A COMPARATIVE STUDY OF THE METHODS OF PREPARING THE TOLUIC ACIDS

A STUDY OF THE OXIDATION PRODUCTS OF VARIOUS PHTHALIDES

by

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A STUDY OF THE OXIDATION PRODUCTS OF VARIOUS PHTHALIDES

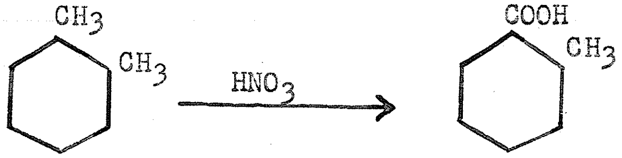
PART I

A COMPARATIVE STUDY OF THE METHODS OF PREPARING THE TOLUIC ACIDS

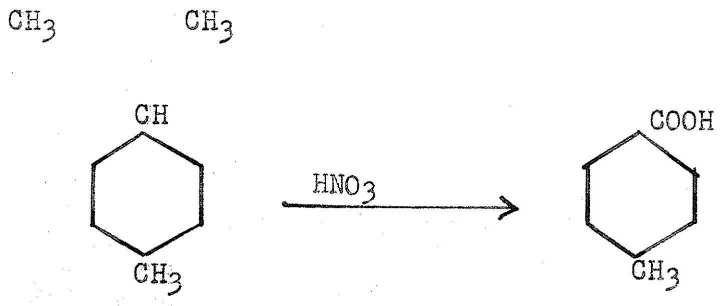
INTRODUCTION AND LITERATURE SURVEY

At the present time there are two methods of preparing the toluic acids on a large scale in the laboratory. These methods are the preparation of the toluic acid from the toluamine by means of the Sandmeyer reaction, and the oxidative preparation of the acid from a suitable aromatic hydrocarbon. Ortho toluic acid has been prepared on a small scale by the action of o-magnesium bromotoluene on solid carbon dioxide (1). This research was undertaken to determine the possibility of preparing the toluic acids on a large scale by the Grignard reaction, and to compare the results obtained with those of the commoner methods of preparation.

Zaugg and Rapala (23) prepared o-toluic acid in good yield (60%) by refluxing o-xylene for 55 hours with dilute nitric acid. The reaction proceeded quite smoothly until the oxidation was complete. Unfortunately, the reaction also produced phthalic acid and a small amount of the nitro derivatives of the two acids. The resulting mixture was difficult to separate into the component parts.

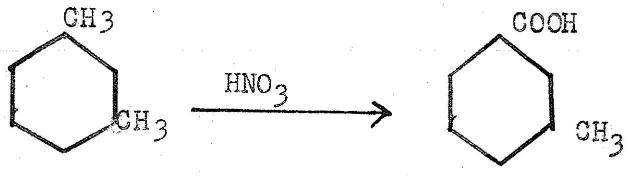


Tulay and Marvel (22) prepared p-toluic acid in a similar manner from p-cymene by oxidation with dilute nitric acid. The reaction illustrated the preferential oxidation of a tertiary carbon over the primary carbon in the side chain.

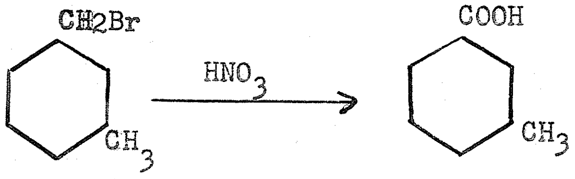


Some terephthalic acid was formed in the reaction. It was rather easily separated from the p-toluic acid, but the nitro compounds formed, which may be nitro derivatives of p-toluic acid and terephthalic acid, were very difficult to remove. Thus, this preparative method was found to suffer from the same difficulties as the preparation of o-toluic acid.

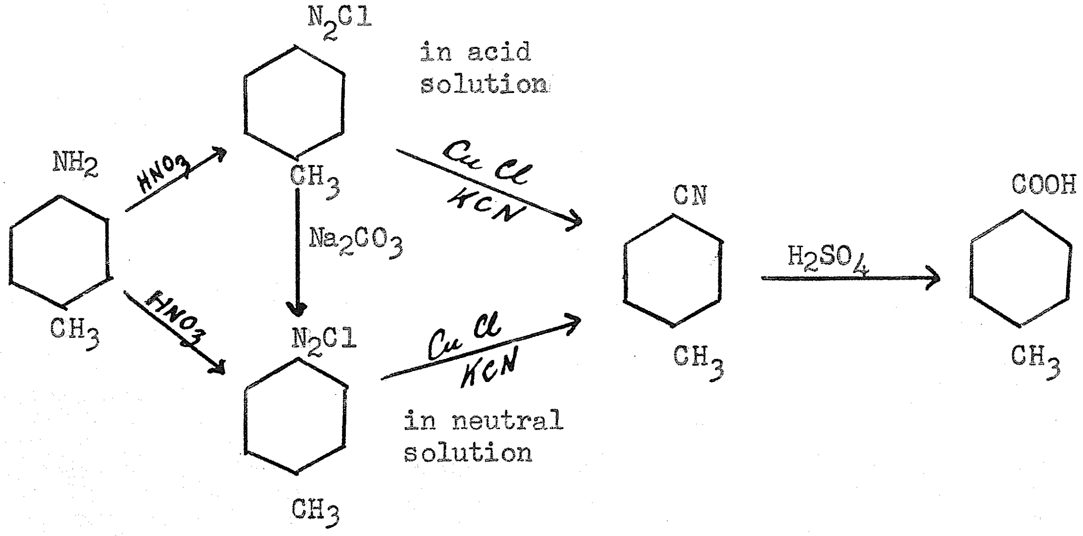
Reuther (17) oxidized m-xylene to m-toluic acid. The yields obtained were not mentioned, but judging from the results obtained by Stewart (20) in the oxidation of m-xylyl bromide, it is probable that the yields were low.



Stewart (20) attempted the synthesis of m-toluic acid from m-xylyl bromide. He used a variety of oxidizing agents such as dilute nitric acid, potassium permanganate in acetone, potassium permanganate in acid solution and potassium permanganate in basic solution. In all cases but the last, the acidic material obtained from the oxidation was isophthalic acid. The last mentioned oxidation gave isophthalic acid and 13.6% of m-toluic acid.



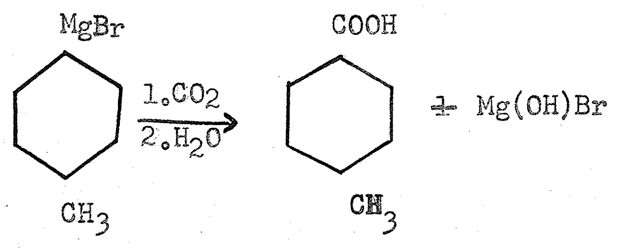
The commonest and most convenient method of preparing the toluic acids is based upon the Sandmeyer reaction. There are two methods of preparing the diazonium salt, differing in detail only. The first of these was given by Clarke (5), and in it the p-toluene diazonium chloride was prepared in an acid solution. In the second method, given by Clarke and Read (4), the diazonium salt was prepared in an acid solution and then all excess acid present in the solution was neutralized. Once the diazonium salt was formed. it could be treated with potassium cyanide in the presence of cuprous chloride as in a normal Sandmeyer reaction. The only advantage of the second method was that the addition was carried out in a neutral solution and therefore hydrogen cyanide gas was not evolved during the reaction. Hydrolysis of the resulting nitrile in sulphuric acid gave the toluic acid (5). This method of preparation was commonly used for ortho and para toluic acids and may also be applied to meta toluic acid.

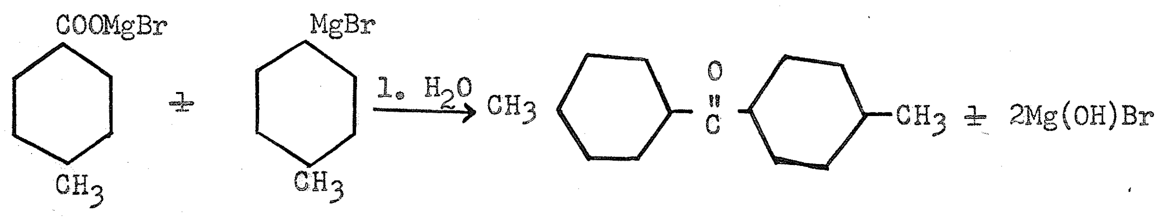


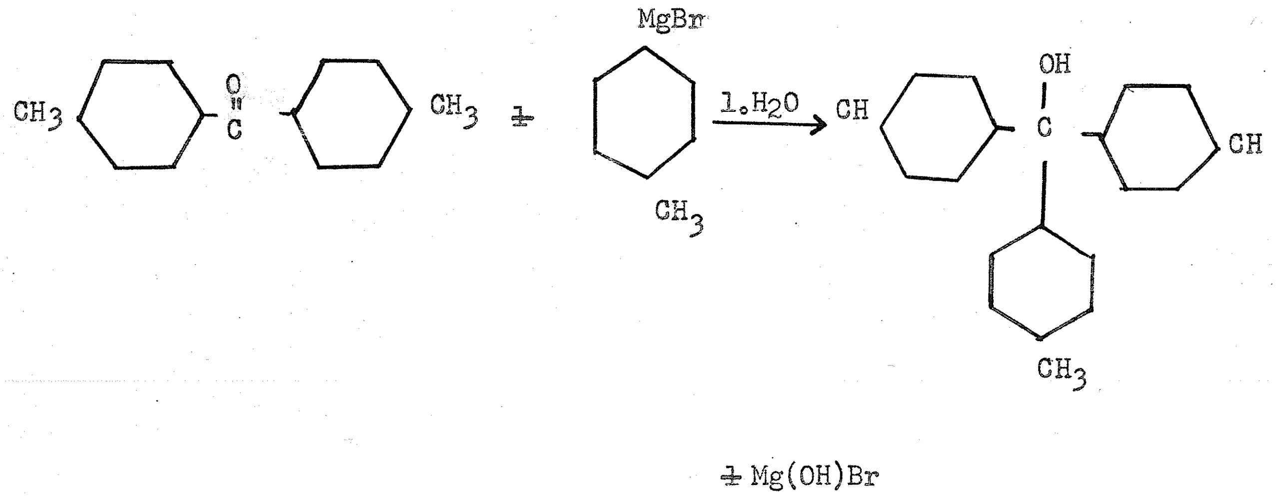
A search of the literature showed that o-toluic acid has been prepared on a small scale by the action of solid carbon dioxide on the Grignard reagent prepared from o-bromotoluene. This synthesis was accomplished by Austin and Johnson (1).

Because the preparation of organic acids by the Grignard method has been a thoroughly studied field, some of the results of such studies as are pertinent to this investigation are considered here before further discussion of the preparation of the toluic acids.

The synthesis of organic acids from the corresponding halide was accomplished very shortly after the introduction of the Grignard reaction into Organic Chemistry. Early workers such as Grignard (13), Houben (14), Schlenk and Ochs (18), Meyer (15), and Schmidlin (19) were able to show that if a Grignard reagent be prepared and treated with carbon dioxide, three products could be obtained, depending on the experimental conditions. These products were found to be an acid, a ketone, or a tertiary alcohol. The formation of these products is readily explainable if the following reactions be considered.







The following results were obtained by Bodroux (3) when he treated the mono Grignard reagent of p-dibromobenzene and p-dichlorobenzene with carbon dioxide under the temperature conditions indicated. The table shows quite clearly that the product of the reaction of a Grignard reagent with carbon dioxide depends upon the temperature.

Starting Material	Product	Yields obtained when carbon dioxide added at		
		36°C. (%)	0°C. (%)	-40°C. (%)
Mono Grignard reagent of p-dibromobenzene	p-bromobenzoic acid	10	61	76
	p_1p'-dibromobenzophenone	58	26	6
Mono Grignard reagent of p-dichlorobenzene	p-chlorobenzoic acid	4	64	80
	p_1p'-dichlorobenzophenone	50	18	4

A gradual evolution in the method of reacting the Grignard reagent with carbon dioxide occurred. Schlenk and Ochs (18) bubbled carbon dioxide gas through a cooled Grignard solution. This led to a number of difficulties, the chief of which was the tendency of the bubbling tube to clog with the resulting carbon dioxide - Grignard complex. Another method, used by Houben (14), was to cool the Grignard reagent to 0°C. and add small pieces of solid carbon dioxide, slowly at first, to the solution. The method used by Austin and Johnson (1) was finally evolved whereby a slush composed of solid carbon dioxide and ether was prepared, and the Grignard complex poured into it with vigorous stirring. This method employed the solid carbon dioxide as its own refrigerant.

It was reported in the literature that a low temperature hindered the preparation of triphenyl acetic acid from triphenyl methyl bromide. The reaction had to be warmed to assist the formation of the acid (19).

A great deal of study has been carried out upon the Grignard reagent itself. Meyer and Tögel (15) in Germany made a study of the effect obtained by adding water at various stages of the reaction of a Grignard reagent with carbon dioxide. It was found that traces of water at certain stages in the formation of benzoic acid from bromobenzene actually catalysed the reaction.

More recently, Gilman in the United States published a series of papers in collaboration with other workers dealing with the preparation of Grignard reagents. Gilman and McCracken (8) determined the yields of various Grignard reagents, several that are of interest for comparative purposes are:

Organic Halide	Percentage Yield of the Grignard Reagent from the Organic Halide
bromobenzene	94.37
iodobenzene	84.58
o-bromotoluene	86.65
m-bromotoluene	84.75
p-bromotoluene	88.16
a-bromonaphthalene	70.50
cyclohexyl bromide	68.32
benzyl chloride	94.28

The method of determining the amount of Grignard reagent present followed the method given by Gilman and Wilkinson (12). It was accomplished by hydrolysing the Grignard reagent with water and collecting the hydrocarbon produced. Another method would be to add the organic halide and the magnesium mole for mole. When the Grignard reagent was prepared, it could be poured or filtered from the residual magnesium. The magnesium remaining would give a direct measure of the amount of unreacted organic halide.

Gilman and Meyers (9) investigated the conditions that would give a maximum yield of a Grignard reagent. Maximum yields resulted if the organic halide was added slowly to the magnesium, but no increase would occur if the addition took longer than 45 minutes. Stirring during the above mentioned addition also increased the yield. Two somewhat surprising facts demonstrated were that there was no advantage in having an excess of magnesium present, and that it was not necessary to reflux the Grignard complex after addition has been carried out if the mixture was stirred efficiently for 15 minutes instead.

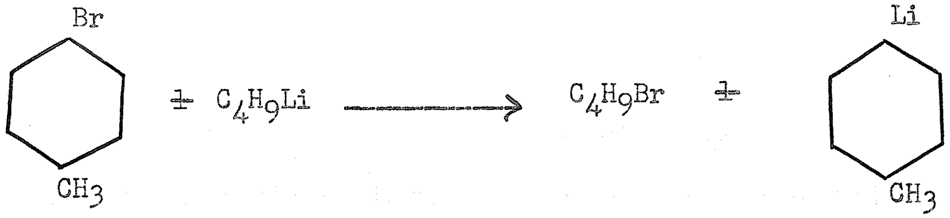
It is now desirable to consider the paper by Austin and Johnson in more detail. These workers studied the reactions of benzyl magnesium chloride with reagents such as carbon dioxide, acid chlorides, chlorocarbonate ester, aldehydes, ketones and ethoxides. To explain the reaction mechanism in some of these cases, it was necessary to react carbon dioxide with the Grignard reagent of o-bromotoluene. To do this, they prepared the

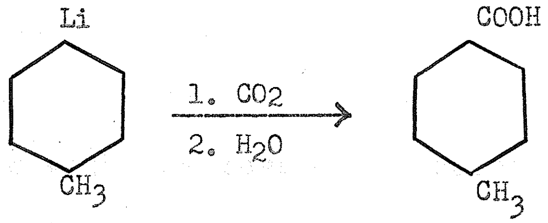
Grignard reagent in the normal manner and stirred it into a slush composed of solid carbon dioxide and ether. The temperature of such a mixture of carbon dioxide and ether drops quickly to a eutectic temperature of about -40°C. The o-toluic acid was obtained by hydrolysing the magnesium complex. The authors reported a yield of 8.5 grams or 62% based upon the amount of o-bromomagnesium toluene present. If the yields of o-bromomagnesium toluene on page 7 be considered, the yield of o-toluic acid obtained by these authors is 53% of the o-bromotoluene.

Although the following method of producing the toluic acids, carried out by Gilman, Moore and Langham (10), could not be readily adapted to a large scale preparation because of the high cost of the reagents used, this synthesis of the toluic acids was of interest because of its great similarity to the Grignard reaction.

Butyl lithium reagent was prepared in a 90% yield by treating n-butyl bromide with lithium metal in ethyl ether at -10°C. The butyl lithium was then reacted with any of the bromotoluenes to form an aromatic lithium complex. This complex was poured onto solid carbon dioxide giving an excellent yield of the corresponding toluic acid.

$$C_4H_9Br + 2\ Li \longrightarrow C_4H_9Li + LiBr$$





DISCUSSION OF RESULTS

Meta and para toluic acids have been prepared for the first time by the action of the Grignard reagent of the bromotoluene on solid carbon dioxide. Ortho and para toluic acids have been prepared on a large laboratory scale by means of the Grignard reaction. The results of these experiments have been compared with the results of the oxidative and the Sandmeyer preparations carried out in this investigation, and they have also been compared with the results of several oxidative methods given in the literature.

The Grignard Reaction

The reason for the various techniques used in the preparation of the toluic acids by the Grignard method will not be discussed here. They are explained either in the Experimental Section or in the Literature Survey.

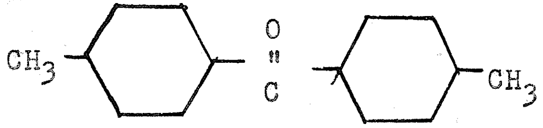
There is one part of the Experimental Procedure that does require some discussion. It may be thought inconsistent that a carefully prepared Grignard reagent should be poured into an open beaker in the fume chamber. It would seem that the yields would be reduced drastically because of the condensation of moisture upon the solid carbon dioxide in the open beaker. The yields of the acid obtained by the reaction do not appear to have been seriously affected by this danger. It must be concluded therefore, that the solid carbon dioxide was subliming at such a rate that the heavy layer of carbon dioxide gas prevented the admission of moisture laden atmospheric gases, and no condensation of moisture could occur.

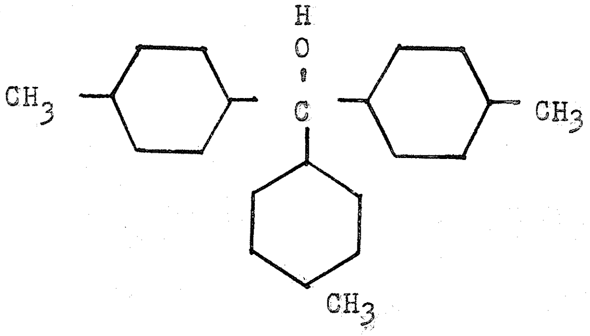
This was verified by the fact that on the outside of the beaker containing the carbon dioxide - ether slush, was deposited an extremely thick layer of frost; while on the inside of the beaker, at the very same level above the slush level, there was no frost deposit.

