TO

DR. E. HAROLD CHARLESWORTH

For invaluable advice and kindly guidance in this first venture of research, the author is deeply grateful.

Condensations of Aromatic Acids with Aliphatic Aldehydes In the Presence of Halogen Acids and Synthesis of α-Ethanolglutaric Acid Lactone And Related Substances

By

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CONDENSATIONS OF AROMATIC ACIDS WITH ALIPHATIC ALDEHYDES IN THE PRESENCE OF HALOGEN ACIDS

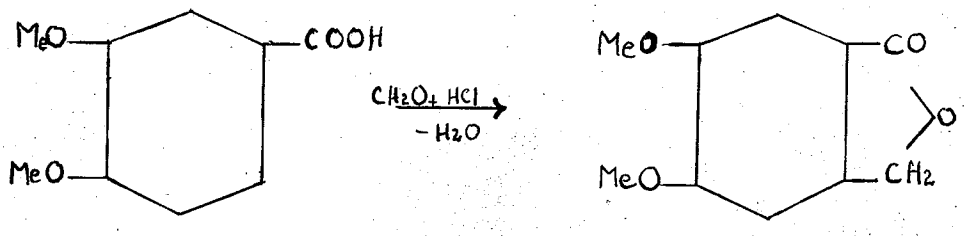
INTRODUCTION

In 1898, Grassi and Maselli (10) published the first report of the chloromethylation of the benzene nucleus by the action of paraformaldehyde and hydrochloric acid. Since then, the reaction has been widely studied with respect to numerous types of aromatic compounds. Of these, the aromatic acids have only recently been subjected to a systematic investigation.

Since the reactions involving these acids utilized only formaldehyde and hydrochloric acid, the present investigation was carried out in order to ascertain what effect analogous reagents, namely, hydriodic and hydrobromic acids, as well as the higher aliphatic aldehydes including acetaldehyde and propionaldehyde, would have on some of the same acids. Because certain condensations of aromatic acids with hydrochloric acid and formaldehyde, studied in previous researches, produced somewhat dubious results, a re-investigation of some of these reactions was also included in this work.

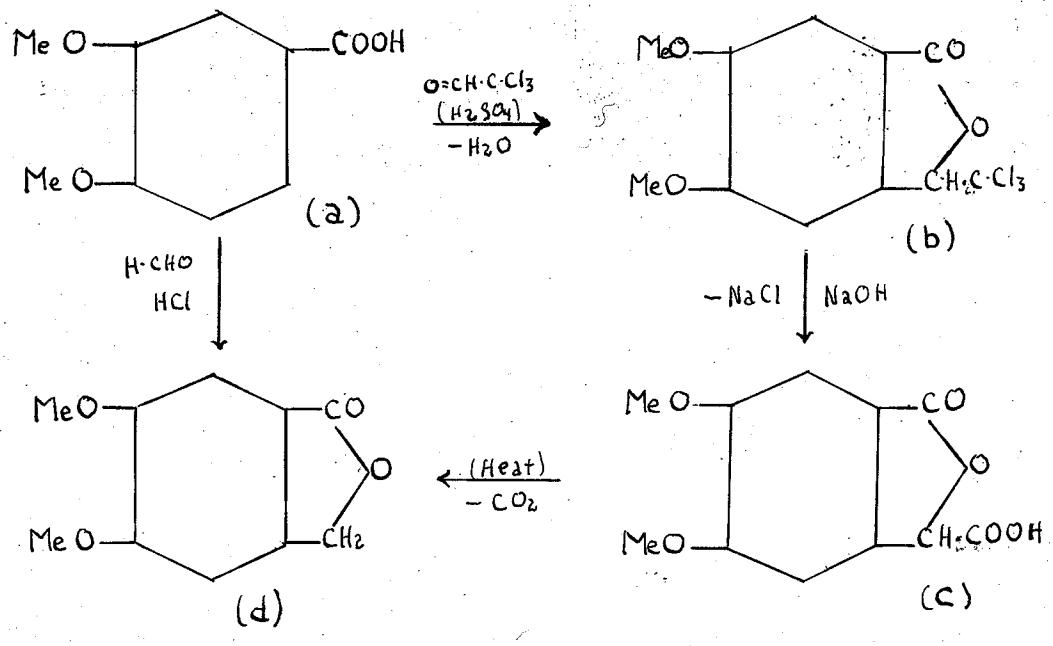
When definite products are obtained from condensations of the latter type, they are normally one of two kinds: a simple phthalide or a chlorinated compound.

