ml. per g.) was

necessary before the product was suitable for sulphonation.

The water recrystallized material appeared as very light, fluffy, white needles of m.p. 100-101°C. The yield of pure o-toluic acid was generally about 145g., or 69% of the theoretical. This is 15-20% higher than that claimed in the published method.

b) The preparation of 5-hydroxy-o-toluic acid

(i) Sulphonation of o-toluic acid

A mixture of 50 g. (0.37 moles) recrystallized o-toluic acid and 300 ml. fuming (20%) sulphuric acid was heated on a steam bath for 8 hours. When cool, the reaction mixture was added with stirring to 200 ml. water in a 1 liter beaker. The clear, deep red solution was chilled in the refrigerator overnight, when it set to a solid mass of crystals. The product was filtered with suction, and then dissolved in 500 ml. water. The solution was boiled for 15 minutes with 2 grams of decolorizing carbon and filtered. The filtrate was again heated to boiling, and salt was added until saturation was produced. Upon cooling the sodium salt of o-toluic acid-5-sulphonic acid recrystallized in quantitative yield. The sodium salt was filtered off, dried in the oven and powdered for fusion.

(ii) Alkali fusion of the sulphonic acid

A mixture of 240 g. potassium hydroxide and 10 ml. water was heated in a nickel crucible until the temperature reached 250°C. The flame was removed and 45 g. (0.21 moles)

of sodium o-toluic acid - 5-sulphonate was stirred into the melt. The temperature was raised to 290°C . over a period of 5 minutes, and maintained at that temperature for 5 minutes. The temperature was then raised quickly to $315-320^{\circ}\text{C}$., and the mixture was then allowed to cool to the consistency of a thick paste. It was then ladled out onto 200 g. ice in a 2 liter beaker. The resultant mixture was then acidified with 50% sulphuric acid, and brought back just to the alkaline side with potassium hydroxide pellets. After the mixture cooled, the precipitated potassium sulphate was filtered off, and the filtrate evaporated on the hot plate with mechanical stirring to a volume of 150 ml., removing precipitated potassium sulphate whenever necessary. The residual liquid was cooled, and any potassium sulphate filtered off. The filtrate was acidified with concentrated hydrochloric acid, and the 5-hydroxy-o-toluic acid filtered off. After drying the light tan crude product melted at 182°C . (value for pure product $183-184^{\circ}\text{C}$.) and was pure enough for synthetic work. The yield was 25g. or 80% of the theoretical based on o-toluic acid.

The above directions for the sulphonation and fusion are modifications of those of Radych (15).

c) Condensation of 5-hydroxy-o-toluic acid with formaldehyde and hydrochloric acid

The method for this condensation is a modification of that of Radych (15) also.

In a 2 liter interjoint flask equipped with a 1 meter length of reflux condensation attached to a gas absorption trap was placed a mixture of 300 ml. formaldehyde and

30 g. (0.2 moles) of 5-hydroxy-o-toluic acid. The mixture was heated on a wire gauze until the acid was dissolved. At this point 300 ml. of concentrated hydrochloric acid was added through the top of the reflux condenser. When the mixture had just begun to boil, a flocculent white precipitate settled out. A small sample of this material was removed, and was found to be the simple phthalide, m.p. 223-224°C. Upon further boiling, the mixture frothed badly, until the precipitate went back into solution. After about 15 minutes further boiling, the final product began to settle out in light brown granules. After a total of one hour's boiling, the mixture was cooled and filtered. The yield of the crude dioxanyolphthalide amounted to 30 g., or 75% of the theoretical. No modification of the above procedure could be found which would increase the yield, neither could the material not accounted for be recovered.

The material was recrystallized from 2 liters of 95% ethanol to give coarse white needles of m.p. 171-172°C. A small amount of material was recrystallized from acetone for combustion analyses. The analytical results were:

% C	<u>Found</u> 63.24	<u>Calculated</u> 64.07
% H	4.94	4.89

The First Oxidative Degradation Series of the Dioxanyl-phthalide

- a) The lactone of 8-hydroxymethyl-6-methyl-1,3-benzodioxan-4-one-7-carboxylic acid (II)

The dioxanyolphthalide (I) (10 g., 0.05 moles) was

dissolved in 250 ml. glacial acetic acid in a 4 liter beaker by heating. When the temperature of the solution had dropped to 75°C., the beaker was placed in a cold water bath. Finely ground chromium trioxide was added with stirring at such a rate that the temperature was maintained between 65°C. and 70°C. When the reaction appeared to be complete, the mixture was diluted to a volume of 2 liters, and the dark green solution was allowed to stand overnight. It was then refrigerated for 4 hours, during which time white crystals appeared. These were filtered off, and amounted to 2.5 g., (23% of the theoretical) of white, fluffy needles. Upon recrystallization from acetone, the product was obtained as white needles of m.p. 184-185°C. Combustion analysis gave the following results:

	<u>Found</u>	<u>Calculated</u>
% C	60.41	60.01
% H	3.64	3.66

b) 3-Hydroxy-4-carboxy-6-methylphthalide (111)

This compound was prepared by refluxing a mixture of 5 g. (0.23 moles) of the dioxanonephthalide (11) and 50 ml. 10% aqueous sodium hydroxide for one hour. A homogeneous solution gradually developed with the evolution of formaldehyde. The reaction mixture was cooled, filtered, and made acid with concentrated hydrochloric acid. The precipitate, when filtered and dried, weighed 4 g. (84% of the theoretical). Upon recrystallization from water, the compound was obtained as a white powder, m.p. 238°C., and giving a dark violet colour with 1% ferric chloride solution.

Due to the high melting point of the compound, and

its habit of charring when heated, no satisfactory combustion analyses could be made with the equipment at hand. The presence of the phenolic group also made neutralization equivalent determinations useless. Lately a p-nitrobenzyl derivative was prepared, but time did not allow for its analysis.

c) 3-Methoxy-4-carboxy-6-methylphthalide (IV)

The hydroxy compound (III) (7.5 g., 0.03 moles), was dissolved in 75 ml. 10% aqueous sodium hydroxide. Methyl sulphate (12 ml.) was added, and the mixture was stirred for 1 hour at room temperature. An additional 25 ml. base was added along with another 12 ml. methyl sulphate, and the mixture was stirred for another hour. Another 40 ml. base was added, and the mixture was heated on a steam bath for two hours. Upon acidification of the mixture, 7 g. of crude product was obtained. After two recrystallizations from water, 6 g. (77% of the theoretical) of white needles were obtained, m.p. 150-151°C., which gave no phenol test with ferric chloride. The crystals gradually turned brown, as did the powder when dried for combustion analysis. The analytical results are:

	<u>Found</u>	<u>Calculated</u>
% C	59.62	59.49
% H	4.47	4.54
Neutralization Equivalent	218	222

d) Decarboxylation of Compounds (III) and IV)

Compounds (III) and IV) were decarboxylated by

heating one gram of the compound dissolved in 15 ml. quinoline at 180°C., a catalytic amount of copper chromite being added. After a period of 15 minutes, when the bubbles of carbon dioxide had ceased coming off, the mixture was cooled and poured into 150 ml. of 10% hydrochloric acid. The product settled out as white needles. From 3-hydroxy-4-carboxy-6-methylphthalide was obtained in this manner 3-hydroxy-6-methyl phthalide, as determined by a mixed melting point with a synthetic specimen. Similarly, 3-methoxy-4-carboxy-6-methylphthalide was found to produce 3-methoxy-6-methylphthalide by comparison with a synthetic specimen. The synthesis of these two compounds is described below.

e) The synthesis of 3-methoxy- and 3-hydroxy-6-methylphthalide

(i) 5-Methoxy-o-toluic acid (XIII)

The 5-hydroxy-o-toluic acid (8.4 g.) was dissolved in 42 ml. 20% aqueous sodium hydroxide in a three-necked flask. While the solution was stirred in an inert atmosphere of nitrogen and cooled in an ice-water bath, 12.2 g. methyl sulphate was added dropwise over a period of 15 minutes. After an additional half hour's stirring, 2.1 g. sodium hydroxide was added and the solution was refluxed for 45 minutes. The solution was cooled, filtered to remove any sodium sulphate, and acidified with concentrated hydrochloric acid. The white precipitate was filtered, washed, and dried. The product, m.p. 144-145°C., was obtained in 70% yield.