From the percentage yields given at the end of the section for the Grignard preparation of the toluic acids, it will be noticed that the yield of p-toluic acid was very much greater than the yields of the ortho and para acids. It is presumed that the difference in yields was the result of experience gained by the experimenter in handling the reaction. From the yields of the Grignard reagents given on page 17, it would be expected that the yields of the three acids by the Grignard method would be approximately equal.

After the ethereal layer from the preparation of p-toluic acid by the Grignard method had been thoroughly extracted with sodium hydroxide to remove the p-toluic acid, the layer was dried and evaporated to recover the ether. There was found to be a residue of 4.2 grams of a material melting at 116-120°C. This material was non acidic in nature and had a pleasant odour.

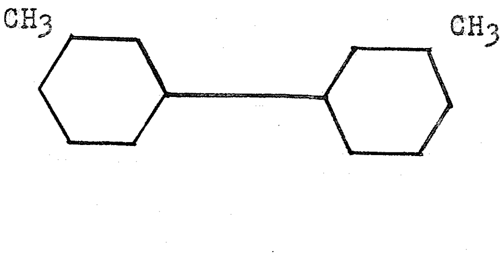
It might be a mixture of di-p-tolyl ketone, which melts at 95°C., and tri-p-tolyl carbinol. This low melting compound formed enormous, clear, crystals on crystallizing from ether.





The ethereal residues of the o-toluic acid and the m-toluic acid preparations were not investigated to see if similar compounds could be obtained in their cases. However, in the case of o-toluic acid, an oil was observed floating on the surface of the aqueous solution during recrystallization. This was probably an oil that often appears when a substance, having a melting point (103°C.) close to the boiling point of water, is recrystallized from water.

When the Grignard reagent from m-bromotoluene was being formed, there was observed to be a white solid in the ethereal solution. Since the reaction was carried out on a small scale this product was not isolated. This material might have a diphenyl structure produced by a Grignard coupling reaction.



The Oxidative Reaction

It was decided to attempt the oxidation of each of the three xylenes with nitric acid. Experimental details were given by Zaugg and Rapala (23) for the oxidation of o-xylene. The instructions for the oxidation of p-cymene by Tulay and Marvel (22) were adapted for the oxidation of p-xylene. Modifications of these experimental conditions were used for the oxidation of m-xylene. The reason for the lack of literature covering the oxidation of the xylenes was quickly discovered, once the oxidation with nitric acid was completed.

It was found that nitro derivatives, presumably of the two acids obtained from the xylenes, contaminated any attempts for a simple separation of the mono and dicarboxylic acids so badly, that reduction of the nitro compounds was necessary to achieve separation. In the case of m-xylene, the reduction was completed and a small amount of fairly pure m-toluic acid was obtained. The reduction of the nitro compounds of the p-xylene oxidation was also attempted, but it was found to be incomplete. No attempt was made to repeat the purification because of the great length of time involved. It was felt that the difficulties encountered in this type of preparation had been amply illustrated.

It is noticeable in the table at the end of this Section, that there is a wide variation between the literature yield of 53% for the preparation of o-toluic acid from o-xylene and the yield obtained in this research of 18%. This discrepancy was introduced when a 40-inch condenser used for refluxing was found to be of insufficient cooling capacity to prevent the escape of a considerable quantity of o-xylene. The single 40-inch condenser was replaced by two 40-inch condensors and the oxidation continued.

The Sandmeyer Reaction

The Sandmeyer method of preparing the toluic acids was found to proceed quite smoothly. The yields obtained were less than those given in the literature. It was felt that an increased familiarity in handling the reaction would result in increased yields.

The Sandmeyer reaction was found to occupy a great deal of experimental time. It was necessary to carry out two preparative reactions, and an addition reaction followed by a long procedure to ensure maximum yield of the nitrile. The crude nitrile must be steam distilled and then fractionally distilled at least once before the hydrolysis can be attempted. The hydrolysed product was found to be contaminated with some foreign substance, therefore a purification of the acid followed. In the case of the Grignard reaction, only one preparative reaction and one addition reaction need be carried out. The purification after a simple hydrolysis reaction was very easily accomplished. The yield obtained from the Grignard reaction was a large as the yield obtained from the Sandmeyer reaction.

Comparison of Results

The following table gives a comparison of the various methods of preparing the toluic acids. Included is the cost to prepare one kilogram of the acid. This cost is based upon the price of the chief chemical reagent required in the experiment. (24) This does not include the cost of sodium cyanide for the Sandmeyer reaction or of magnesium for the Grignard reaction. The time required to carry out the experiment has been estimated. This includes the time actually devoted to the experiment, and would include, for example, the time required to regulate the temperature of the o-xylene oxidation mixture to 135°C., but would not include the time the mixture refluxed at 135°C. when the experiment was not closely watched, neither does it include the time needed to prepare the apparatus for the experiment. The labour cost has been conservatively estimated at $1.00 per hour. Also included in the table, are oxidative preparations given in the literature; the time required to carry out the experiment is assumed to be the same as in those oxidations actually carried out.

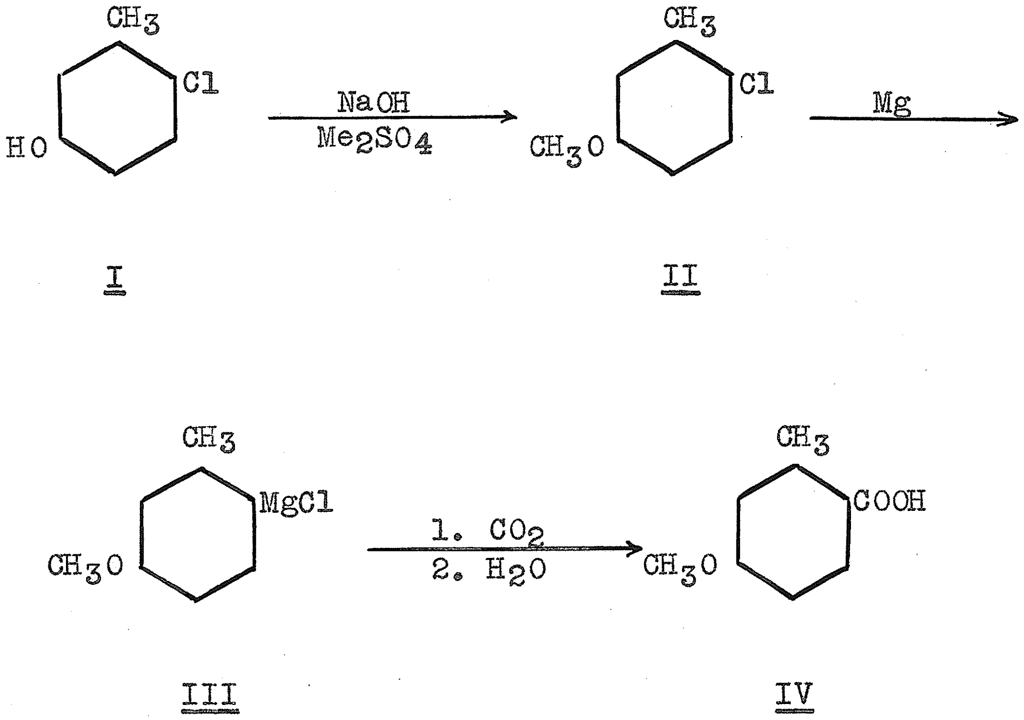
The table shows that the cost of preparing the toluic acids, except in the oxidative preparation of m-toluic acid, is approximately equal for each of the methods listed. They might be considered to be equal, except for the one mentioned, because of the rough method of estimating the time required to perform the experiment. Because of the rising wages of workers, those experiments requiring the least time to accomplish would become increasingly cheaper to carry out when compared with the cost of the other methods of preparation.

Material Prepared	Source	Yield (%)	Time (hrs.)	Cost/kg.	Labour	Total Cost
o-toluic acid	o-xylene	18	40	$ 24.98	$40.00	$ 64.98
m-toluic acid	m-xylene	5	40	400.00	40.00	440.00
p-toluic acid(22)	p-cymene	55	40	4.00	40.00	44.00
o-toluic acid(23)	o-xylene	53	40	9.21	40.00	49.21
p-toluic acid	p-tolunitrile	47	27	20.14	27.00	47.14
o-toluic acid	o-bromotoluene	45	18	35.52	18.00	53.52
m-toluic acid	m-bromotoluene	37	18	24.30	18.00	42.30
p-toluic acid	p-bromotoluene	65	18	24.64	18.00	42.64

The Sandmeyer and Grignard methods of preparing the toluic acids were much easier to carry out and should be preferred over the oxidative methods. The Grignard method cost approximately the same as the Sandmeyer method but it gave a purer product in a shorter time. The Grignard preparation of the toluic acids should be preferred to the Sandmeyer preparation for these two reasons.

An Attempt to Prepare the Grignard Reagent of 4-Methoxy-2-chloro toluene (IV)

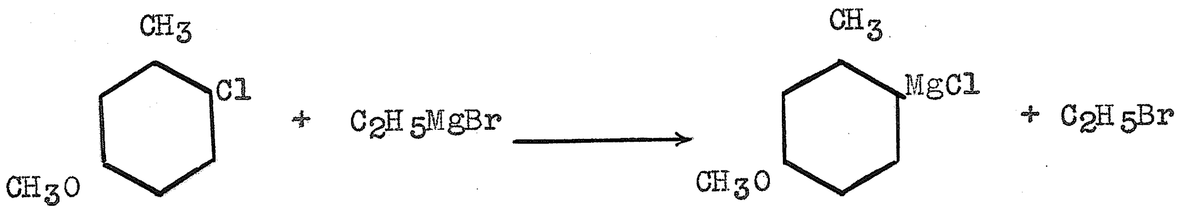
An attempt was carried out to produce 4-methoxy o-toluic acid by a Grignard method. It was hoped to be able to methylate 2-chloro-5-hydroxy toluene (I). The methylated product (II) was to be treated with magnesium to form the Grignard reagent (III) and this was to be poured onto solid carbon dioxide to produce 4-methoxy o-toluic acid (IV).



Methylation was necessary to prevent the reaction of the phenolic group with the Grignard reagent of another molecule. This synthesis would result in a much shorter method of preparing the acid (IV) than the method of sulphonation of o-toluic acid followed by alkali fusion that must be employed at present.

It was found possible to methylate the chlorocresol (I) but it was not possible to form the Grignard reagent (III) of the methylated product. The starting techniques tried in an attempt to initiate the reaction were crushing the magnesium, adding methyl iodide, adding a crystal of iodine, refluxing for several hours, and allowing to stand overnight. Since the reaction did not start, it was therefore concluded that it was impossible to prepare the Grignard reagent of 2-chloro-5-methoxy toluene under the conditions described.

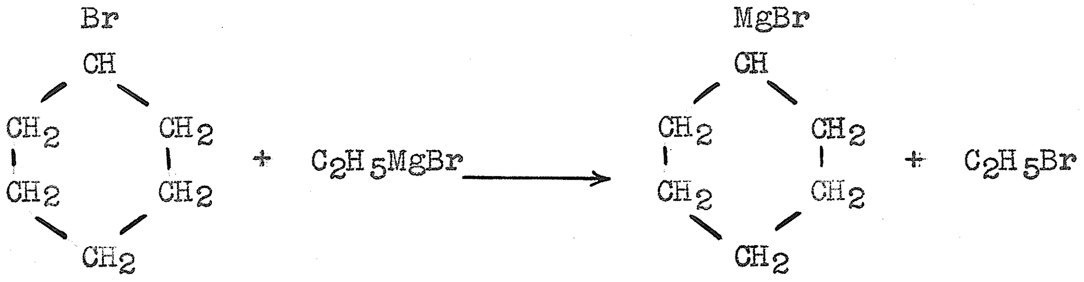
One method of initiating such a reaction, known as the Entrainment method, was not attempted. This methodw would consist of mixing equal moles of 2-chloro-5-methoxy toluene and ethyl magnesium bromide. The temperature of the mixture would be kept at the boiling point of ethyl bromide. The ethyl bromide, distilling off, would leave the Grignard reagent of 2-chloro-5-methoxy toluene in the reaction flask.



II

III

This method of forming a Grignard reagent was first accomplished by Grignard (13). One of the reactions described by this author was the reaction of ethyl magnesium bromide with cyclohexyl bromide (V). The yield of cyclohexyl magnesium bromide (VI) from this reaction was small.



V

VI

EXPERIMENTAL

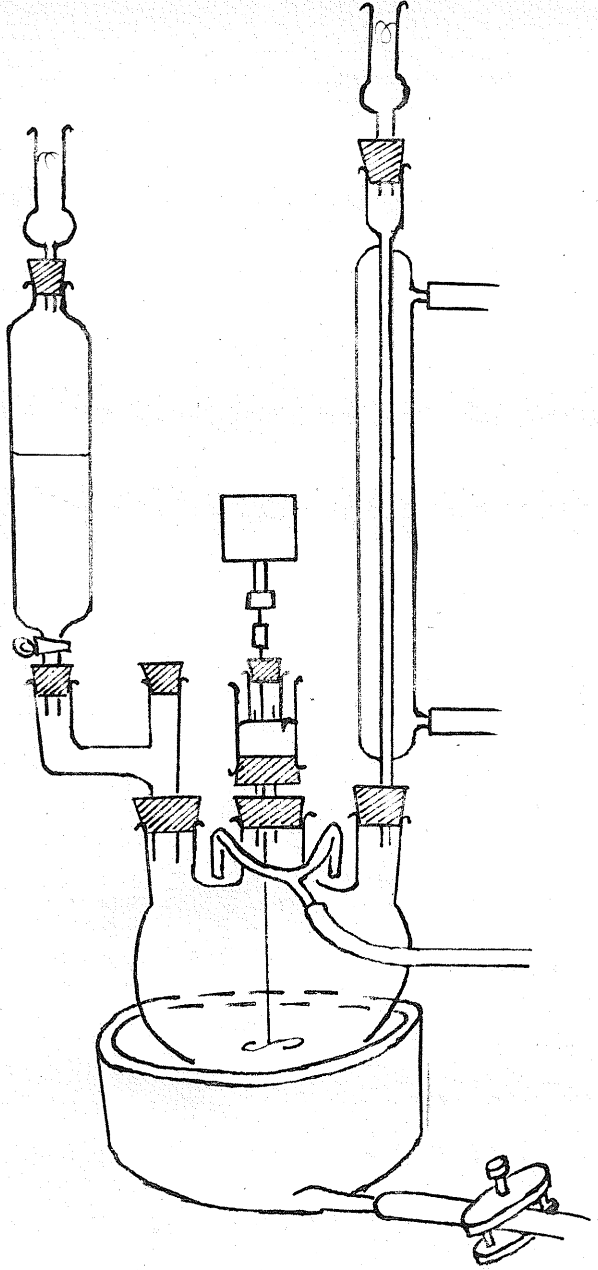
The Grignard Preparation of the Toluic Acids

(a) The Preparation of p-Toluic Acid

The apparatus used in the experiment was that shown in Figure 1. It was carefully cleaned of all moisture and assembled. A little magnesium was added (1 gram) and the reaction flask was gently heated to evaporate the small puddle of ether that had collected. This was done to expel moist air from the apparatus and to wash the last trace of moisture onto the magnesium where it would be destroyed.

A p-bromotoluene solution (50 ml.) was added to the reaction flask from the dropping flask. Magnesium (4 grams) was also added. The p-bromotoluene solution was prepared by mixing p-bromotoluene (200 grams, 1.17 moles) and ether (600 ml.). A small crystal of iodine was added to the solution and it was allowed to reflux, with mechanical stirring, by heating with hot water until the violet colour of the solution disappeared and a greenish turbidity appeared. The solution was mechanically stirred.

The total amount of magnesium required for the experiment was 28.4 grams or 1.17 moles. If this large amount of magnesium was added to the solution all at once, the reaction would be impossible to control. It was found to be sufficiently



vigorous to force the reaction mixture out the top of the condenser. Therefore the magnesium was added in 5-gram lots accompanied by gradual additions of the p-bromotoluene solution at such a rate that the reaction refluxed from the heat of reaction. If the reaction became too vigorous, it may be stopped by filling the pan about the reaction flask with cold water from the water jets. When all the halide and the magnesium were added, the solution was stirred until all refluxing had ceased, and was stirred for 20 minutes after that.

While the Grignard solution was being stirred, solid carbon dioxide (770 grams, 17.5 moles) was crushed by wrapping in a newspaper and striking with a flat object. The fine lumps were added to ether (800 ml.) in a 4-litre beaker. The Grignard reagent was then poured onto the carbon dioxide - ether slush. When the surface of the slush was covered with the addition complex, the addition was stopped until stirring with a heavy glass rod exposed the surface again. When the addition was completed, the cold mixture was stirred until it set to a glassy mass. Stirring was continued until the temperature reached 0°C.

To the ethereal solution was added a solution composed of ice (500 grams), hydrochloric acid (150 ml.) and water (150 ml.). The resulting mixture was stirred by hand until all the magnesium salt was hydrolysed. The acidic aqueous layer was discarded, and the ethereal layer was extracted three times with 20% sodium hydroxide (200 ml.). The basic solution was heated with charcoal and norite and filtered. Acidification produced the crude acid. After drying, the acid was recrystallized from the least amount of ethyl alcohol. Evaporation of the alcohol by 2/3 gave a second crop. The total yield of p-toluic acid was 106 grams or 65.5% of the p-bromotoluene. It melted at 179-181°C.

The ethereal solution was dried with anhydrone after washing with water to remove any base. The ether was distilled off and a residue was left which was insoluble in sodium bicarbonate. This was recrystallized from ether once to give enormous crystals melting at 116-120°C. and weighing 4.3 grams.

The acid was also prepared on a small scale similar to the preparation of m-toluic acid. The yield obtained was 36% of the p-bromotoluene used.

(b) The Preparation of o-Toluic Acid

o-Bromotoluene (24.5 grams, 1.43 moles) was dissolved in ether (600 ml.) and treated with magnesium (36 grams, 1.43 moles) and solid carbon dioxide (770 grams, 17.5 moles) in the manner described for the preparation of p-toluic acid. There was one difference in experimental technique. The blue-green Grignard complex was blown through a glass tubing circuit from the reaction flask onto the solid carbon dioxide - ether mixture using nitrogen gas. The method was found to introduce unnecessary difficulties and was abandoned. Purification of the crude acid was accomplished in the same manner that p-toluic acid was purified. Some of the acid was recrystallized from water to give very pure o-toluic acid melting at 103-104°C. The total yield obtained was 109 grams or a yield of 45% based on the amount of o-bromotoluene used.

o-Toluic acid was also prepared on a small scale similar to the m-toluic acid preparation. The yield was 41% of the o-bromotoluene.