The isolation of a phthalide by this method, was first effected by Perkin, Edwards, and Stoyle (18) in 1925. By boiling the veratric acids with formaldehyde and hydrochloric acid, they obtained the corresponding meconines.



Veratric Acid — Meconine

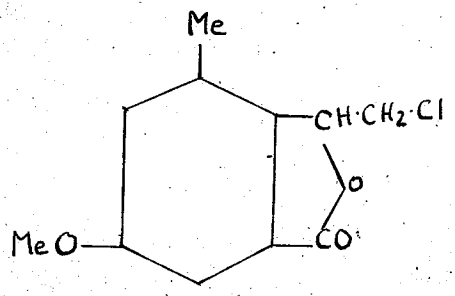
Previously, the only method by which phthalides were produced from their acids, was the classical Fritsch reaction (7). In this case the acid is first condensed with chloral hydrate and sulphuric acid yielding a trichloromethylphthalide. The latter is then converted by aqueous alkali to a carboxylic acid which in turn is decarboxylated, giving the desired phthalide. By this method the production of meconine (d) from veratric acid (a) must pass through stages (b) and (c).

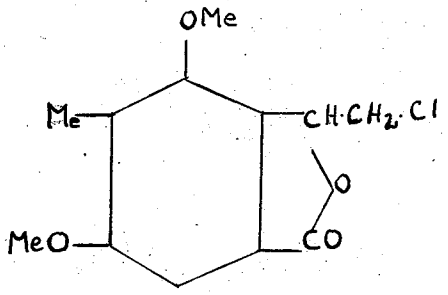


Obviously, by the condensation of the acid with formaldehyde and hydrochloric acid, Perkin, Edwards, and Stoyle (18) eliminated steps (b) and (c).

Recognizing this fact, Raistrick, Robinson, and Todd (21) attempted to obtain the phthalide of 5-methoxy-m-toluic acid in exactly the same manner. However, instead of the desired product, they isolated a chlorinated compound. Furthermore, Charlesworth and Robinson (3) obtained a chloroproduct when they attempted the same reaction with 3:5-dimethoxy-p-toluic acid.

Cameron (2) in a study of the action of formaldehyde and hydrochloric acid on 5-methoxy-m-toluic acid and 3:5-dimethoxy-p-toluic acid, again isolated these chlorinated products. On the basis of theoretical deductions, Cameron offered the following structures for these compounds.