(ii) 3-Methoxy-6-methylphthalide (XV) ~~XIV~~

A mixture of 5.9 g. 5-methoxy-o-toluic acid, 35 ml. concentrated hydrochloric acid, 35 ml. formaldehyde was refluxed on a wire gauze for one hour. The filtered product was washed, dried, and then recrystallized from 95% ethanol to give 4 g. (60% of the theoretical) of the desired product. This melted at 165-166°C.

(iii) 3-Hydroxy-6-methylphthalide (XIV) ~~XV~~

A mixture of 1.1 g. 3-methoxy-6-methylphthalide and 2.7 g. anhydrous aluminum chloride in 40 ml. dry benzene was refluxed for 10 hours on a water bath. The solid was filtered, washed, and dried. Recrystallization from 95% ethanol gave 0.5 g. (47% of the theoretical) of the product, m.p. 223-224°C.

f) 4-Methoxytoluene-2,3,5-tricarboxylic acid (V)

A solution of 3 g. (0.013 moles) of the phthalide (iv) in 200 ml. 3.5% aqueous potassium hydroxide was heated at 60°C. and stirred while 105 ml. 0.27M potassium permanganate was run in over a period of 1 hour. Excess permanganate was decomposed with sodium bisulphite, and the manganese dioxide was filtered off. The filtrate was acidified with concentrated sulphuric acid, and the resultant precipitate filtered off. On recrystallization from 50% acetic acid, 2 g. (62% of the theoretical) of grey-white crystals were obtained. The compound had a m.p. of 238°C. and gave the following analytical results:

	<u>Found</u>	<u>Calculated</u>
% C	52.00	51.97
% H	4.09	3.96
Neutralization Equivalent	250	254

g) 4-Methoxybenzene-1,2,3,5-tetracarboxylic acid (VI)

The methoxy compound (V), 1 g. (0.004 moles) was dissolved in 80 ml. 5% aqueous potassium hydroxide. The solution was heated on a steam bath and stirred while 242 ml. 0.117 M. potassium permanganate was added dropwise over a 4 hour period. The excess permanganate was then decomposed with bisulphite, and the manganese dioxide filtered off. The filtrate was evaporated to a small volume, refiltered, and acidified with concentrated sulphuric acid. The solution was then extracted three times with 50 ml. portions of ethyl acetate. The extract was evaporated to dryness, and the residue recrystallized from 50% acetic acid. The tetracarboxylic acid was obtained as a white powder of m.p. 167-168 C. with effervescence. Analytical results are:

	<u>Found</u>	<u>Calculated</u>
% C	45.24	46.51
% H	3.00	2.83
Neutralization Equivalent	$\frac{1}{4} \times 268$	284

h) Tetramethyl 4-methoxybenzene-1,2,3,5-tetracarboxylate (VII)

A solution was made of 1 g. (0.0035 moles) of the tetracarboxylic acid (VI) in 20 ml. absolute

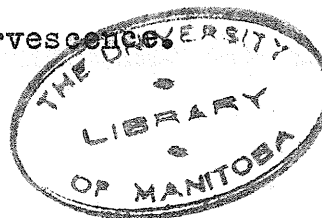
methanol. A solution of diazomethane in absolute ether was added until an excess was present as indicated by the persistence of the yellow colour of diazomethane. The solution was then placed on the water bath and heated until the excess diazomethane and the ether were driven off. Ten ml. water was then added and the solution chilled in the refrigerator. The solution was then extracted with two 10 ml. portions of ether. The ether extract was dried and the ether evaporated off. A small amount of a gummy yellow liquid remained which was insoluble in sodium bicarbonate solution, and was thus presumably the tetramethyl ester of (VI). The liquid did not solidify at temperatures down to -10°C . Since the melting points of similar compounds are above room temperature, the ester was probably obtained as a supercooled liquid. Since this ester (VII) was obtained only in very small amounts, and since it was a liquid, no further work or analyses were done on the compound as it was useless for identification purposes. Although the esters of benzene polycarboxylic acids are more useful for identification purposes than the free acids, the tetracarboxylic acid (VI) would have to be used in this case.

The Second Oxidative Degradation Series of the
Dioxanyolphthalide

a) 6-Methyl-1,3-benzodioxan-7,8-phthalic acid (VIII)

The first method tried for oxidizing the phthalide ring of the dioxanyolphthalide (1) to produce the dioxanyolphthalic acid (VIII) was that of Buehler and coworkers (8).

A solution of 5 g. of the lactone (1) in 300 ml. 20% aqueous hydroxide was prepared by heating the mixture to 75-85°C. The solution was filtered, and its temperature raised to 60°C. The temperature was maintained at this point while a solution of 10 g. potassium permanganate was added with stirring over a period of 20 minutes. The solution was cooled, filtered, and made just acid to litmus with concentrated hydrochloric acid. The resulting yellow fluorescent solution was evaporated to 50 ml. at a temperature of less than 75°C. The resultant solution was reacidified and chilled for one hour, then filtered. The solid material was dissolved in a minimum quantity of hot, aqueous 5% sodium carbonate, boiled with decolourizing carbon and filtered. The filtrate was cooled and acidified. The precipitated acidic material was filtered off, washed, and dried. The light brown solid was not homogeneous, and could be separated into three apparently pure substances by fractional crystallization from water-alcohol. The first fraction melted at 126°C., the second at 139°C., and the third at 159-160°C., none with effervescence.



The third fraction predominated, about one gram being obtained from each oxidation. None of these substances were the desired phthalic acid, as they were unable to form anhydrides.

The cold oxidation method of Thompson (20) was then tried, and the desired compound was obtained in poor (ca. 10% of the theoretical) yield. The oxidation was carried out as follows:

A solution was made of 6 g. of the lactone in 300 ml. of 3.5% potassium hydroxide solution by heating. The solution was cooled, filtered, and placed in an ice-water bath. It was kept at 5-10°C. while a solution of 24 g. potassium permanganate was added over a period of one hour. The resultant mixture was allowed to stand overnight. It was then filtered, made just acid to litmus with concentrated hydrochloric acid, and evaporated to a volume of 100 ml. at a temperature of 65°C. The residual mixture was filtered to give a solid comprised of both organic and inorganic material. The acidic organic material was separated by dissolving in 5% aqueous sodium carbonate, filtering, and acidifying. The resultant precipitate was 1-1.5 g. of a dark brown powder, which when recrystallized from alcohol-water appeared as a light yellow powder melting at 223-224°C. with effervescence. Anhydride formation and combustion analysis showed this to be the desired compound. The analytical results are:

	<u>Found</u>	<u>Calculated</u>
% C	69.11	69.00

	<u>Found</u>	<u>Calculated</u>
% H	4.84	4.87

If at any time a solution of the phthalic acid became sufficiently acid to darken Congo Red paper, the compound was isolable only as a dark brown tar which liquified at about 80°C. Presumably the dioxane ring of the phthalide opens under the influence of a strong acid as is common with these compounds. The resultant chloromethyl group probably condenses with the carboxyl group of another molecule to form a polymer. This tar could be converted to the phthalic acid by boiling with 10 times its weight of 10% sodium hydroxide solution, and careful acidification of the solution. The resultant material was very pure and gives better combustion results than the material isolated as above.

b) 6-Methyl-1,3-benzodioxan-7,8-phthalic anhydride (IX)

The phthalic acid (Vlll), (2 g.) was dissolved in 20 ml. acetic anhydride by gentle heating. After one hour's additional warming, the solution was filtered and placed in the refrigerator for at least 24 hours. The desired product crystallized out in stout needles of a light brown colour. When recrystallized from dry toluene, the compound appeared as white crystals of m.p. 130°C. The anhydride quickly reverted to the free acid, and was not analysed. As with the phthalic acid (Vlll), too much acid, as would result from reacting too much material at one time, caused the product to turn to a tar.

c) 6-Methyl-1, 3-benzodioxan-7, 8-phthalimide (X)

An intimately powdered mixture of 2 g. of the phthalic anhydride (IX) and 2 g. urea was heated in an oil bath until evolution of ammonia ceased. The molten mixture was poured into 1 liter of boiling water in which it dissolved quickly. Upon cooling of the solution, the phthalimide (X) separated out as orange plates. The yield of crude material was poor because ^{of} its hydrolysis to the free acid by the boiling water. Recrystallization from boiling water gave a small amount of white powder of m.p. 162°C. It was later found that alcohol-water was a better recrystallizing medium as no material was lost. Combustion analysis gave the following results:

	<u>Found</u>	<u>Calculated</u>
% C	60.93	60.02
% H	4.13	4.14

d) Oxidation of the dioxanyolphthalic acid (Vlll)

As the yields of the dioxanyolphthalimide were extremely poor based on the dioxanyolphthalide, it was not feasible to continue the degradation on from this compound. Thus it was necessary to attempt the direct oxidation of the dioxanyolphthalic acid (Vlll). This was done as follows:

A solution of 3 g. of the dioxanyolphthalic acid in 80 ml. glacial acetic acid was prepared by heating the mixture. When the solution had cooled to a temperature of 75°C., it was placed in a cold water bath. Finely powdered chromium trioxide (10.5 g.) was added in small portions

At such a rate that the temperature was maintained at 65-75°C. The beaker was then placed on a steam bath until all reaction had ceased. The solution was then diluted to 600 ml. with water, and the dilute acetic acid evaporated off in vacuo. The remaining solid was dried and ground. Inorganic material was removed by digesting the material with 50 ml. 5% aqueous sodium carbonate and filtering. The crude dioxanonephthalic acid was obtained by acidification of the filtrate as a brown tar. Tar formation probably resulted from the high acid concentration present during the oxidation. Since the tar could not be purified without hydrolysis of the dioxanone ring, no pure material could be obtained for analysis.

The tar was boiled for 1 hour with 30 ml. 10% aqueous sodium hydroxide. Acidification of the reaction mixture gave a brown powder which gave a phenol test with ferric chloride, and was apparently the 4-hydroxytoluene-1,2,5-tricarboxylic acid. As the amount of this material was quite small, purification was not attempted, and the whole amount was methylated.

Methylation of the supposed toluene acid (XIII) was accomplished in alkaline solution in the usual manner. Upon acidification of the reaction mixture, a small amount of light brown powder precipitated which melted at 228°C. Recrystallization from 50% acetic acid gave a yellow-brown powder of m.p. 231°C. A mixed m.p. with the 4-methoxytoluene-1,2,5-tricarboxylic acid (V) produced in the first degradative series indicated that these two compounds were identical.

The Attempted Synthesis of 4-Methoxybenzene-1,2,3,5-tetracarboxylic Acid

a) The Preparation of Bromomesitylene

Bromomesitylene was synthesized by the directions of Smith (17), outlined in the next paragraph.

In a 500 ml. three-necked flask provided with a reflux condenser, stirrer, and separatory funnel was placed a solution of 106 g. mesitylene (0.88 moles) in 70 ml. carbon tetrachloride. The flask was cooled in an ice-salt bath until the temperature of the mixture had dropped below 10°C. A solution of 150 g. bromine (48 ml., 0.93 moles) in 95 ml. carbon tetrachloride was then added to the well stirred solution. The hydrogen bromide evolved was lead from the top of the condenser to a gas absorption trap. 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 off through a fractionating column until the vapour temperature was 120°C.

The residue was added to a solution of 8.5 g. of sodium in 200 ml. absolute ethanol. The resultant solution was boiled under reflux for one hour and then allowed to stand overnight. The reaction mixture was then diluted with 1 liter of water and the two layers separated. The

Aqueous layer was extracted with three 100 ml. portions of carbon tetrachloride, and the extract added to the bromomesitylene. This solution was washed thoroughly with water and then dried over calcium chloride. The carbon tetrachloride was then distilled off, and the residue was transferred to a Claisen flask. The fraction boiling at 100-101°C. at 10mm. was collected and amounted to 135g. (77% of the theoretical).

b) The preparation of isodurene

Isodurene was synthesized according to the directions of Smith (18), which are outlined in the next paragraph.

A 1 liter three-necked flask fitted with a reflux condenser protected from the air by a calcium chloride tube, a separatory funnel, and a stirrer was mounted on a steam bath. In the flask was placed 16 g. (0.66 moles) magnesium turnings, 50 ml. anhydrous ether, 33 ml. bromomesitylene, and a crystal of iodine. The reaction started after the application of gentle heat. Then the remaining 100 g. bromomesitylene (total of 2 moles) in 250 ml. dry ether was added at such a rate that the ether refluxed gently. When the addition was complete, the mixture was heated on the steam bath until the magnesium had dissolved.

The solution of the Grignard reagent was cooled to 10°C. and to it was added 200 g. (1.6 moles) of pure methyl sulphate in 100 ml. ether. The addition required 3 hours. After standing for 24 hours, the mixture was

decomposed by the addition of dilute hydrochloric acid through the addition funnel. Stirring was started as soon as possible. When all magnesium salts had gone into solution, the ether layer was separated, and washed three times with water. The ether layer was evaporated, and the residue added to a solution of 10 g. sodium in 125 ml. absolute methanol. This mixture was boiled for half an hour to decompose excess methyl sulphate, and the solution was then cooled. To the cold solution was added 60 ml. ether, and all alkali and alcohol were removed by washing with water. The ether solution was dried over calcium chloride, filtered, the ether was distilled, and the residue heated on a steam bath with 10 g. sodium cuttings for 3 hours. The mixture was filtered, and the filtrate fractionated under reduced pressure in a Claisen flask. A large amount of low boiling material was obtained which was impure mesitylene. The isodurene boiled at 82-85°C./15 mm., and amounted to 30 g. (39% of the theoretical).

c) The preparation of isodurene sulphonic acid

This material was prepared according to the directions of Smith and Cass (19), as outlined in the next paragraph.

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 a Turkey red colour. The reaction mixture was then poured into a 100 ml. beaker filled with crushed ice. Filtration gave the sulphonic acid in quantitative yield. This

crude material liquified upon standing, so it was necessary to recrystallize it almost immediately. This was accomplished as follows: The crude sulphonic acid was dissolved in 50 ml. ice water, and the solution saturated with hydrogen chloride gas. The pure product separated out as white leafy crystals of m.p. 72°C . On standing, they gradually acquired a slight green tinge.

d) The oxidation of isodurene sulphonic acid

This and the following steps are modifications of methods outlined in French (10) and German (11) patents for the oxidation and fusion of hemimellitene sulphonic acid.