(c) The Preparation of m-Toluic Acid

m-Bromotoluene (10 grams, 0.11 mole) was dissolved in ether (56 ml.) in a dry flask fitted with a reflux condenser topped by a calcium chloride tube. Magnesium (2.6 grams, 0.10 mole) was added and it was followed by a crystal of iodine. After refluxing for half an hour, the reaction began. The Grignard complex in the present case had an orangish colour. When the reaction was completed, the solution was refluxed for half an hour longer and allowed to cool. A small amount of white precipitate was observed to be present. The Grignard reagent was poured into a slush composed of solid carbon dioxide (80 grams, 1.82 moles) and ether (100 ml.). The solution was hydrolysed with hydrochloric acid (1:1) and purified in the manner described above. It was further purified by recrystallizing from water. 5.4 Grams of m-toluic acid was obtained melting at 111-113°C.

The Oxidative Preparation of the Toluic Acids

(a) The Preparation of o-Toluic Acid

Nitric acid (200 ml., s.g. 1.40) was diluted with water (800 ml.) and the solution added to o-xylene (200 ml., 182 grams, 1.5 moles) in a round bottomed flask. The mixture was heated at 145-155°C. for 55 hours on an oil bath. It was found that one 40 cm. condenser was not of sufficient cooling capacity to prevent the slow distillation of o-xylene from the solution. A second condenser was added, but not before a considerable amount of o-xylene had distilled off. After 55 hours, the organic layer settled to the bottom of the flask.

The hot reaction mixture was poured, with stirring, onto ice (500 grams). The resulting solid was filtered and suspended in water (1 litre). It was filtered and dissolved in 10% sodium hydroxide (500 ml.) and shaken with ether (125 ml.). The aqueous layer was added with vigorous stirring to hydrochloric acid (1:1) (238 ml.). It was filtered on a Buchner funnel and was washed and dried.

The crude acid was further purified by dissolving in ethyl alcohol (175 ml.). It was heated with charcoal and norite for one hour. The solution was filtered through a heated funnel and the filter paper washed with 50% alcohol (35 ml.). The combined solutions were diluted with water (480 ml.). After refrigeration, the precipitate was filtered. This material melted at 98-102°C. It weighed 38 grams and represented a yield of

18% based on the amount of o-xylene used.

(b) The Preparation of m-Toluic Acid

m-Xylene (23 grams, 0.21 mole) was mixed with concentrated nitric acid (72 ml., s.g. 1.40) and water (108 ml.). The mixture was heated on an oil bath, under reflux, for 50 hours at 130°C. The hot mixture was poured onto ice (100 grams). The resulting precipitate was refrigerated and filtered. It was dissolved in 10% sodium hydroxide (250 ml.), and zinc (6.45 grams, 0.099 mole) was added. The mixture was heated under reflux until the solution was clear. The unreacted zinc was filtered off and the resulting filtrate poured with stirring into 5 N hydrochloric acid (134 ml.). The precipitate was cooled and filtered. After being dried, the precipitate was refluxed for 6 hours with benzene (161 ml.). Removal of the benzene layer left impure m-toluic acid. No attempt was made to purify the acid any further. It weighed 1.3 grams (5.2% of the m-xylene used) and melted at 104-108°C.

(c) The Preparation of p-Toluic Acid

A dilute nitric acid solution composed of concentrated nitric acid (220 ml., s.g. 140) and water 814 ml.) was added carefully to p-xylene (86 grams, 0.81 mole). The mixture was heated under reflux for 55 hours at 130-135°C. The resulting solution was poured into a beaker and refrigerated. The precipitate was washed with water (200 ml.). It was dissolved in 10% sodium hydroxide (880 ml.) and zine (21 grams, 0.32 mole) was added and the mixture refluxed until it was clear. The solution was filtered from the unreacted zinc and poured into 5 N hydrochloric acid (500 ml.). The precipitate was filtered and washed well. After drying, the solid precipitate was extracted with toluene (630 ml.). On cooling, a brown material was deposited. Evaporation of the toluene left a brown mass identical in appearance with the first. The melting points of both precipitates extended from about 125°C. to 250°C. It was assumed that the complete reduction of the nitro compounds present had not been accomplished. The experiment was abandoned at this point for it was thought that the time required to finish the experiment was worth more than the results that would be obtained.

The Sandmeyer Preparation of p-Toluic Acid

(a) The Preparation of p-Tolunitrile

The procedure followed in this preparation was that given by Clarke and Read (4). Copper sulphate (292 grams, 2.08 moles) and sodium chloride (75.8 grams, 1.31 moles) were dissolved in water (936 ml.). While the solution was stirred, a second solution composed of sodium bisulphite (63 grams, 0.525 mole) and water (468 ml.) was quickly added to it. The resulting cuprous chloride was allowed to cool and was then washed by decantation. The cuprous chloride was suspended in water (468 ml.) and a solution composed of sodium cyanide (152 grams, 3.10 moles) in water (234 ml.) was added to it. The resulting cuprous cyanide was allowed to cool.

The p-toluene diazonium salt was prepared by dissolving p-toluidine (100 grams, 0.93 mole) in concentrated hydrochloric acid (234 ml., s.g. 1.14). Ice (936 grams) was added to bring the temperature to 0°C. To this solution was added a solution composed of sodium nitrite (75 grams, 1.09 moles) in water (186 ml.) over a period of fifteen minutes. The temperature was carefully maintained at 0-5°C. When the mixture showed a distinct and permanent test for the nitrite ion on starch-iodide paper, it was carefully neutralized with sodium carbonate.

The solution of cuprous cyanide was cooled to 0-5°C. and toluene (240 ml.) added to it. The cooled diazonium salt was added to the cuprous cyanide solution over a period of half an hour with vigorous stirring. The solution was kept cool for 30 minutes longer and then allowed to rise to room temperature over a period of 3 hours. The solution was stirred for 2 hours longer and the stirring was discontinued. The reaction mixture was heated to 50°C. and allowed to cool.

The upper oily layer was separated and steam distilled. The oily material so obtained was distilled. The toluene fraction was discarded and the fraction boiling from 215-220°C. was collected. This gave 63 grams of p-tolunitrile or 60.8% yield.

(b) <u>The Hydrolysis of p-Tolunitrile</u>

The p-tolunitrile was hydrolysed by the method of Cohen (6). The nitrile (63 grams, 0.538 mole) was added gradually to a solution of concentrated sulphuric acid (190 ml.) and water (126 ml.). The solution was refluxed until crystals of p-toluic acid appeared in the condenser. The acid crystallizes out on cooling the solution. It was separated by filtration and washed with water. It was dissolved in the least amount of sodium hydroxide and treated twice with charcoal and norite. Acidification produced p-toluic acid. This acid was recrystallized from the least amount of alcohol. The acid obtained weighed 56.5 grams and melted at 215-220°C. The yield of p-toluic acid from p-toluamine was 47%.

An Attempt to form the Grignard Reagent of 2-Chloro-5-methoxytoluene

The Methylation of 2-Chloro-5-hydroxy toluene

2-Chloro-5-hydroxy toluene was methylated by the method of Tambor (21) by dissolving it (26.8 grams 0.18 mole) in sodium hydroxide (10 grams, 0.25 mole). Methyl sulphate (26.5 ml. 0.28 mole) was added at such a rate that the temperature did not rise above 40°C. An oily layer separated which, after heating the solution with sodium hydroxide (2 grams), was extracted with ether (50 ml.). The ethereal layer was dried with anhydrone and distilled. The ether fraction was discarded and the fraction boiling at 214-215°C. was collected. The weight of the liquid collected was 18.9 grams or a 70% yield. Gibson (7) gave a boiling point of 213.5°C. for 2-chloro-5-methoxy toluene.

The Attempt to Prepare the Grignard Reagent of 2-Chloro-5-methoxy toluene

The 2-chloro-5-methoxy toluene (18.9 grams) was dried with anhydrone and distilled in a dry apparatus, the fraction boiling at 214-215°C. being collected. This material (10 grams, 0.064 mole) was dissolved in ether (40 ml.) and magnesium (1.7 grams, 0.071 mole) was added. A crystal of iodine was added and the solution heated under reflux for 5 hours. No reaction occurred. Adding methyl iodide and refluxing for 2 hours longer did not start the reaction. Crushing the magnesium was of no avail. The reaction did not start, or proceed slowly after the solution had stood overnight. There was no change in the appearance of the magnesium, nor did the solution lose the violet colour of the iodine. It was assumed that 2-chloro-8-methoxy toluene does not react with magnesium under the conditions described.

SUMMARY

1. Meta and para toluic acids have been prepared for the first time by the action of solid carbon dioxide on the Grignard reagent prepared from the bromotoluene.

2. Ortho and para toluic acids have been prepared for the first time on a large laboratory scale by the Grignard method.

3. A comparison of the Grignard method of preparing the toluic acids with the Sandmeyer and the oxidative methods has been made. The Grignard method was shown to be a slightly superior preparative method for the toluic acids.

4. It has been found impossible to prepare the Grignard reagent of 4-methoxy-2-chloro toluene by the methods attempted. A possible method of accomplishing this has been suggested.

5. The possible structure of a non-acidic material, obtained from the ethereal solution of the Grignard preparation of p-toluic acid, has been suggested.

RECOMMENDATIONS FOR FUTURE WORK

1. Further investigation of the non-acidic material isolated from the ethereal solution obtained from the Grignard preparation of p-toluic acid might be carried out.

2. Similar non-acidic materials, as mentioned above, may be found in the ethereal solutions from the Grignard preparations of ortho and meta toluic acids.

3. A method of preparing the Grignard reagent of 4-methoxy-2-chloro toluene mentioned on page 19 might be carried out.

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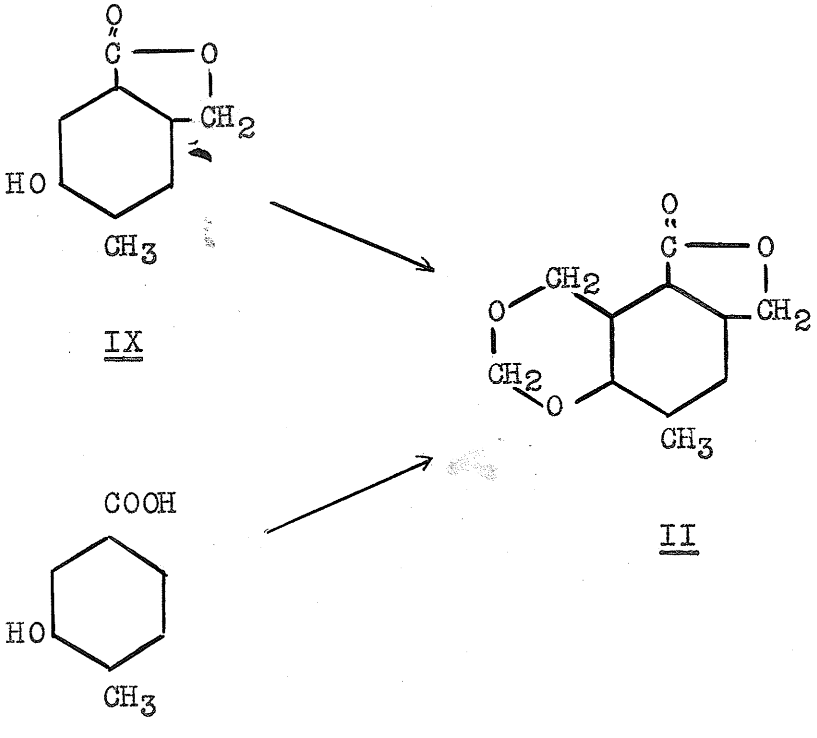
PART II

A STUDY OF THE OXIDATION PRODUCTS OF VARIOUS PHTHALIDES

INTRODUCTION

Anderson (1) condensed 5-hydroxy-4-methyl phthalide (IX) with 40% formaldehyde in the presence of concentrated hydrochloric acid and obtained a condensation product whose likely structure was (II) and which was identical with a compound obtained by earlier workers (20)(21) when 3-hydroxy-p-toluic acid (I) was condensed with formaldehyde.



IX

II

I

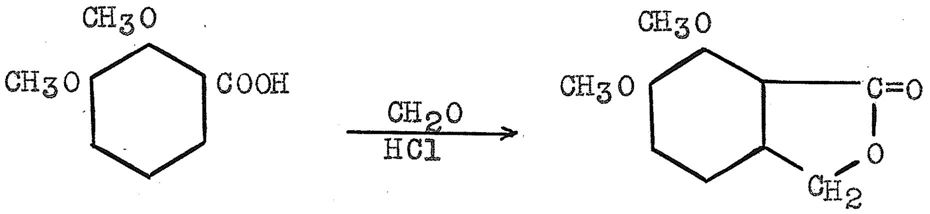
This investigation consists of a series of oxidative and degradative reactions carried out in an effort to elucidate more clearly the structure of this condensation product (II). Although, from the structural formula given above, it

wo

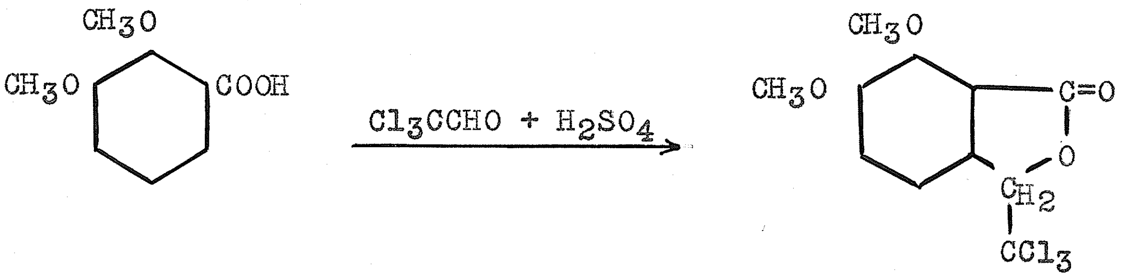
would appear more advantageous to attack the dioxane ring directly in order to show the existence of that component, it was found that the oxidation of the phthalide ring permitted an indirect attack on the dioxane ring and led eventually to a known degradation product. The facts derived in this manner, together with the knowledge gathered by earlier workers, give evidence that indicates formula (II) as representing the structure of the condensation product.

LITERATURE SURVEY

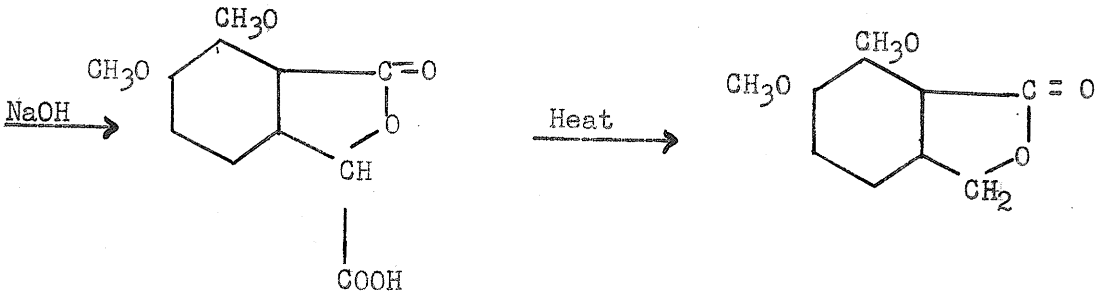
The condensation of formaldehyde in the presence of concentrated hydrochloric acid, with a phenolic acid or methoxy aromatic acid, was first performed by Edwards, Perkin and Stoyle (12). They condensed o-veratric acid with these reagents and obtained meconine.



This reaction promised at first to replace the earlier Fritsch reaction (13) that was used to prepare phthalides from aromatic acids. The Fritsch reaction consists of a condensation of an organic acid, for example o-veratric acid, with chloral in the presence of dilute sulphuric acid. The resulting chloro condensation product (a) is hydrolysed to a carboxylic acid (b), and this acid may be decarboxylated to the phthalide meconine (c).



(a)

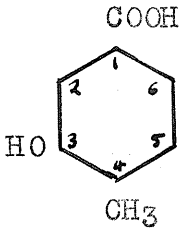


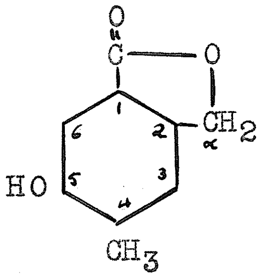
(b) (c)

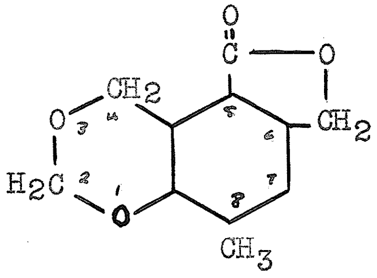
Unfortunately, the Edwards, Perkin and Stoyle Reaction did not always lead to the desired product. Investigators such as Charlesworth and Robinson (11), attempting to prepare phthalides, often found other compounds were produced. It therefore became of interest to examine the Edwards, Perkin and Stoyle Reaction in order to find out when phthalide formation would occur, and when some other reaction would occur.

It was found in the case of 3-hydroxy-p-toluic acid, that when condensed in the Edwards, Perkin and Stoyle Reaction (20)(21), a compound consisting of a phthalide ring and a 1,3-dioxane ring attached to the benzene nucleus was formed. A survey of the literature concerning the 1,3-benzodioxane ring was carried out. Since most of the literature concerning the phthalide ring has been surveyed by Anderson (1) and Winestock (20), only the relevant parts of this previously surveyed material will be considered in any detail.

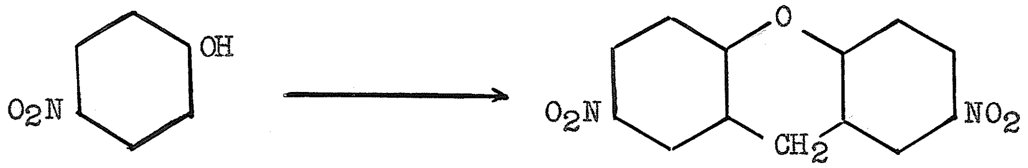
The numbering of the positions of the heterocyclic molecules will follow the conventions given below, based on Patterson's Ring Index.





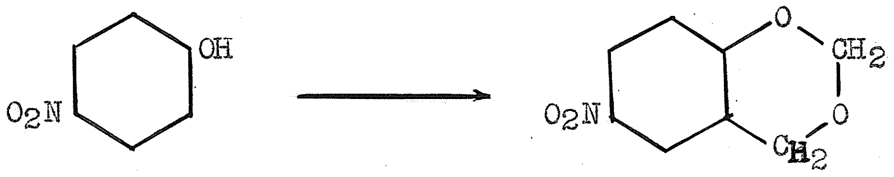


The first recorded mention of a 1,3-benzodioxane structure in the literature was made by Borsche and Berkhout (3). These authors were re-investigating a material obtained by Borsche (2) from the condensation of p-nitrophenol with formaldehyde in the presence of sulphuric acid. This product, originally prepared by Borsche, was claimed to have an xanthene structure (d).