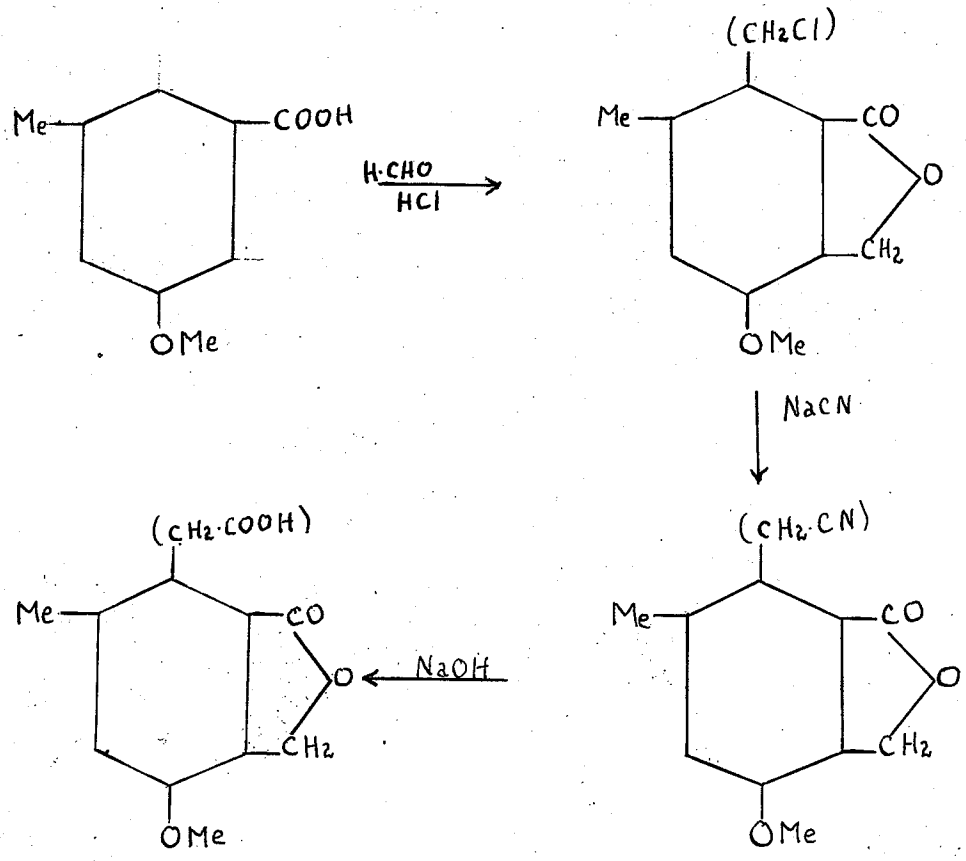


It will later be shown, however, that these formulae are incorrect.

The production of simple phthalides was obtained by Rennie (23) who worked with 2:4-dimethoxybenzoic acid, 5-methoxy-o-toluic, and 3:5-dimethoxy-o-toluic acids. However, the constitution of the product obtained from 2:4-dimethoxybenzoic acid is questionable, in view of results obtained in this investigation.

Another simple phthalide was reported by Yan (31) when he condensed 3-methoxy-p-toluic acid with formaldehyde and hydrochloric acid. Yan also carried out work with 5-methoxy-p-toluic acid in order to characterize definitely the chloroproduct which Cameron obtained in his work.

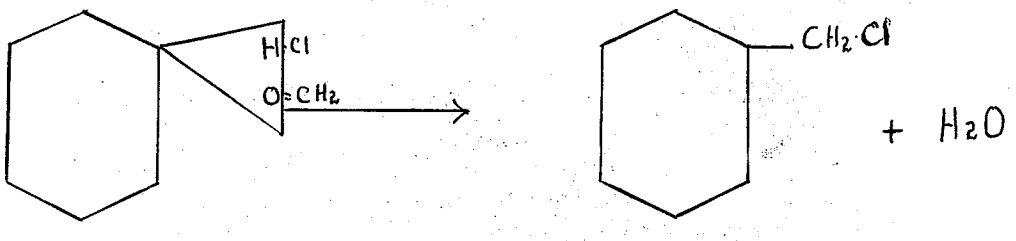
By a definite sequence of reactions in which Yan converted the chloroproduct to a nitrile, thence to a phenylacetic acid, he proved that the chloromethyl group was in the ring and not as suggested by Cameron.



Although Yan failed to orientate the position of substituent groups, he did produce a tricarboxylic acid from the phenylacetic acid. He pointed out that if this acid can be subjected to degradative processes, it would provide the necessary evidence.

The fact that the chloromethyl group is nuclearly substituted as indicated by Yan, is substantiated by the work of Stephen, Gladding and Short (27), Quelet (19), and many others.

In connection with this point, Stephen, Gladding, and Short provided a logical explanation for the mechanism of the reaction. They submitted that the chloromethyl group was probably introduced through an intermediate stage, rather than by the direct action of the hydrochloric acid and formaldehyde.