In a 1 liter three-necked flask equiped with a reflux condenser and stirrer were placed 10 g. isodurene sulphonic acid and a solution of 5.5 g. potassium hydroxide in 250 ml. water. The resultant solution was heated to 90°C . with a heating mantle. While the solution was stirred vigorously, 62.8 g. powdered potassium permanganate was added at such a rate that the temperature did not rise above 95°C . After the addition was complete, the oxidation was continued for another 24 hours at this temperature. Excess permanganate was decolorized with alcohol, and the manganese dioxide was filtered off and washed with two 150 ml. portions of boiling water. The resultant yellow solution was evaporated to dryness, and the residue dried and pulverized. The crude product was not purified, but put immediately into the next reaction.

e) Fusion of the crude oxidation product

The crude sulphonic acid carboxylic acid (XVI) was mixed with 40 g. potassium hydroxide and 5 ml. water, and fused at 200-220°C. for 5 hours in a nickel crucible. The melt was mixed with 60 ml. water after it had cooled to a slush, and cautiously acidified with concentrated hydrochloric acid. After the addition of 150 ml. water the mixture was heated to boiling and filtered. The filtrate was evaporated to dryness. The residue was recrystallized from 60 ml. hot 5% hydrochloric acid to give 4 g. of white powder, m.p. 260°C.

Combustion results indicate that the supposed 4-hydroxybenzene-1,2,3,5-tetracarboxylic acid (XVII) was not pure due to the incomplete oxidation of the isodurene sulphonic acid. The final product appeared to have 0.8 unoxidized methyl groups per molecule. Unfortunately, there was insufficient time to methylate the compound and complete the oxidation.

The Synthesis of 3-Methoxy-4-methylphthalic Acid

a) The preparation of 3-methoxy-p-toluic acid

The preparation of 3-hydroxy-p-toluic acid has been given by Thompson (20). This substance was methylated as directed by Anderson (1).

b) This and the remaining steps of this synthesis were accomplished by a modification of the method of Simonsen and Rau (16). The method has been outlined on p. 18.

Finely powdered 3-methoxy-p-toluic acid was added slowly to a mixture of 8 ml. fuming nitric acid and 28 ml. acetic anhydride, the mixture being well cooled in an ice-water bath. When the addition was complete, the mixture was allowed to stand for 15 minutes at room temperature, and was then poured onto 100 g. ice. A yellow material precipitated out which crystallized after refrigeration for 1 hour. The acid was collected, and amounted to 3.5 g. of the 2-nitro-3-methoxy-p-toluic acid. Upon recrystallization from hot water, the nitro acid was obtained as a light yellow crystalline material of m.p. 164°C . in 46% yield. Simonsen and Rau report a white product melting at 165° obtained in quantitative yield.

c) The preparation of 2-amino-3-methoxy-p-toluic acid

Simonsen and Rau reported a reduction of the nitro acid with ferrous sulphate. This was tried several times, but none of the desired amino acid was obtained. Thus the reduction was carried out in the following manner.

The nitro acid (5 g.) was dissolved in 25 ml. 6N ammonia, and the solution was placed in a 100 ml. flask cooled in a water bath. The solution was saturated with hydrogen sulphide for 3 hours. The mixture was then boiled until ammonia and hydrogen sulphide ceased being driven off.. The boiling solution was filtered and the filtrate poured into 2 ml. glacial acetic acid. The precipitate was filtered off and recrystallized from water to give 2.3 g. (50% of the theoretical) of the

amino acid, m.p. 160° . Simonsen and Rau give the m.p. for this compound as 162°C .

A method for the simpler catalytic reduction of the nitro acid was later found, as published by Grewe (12). A mixture of 2 g. of the nitro acid, 50 ml. glacial acetic acid, and 50 mg. palladium charcoal catalyst were shaken under hydrogen at 50 lbs. pressure for one half hour at room temperature. The catalyst was filtered off, and the filtrate was evaporated to a small volume in vacuo. Upon cooling colorless needles of the amino acid separated out in good yield, of m.p. $164\text{--}165^{\circ}\text{C}$.

d) The preparation of 2-cyano-3-methoxy-p-toluic acid

Simonsen and Rau (16) prepared the amino acid for diazotization by dissolving it in 5 volumes of a 20% hydrochloric acid solution. When this was tried, it was found that a prohibitively large volume (about 300 ml.) of dilute hydrochloric acid was necessary to dissolve the amino acid. The published method was therefore modified and runs as follows.

A solution was prepared of 1 g. of the amino acid, 0.4 g. sodium nitrite, and 0.5 g. sodium hydroxide in 5 ml. water. The solution was chilled and added in small portions to an ice-cold solution of 3 ml. concentrated hydrochloric acid in 2 ml. water. Each succeeding portion was not added until the previous one had reacted completely. The resultant solution was then added to a hot solution of 1.4 g. copper sulphate and 1.6 g. potassium cyanide in 20 ml. water. When evolution of nitrogen was complete,

the mixture was chilled for 4 hours and filtered. The mixture of the nitrite and copper cyanide was dissolved in dilute ammonia and filtered. The filtrate was acidified, and the deposited cyano acid was collected and dried. The yield was 0.47 g. (50% of the theoretical) of grey needles with a melting point of 183°C . Although this m.p. is 3° below the published value, the material was not purified.

e) The preparation of 3-Methoxy-4-methylphthalic acid

The phthalic anhydride was prepared by heating 0.3 g. of the cyano acid with 0.5 ml. 75% sulphuric acid on a steam bath for 3 hours. On pouring the reaction mixture onto a small amount of ice, the anhydride separated as a white powder. The anhydride was boiled under reflux with 5 ml. water for 1 hour. On cooling, the phthalic acid crystallized out as small white crystals. The compound had a m.p. of $174-175^{\circ}\text{C}$., in agreement with the published value.

SUMMARY

1. The degradative proof of structure of the dioxanyl-phthalide resulting from the condensation of 5-hydroxy-o-toluic acid with formaldehyde and concentrated hydrochloric acid has been accomplished.
2. An attempt to synthesize the end-product of this degradation has been made.
3. The end-product of the degradation of the dioxanyl-phthalide resulting from the condensation of 3-hydroxy-p-toluic acid with formaldehyde and concentrated hydrochloric acid has been synthesized. This degradation was carried out by Thompson (20), and the end-product obtained by him was identical with the one synthesized by this research worker.