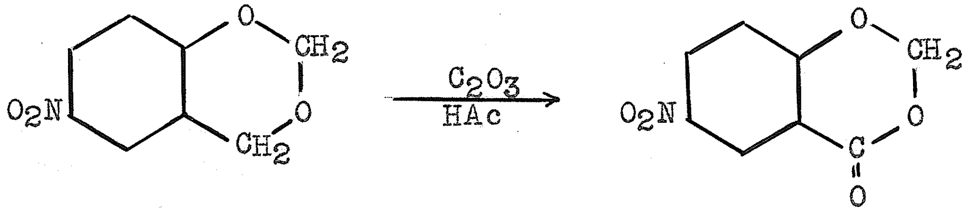
(d)

The paper by Borsche and Berkhout (3) continued the investigation of the condensation product, and these authors were able to show that the product formed in the condensation was a dioxane compound (e) and not the xanthene structure as originally claimed.

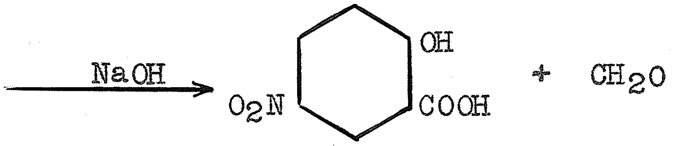


(e)

By oxidizing the condensation product obtained with chromium trioxide in glacial acetic acid a non-acidic material (f) was obtained. This product was then hydrolysed by means of sodium hydroxide with a loss of formaldehyde. Acidification of the solution gave 5-nitrosalicylic acid (g).



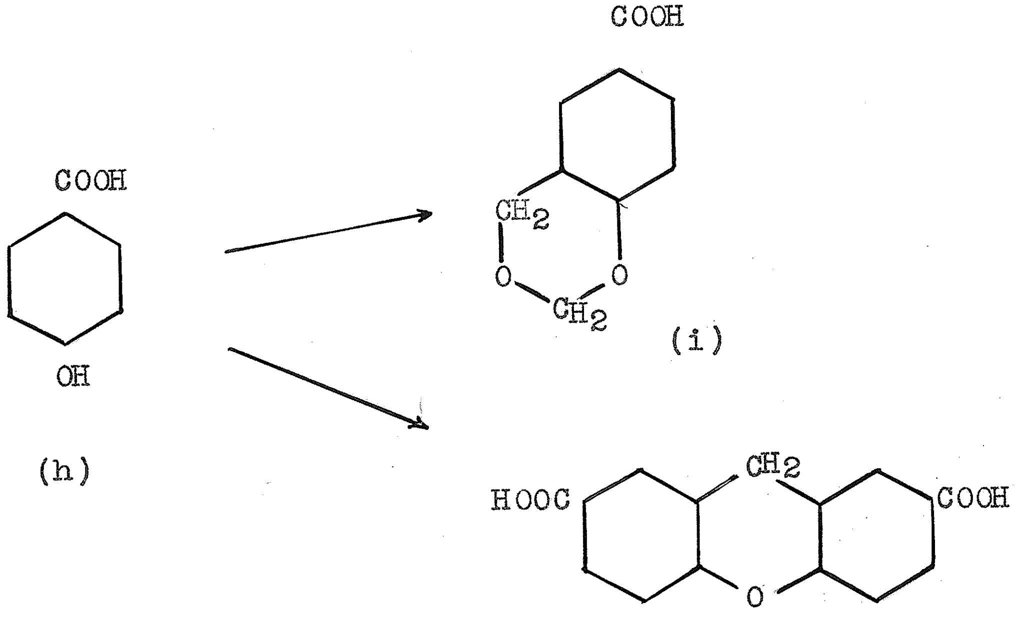
(f)



(g)

Borsche and Berkhout also condensed 5-nitrocresol, 6-nitrocresol, α nitronaphthol and nitroresorcinol as well as p-nitrophenol, and obtained a dioxane structure in each case. This dioxane compound was oxidized in all cases to an o-hydroxy carboxylic acid.

Mejuto and Calvet (14) were the next workers to give any new information concerning the dioxane ring. They were able to condense p-hydroxy benzoic acid (h) with formaldehyde in the presence of concentrated sulphuric acid. If the reaction was carried out at -15°C., 6-carboxylic acid -1,3-benzodioxane (i) was obtained. If the reaction was carried out at a higher temperature, an xanthene type of structure was isolated (j).

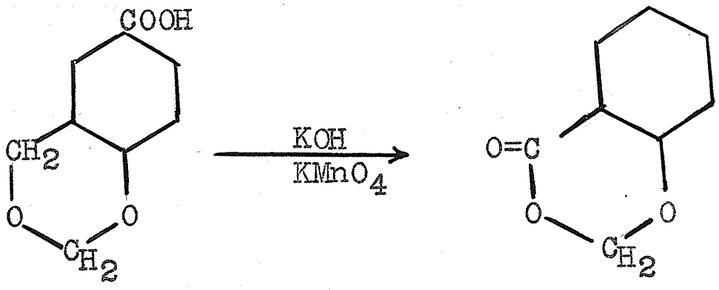


(h)

(i)

(j)

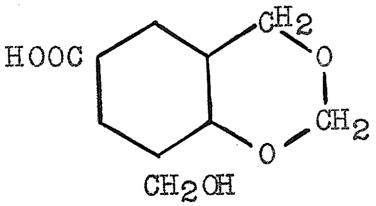
Treatment of 6-carboxylic acid-1,3-benzodioxane in potassium hydroxide solution with potassium permanganate resulted in the evolution of carbon dioxide and the formation of 4-keto-1,3-benzodioxane (k).



(i)

(k)

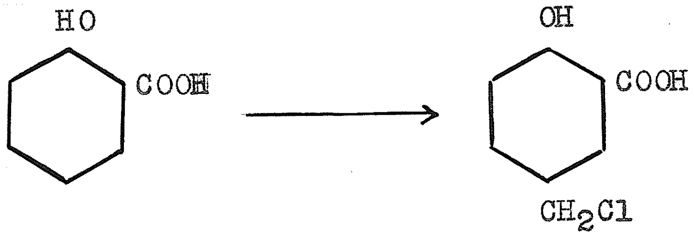
Another compound isolated by Mejuto and Calvet from the condensation mixture was 8-hydroxymethyl-6-carboxy-1,3-benzodioxan (1).



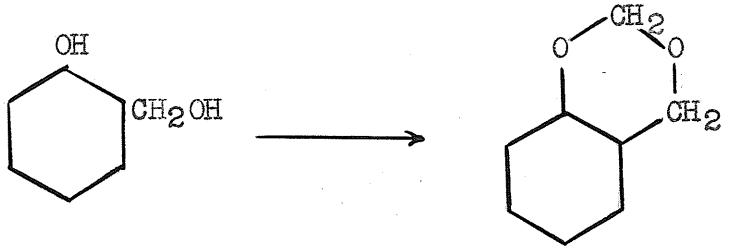
(1)

Many important advances in the study of 1,3-benzodioxane structures were accomplished by Buehler and his co-workers. Buehler, Brown, Holbert, Fulmer and Parker (5) condensed various phenols with formaldehyde in the presence of a variety of condensation reagents and obtained dioxane structures as well as diphenyl derivatives of the phenols.

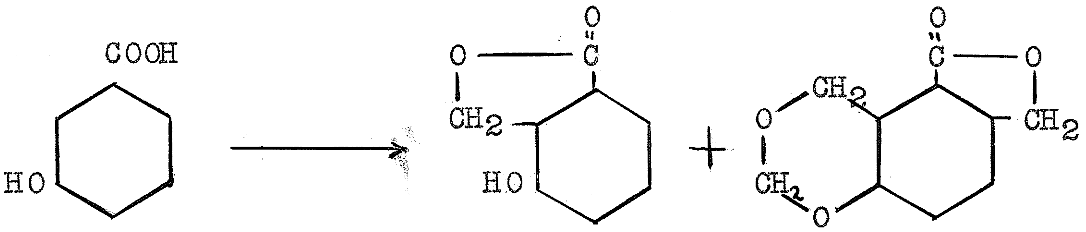
Buehler and his co-workers showed that phenols may be chloromethylated, and may also be condensed to form various benzodioxan structures. For example, condensing salicylic acid under suitable conditions gave 2-hydroxy-5-chloromethyl benzoic acid.



They also showed that o-hydroxybenzyl alcohols react readily with formaldehyde to form benzodioxane.

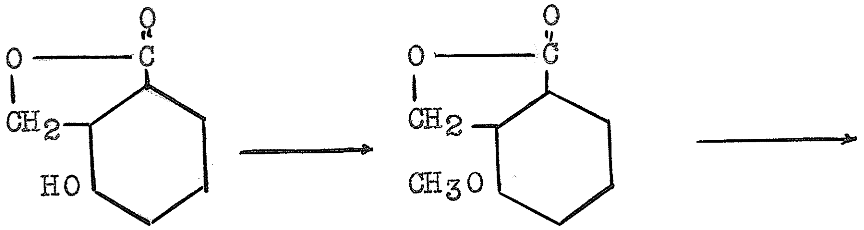


In 1944, Buehler, Powers and Michels (9) described the condensation of 3-hydroxy benzoic acid and hydrogen chloride. Two products were obtained, one melting at 254°C. and the other melting at 175°C.

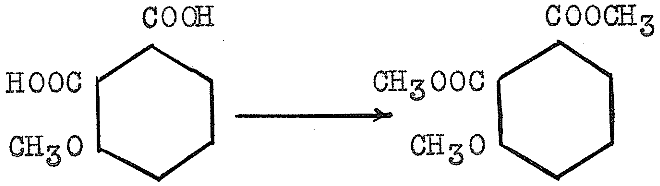


X XI XII

Buehler, Powers and Michels were able to determine the structure of the higher melting compound in the following manner. The hydroxy phthalide (XI) was methylated. This product (XIII) was oxidized with alkaline permanganate solution to give a methoxyphthalic acid (XIV). This acid was treated with diazomethane to give the known di-methyl ester of 3-methoxyphthalic acid (XV).

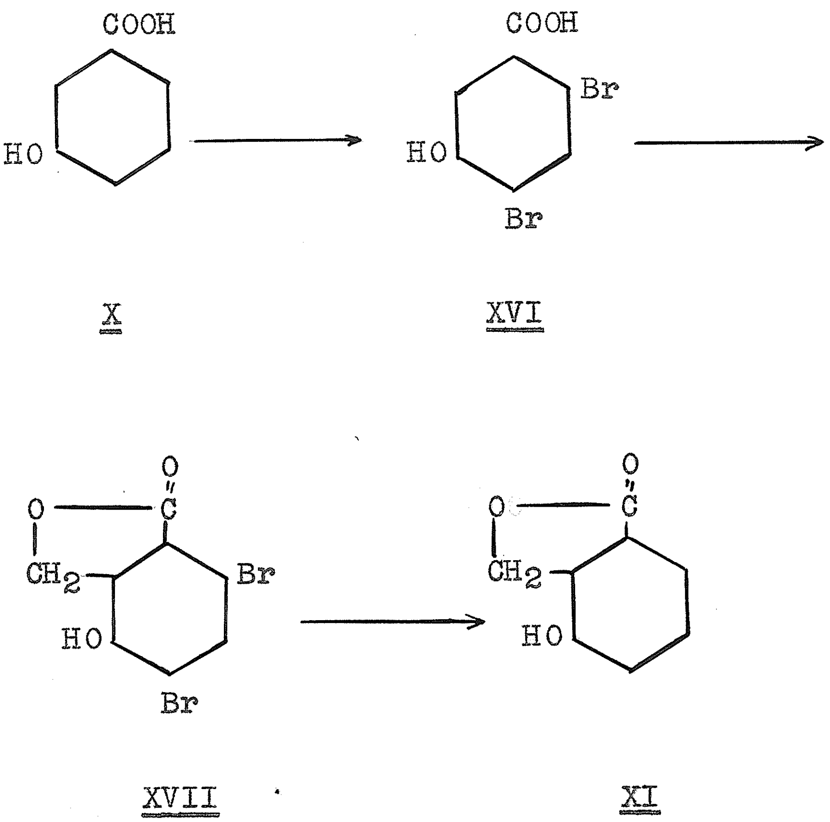


XI XIII

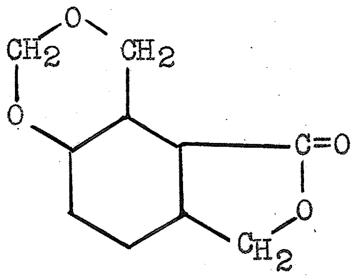


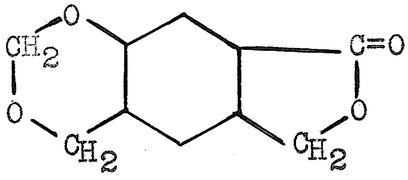
XIV XV

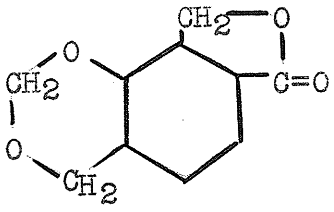
Additional proof of the structure of compound (XI) was presented in the following synthesis carried out by the above mentioned authors. M-hydroxy benzoic acid (X) was brominated to give a known di-bromo derivatives (XVI). When this acid was condensed with formaldehyde, only one possible phthalide could result. The dibromo phthalide (XVII) was debrominated using nickel and hydrogen to give 3-hydroxyphthalide (XI).



Buehler, Harris, Shacklett and Block (6) began the investigation concerning the other substance isolated from the reaction mixture. After a series of tests, they came to the conclusion that the molecule contained a phthalide ring and a dioxane ring. They showed that three isomers containing these groups could be derived from 3-hydroxybenzoic acid, (XII) (XIX) and (XX).

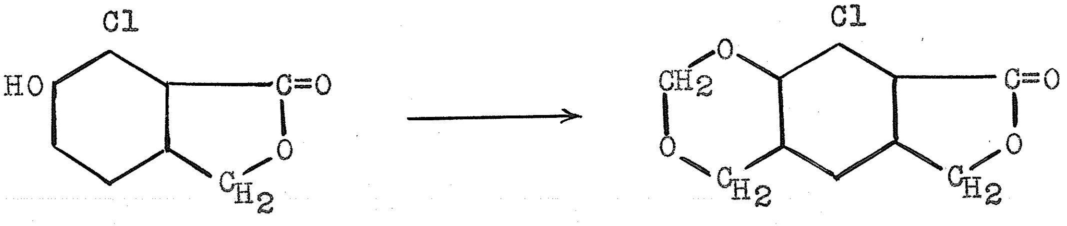

XII


XIX

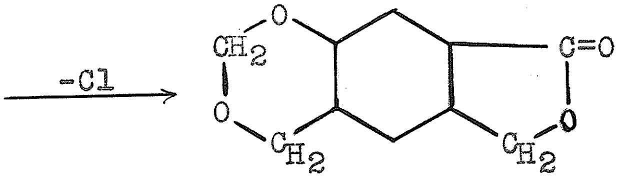


XX

To avoid confusion, it is perhaps best to state here that a mixture of compounds (XII) and (XIX) seem to have been isolated by Buehler. He has been able to show that molecule (XVIII) was produced in the condensation, but he has not given positive proof of the isolation of compound (XIX) from the reaction. The chief condensation product was shown to be (XII). It was shown not to be (XIX) by condensing 5-hydroxy-6-chlorophthalide (XXI) with paraformaldehyde and sulphuric acid. The resulting chlorophthalide (XXII) was dechlorinated and compound (XIX) was produced. This material (XIX) was not the same as the chief condensation product of m-hydroxy benzoic acid.

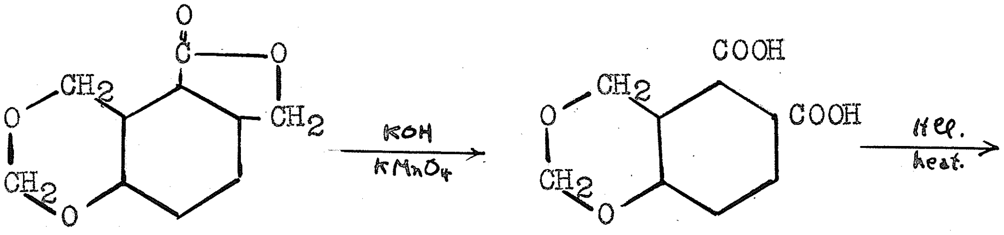


XXI XXII



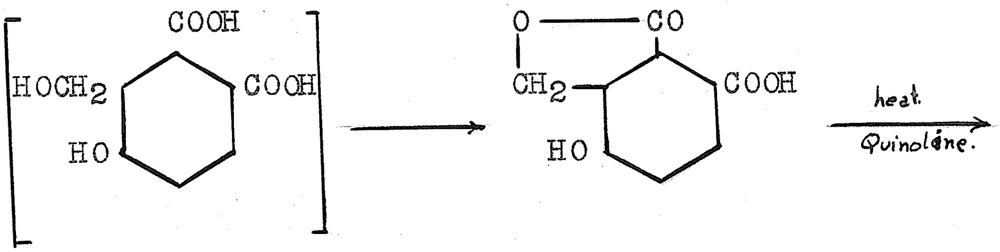
XIX

The dioxanylphthalide (XII) was dissolved in potassium hydroxide and oxidized with warm potassium permanganate. The resulting phthalic acid (XXIII) was converted into the monocarboxylic acid (XXV) with a loss of formaldehyde by refluxing with hydrochloric acid. The intermediate compound (XXIV) was postulated by Buehler and has not been isolated. The monocarboxylic acid (XXV) was decarboxylated by heating in quinoline solution and the known 3-hydroxyphthalide was produced (XI).