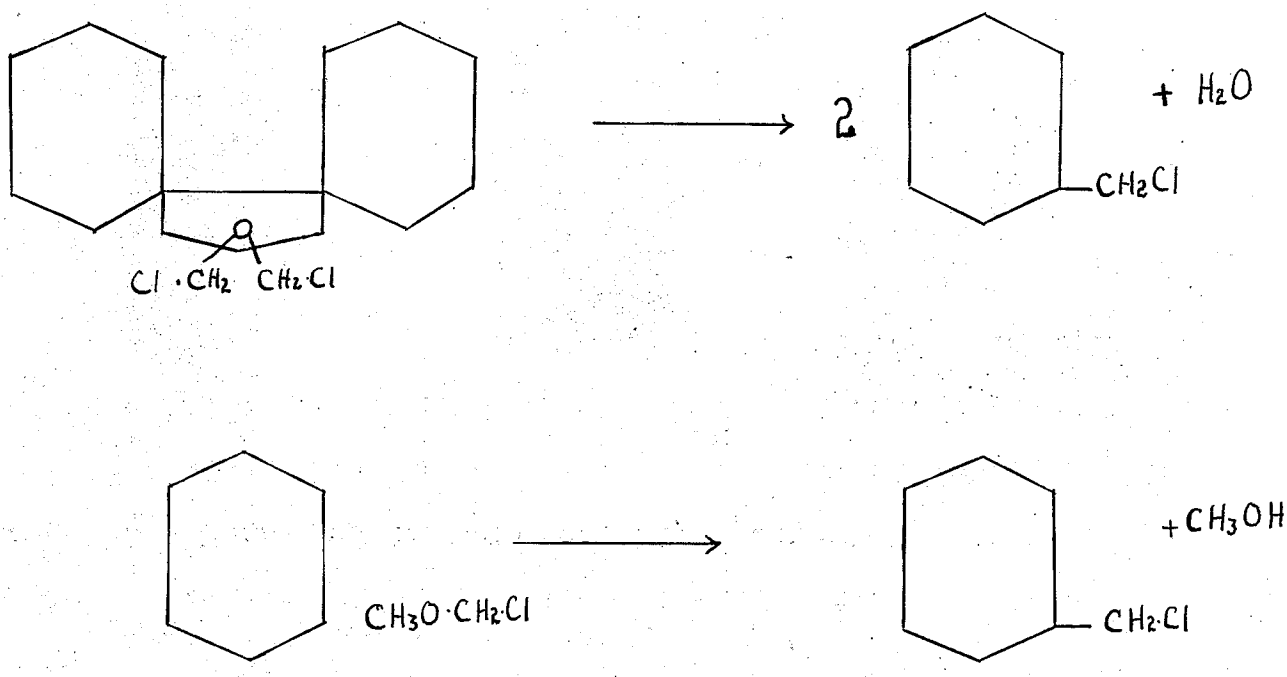
Working on this assumption, Stephen, Gladding and Short, isolated two compounds from the reaction of formaldehyde and hydrochloric acid alone: s-dichloromethyl ether and mono-chlorodimethyl ether. The former product is obtained by the direct combination of hydrochloric acid and formaldehyde.

$$2\ H{\cdot}CHO + 2\ HCl \longrightarrow (CH_2Cl)_2{\cdot}O + H_2O$$

The other compound could only be explained by the presence of methyl alcohol in the commercial formaldehyde. The alcohol and hydrochloric acid react to form the mono-chlorodimethyl ether.

$$2\ CH_3OH + HCl \longrightarrow CH_3O{\cdot}CH_2{\cdot}Cl$$

Both these intermediate products may react with the aromatic nucleus to introduce the chloromethyl group.



In the condensations with the aromatic compounds, both Quelet and Stephen, Gladding, and Short reported the formation of diarylmethane derivatives. The latter suggested that when the chloromethyl derivative was formed, some of it probably reacted with the unchanged aromatic reagent to produce these substances.

$$C_6H_5 \cdot CH_2 \cdot Cl + C_6H_6 \longrightarrow C_6H_5 \cdot CH_2 \cdot C_6H_5 + HCl$$

Although phthalide formation is the expected result in the formaldehyde, hydrochloric acid condensation with aromatic acids, it is evident from Table I that not all the acids studied, yielded the desired product.