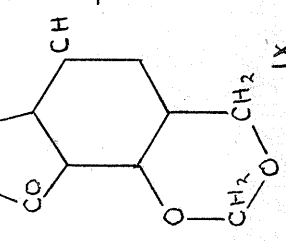
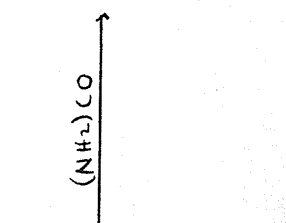
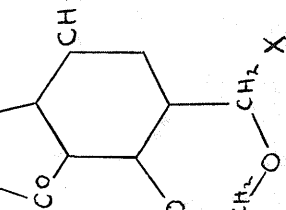
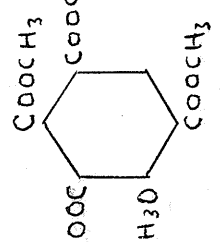
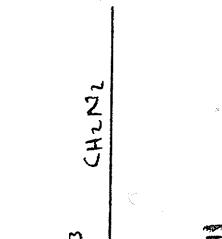
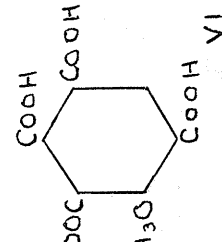
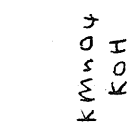
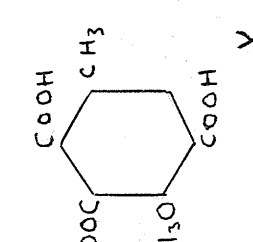
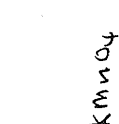
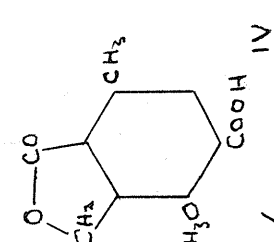
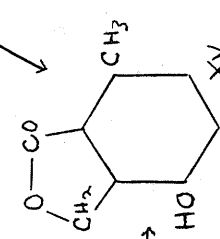
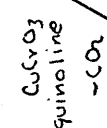
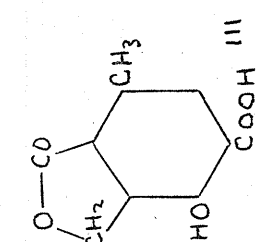
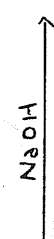
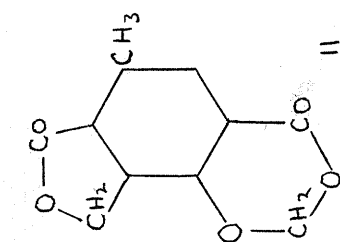
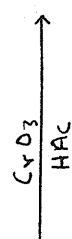
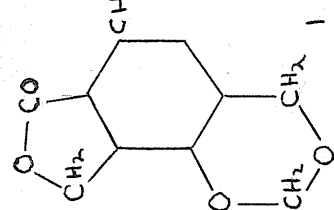
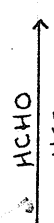
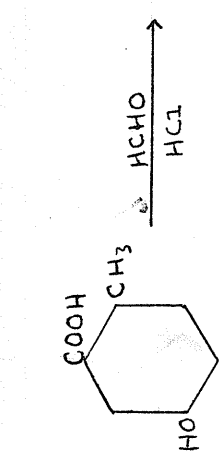
SUGGESTIONS FOR FUTURE WORK

1. The synthesis of the degradative end-product, 4-methoxy-benzene-1,2,3,5-tetracarboxylic acid should be completed.
2. It would be interesting to ascertain the nature of the substances obtained from the hot alkaline permanganate oxidation of the dioxanyolphthalide.
3. It would be of interest, although not directly related to the project, to determine the products resulting from the photo- and catalytic halogenation of the dioxanyolphthalide.
4. The air oxidation of the dioxanyolphthalide as described by Thompson (20) should be undertaken with a view to finding out what substances are produced.
5. The work of Meldrum and Kapadia (14) based on the Fritsch condensation product with 3-hydroxy-p-toluic acid might be repeated (this was done, but the results were of insufficient value to report in this Thesis), and its extension to 5-hydroxy-o-toluic acid might be attempted.

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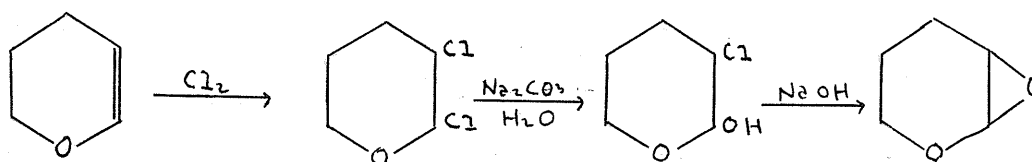
PART II

A SURVEY OF METHODS OF SYNTHESIS OF ³-DIHYDROPYRAN

INTRODUCTION

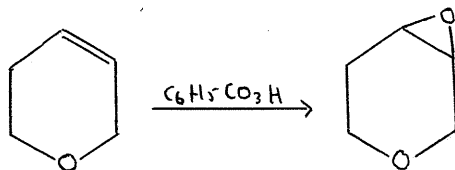
Cyclic oxides have been found useful intermediates for the preparation of certain types of organic compounds, such as cyclohexyl substituted aliphatic acids (5, 8, 9). In order to try some of these, Giesinger (3) attempted oxide formation with the heterocyclic cyclohexene compound Δ^2 -dihydropyran.

This oxide was to be synthesized by the following series of reactions:



However, no oxide could be isolated from the dehydrohalogenation reaction mixture, as the oxide would very likely be quite unstable.

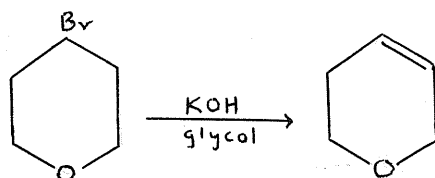
Thus it was thought to be of interest to work out a good method of synthesis of the structural isomer of this compound, Δ^3 -dihydropyran, as Paul and Tchelitchev (11) have reported oxide formation with this compound using perbenzoic acid:



This compound could then be used for the work mentioned.

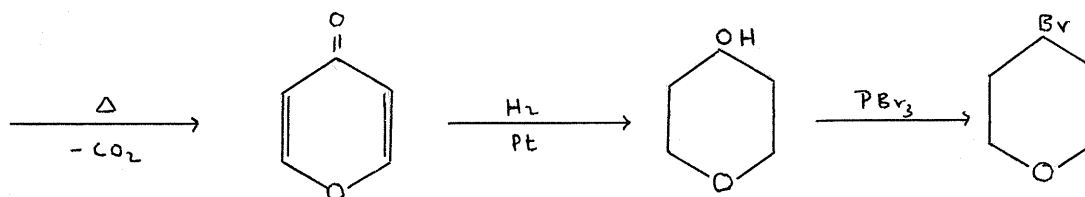
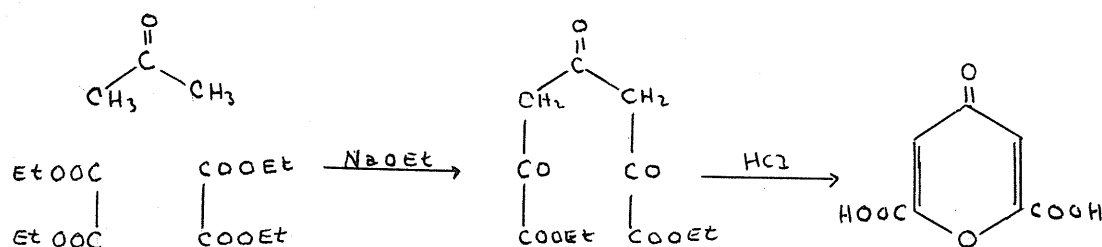
LITERATURE SURVEY

The compound Δ^3 -dihydropyran was first mentioned in the literature by Paul and Tchelitchev (11), in 1947. These research workers prepared the isomer by the slow distillation of a solution of 4-bromotetrahydropyran and potassium hydroxide in glycol:

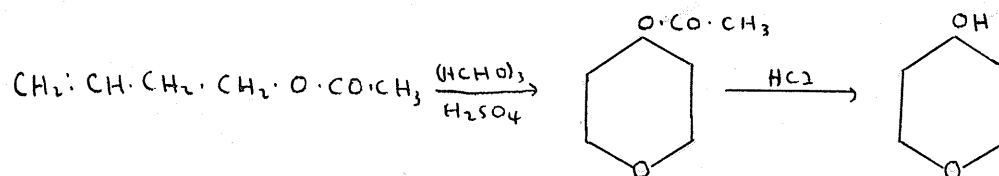
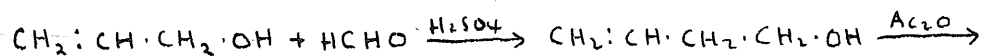


The synthetic source of the 4-bromotetrahydropyran was not mentioned in this paper, but a literature search indicates that only two methods of synthesis of this compound have been reported up to the present time.