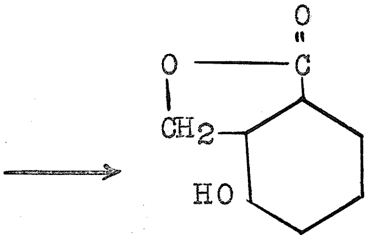
XII

XXIII



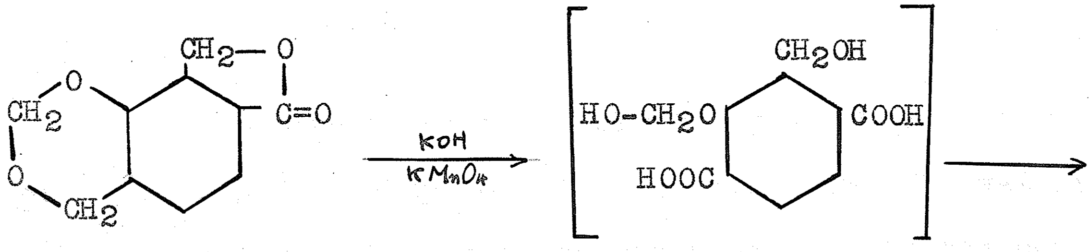
XXIV

XXV

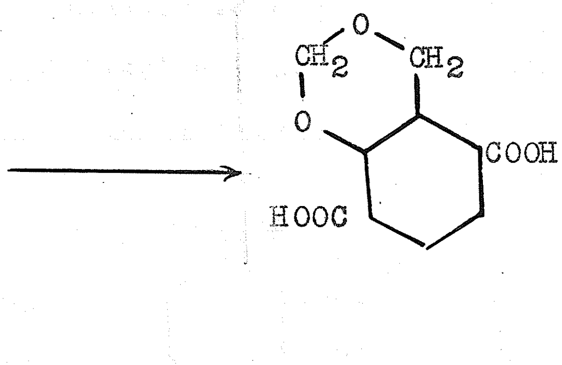


XI

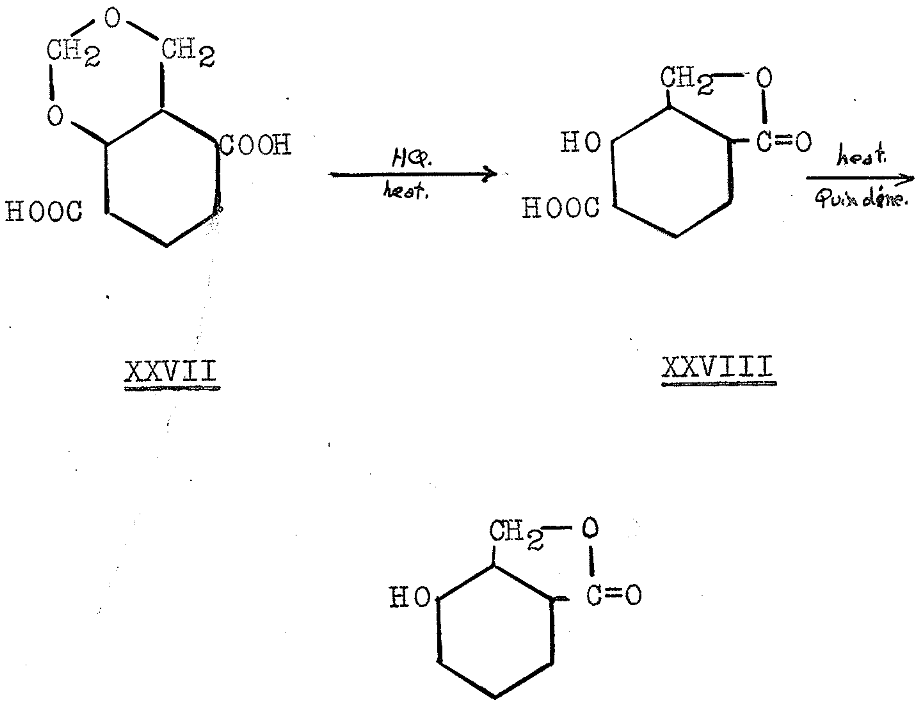
It is apparent that his analysis of the molecule limits the original structure from which (XI) was derived to either (XII) or (XX). If it had been proved that molecule (XXIII) was an orthodicarboxylic acid, only structure (XII) could represent the parent compound. As it is, the results may be interpreted in the following manner:



XX XXVI



XXVII

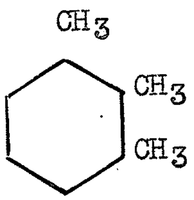


XXVII

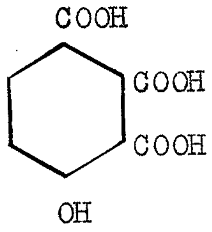
XXVIII

XI

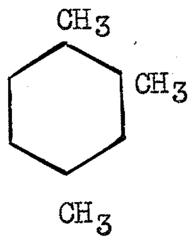
In order to prove conclusively which of the three dioxanyl phthalide compounds (XII), (XIX), or (XX) was produced in the larger amount when m-hydroxy-benzoic acid was condensed with formaldehyde, Buehler, Spees and Sanguinetti (8) prepared 4-hydroxybenzene,-1,2,3-tricarboxylic acid (XXIX) and 5-hydroxybenzene-1,2,4-tricarboxylic acid (XXX) from hemimellitene (XVIII) and pseudododocumene (XXXI).



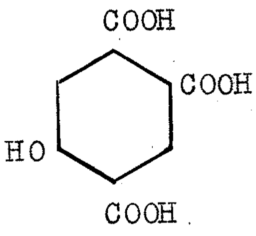
XVIII



XXIX



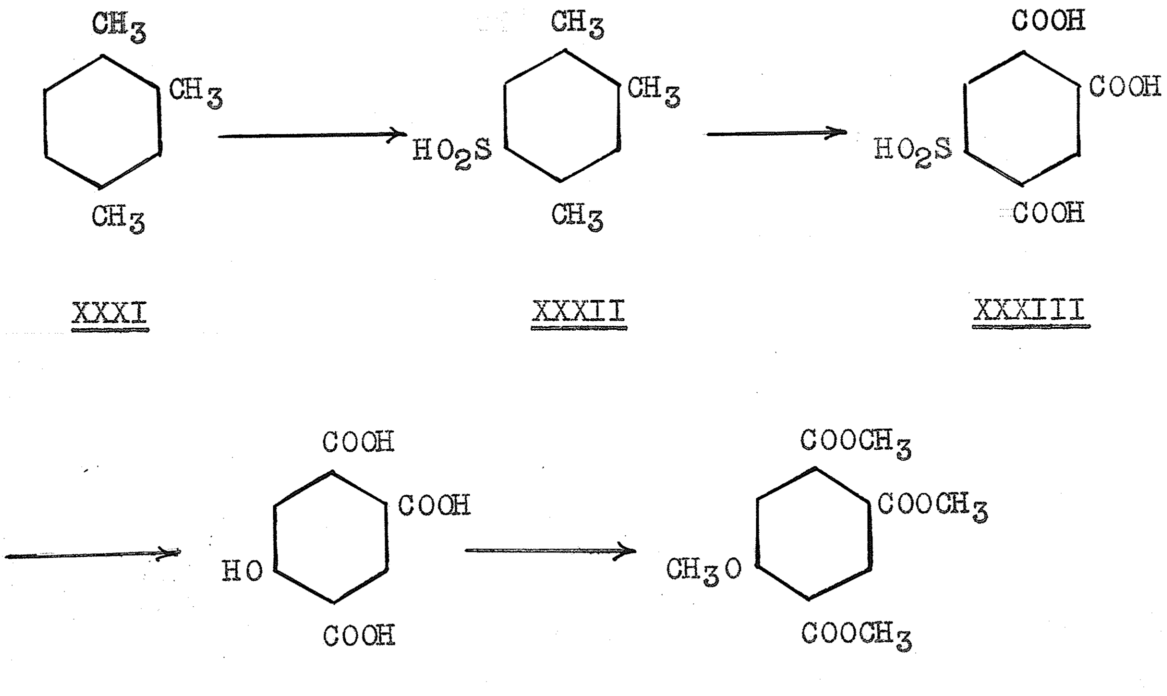
XXXI



XXX

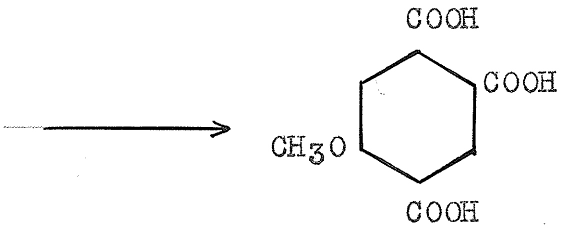
The methoxy methyl ester of these acids was also prepared since it was found that the acids shown above were difficult to purify and difficult to identify.

The synthesis of 5-hydroxybenzene-1,2,4-tricarboxylic acid (XXX) was accomplished by sulphonating the aromatic hydrocarbon pseudodocumene (XXXI) with sulphuric acid to give the sulphonic acid (XXXII). Oxidation of (XXXII) with alkali potassium permanganate gave the acid (XXXIII). This new acid was fused with potassium hydroxide to replace the sulphonic acid group with a hydroxyl group. The resulting hydroxy acid (XXX) was treated with diazo-methane to produce the methoxy trimethyl ester (XXXIV). Saponification of this ester gave 5-methoxybenzene-1,2,4-tricarboxylic acid (XXXV). Oxidation of hemimellitene (XVIII) to (XXIX) was accomplished in the same manner.



XXXI XXXII XXXIII

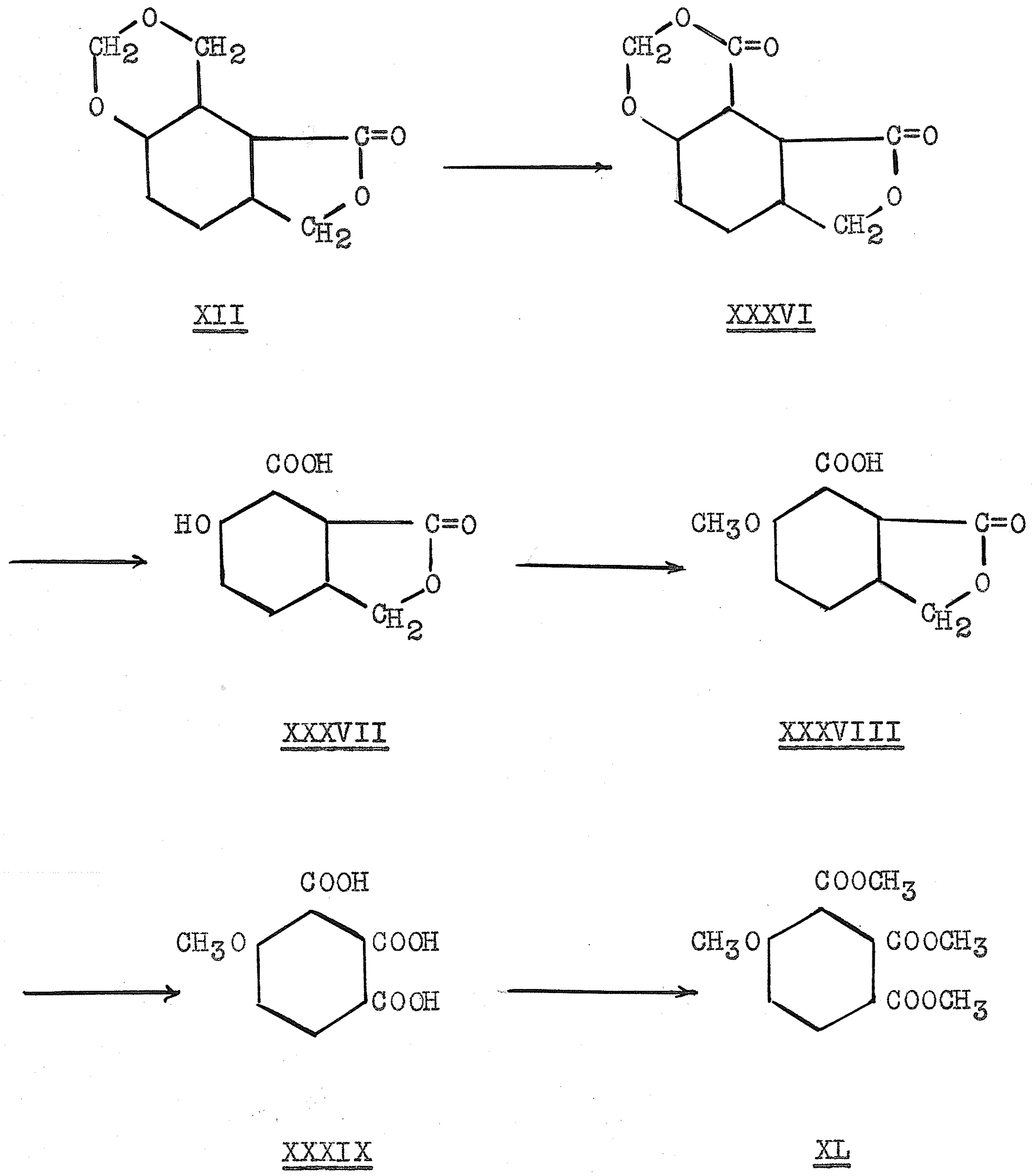
XXX XXXIV



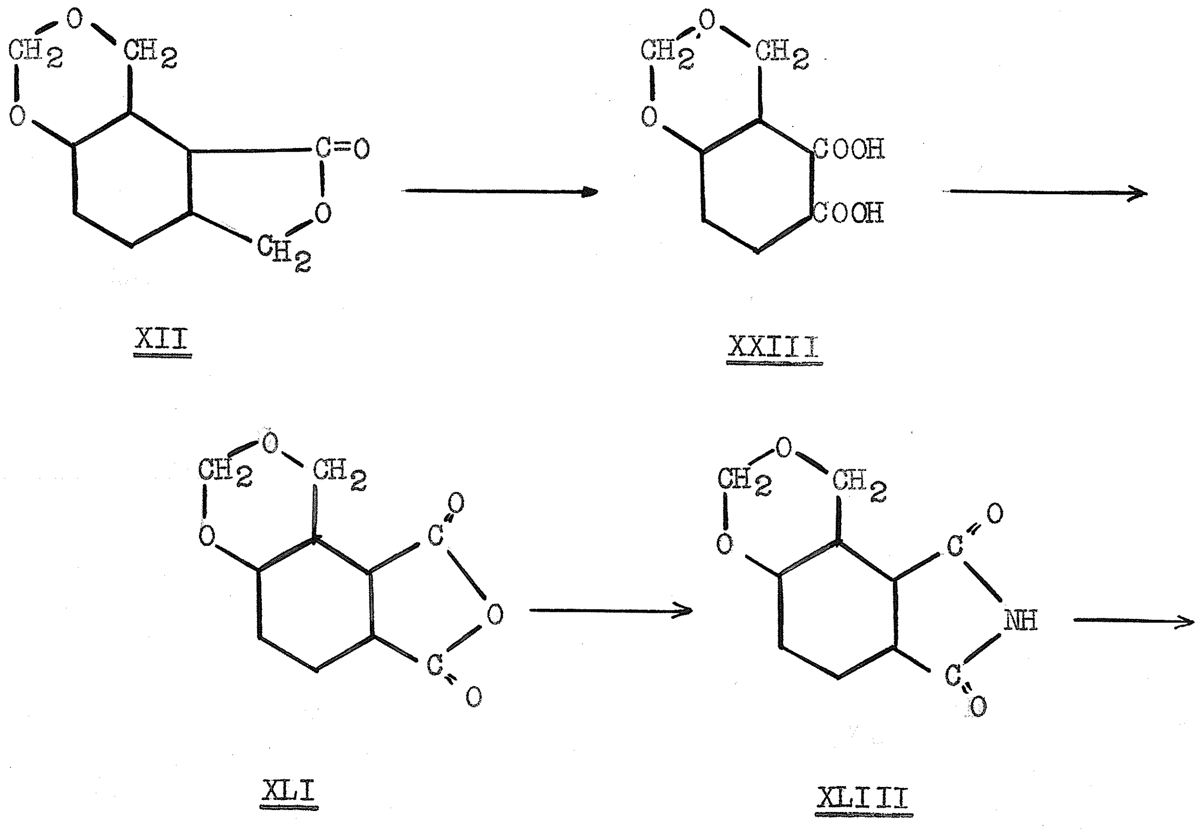
XXXV

The final stage of the identification of the condensation product was accomplished by Buehler, Slack, Shirley, Sanguinetti and Frey (7). These authors found it impossible to oxidize the dioxanyl phthalide under question directly to the tricarboxylic acid. It was necessary to accomplish this by stages. In order to give further evidence for the existence of the dioxane ring and the phthalide ring, these authors oxidized the molecule by two different routes, breaking one ring first in the first method, and breaking the other ring first in the second method. As a result of these degradative reactions, Buehler was able to show that the dioxanyl phthalide he had isolated had structure (XII).

In the first degradative method attempted the dioxane ring of the dioxamyl phthalide, (which was finally shown to be (XII)), was oxidized with chromium trioxide in glacial acetic acid to give the methylene ether - ester type of compound (XXXVI). Saponification of this product with sodium hydroxide gave the o-hydroxy carboxylic acid (XXXVII). This compound (XXXVII) was methylated to produce the methyl ether (XXXVIII). The methyl ether (XXXVIII) was then oxidized with alkali potassium permanganate to give the known methoxy-tricarboxylic acid (XXXIX). This acid was further identified by preparing the methyl ether (XL) by treating (XXXIX) with diazomethane. The isolation of this acid meant the dioxanyl-phthalide must have had structure (XII).

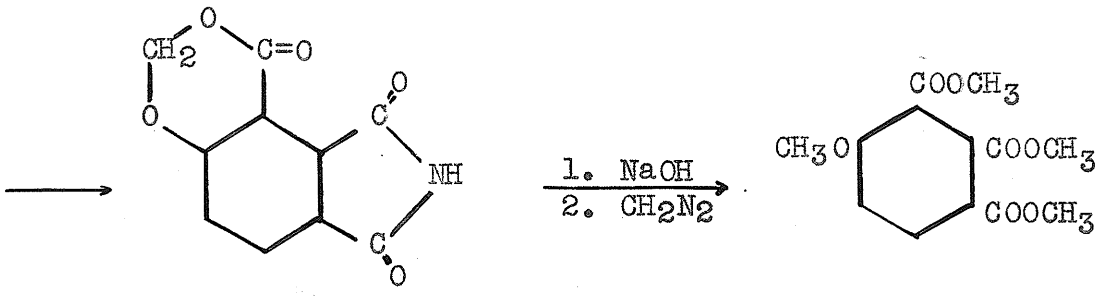


The other method of oxidation carried out by the above mentioned authors was to oxidize the dioxanyl phthalide (XII) with potassium permanganate. This reagent oxidized the phthalide ring and produced the dicarboxylic acid (XXIII). Treatment of (XXXIII) with acetic anhydride gave the anhydride (XLI) of the acid. Further treatment of (XLI) with ammonia gave the imide (XLII). The imide (XLII) was oxidized with chromium trioxide in the presence of glacial acetic acid. The nitrogenous methylene ether - ester compound (XLIII) was the result. This product was hydrolysed with sodium hydroxide to give 4-hydroxy benzene-1,2,3-tricarboxylic acid (XXIX). This acid was treated with diazomethane producing the easily identified methoxy methyl ester (XL).