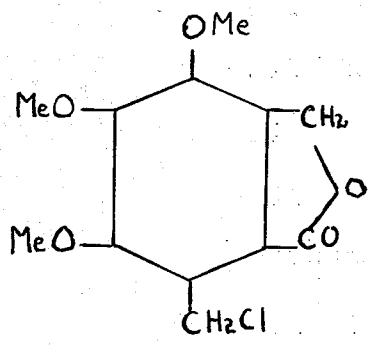
TABLE I

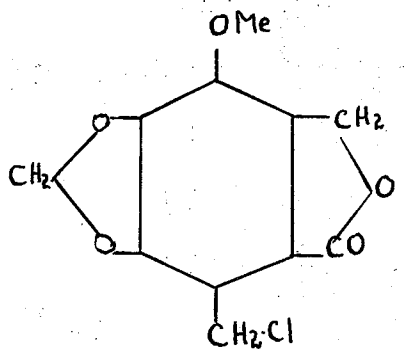
FORMALDEHYDE AND HYDROCHLORIC ACID CONDENSATIONS

ACID	RESULT	
Benzoic	No reaction	(23)
o-Methoxybenzoic	No reaction	(23)
p-Methoxybenzoic	No reaction	(23)
m-Toluic	No reaction	(23)
p-Toluic	No reaction	(23)
4:5-Methylenedioxybenzoic	No reaction	(18)
5:6-Methylenedioxybenzoic	Phthalide	(29)
2:3-Dimethoxybenzoic	Phthalide	(18)
3:4-Dimethoxybenzoic	Phthalide	(18)
2:4-Dimethoxybenzoic	Phthalide	(23)
1-Bromo-2:3-dimethoxybenzoic	Phthalide	(22)
3-Methoxy-p-toluic	Phthalide	(31)
5-Methoxy-o-toluic	Phthalide	(23)
5-Methoxy-m-toluic	Chloromethylphthalide	(2)(31)
3:5-Dimethoxy-o-toluic	Phthalide	(23)
3:5-Dimethoxy-p-toluic	Chlorocompound	(2)
3:4:5-Trimethoxybenzoic	Chloromethylphthalide	(16)(12)
3:4:5-Trimethoxybenzoic	Phthalide	(12)
3-Methoxy-4:5-methylene-dioxybenzoic	Phthalide Chloromethylphthalide	(16) (16)
3:5-Dimethoxy-4-hydroxybenzoic	Phthalide Chloromethylphthalide	(12) (12)

The apparent resistance to phthalide formation on the part of some acids, led Rennie (23) to suggest that the influence of substituent groups is an important factor. In this respect, he pointed out that the groups CH_3 and CH_3O favor phthalide formation, whereas the COOH group has an opposite effect. Nevertheless, he could not correlate this with his failure to obtain the phthalide of tri-methyl gallic acid.

In a later communication, Paul (16) reported that he definitely obtained a chloromethylphthalide from trimethyl gallic acid and also myristicinic acid, after adding acetic acid to the condensation mixture. He also isolated the simple phthalide of myristicinic acid and possibly that of trimethyl gallic acid.