The first of these is rather involved, and would not be useful for any other than small scale preparations. It involves the condensation of ethyl oxalate and acetone to give acetone dioxalic ester, which can be hydrolysed and cyclized to chelidonic acid. These reactions have been published by Riegel and Zwillgmeyer (13). Chelidonic acid has been decarboxylated by Willstatter and Pummerer (16) to give γ -pyrone. Prelog and coworkers (12) have described the hydrogenation of γ -pyrone to tetrahydropyranol-4, and the conversion of the alcohol to 4-bromotetrahydropyran by treatment with phosphorus tribromide. This reaction scheme can be represented as follows:



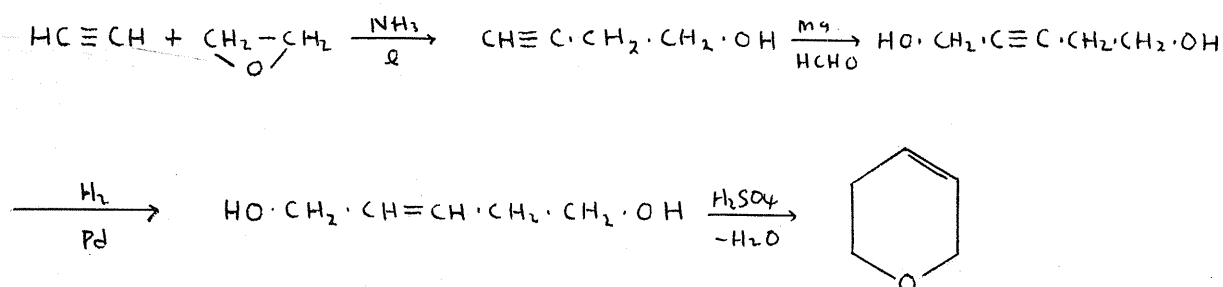
The second method for the synthesis of tetrahydropyranol-4 is that of Olsen (10). This is a rather more direct synthesis, and uses inexpensive starting materials, but the yields are low. Here, allyl alcohol was condensed with formic acid to give butene-3-ol-1, which was acetylated with acetic anhydride. This acetate was refluxed with paraformaldehyde in benzene to give the acetate of tetrahydropyranol-4, which could be hydrolysed with dilute hydrochloric acid to give the free alcohol.



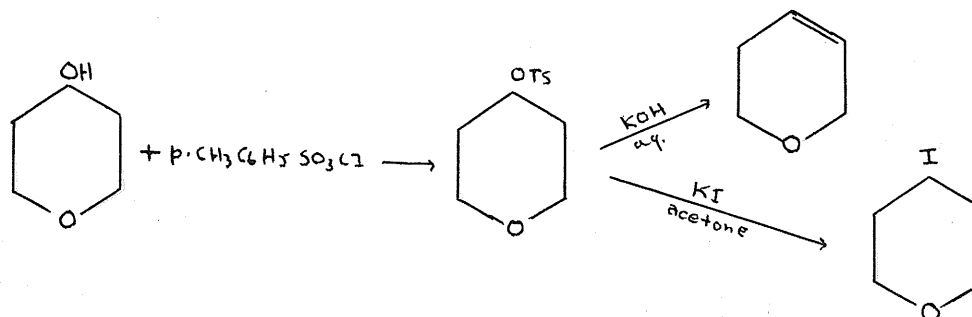
The tetrahydropyranol-4 could be converted to the bromide

as described above.

A recent publication of Heuberger and Owen (6) gave a total synthesis of Δ^3 -dihydropyran starting with acetylene and ethylene oxide. These were condensed in liquid ammonia to give butyne-3-ol-1. This was transformed into pentyne-2-diol-1,5, which was cyclized with sulphuric acid to produce the desired compound. The reaction scheme is shown below:

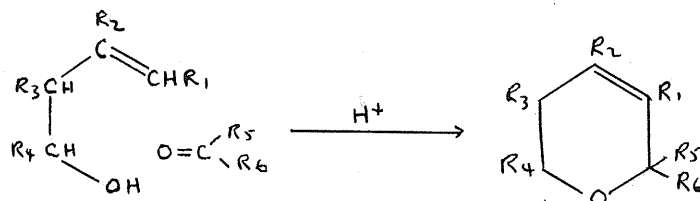


These authors also describe another method for the transformation of tetrahydropyranol-4 into Δ^3 -dihydropyran, and also into 4-iodotetrahydropyran. Tetrahydropyranol-4 was condensed with p-toluenesulphonyl chloride, and the tosyl derivative was treated with aqueous alkali to give Δ^3 -dihydropyran. On refluxing the tosyl derivative with potassium iodide in acetone, 4-iodotetrahydropyran resulted.



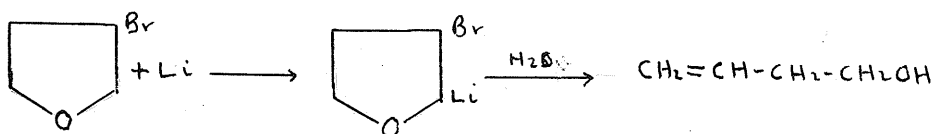
Siever and Ballard (15) have published a method for

the synthesis of substituted Δ^3 -dihydropyrans. This involves the condensation of variously substituted butene-3-ol-1 compounds with substituted aldehydes or ketones to produce the corresponding Δ^3 -dihydropyran:

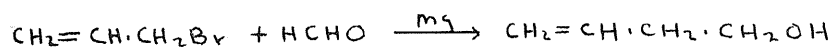


Although preparation of the unsubstituted compound was not reported in this paper, it was felt that butene-3-ol-1 could be condensed with formaldehyde to give the desired compound.

Thus the problem arose of obtaining a good method of synthesis of butene-3-ol-1. That of Olsen (10), as was mentioned above, gives poor yields. Besides this, the literature lists only two other methods. The first was published by Yu'rev and coworkers (18), and involves the condensation of 3-bromotetrahydrofuran with lithium, followed by hydrolysis of the adduct with water:

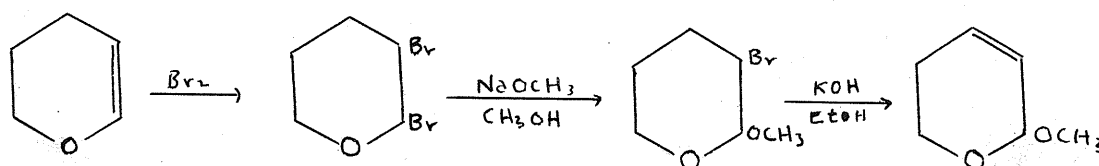


However, the literature lists no useful synthesis of 3-bromotetrahydrofuran. The other method is the Grignard synthesis using allyl bromide and formaldehyde:



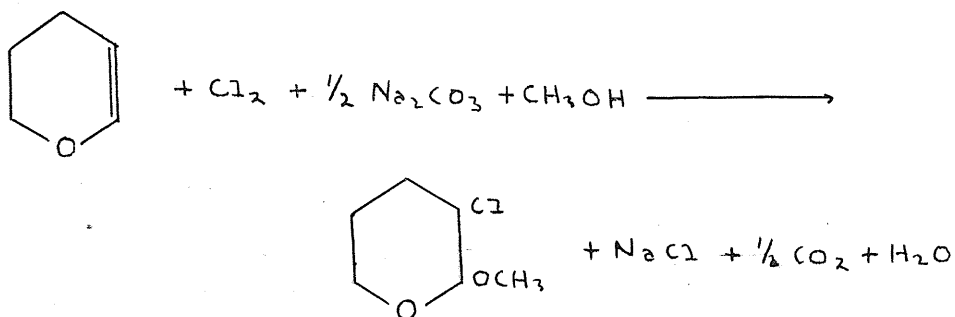
Allyl bromide is very reactive and the magnesium derivative is difficult to prepare (4). The yield of the overall reaction is quite poor due to the formation of large quantities of biallyl and biallyl ether.