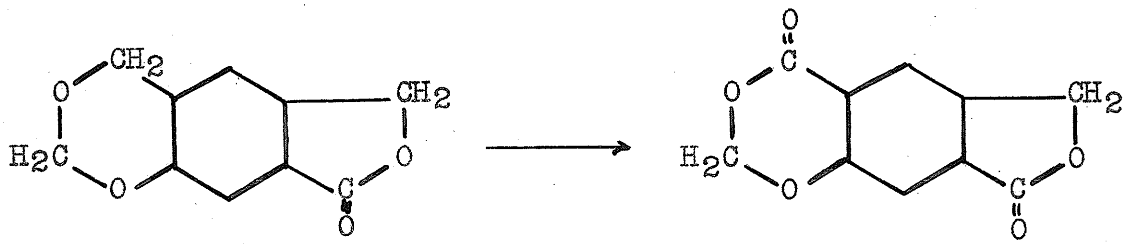
XII XXIII

XLI XLIII

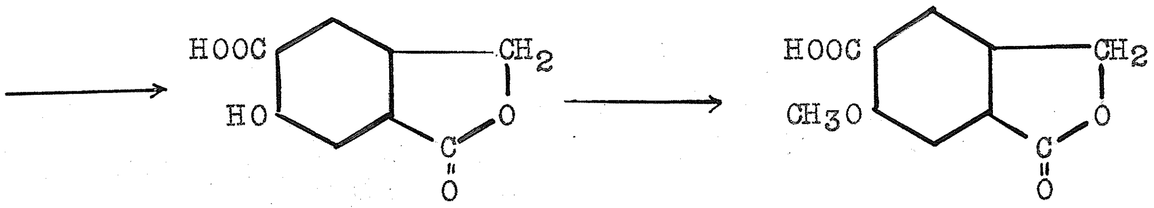


XLIII XL

Buehler and Block (4) describe the oxidation of the lactone of 6-hydroxymethyl-1,3-benzodioxane-7-carboxylic acid (XIX). They did not state the source of this material, but presumably it was prepared by that method mentioned on page 50. This dioxanyl phthalide (XIX) was oxidized with chromium trioxide to give a methylene ether - ester compound (XLIV). Hydrolysis produced an acidic material (XLV). This salicylic acid was methylated to demonstrate the presence of the phenolic group and the methyl ether (XLVI) was isolated.



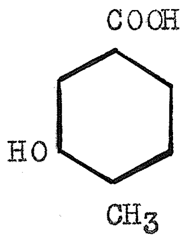
XIX XLIV



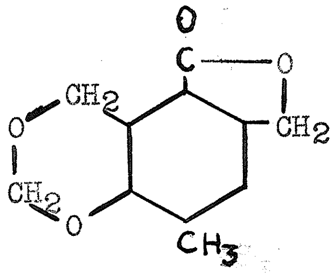
XLV XLVI

Most of the literature surveyed on the previous pages has dealt with one of the products obtained from the condensation of m-hydroxy benzoic acid with formaldehyde. The succeeding pages will deal with the condensation product of 3-hydroxy p-toluic acid with formaldehyde.

The condensation of 3-hydroxy p-toluic acid with formaldehyde was first carried out by Yan (21). He isolated a non-acidic condensation product melting at 165°C. This work was repeated by Winestock (20) and he was able to verify Yan's work. He also came to the conclusion that this condensation product, melting at 165°C., was a dioxanyl phthalide type of structure (II).



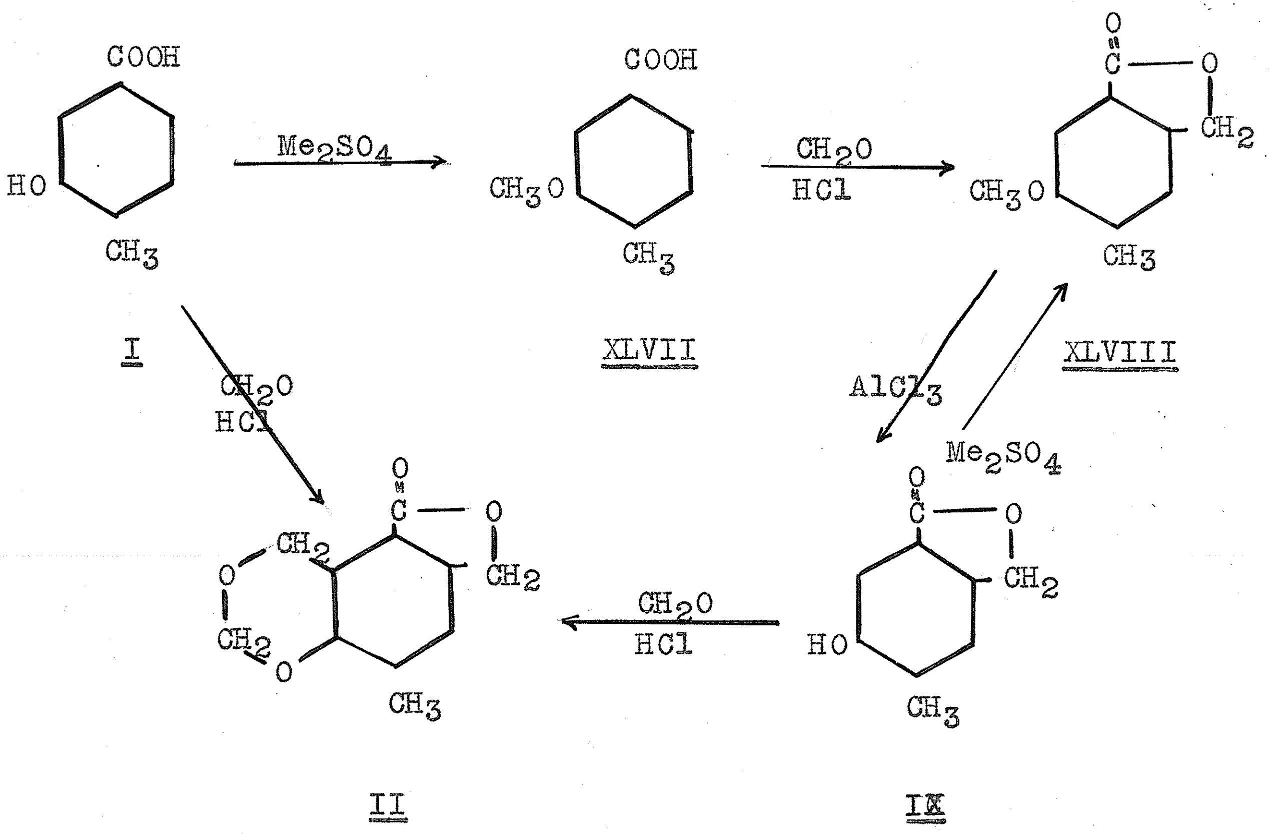
I



II

Winestock attempted to methylate the dioxanyl phthalide (II) with methyl iodide and silver oxide, but he was unsuccessful. This demonstrated quite clearly that the phenolic group that was present in 3-hydroxy-p-toluic acid was not present in the dioxanyl phthalide (II).

Anderson (1) was able to accomplish a synthesis of the dioxanyl phthalide (II) from 5-hydroxy-4-methyl phthalide. He did this by first methylating 3-hydroxy-p-toluic acid (I). The resulting 3-methoxy-p-toluic acid (XLVII) was condensed with formaldehyde in the presence of hydrochloric acid to give the known 5-methoxy-4-methyl phthalide (XLVIII). This phthalide may be demethylated by means of aluminum chloride in benzene to give 5-hydroxy-4-methyl phthalide (IX). The hydroxy phthalide (IX) may be methylated to give (XLVIII). The hydroxy phthalide (IX) was treated with formaldehyde and hydrochloric acid and the dioxanyl phthalide (II) was isolated from the condensation mixture. In addition, (II) was prepared by treating 3-hydroxy-p-toluic acid with formaldehyde.



DISCUSSION OF RESULTS

The Structure of the Condensation Product of 3-Hydroxy-p-Toluic Acid

After carrying out the series of degradative reactions as described below, on the condensation product of 3-hydroxy-p-toluic acid with formaldehyde, it was possible to isolate an acidic material that has been identified as 3-methoxy-4-methyl phthalic acid (VII).

For convenience a schematic diagram of the degradative work carried out has been placed at the rear of the Thesis and it may be folded over and referred to while reading this Section. Each compound has been given the Roman numeral that it keeps whenever it is referred to in Part II. A simple derivative of a compound has a Roman numeral corresponding to its parent substance, and a suffixed letter to differentiate it from other derivatives.

3-Hydroxy-p-toluic acid (I) was condensed with formaldehyde in the presence of concentrated hydrochloric acid to give a compound that was thought to be a dioxanyl phthalide derivative (II). This compound was dissolved in potassium hydroxide and oxidized, in the cold, with potassium permanganate. Since boiling the solution would cause decomposition of the desired product and lessen the yield, it was necessary to evaporate the solution slowly, at 80°C.; until its volume was small enough to permit isolation of an acidic material (III) by acidification. This material (III) melted with the evolution of a gas at 200°C. The gas was positively identified as water by sealing a small amount of the acid in a melting point tube. Above the acid (III), resting on cotton, was anhydrous copper sulphate. Melting the organic material resulted in the condensation of a liquid about the anhydrous copper sulphate, and after standing for an hour, the copper sulphate turned blue. The acidic material was also identified as an ortho dicarboxylic acid by the neutralization equivalent, and by the formation of the anhydride (IIIa).

If the acid (III) was refluxed with strong hydrochloric acid, formaldehyde evolved, and the acid converted into a monocarboxylic acid (IV). A free hydroxyl group was formed that was not present before, as compounds (IVa) and (IVb) indicate. The monocarboxylic acid acid (IV) melted at 269-271°C. with decomposition.

The monocarboxylic acid was dissolved in quinolene and decarboxylated by heating the solution. It was found that the presence of a very small amount of copper chromite hastened the decomposition, but did not lower the temperature at which the decomposition occurred. The resulting material (V) was difficult to purify. It was found to be non-acidic in character and behaved in a manner typical of phthalides. It also had a free hydroxyl group and it melted at 190-191°C.

Compound (V) was dissolved in potassium hydroxide and was methylated with methyl sulphate. It is recommended that diazomethane be employed as a methylating agent. The methylation was not brought to completion, but it was found possible to isolate a methylated substance (VI) by fractional crystallization. The pure compound (VI) melted at 118.5-119.5°C.

A somewhat impure sample of compound (VI) melting at 117-119°C. was dissolved in potassium hydroxide and oxidized with potassium permanganate. It was assumed that a small amount of hydroxy phthalide would not affect the oxidation, for it was found that phenolic compounds on oxidation tended to produce tars which were easily separated. The crude phthalic acid (VII) was found to be contaminated with such a material. Simonsen and Rau (18), in their preparation of the acid, did not give a method of purification, but they did state that the acid was insoluble in chloroform. It was found that the acid could be recrystallized very well from water. In an impure state, it tended to form supersaturated solutions but scratching assisted precipitation. It was finally recrystallized from an acetone-chloroform mixture. Combustion results agreed with the empirical formula $C_{10}H_{10}O_5$. Its melting point of 172-173°C. (uncorrected) or 175-176°C. (corrected) agreed very well with the literature value of 175°C.

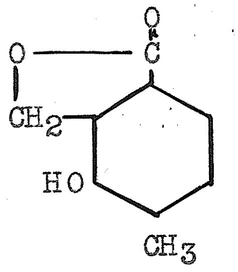
A small amount of compound (VII) was placed overnight in a sulphuric acid desiccator to dry before analysis. The material originally melted at 170-173°C. In the morning, the sample had changed in appearance and melted at 143-160°C. It was assumed that partial anhydride formation had occurred. This material (VIIa) was heated in an oil bath until all bubbling had ceased and was then recrystallized from toluene. The first fraction melted at 133-134°C. The anhydride prepared by Simonsen and Rau melted at 135°C. The acid (VII) was therefore assumed to be the same as 3-methoxy-4-methyl phthalic acid prepared by Simonsen and Rau.

The structure of the dioxanyl phthalide (II) may be derived using the information obtained by Anderson (1), Winestock (20) and the clues supplied by this investigation.

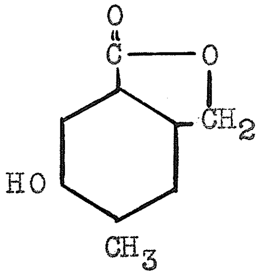
The phthalic acid (VII) was derived from a phthalide (VI) by oxidation. This structure was indicated because (VI) was an acid weaker than carbonic acid and it was oxidized to give a dicarboxylic acid. Since the phthalide was obtained indirectly from 3-hydroxy-p-toluic acid, and since the acid carbon contributed by (I) was not lost in the decarboxylation, the only possible structure of the methoxy phthalide must be VI.

The methoxy phthalide (VI) was derived by methylation from a hydroxy phthalide. Therefore the structure of the hydroxy phthalide must be V and V is a degradation product of the condensation product (II) of 3-hydroxy-p-toluic acid (I).

Anderson was able to show that the condensation product referred to above, could also be obtained from the condensation of 5-hydroxy-4-methyl phthalide (IX) with formaldehyde. Therefore the condensation product (II) must incorporate features of the two isomeric hydroxy phthalides, (V) and (IX).

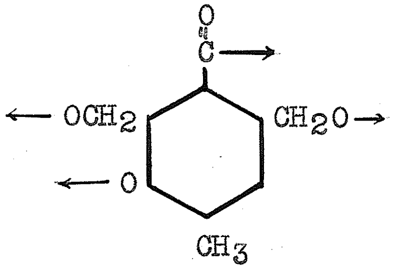


V



IX

A partially complete molecule containing the arrangement of atoms suggested by the two hydroxy phthalides is structure (L).



L

This structure (L) has unsatisfied bonds indicated by the arrows. The phenolic group, present in 3-hydroxy-p-toluic acid, was shown by Winestock (20) to be absent after an unsuccessful attempt was made to methylate it. For this reason the hydrogen was left off the unfinished structure (L).

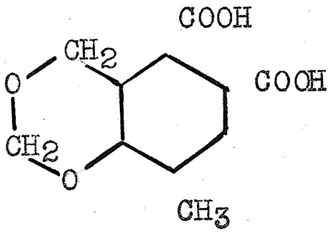
If this partially complete structure (L) is to be arranged into the structure of the condensation product thought to be (II) it must have one carbon and two hydrogens added to it. This fact was determined by comparing the empirical formula of (II) found from the combustion results $C_{11}H_{10}O_4$ with the empirical formula of structure (L) $C_{10}H_8O_4$. In addition there must not be an active phenolic group present. One other fact that was derived from the information obtained from the degradative work was that the phthalide ring must be located on the right hand side of the partially completed molecule (L) as it was drawn on page 64.

The latter requirement was necessitated by the fact that oxidation of the condensation product thought to have structure (II) with alkali potassium permanganate gave an ortho dicarboxylic acid. This acid was degraded through a number of steps to a phthalide after the loss of one of these acid groups. Since the structure of the phthalide was known, the position of its acid carbon was known, and the lost acid carbon must have been ortho to it. Therefore the lost acid carbon must have been situated at position 2 of the partially complete structure (L). The ortho dicarboxylic acid was obtained by oxidation of a phthalide ring, therefore the ring must have had the position predicted above.

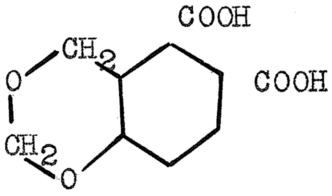
Since the right hand side of the molecule (L) was no longer available for the possible addition of a CH_2 group, the left hand side had to be used. There was only one way in which a CH_2 group could be added to the molecule and neutralize the active phenolic group and that way was to form a 1,3-dioxane ring. Structure (II) was the only one fulfilling all the requirements. It was also the only structure that could explain the results of the degradative work.

The evidence given for the existence of the dioxane ring was indirect and should be verified by experimental evidence. The beginning of such experimental work was started and has been discussed in the section dealing with the chromic oxide oxidation. It was possible to show in a qualitative manner the existence of the 1,3-dioxane ring. Saponification of the chromium trioxide product resulted in the evolution of formaldehyde and the formation of an acid, as structure (VIII) demands.

The rearrangement of a benzodioxane dicarboxylic acid to a monocarboxylic acid with the loss of formaldehyde and the formation of a phthalide ring was discovered by Buehler, Harris, Shacklett, and Block. The only compounds known to undergo "Buehler's Rearrangement" are compounds (II) and (XII). These compounds have identical arrangements of their functional groups and differ by a methyl group only.