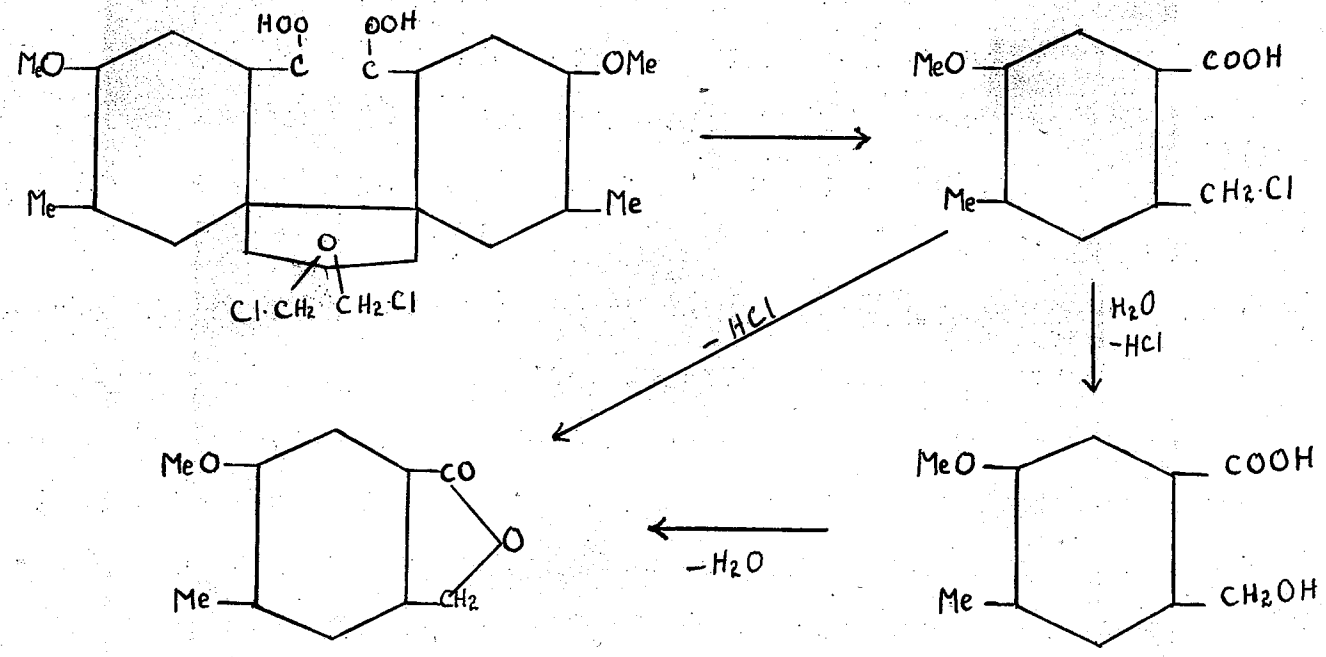
When Yan (31) attempted to repeat Paul's work, he was unable to reproduce the same results. This was in agreement with Rennie's experiments which were also negative.

Within the past few months, King and King (12) have re-investigated the problem of the trimethyl gallic acid. These men obtained both the simple phthalide, which they proved by the Fritsch (7) synthesis, and the chloromethylphthalide. Unlike Paul, they did not require the use of acetic acid in the condensation.

King and King showed that by altering the quantity of hydrochloric acid they could produce either the simple phthalide or the chloromethyl product. Using only a small quantity of the mineral acid they obtained the non-chlorinated phthalide; by increasing the amount of the hydrochloric acid, they isolated the chloromethylphthalide.

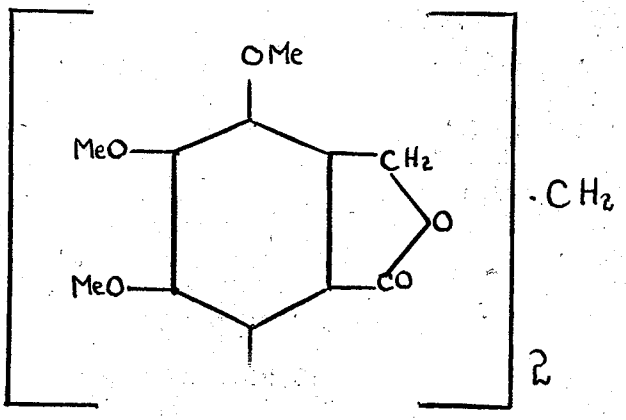
Evidently, the normal phthalide must be formed first in the reaction. To prove this point, King and King condensed this phthalide with a further quantity of formaldehyde and hydrochloric acid, obtaining thereby, the chlorinated substance.

The mechanism involved in the production of all these phthalides can readily be explained on the basis of Stephen, Gladding, and Short's (27) theory. Firstly, the chloromethyl group is introduced into the ring ortho to the carboxyl group. Once this group is in the ring, the phthalide may form by either splitting out hydrochloric acid directly, or the chloromethyl group will be hydrolysed to the alcohol, followed by lactonization.



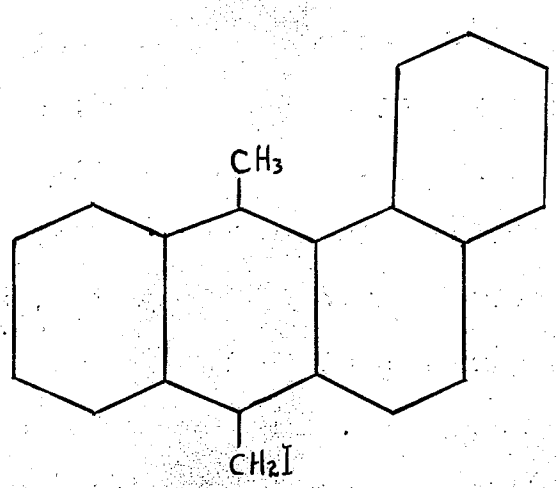
If the work of King and King (12) can be considered general, the formation of the chloromethylphthalide will take place only after the normal phthalide has been produced.