A paper of Woods and Sanders (17) gives a method of synthesis of the 2-methyl- and 2-ethyl-ethers of Δ^3 -dihydropyran. The preparation was carried out by brominating Δ^2 -dihydropyran to give the dibromotetrahydropyran, which was then reacted with ammoniacal absolute methanol or sodium methoxide in absolute methanol to give the 2-methyl ether. This was refluxed with alcoholic potassium hydroxide to give the desired compound:



The ethyl ether is made in an entirely analogous manner.

In a British patent, Jones and Bremner (7) give details for carrying out the chlorination and etherification simultaneously by dissolving the starting material in absolute methanol containing sodium carbonate, and passing in the calculated amount of chlorine:



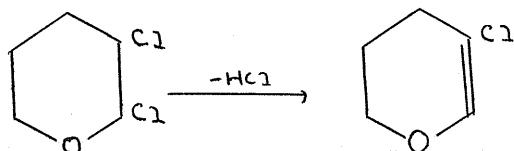
Woods and Saunders gave proof that the dehydrohalogenation of the 2-methoxy-3-chlorotetrahydropyran occurred to give a double bond in the 3,4-position rather than the 2,3-position by hydrolysing the unsaturated compound and preparing the dinitrophenylhydrazone of the resultant pentenal. The mixed melting point test showed that the aldehyde produced by the hydrolysis was 5-hydroxy- Δ^2 -pentenal, thus fixing the double bond of the dihydropyran to be 3,4.

DISCUSSION OF RESULTS

Of the various synthetic methods listed in the Literature Survey, three were chosen for investigation. These were: the oldest method, starting with chelidonic acid; the method of Woods and Sanders (17), and the cyclization of butene-3-ol-1 with paraformaldehyde. Although the best method for turning out large quantities of Δ^3 -dihydropyran appeared to be that of Heuberger and Owen, lack of the necessary equipment ruled this method out.

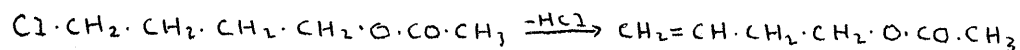
Chelidonic acid was synthesized by the method of Riegel and Zwillgmeyer (13). All attempts at thermal decarboxylation of this compound according to the method of Willstatter and Pummerer (15) as improved by Cornubert and Robinet (2) gave no results. Cornubert and Robinet claim that the method of Riegel and Zwillgmeyer for the synthesis of chelidonic acid gives a product unsuitable for the purpose of decarboxylation, and suggest a series of modifications of the method whereby a product can be turned out which will give good yields of γ -pyrone on decarboxylation. Time did not allow an investigation of these claims. Attempts were also made to pyrolyze the copper salt of chelidonic acid, and to decarboxylate chelidonic acid in quinoline with copper chromite according to Shepard and coworkers (14). These attempts were also failures. This approach was therefore dropped as being too difficult for practical purposes.

The method of Woods and Sanders (17) seemed worthy of trial, since the 2-ethers of Δ^3 -dihydropyran would be suitable for the required purpose, and according to the publication should be quite easy to synthesize. For purposes of convenience, it was decided to chlorinate the Δ^2 -dihydropyran rather than brominate it, as the dichloro compound would be just as suitable for the desired purpose as the dibromo compound. Thus Δ^2 -dihydropyran was chlorinated according to the directions of Giesinger (3) to give 2,3-dichlorotetrahydropyran in quantitative yield. The dichloro compound was reacted with a solution of sodium methoxide in absolute methanol to produce a product which did not appear to be that desired. Although a sodium fusion showed that the compound still contained chlorine, it showed unsaturation on testing with bromine in carbon tetrachloride and potassium permanganate solution.. Its boiling point under reduced pressure deviated approximately 10° from that expected, and it did not have a correct refractive index. It was first thought that the 2,3-dichlorotetrahydropyran had lost HCl in the etherification reaction to produce 3-chloro-dihydropyran instead of the desired ether:



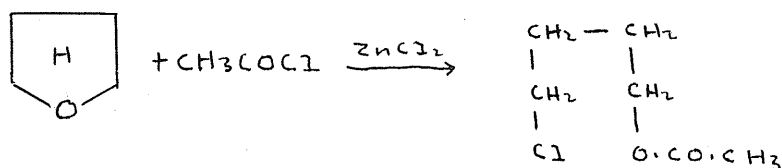
However, the normal boiling point of the isolated liquid was about 10° too high for 3-chloro- Δ^2 -dihydropyran. Thus the conclusion was arrived at that the etherification had gone to completion, but when the excess methanol was distilled off after the completion of the reaction, some of the reaction product lost HCl to give the final product, 2-methoxy- Δ^3 -dihydropyran. In order to verify this conclusion, the isolated liquid was hydrolysed by a dilute solution of hydrochloric acid in ethanol, and the 2,4-dinitrophenylhydrazone of the resultant aldehyde prepared. Upon recrystallization, this derivative melted at $162-3^{\circ}\text{C}$. as compared with the derivative prepared from 2-methoxy- Δ^3 -tetrahydropyran by Woods and Sanders which had a m.p. of 159° . Lack of time did not permit further work on this line of approach.

The third line of approach to Δ^3 -dihydropyran was through the cyclization of butene-3-ol-1 with formaldehyde, by the directions of Siever and Ballard (14), or of Olsen (10). Thus a practical method of synthesis of butene-3-ol-1 was sought. The best method of preparation of this compound appeared to be the dehydrohalogenation of 4-chlorobutyl acetate:

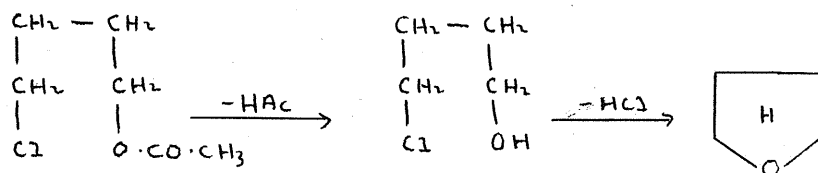


4-Chlorobutyl acetate could be synthesized easily and in good yield by the method of Cloke and Pilgrim (1). Here the cyclic ether tetrahydrofuran is split under the

catalytic influence of anhydrous zinc chloride:



The dehydrohalogenation of 4-chlorobutyl acetate proved to be more difficult than was anticipated. The first method tried involved the use of potassium hydroxide in glycol. It was hoped that this reagent would split out HCl before saponifying the ester. However, tetrahydrofuran was recovered from the reaction mixture in almost quantitative yield, indicating that the reverse reaction sequence had taken place:



Refluxing 4-chlorobutyl acetate in dry pyridine gave a product which was water soluble, and so could not have been the desired ester. However, refluxing with pure dry quinoline proved to be successful, except that the product was none too pure. As this section deals with a secondary research project, only a limited amount of time was available for research along these lines. Thus the above point was reached quite late, and this approach to the problem also had to be abandoned before its completion.