II



XII

It is quite possible that benzodioxane dicarboxylic acids will be discovered having a different arrangement of atoms to those given above. Radych * prepared a dioxanylphthalide by

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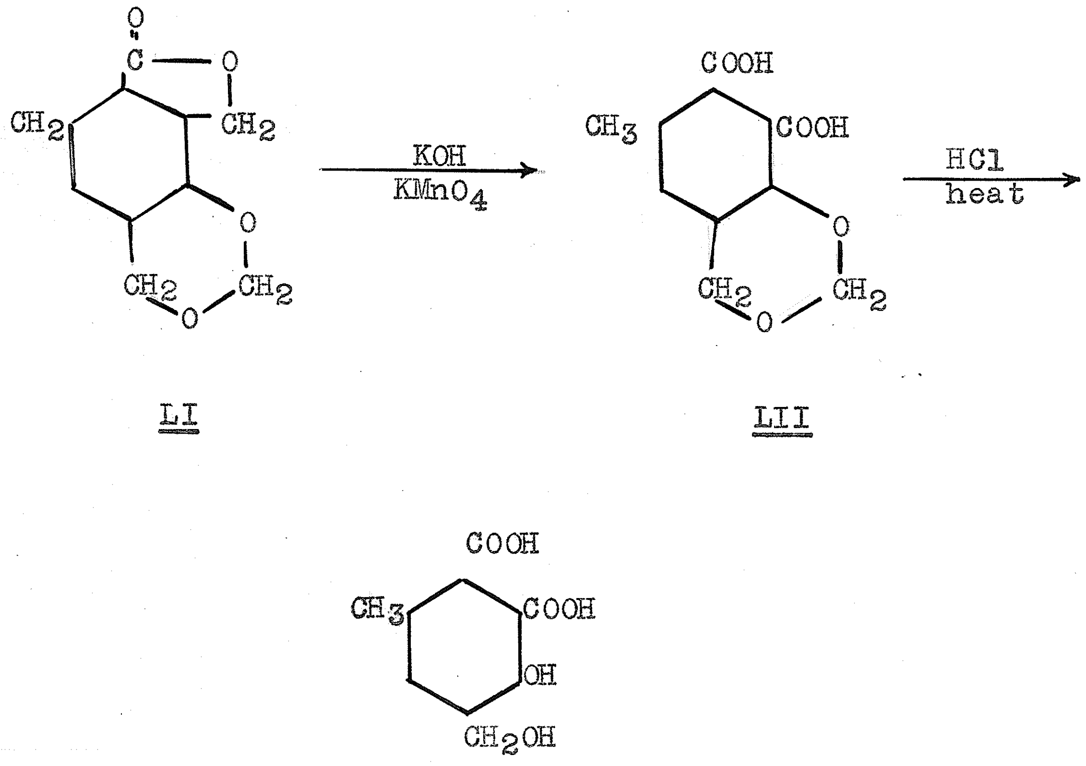
* M.Sc. Student, University of Manitoba, private communication

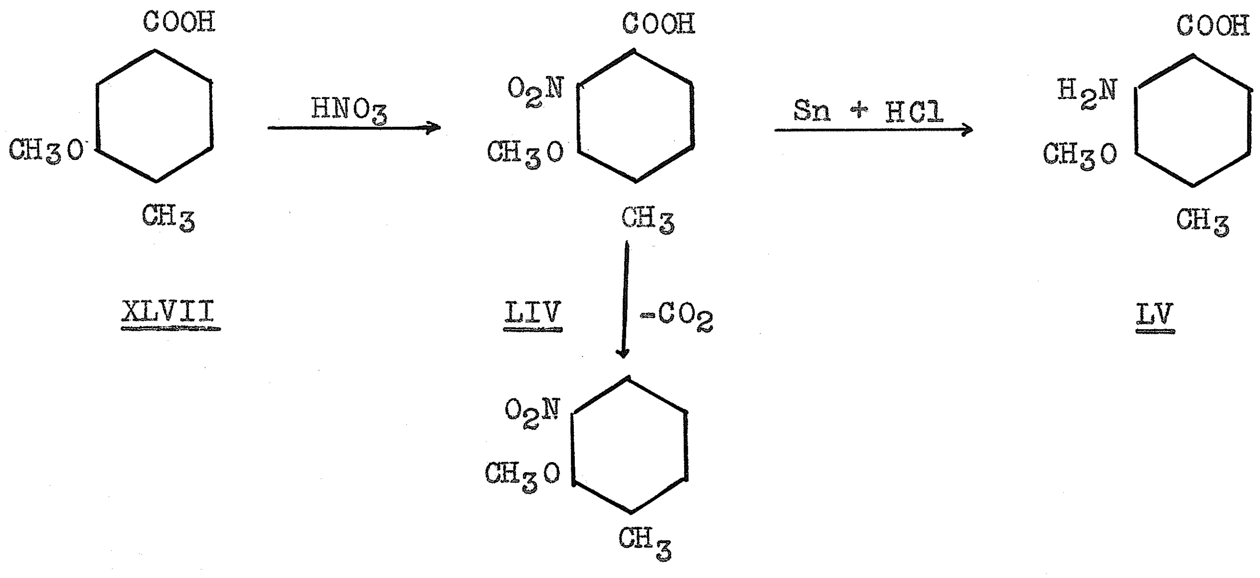
a method similar to that employed by Anderson (1). It was thought to have the structure (LI). Oxidation of this dioxanyl phthalide (LI) in basic potassium permanganate would be expected to attack the phthalide ring and produce the dicarboxylic acid (LII). It would not be expected that this acid could be rearranged to a monocarboxylic acid, because the arrangement of the functional groups is not such as to permit the formation of a phthalide ring. The two acid groups might weaken the dioxane ring sufficiently to permit hydrolysis of that component.



LI

LII

It is of importance to this Thesis that the method by which Simonsen and Rau (18) were able to prepare 4-methyl-3-methoxy phthalic acid (VII) be considered. The synthesis of this acid (VII) was accomplished by nitrating 3-methoxy-p-toluic acid. The position of the nitro group of the acid (LIV) was determined by decarboxylating the acid. The known compound 3-nitro-2-methoxy toluene was obtained. The nitro acid (LIV) was reduced to give 4-methyl-2-amino-3-methoxy benzoic acid (LV). This acid was diazotized and treated, in a Sandmeyer reaction, with cuprous cyanide. The resulting nitrile acid (LVI) was hydrolysed with sulphuric acid, and a mixture of 4-methyl-3-methoxy phthalic acid (VII) and its anhydride (VIIa) was obtained.

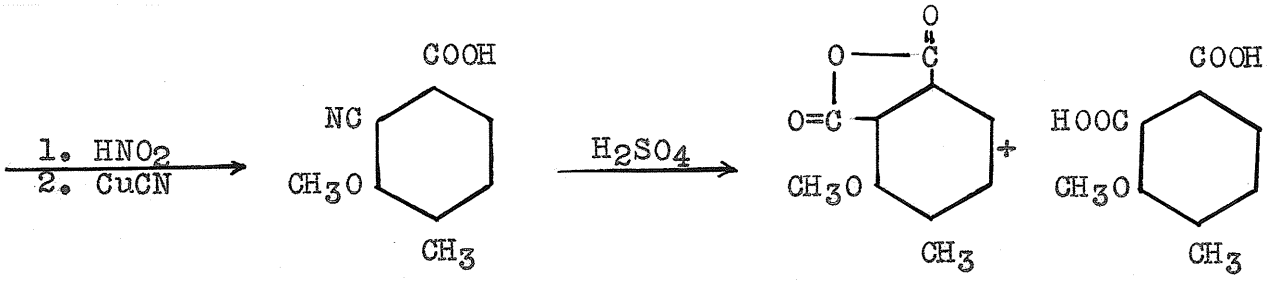


XLVII

LIV

LV

LVII



LVI

VIIa

VII

The Chromium Trioxide Oxidation

It has been shown by several workers (2)(4) and (7) that it is possible to oxidize a 1,3-benzodioxane ring with chromium trioxide in glacial acetic acid. A non acidic methylene ether - ester type of molecule would be obtained.

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

Oxidation of the dioxanyl phthalide was first attempted by Anderson * . The oxidation was repeated with some modifications and a compound (VIII) melting at 248-250°C. was isolated. This compound had the characteristics of the methylene ether - ester compound expected from this oxidation. It was hoped to be able to hydrolyse the methylene ether - ester (VIII) with sodium hydroxide to the o-hydroxycarboxylic acid (LVIII). This was not accomplished for reasons that will be mentioned later. This series of reactions would demonstrate the existence of the 1,3-dioxane ring, and decarboxylation of molecule (LVIII) would give a hydroxy phthalide (IX) from which the position the dioxane ring had may be deduced.

The oxidation product (VIII) has been referred to as a methylene ether - ester. Examination of the molecule will show

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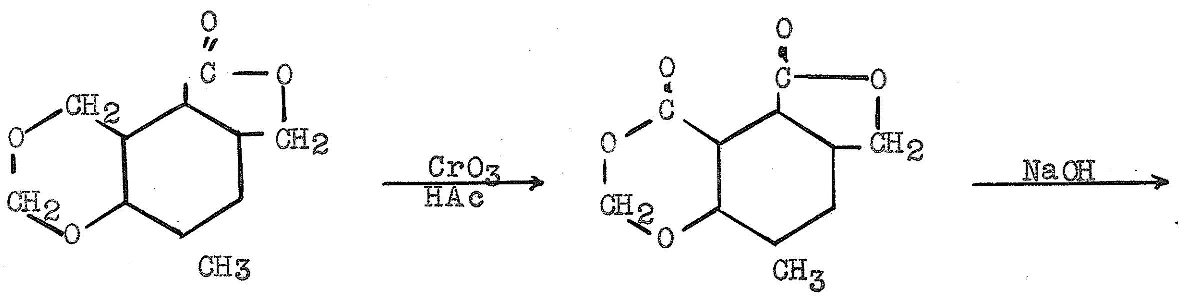
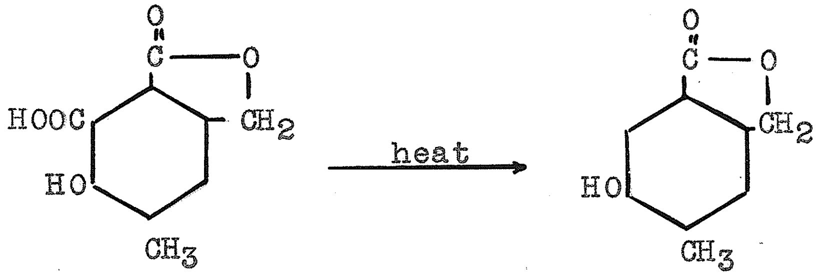
* Private communication



II VIII



LVIII IX

the reason for this. The term was first applied to this type of molecule by Borsche and Berkhout (3). Their method of nomenclature was abandoned, but the shortened form of it was used here for convenience only. The name of the compound by modern conventions of nomenclature is the lactone of 6-hydroxymethyl-8-methyl-1,3-benzodioxan-4-one-5-carboxylic acid.

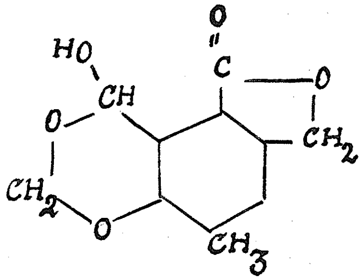
It was found that the dioxanyl phthalide (II) was much more reactive than the dioxanyl phthalide (XII) oxidized by Buehler. This was noticeable in both the potassium permanganate and the chromium trioxide oxidations where the temperature of the oxidations had to be kept below the temperatures reported by Buehler.

It was found that only a 10% by weight yield of the methylene ether - ester could be obtained. The carbon and hydrogen determinations of this material agreed with the empirical formula $C_{11}H_8O_5$. It was felt for some time that the methylene ether - ester (VIII) might be impure. It would be very difficult to detect the presence of a foreign material having an empirical formula $C_{11}H_{10}O_5$. However, since the same melting point may be arrived at using different purification procedures, the chances are that the compound was pure. The final test would be to hydrolyse the pure material (VIII) to the acid (LVIII). This was not attempted because of a shortage of time. More of the methylene ether - ester, than was already on hand, would have to be prepared if the investigation were to be pursued. This would be the case if the compound thought to be (VIII) proved to be a mixture. Therefore the pure compound (VIII) that was prepared has been left for whoever continues the investigation.

A small amount of impure methylene ether - ester (VIII) melting at 235-243°C. was hydrolysed with sodium hydroxide. Formaldehyde was evolved and a material melting from 190-238°C. was obtained. This material contained an acidic component which could not be isolated and a non-acidic component which was isolated and melted at 188.5 to 192°C. Since the melting point of the unreacted dioxanyl phthalide was 165°C., it would appear that a second oxidation product was formed in the chromic acid oxidation. The hydrolysis did show in a qualitative manner the presence of the 1,3-benzodioxane structure.

The existence of the second oxidation product was verified when, by varying the purification procedure of the first oxidation product, a second non-acidic material was obtained melting in the range 184-189°C. It was also possible to isolate a material melting at 185-195°C. from the air oxidation of the dioxanyl phthalide. It was thought the materials melting at 184-189°C., 188-192°C., and 185-195°C. were impure samples of the same oxidation product.

A possible structure of this new oxidation product might be (LXI). This structure (LXI) could represent an intermediate oxidation product in the formation of the methylene ether-ester (VIII). An alcohol of this type, tetralol, was obtained during the oxidation of tetralin to tetralone (17) and would tend to support this hypothesis.



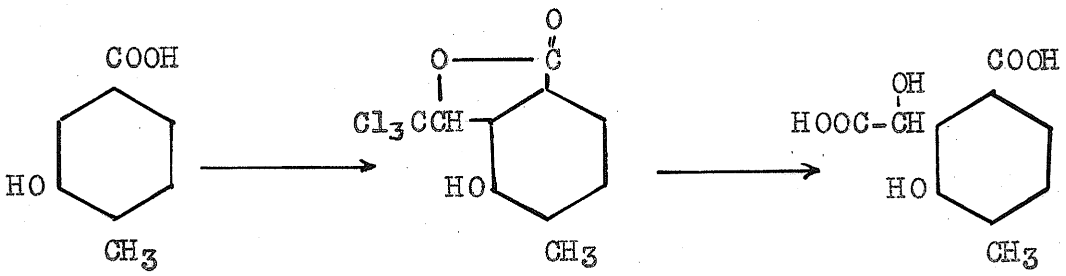
LXI

Other Condensations

Meldrum and Kapadia (16) carried out a large amount of work on the products obtained from the action of chloral on

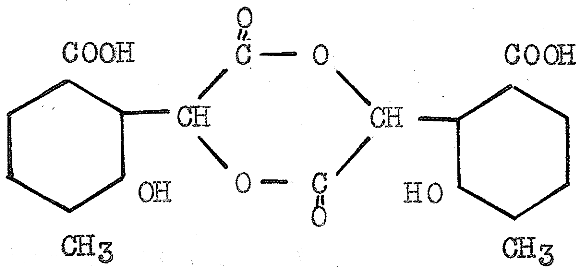
3-hydroxy-p-toluic acid. One of the products obtained was of interest since it was thought it might be used to prepare one of the degradation products obtained in this investigation.

These workers condensed chloral with 3-hydroxy-p-toluic acid. They were able to isolate a chlorine containing compound identified as 3-hydroxy-4-methyl-α-trichloromethyl phthalide (16). On hydrolysis, this chloro compound was changed to 2-hydroxy-3-methyl-6-carboxy mandelic acid.



I   X   XI

It was hoped to be able to carry out a pyrolysis reaction on the mandelic acid (XI) to produce the hydroxyphthalide (V). However, the mandelic acid, melting at 115°C. could not be isolated. A red oil of no definite melting point was isolated. If the hydrolysis conditions were changed, an acidic material melting at 263-265°C. was isolated. A possible structure of this acidic material is (X).



X

EXPERIMENTAL

Determination of the Structure of the Condensation Product of 3-Hydroxy-p-toluic Acid

(a) Sulphonation of p-Toluic Acid

p-Toluic acid (100 grams, 0.66 mole) was heated with a sulphuric acid solution (250 ml.) composed of 20% oleum (360 grams) and concentrated sulphuric acid (100 ml.) at a temperature of 145-155°C. for 12 hours. This material was cooled and poured into water (350 ml. It was heated to cause the precipitate to dissolve and then refrigerated. The precipitate was filtered on a sintered glass funnel and was redissolved in the least amount of boiling water. The precipitate obtained on cooling was filtered and was sucked all night in the funnel by means of the aspirator pump. It was placed in an alkali desiccator to complete the drying. The yield obtained was 140 grams.

(b) Alkali Fusion of the Sulphonic Acid

Potassium hydroxide (248 grams, 4.44 moles) was heated in a nickel crucible with water (14 ml.) until a temperature of 200°C. was reached. The sulphonic acid (45 grams, 0.21 mole) was then added quickly to the solution while the temperature was maintained at 200-210°C. The solution was heated as rapidly as possible, without foaming over, to a temperature of 260°C. After 25 minutes, the solution was cooled and leached with water (780 ml.). The aqueous solution was neutralized with concentrated hydrochloric acid and was then made alkaline with a few pellets of potassium hydroxide. It was evaporated to 500 ml.; the precipitate formed on cooling was filtered off. Acidification with hydrochloric acid gave an impure, yellow, precipitate of 3-hydroxy-p-toluic acid. Stirring the inorganic precipitate with boiling water gave, on acidification, a further quantity of the acid. The acid was recrystallized from water given 20 grams of white crystals. The over-all conversion from p-toluic acid to 3-hydroxy-p-toluic acid was 56%.

(c) The Preparation of the Lactone of 6-Hydroxymethyl-1,3-benzodioxan-8-methyl-5-carboxylic acid (II).

3-Hydroxy-p-toluic acid (20 grams, 0.13 mole) was heated for half an hour under reflux with concentrated hydrochloric acid (100 ml.) and 40% formaldehyde solution (100 ml.). The resulting material was poured into cold water (300 ml.) and allowed to stand. The precipitate was filtered and washed with water until the odour of formaldehyde was no longer present. After the solid had dried, it was dissolved in boiling alcohol (500 ml.) and filtered. The solid, precipitated on standing overnight, was filtered off. A further quantity of the condensation product may be obtained by evaporating the alcohol by 2/3. The total yield of dioxanyl phthalide (II) was 14 grams. It was suitable for further reaction but not for analysis.

The condensation product (II) was found to be slightly soluble in boiling water contrary to earlier reports (20). It was very soluble in sodium hydroxide, concentrated sulphuric acid, and glacial acetic acid. It dissolved in organic solvents such as ethyl alcohol, ether and acetone. It did not dissolve in sodium bicarbonate or cause an evolution of carbon dioxide when added to that reagent. It may be recovered from sulphuric acid and acetic acid solutions by dilution of the solvent with water.

	Theoretical for $C_{11}H_{10}O_4$	Experimental	
% Carbon	64.08	63.92	64.09
% Hydrogen	4.86	4.85	4.87
Neutralization equivalent	206	201	

(d) The Preparation of 1,3-Benzodioxan-8-methyl-5,6-dicarboxylic Acid (III)

The dioxanyl phthalide (II) (6.0 grams, 0.029 mole) was dissolved in potassium hydroxide (10 grams, 0.18 mole) water (300 ml.) by allowing the mixture to stand overnight. The solution was cooled in an ice bath to 5-10°C. and maintained at this temperature during the oxidation. A solution of potassium permanganate (24 grams, 0.15 mole) in water (700 ml.) was added to the first solution over a period of one hour. When the addition was completed, the green solution was allowed to stand overnight at room temperature. The brown manganese dioxide was filtered off and leached with water (300 ml.). The combined filtrates were acidified with hydrochloric acid until the solution was acid to litmus paper and basic to Congo-red paper. It was evaporated on the hot plate at 80°C. to 300 ml. The solution was acidified with hydrochloric acid and the resulting precipipitate was filtered. This white, chalky, material was dissolved in sodium bicarbonate, filtered, and treated with charcoal and norite. The crude acid obtained on acidification may be used for further reactions. Further purification was obtained by recrystallization from acetone. The weight of the acid obtained was 4 grams. It decomposed and melted with the evolution of water at 199.5-200°C.

The acid was soluble in sodium hydroxide, water, and sodium bicarbonate with the evolution of carbon dioxide. It dissolved in organic solvents such as ether, acetone, ethyl and methyl alcohols. The neutralization equivalents given below were determined by titrating 7 milligrams of the acid with .01 N sodium hydroxide.

	Theoretical for $C_{11}H_{10}O_6$	Experimental	
% Carbon	55.46	55.08	55.33
% Hydrogen	4.20	4.18	4.15
Neutralization equivalent	119	120	125
Molecular weight	238	226	

(e) The Preparation of the Lactone of 3-Hydroxymethyl-4-hydroxy-8-methyl-1,2-phthalic acid (IV)

The dicarboxylic acid (III) (6.0 grams, 0.025 mole) was heated under reflux for six hours with concentrated hydrochloric acid (100 ml.) and water (100 ml.). The resulting yellowish needles were recrystallized from an alcohol petroleum - ether mixture. Formaldehyde was evolved while the acid was refluxed. The solid obtained on recrystallization weighed 4.5

grams and melted at 269-270°C.