EXPERIMENTAL

The Preparation of Chelidonic Acid

This was prepared according to the directions of Riegel and Zwillgmeyer (13), which are outlined below.

In a 1 liter flask fitted with a reflux condenser protected with a calcium chloride tube, 46 g. (2 gram atoms) sodium was dissolved in 600 ml. absolute methanol. About half the sodium methoxide solution was poured into a 3 liter three-necked flask equipped with a reflux condenser and a mercury sealed stirrer, the other half was kept warm with a small flame. The first half was allowed to cool until solid began to separate, then a mixture of 58 g. dry acetone and 150 g. redistilled ethyl oxalate was added at once with stirring. Heat was evolved, and the liquid turned brown. As soon as turbidity began to appear, the remaining sodium methoxide was added along with 160 g. additional ethyl oxalate. As stirring was continued, the mixture thickened gradually to the point where the stirrer jammed. The condenser on the flask was then set for downward distillation, and heated at 110°C . in an oil bath until 150 ml. alcohol distilled. The sodium derivative was scooped from the flask into a beaker containing 300 ml. concentrated hydrochloric acid and 800 g. cracked ice. After crushing all lumps, the creamy yellow acetone dioxalic ester was filtered off and washed.

For hydrolysis, the crude ester was heated with 300 ml. concentrated hydrochloric in a 5 liter flask for 20

hours on a steam bath. When cold, the solid hydrated acid was filtered off, washed and dried, first at 100° , and then at 160° . The yield was 110 g., 61% of the theoretical.

The Preparation of Copper Chelidonate

A solution of 9.2 g. chelidonic acid and 5.3 g. anhydrous sodium carbonate in 300 ml. water was prepared by boiling. This solution was cooled to 50°C. , and to it was added a solution of 12.5 g. copper sulphate crystals in 250 ml. water. A voluminous precipitate of copper chelidonate hydrate appeared, which was heated and stirred until it was transformed to the granular anhydrous salt. This was filtered off and dried.

Decarboxylation of Chelidonic Acid

The first attempt at this reaction was carried out according to Cornubert's modification of Willstatter's method (2). A mixture of 20 g. chelidonic acid and 4 g. powdered copper was layered over 20 g. pumice powder in a 100 ml. distilling flask equipped with an air condenser and stoppered at the top. The chelidonic acid was pyrolyzed by heating to 300°C. A copious evolution of sweet-smelling white fumes occurred, along with one or two crops of a liquid which solidified on cooling. This was presumably γ -pyrone, which melts at 32.5°C. No variation of the method tried produced any better results. One modification was the use of the copper salt of the acid as a catalyst. This was tried in all proportions, from 1/20 molar to total quantity of the reaction mixture. The reaction was also tried in vacuo, but again the yields were insignificant.

The Preparation of Dichlorotetrahydropyran

This was prepared by the method of Giesinger (3). Into ice-cold Δ^2 -dihydropyran (84 g., 1 mole) was passed 71 g. (1 mole) chlorine. Thus a theoretical yield of 2,3-dichlorotetrahydropyran was obtained. This crude material was suitable for the required purpose without the wasteful distillation.

The Preparation of 2-Methoxy-3-chlorotetrahydropyran

To a well cooled, stirred solution of 25 g. sodium in 500 ml. absolute methanol was added 155 g. (1 mole) 2,3-dichlorotetrahydropyran at such a rate that the temperature did not rise above 5°C. Stirring was continued for an additional hour. The precipitated sodium chloride was filtered off, and the excess methanol was removed by distillation. The crude reaction product was washed with water and dried over sodium sulphate. It was then fractionated under reduced pressure, the main fraction boiling at 65-67°C./13 mm. This material weighed 65 g. Upon repeating the distillation at atmospheric pressure, the supposedly pure compound boiled at 163-165°C. The boiling point of this product was thus too high to be the expected product (b.p. 130°C.) as well as too high to be the other possible compound, 3-chloro- Δ^2 -dihydropyran (b.p. 140°C.). A sodium fusion indicated the presence of chlorine, and bromine in carbon tetrachloride, and potassium permanganate solution showed the molecule to contain unsaturation.

The compound was hydrolysed by boiling 1 g. of it in 20 ml. of ethanol containing 6 drops of concentrated hydrochloric acid for 1 hour. To the hot solution was added a solution of 0.4 g. 2,4-dinitrophenylhydrazine in 2 ml. concentrated sulphuric acid and 10 ml. methanol. Upon standing, orange crystals of the 2,4-dinitrophenylhydrazine appeared. These were filtered off, washed, dried, and recrystallized from toluene. The resultant crystals melted at 162-163°C. Woods and Sanders (16) give the melting point of 5-hydroxy- Δ^2 -pentenal as being 159-160°C.

The Preparation of 4-Chlorobutyl Acetate

The method of Cloke and Pilgrim (1) was used here. A mixture of 50 g. tetrahydrofuran, 65 g. acetyl chloride, and 10 mg. zinc chloride was heated gently until the reaction commenced. Cooling was then necessary until the reaction moderated. Boiling was then continued for one hour. The reaction product was transferred to a Claisen flask and fractionated under reduced pressure. Except for a minute fore-run and residue, the whole of the material boiled at 78-79°/15mm. to give an almost quantitative yield of chlorobutyl acetate.

Butene-3-yl-1 Acetate

The dehydrohalogenation of 4-chlorobutyl acetate was first attempted by treatment with potassium hydroxide in glycol. The alkali-glycol mixture was prepared by dissolving 25 g. potassium hydroxide in 125 ml. glycol. To this, 30 ml.

4-chlorobutyl acetate was added in small portions with shaking. The reaction was initiated with gentle heating of the solution, and was then controlled by cooling as necessary. The reaction was completed by boiling the mixture under reflux for 30 minutes. The resultant mixture was distilled through a Vigreux column, when almost a quantitative yield of tetrahydrofuran was recovered.

Pyridine was then tried as a dehydrohalogenating agent. A mixture of 30 ml. dry pyridine and 30 ml. 4-chlorobutyl acetate was boiled under reflux for 2 hours. During this time, a second layer appeared at the bottom of the flask which gradually grew larger until the mixture again became homogeneous. When cold, the reaction mixture was poured into 300 ml. 10% hydrochloric acid. The expected ester layer failed to separate out, and saturating the solution with salt forced nothing to separate out.

Quinoline was then tried under the same conditions. Here no second layer appeared during the refluxing, and when the reaction mixture was worked up, an organic layer did appear. This was separated, washed with dilute hydrochloric acid, dried over anhydrous sodium sulphate, and distilled over a range of 110° to 130°C. The reaction product was thus impure butene-3-yl-1 acetate (b.p. 124°C.).

SUMMARY

1. Chelidonic acid was prepared as a starting material for the synthesis of Δ^3 -dihydropyran, but could not be decarboxylated.
2. A start was made in the synthesis of 2-methoxy- Δ^3 -dihydropyran.
3. A simple method for the synthesis of butene-3-ol-1 has been developed. This substance can be used for the synthesis of Δ^3 -dihydropyran by methods outlined previously.

SUGGESTIONS FOR FUTURE WORK

1. An attempt could be made decarboxylate chelidonic acid as prepared by the directions of Cornubert and Robinet (2).
2. The method of Woods and Sanders (17) for the preparation of 2-methoxy- Δ^3 -dihdropyran should be followed up to completion.
3. Butene-3-ol-1 could be transformed to tetrahydropyranol-4 by the method of Olsen (10), or directly to Δ^3 -dihdropyran by the directions of Siever and Ballard (15).

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