This acid (IV) was soluble in the same solvents as the dicarboxylic acid (III). The solution obtained by treating (IV) with sodium bicarbonate was found very difficult to filter.

	Theoretical for $C_{10}H_8O_5$	Experimental	
% Carbon	57.69	57.24	57.41
% Hydrogen	3.84	3.81	3.87
Neutralization equivalent	208	190	
Molecular weight	208	216	222

(f) The Preparation of 3-Hydroxy-4-methyl Phthalide (V)

The monocarboxylic acid (IV) (4.8 grams 0.025 mole) was dissolved in pure quinolene (40 ml.). Copper chromite (0.01 gram) was added to catalyse the reaction. The solution was heated on an oil bath at 185°C. until carbon dioxide was no longer evolved. The evolution of carbon dioxide was verified by placing a drop of barium hydroxide solution in the gas stream. A white precipitate of barium carbonate was formed. The cooled quinolene solution was acidified with dilute hydrochloric acid (1:1) and extracted with ether. Removal of the ether left a yellow, oily, precipitate which was purified by treating the alkaline solution three times with charcoal and norite and recrystallizing from water. The pure material weighed 2.1 grams and melted at 190-191°C.

The hydroxy phthalide was soluble in hot water, sodium hydroxide, ether, acetone, and alcohol. It does not liberate carbon dioxide from sodium bicarbonate.

	Theoretical for $C_9H_8O_3$	Experimental	
% Carbon	65.85	65.41	65.62
% Hydrogen	4.88	4.82	4.86
Molecular weight	164	147	

(g) The Preparation of 3-Methoxy-4-methyl Phthalide (VI)

The hydroxy phthalide (V) (2.5 grams, 0.015 mole) was dissolved in 10% sodium hydroxide (25 ml.) in a 10-inch test tube. To the tube was attached an 18-inch glass tube, a small glass tube that allowed propane gas to be bubbled through the solution, and a short glass tube with a rubber adapter into which an eyedropper may be inserted. Methyl sulphate (3 ml.) was added to the solution at such a rate that the temperature of the solution did not rise above 40°C. The methyl sulphate tended to be decomposed by the base present in the solution, and in a short time, the solution became acid enough to precipitate the hydroxyphthalide. Solid sodium hydroxide was added to cause solution again and the methylation continued. When the methyl sulphate was used up the methylation procedure was repeated three more times. The basic solution was allowed to stand overnight in contact with 1 ml. of methyl sulphate. The methyl sulphate was decomposed by warming the basic solution. The sodium sulphate that precipitated on cooling was filtered off. Acidification gave a solid composed of the two phthalides.

The methylation was repeated, and on acidification, fairly pure 3-methoxy-4-methyl phthalide was obtained. Purification was accomplished by recrystallizing from an acetone and water mixture. This material melted at 114-119°C. and weighed 1.9 grams. It was recrystallized again from acetone and water. The first 0.2 gram obtained melted at 119-120°C. and was used for analysis. Evaporation of the solvent gave 1.3 grams of phthalide melting at 117-119°C. The methoxy phthalide (VI) was more soluble in water than (V). It also dissolved in bases but would not dissolve in sodium bicarbonate.

	Theoretical for $C_{10}H_{10}O_3$	Experimental	
% Carbon	67.42	66.74	67.02
% Hydrogen	5.62	5.53	5.66
Molecular weight	178	160	

(h) The Preparation of 3-Methoxy-4-methyl Phthalic Acid (VII)

3-Methoxy-4-methyl phthalide (1.1 grams, 0.0062 mole) was dissolved in 10% sodium hydroxide (20 ml.). To this solution was added finely crushed potassium permanganate (1 gram, 0.0064 mole) at such a rate that the temperature did not rise above 22°C. Care was taken to ensure that all of one addition of potassium permanganate had dissolved before the next was added. The solution was allowed to stand at room temperature for 24 hours. The manganese dioxide was decomposed with sodium bisulphite, and after acidification, the solution was thoroughly extracted with ether. Evaporation of the ether gave a white solid. This was extracted with the least amount of sodium bicarbonate. There was left 0.3 gram of unreacted phthalide. The bicarbonate solution was treated with activated charcoal and filtered. The solution was acidified, and after scratching the side of the Wright tube in which it was contained, a white precipitate settled out of solution. This was filtered off and recrystallized three times from water to remove inorganic material. Since the acid was reported by Simonsen and Rau to be insoluble in chloroform, the acid was recrystallized from an acetone and chloroform mixture. The yield of pure acid was found to be 0.3 gram and it melted at 172-173°C.

Simonsen and Rau (18) prepared 3-methoxy-4-methyl phthalic acid by a different method. They reported a melting point of 175°C. The melting point was found to vary with the rate of heating. The similar melting points, the correct combustion percentages for carbon and hydrogen given below, together with the fact that the anhydride of this acid (see next experiment) melts at 132-133°C., as compared with Simonsen's and Rau's value of 135°C., indicate that the acid obtained by the oxidation of a phthalide is the same as that acid prepared by Simonsen and Rau.

	Theoretical for $C_{10}H_{10}O_5$	Experimental
% Carbon	57.14	57.14
% Hydrogen	4.76	5.07

(i) The Preparation of the Anhydride of 3-Methoxy-4-methyl phthalic Acid (VIIa)

The phthalic acid (VII) (0.1 gram) was placed in a sulphuric acid desiccator to dry. It was found that the desiccant was powerful enough to cause partial anhydride formation for on standing overnight, the melting point had changed from 173°C. to 145-160°C. This crude material was heated on an oil bath at 160°C. until all bubbling had ceased. Recrystallization from toluene gave a small amount of non acidic material melting at 132-133°C. Evaporation of the toluene gave a crude material melting at 132-160°C. Simonsen and Rau prepared the anhydride of 3-methoxy-4-methyl phthalic acid and found the melting point to be 135°C. No analysis was carried out.

(j) The Preparation of the Anhydride of 1,3-benzodioxan-8-methyl-5,6-dicarboxylic acid (IIIa)

By the action of heat

The dicarboxylic acid (III) (1.1 grams, 0.0046 mole) was heated on an oil bath at 202-205°C. until the violent evolution of water vapour had subsided. It was found that continued heating at 205°C. or higher caused the evolution of formaldehyde and the formation of a resin. The gas evolved at 202-205°C. turns anhydrous copper sulphate blue indicating the presence of water. The solidified mass was extracted with boiling toluene, filtered while hot, and on cooling, masses of yellowish needles were deposited. This material was recrystallized once again from toluene and weighed 0.5 gram. The melting point was 192-193°C. This material was insoluble in sodium bicarbonate, and was converted back to the acid (III) on standing exposed to the atmosphere.

By the action of acetic anhydride

The dicarboxylic acid (III) 1.2 grams, 0.0080 mole) was heated gently with acetic anhydride (1.90 ml.) until it went into solution. The solution was evaporated on a hot plate until only 1 ml. remained. It was cooled and the liquid solidified. The mass was sucked dry on a funnel and thoroughly washed with anhydrous ether. It was then recrystallized twice from toluene, yielding a mass of fine yellow needles. They melted at 193-194°C. A mixed melting point determination with the anhydride produced above gave 194-195°C.

	Calculated for $C_{11}H_8O_5$	Experimental	
% Carbon	60.00	60.00	59.89
% Hydrogen	3.64	3.65	3.73

(k) The Preparation of 3-Hydroxymethyl-4-methoxy-8-methyl-1,2-phthalic Acid (IVa)

The monocarboxylic acid (IV) 1 gram, 0.0048 mole) was dissolved in 40% sodium hydroxide (10 ml.). Propane gas was bubbled through the solution and methyl sulphate (3 ml.) was added over a period of half an hour. The solution was stirred by the propane gas until all the methyl sulphate was used up. This procedure was repeated twice more, and the alkali solution was allowed to stand overnight in the presence of methyl sulphate. Heating the solution after making it basic destroyed the residual methyl sulphate. On cooling, a fine white precipitate was obtained. This was filtered off. Acidification of the solution produced a gummy residue. The fine white precipitate was recrystallized twice from acetone giving greenish needles. These crystals melted at 153.5-155°C. and weighed 0.1 gram.

	Calculated for $C_{11}H_{11}O_5$	Experimental	
% Carbon	59.45	58.83	59.27
% Hydrogen	4.50	4.71	5.08

(1) The Preparation of 3-Hydroxymethyl-4-acetoxy-8-methyl-1,2-phthalic acid (IVb)

The monocarboxylic acid (IV) (0.5 gram, 0.0024 mole) was mixed with potassium carbonate (0.5 gram) and the mixture stirred into acetic anhydride (2.5 ml.). The mixture was warmed occasionally to keep it in a liquid state. After 30 minutes potassium carbonate (0.2 gram) and acetic anhydride (1.0 ml.) were added. The solution was warmed occasionally for another 20 minutes to keep in a liquid state. Finally the solution was diluted to 10 ml. with water and acidified carefully with concentrated hydrochloric acid. The crystals obtained were recrystallized once from alcohol and once from acetone. The first fraction, consisting of 0.2 gram melting at 188-189.5°C., was collected for analysis. A second fraction of 0.2 gram was also collected. This compound was not analyzed because of a shortage of time.

(m) Oxidation of the Lactone of 6-Hydroxymethyl-1,3-benzodioxan-8-methyl-5-carboxylic Acid (II) with Chromium Trioxide

First Method

The dioxanyl phthalide (II) (2 grams, 0.0097 mole) was added to glacial acetic acid (12 ml.). This mixture was heated on the hot plate to get as much of the dioxanyl phthalide (II) as possible to dissolve. It was allowed to stand until cool. A solution of chromium trioxide (3 grams, .03 mole), dissolved first in the least amount of water and then in glacial acetic acid (5 ml.), was added slowly to the dioxanyl phthalide solution at such a rate that the temperature did not exceed 70°C. The oxidation mixture was allowed to stand at room temperature for 36 hours. The solution was heated on the hot plate to 50°C. and allowed to cool. After 4 hours it was diluted to 250 ml. with water and allowed to stand overnight. The precipitate was filtered off and washed well with water. After drying, the material was extracted with cold acetone (50 ml.). to remove any unreacted dioxanyl phthalide (II). It was then dissolved in the least amount of boiling acetone and filtered. The acetone was evaporated by two thirds, and white crystals were deposited melting at 240-245°C. This material may be recrystallized from acetone again to give a product melting at 244-247°C. Recrystallization from water gives crystals melting at 248.5-250°C. and weighing 0.12 gram.

	Calculated for $C_{11}H_8O_5$	Experimental
% Carbon	60.00	59.89
% Hydrogen	3.64	3.67
Molecular weight	220	211

Second Method

The dioxanyl phthalide (II) (2 grams, 0.097 mole) was dissolved in glacial acetic acid (60 ml.). Chromium trioxide (4 grams, 0.04 mole) dissolved in glacial acetic acid (10 ml.) and the least amount of water, was added to the dioxanyl phthalide solution at such a rate that the temperature did not rise above 50°C. It was allowed to stand overnight and it was then diluted to 700 ml. with water. After standing overnight in the ice-chest, the precipitate was filtered and then washed well with water. This gave 0.48 gram of crude material. This residue was leached with 200 ml. portions of boiling water. The first two fractions contained most of the oxidized product. The precipitate obtained on cooling was filtered and dried. The precipitates from the first two fractions were combined, and the mother liquors combined and kept. The precipitate was leached with ethyl acetate (60 ml.) and it removed 0.10 gram of unreacted dioxanyl phthalide (II). The undissolved residue contained 0.12 gram of yellowish crystals melting at 239-244°C. This was recrystallized from acetone and 0.095 gram of a material melting at 248-250°C. was obtained.

The aqueous layer of the first crystallization was boiled down by two thirds and a solid obtained. The acetone layer of the last crystallization was evaporated and the solids combined. Three portions of three similar oxidations were combined. This crude material was recrystallized twice from ethyl alcohol and 0.03 gram of white needles melting at 186-188°C. were obtained. Evaporation of the alcohol layer gives a residue that melts at 140-155°C.

The crystals melting at 186-188°C. were found to be more soluble in ether than the material melting at 248-250°C. and a partial separation of these two might be effected. If the material recrystallized from water were extracted with ether, the residue melted at 243-245°C. while the ether soluble material melted from 181-190°C.

(n) Hydrolysis of an Impure Sample of the Lactone of 6-Hydroxymethyl-8-methyl-1,3-benzodioxan-4-one-5-carboxylic Acid (VIII)

The impure oxidation product (VIII) melting at 235-242°C. was hydrolysed in the manner described by Buehler and Block (4). The material (0.2 gram) was treated with 20% sodium hydroxide (10 ml.) and heated on a water bath for half an hour. A strong odour of formaldehyde was noticed. The solution was acidified and evaporated to dryness on a hot plate. The residue was extracted with ethyl alcohol and evaporated to dryness. The residue melted from 190 to 235°C. Treatment of the residue with sodium bicarbonate showed the presence of an acid. A white residue was found to be insoluble in this reagent. It melted at 185-195°C., and after recrystallization from ethyl alcohol, it melted at 190-195°C. It was found impossible to isolate the acidic material. Acidification of the bicarbonate solution produced a blue fluorescence which was destroyed by excess acid.

(o) Air Oxidation of the Lactone of 6-Hydroxymethyl-1,3-benzodioxan-8-methyl-5-carboxylic Acid (II).

The dioxanyl phthalide (II) (2.1 grams) was allowed to stand on a glass plate exposed to the atmosphere. After one month had passed, the crumbly, brown material was dissolved in sodium hydroxide and filtered. On acidification, a gas was evolved, and a brown gum was deposited. The aqueous layer was decanted and the gum allowed to dry. It melted from 148 to 210°C. If the brown material is not treated with sodium hydroxide, but recrystallized from water, a product melting at 90 to 135°C. is obtained. When the material melting at 148 to 210°C. was recrystallized three times from acetone, 0.05 gram of a crude brownish material melting at 180-192°C. was obtained.

Other Condensations

(a) The Condensation of 3-Hydroxy-p-toluic Acid (I) with Chloral

3-Hydroxy p-toluic acid (4 grams, 0.019 mole) was heated on the water bath at 70-80°C. for half an hour with chloral (4.7 grams) and a solution of concentrated sulphuric acid (30 ml.) mixed with water (2 ml.). The solution changed from light orange to green. After standing at room temperature for 24 hours, it was diluted with water (30 ml.) and refrigerated for 4 hours. The precipitate was filtered and washed well with water. It was dried overnight and recrystallized twice from acetic acid. A final recrystallization from acetic acid gave a chlorine containing compound melting at 228-229°C. Meldrum and Kapadia (16) report a melting point of 232°C. for 3-hydroxy-4-methyl-α-trichloromethyl phthalide.

(b) Hydrolysis of 3-hydroxy-4-methyl-α-trichloromethyl phthalide (X)

The chloro compound (X), (3.8 grams, 0.014 mole) was dissolved in a sodium hydroxide solution composed of sodium hydroxide (5 grams, 0.218 mole) in water (25 ml.). The solution turned a deep wine colour, and after heating on the steam bath for two hours turned a light red. After acidification, the solution was thoroughly extracted with ether. Evaporation of the ether leaves 1.5 grams of a red oil. The oil, after standing in an alkali desiccator, set to a red tar melting from 189 to 220°C. Attempts to form the barium salt of this material were unsuccessful. The material could not be recrystallized in a crystalline form from ethyl alcohol, ether, or acetone. After standing in an alkali desiccator for three months, a small amount of the material became greyish and melted from 145-157°C. Meldrum and Kapadia report a melting point of 115°C. for 2-hydroxy-3-methyl-6-carboxy-mandelic acid which should be formed in this reaction.

It was found that if the freshly hydrolysed solution were acidified with concentrated hydrochloric acid and allowed to stand overnight, 1.1 grams of a yellow, acidic material was

x

deposited. Three recrystallizations of this acid from acetone resulted in a melting point of 262-265°C. This acid could not be converted into the acid reported by Meldrum and Kapadia.

SUMMARY

1. After a long series of degradative reactions on the condensation product of 3-hydroxy-p-toluic acid (I), it was possible to isolate a material identified as 3-methoxy-4-methyl phthalic acid (VII).

2. The structure of the condensation product of 3-hydroxy-p-toluic acid with formaldehyde has been shown to be the lactone of 6-hydroxymethyl-8-methyl-1,3-benzodioxan-5-carboxylic acid (II).

3. As a result of this degradative work, it has been possible to isolate and identify the following new compounds:
   (a) 1,3-benzodioxan-8-methyl-5,6-phthalic acid (III);
   (b) the anhydride of 1,3-benzodioxan-8-methyl-5,6-phthalic acid (IIIa);
   (c) the lactone of 3-hydroxymethyl-4-hydroxy-8-methyl-1,2-phthalic acid (IV);
   (d) the lactone of 3-hydroxymethyl-4-methoxy-8-methyl-1,2-phthalic acid (IVa);
   (e) 3-hydroxy-4-methyl phthalide (V);
   (f) 3-methoxy-4-methyl phthalide (VI).

4. The lactone of 3-hydroxymethyl-4-acetoxy-8-methyl-1,2-phthalic acid (IVb) was also prepared but it has not been analysed.

5. The chromium trioxide oxidation of the dioxanyl phthalide (II) has been investigated, and a compound thought to be the lactone of 6-hydroxymethyl-8-methyl-1,3-ben-zodioxan-4-one-5-carboxylic acid (VIII) has been isolated and analysed. Evidence was obtained indicating the existence of a second oxidation product but this compound was not isolated. A possible structure has been indicated for this new product.

6. It has been shown in a qualitative manner that the dioxanyl phthalide (II) possesses a 1,3-dioxane ring.

RECOMMENDATIONS FOR FUTURE WORK

1. Analysis of the sample of material obtained by treating the lactone of 3-hydroxymethyl-4-hydroxy-8-methyl-1,2-phthalic acid (IV) with acetic anhydride might be attempted.

2. Continuation of the chromium trioxide oxidation of the lactone of 6-hydroxymethyl-8-methyl-1,3-benzodioxan-5-carboxylic acid (II) might be carried out.

3. The air oxidation of the dioxanyl phthalide (II) might be repeated in an attempt to isolate the oxidation product.

4. The lactone of 6-hydroxymethyl-8-methyl-1,3-benzodioxan-4-one-5-carboxylic acid (VIII), produced by the oxidation of the dioxanyl phthalide (II), might be hydrolysed.

5. Determination of the structure of the hydrolysis product obtained from 3-hydroxy-α-trichloromethyl phthalide (X) that melts at 263-265°C. might be attempted.

6. The possibilities of an acid-permanganate oxidation and an acid-dichromate oxidation of the dioxanyl phthalide (II) might be investigated.

7. It is recommended that diazomethane be tried as a methylating agent for the preparation of 3-methoxy-4-methyl phthalide (VI) from 3-hydroxy-4-methyl phthalide (V) if the reaction be repeated.

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