Along with the synthesis of the simple phthalide or the chlorinated substance, diphthalidemethane derivatives similar to the diarylmethane products obtained in condensations with other aromatic compounds, could be expected. Cameron (2) had previously attempted to show the existence of such substances, but without success. King and King, however, have isolated and analysed a diphthalidemethane derivative from the trimethyl gallic acid condensation.



Up to this point the discussion has dealt with the action of formaldehyde and hydrochloric acid on the aromatic acids. It is pertinent therefore, to see what effect hydrobromic and hydriodic acids would have on the course of such a reaction.

Various workers have reported successful bromomethylation and iodomethylation of aromatic compounds by this reaction. Darzens and Levy (5) made α-bromo-methylnaphthalene; Stephen, Gladding, and Short (27) reported the isolation of p-chlorobenzyl bromide. Sandin and Fieser (24) converted 9-methyl-1:2-benzanthracene to 9:10-dimethyl-1:2-benzanthracene through the iodomethyl derivative.



The use of hydrobromic and hydriodic acids has, however, thus far not been recorded in connection with condensations of aromatic acids.

Higher aliphatic aldehydes in place of formaldehyde in the presence of hydrochloric acid, have been used successfully in condensations with various aromatic compounds. Chloroethyl, chloropropyl, and chlorobutyl nuclearly substituted derivatives have been reported.

Quelet (20) chloroethylated anisole and a large number of its homologs. In his synthesis of anethole from anisole, Quelet used the chloropropyl derivative. Both Ducasse (6) and Sommelet and Marszak (26) successfully chlorobutylated several compounds. No record of the use of higher aliphatic aldehydes with aromatic acids has been found in the literature.

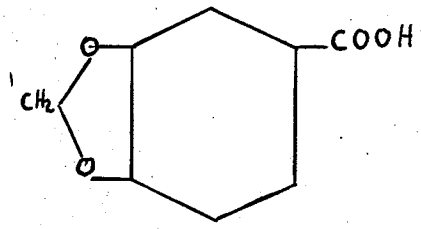
DISCUSSION OF RESULTS

The following table includes a summary of the various substances investigated during the course of this work.

TABLE II

ACID	REAGENTS	RESULT
Piperonylic	HCHO + HCl	Low-melting substance
	HCHO + HCl+acetic	No reaction
	HCHO + HCl+H_3PO_4	No reaction
3:5-Dimethoxy-p-toluic	HCHO + HCl	Chloromethylphthalide
2:4-Dimethoxybenzoic	HCHO + HCl	High-melting resin
Veratric	HCHO + HCl	Meconine
	HCHO + HBr	Meconine
	HCHO + HI	Meconine
3-Methoxy-p-toluic	HCHO + HBr	Phthalide
	HCHO + HI	Phthalide
3-Methoxy-p-toluic	CH_3-CHO + HCl	No reaction
3-Methoxy-p-toluic	CH_3-CH_2-CHO +HCl	No reaction

At the time Perkin, Edwards, and Stoyle (18) prepared the meconines by the condensation of the veratric acids with formaldehyde and hydrochloric acid, they also attempted a similar reaction with piperonylic acid (I). In this instance, however, they failed to isolate any new product. This seemed rather strange, since the very closely related substance, o-piperonylic acid (LL), readily yielded its corresponding phthalide. In view of this fact, several condensations with piperonylic acid were repeated under various conditions, in this investigation.



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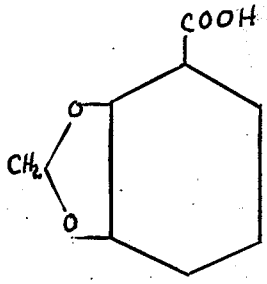
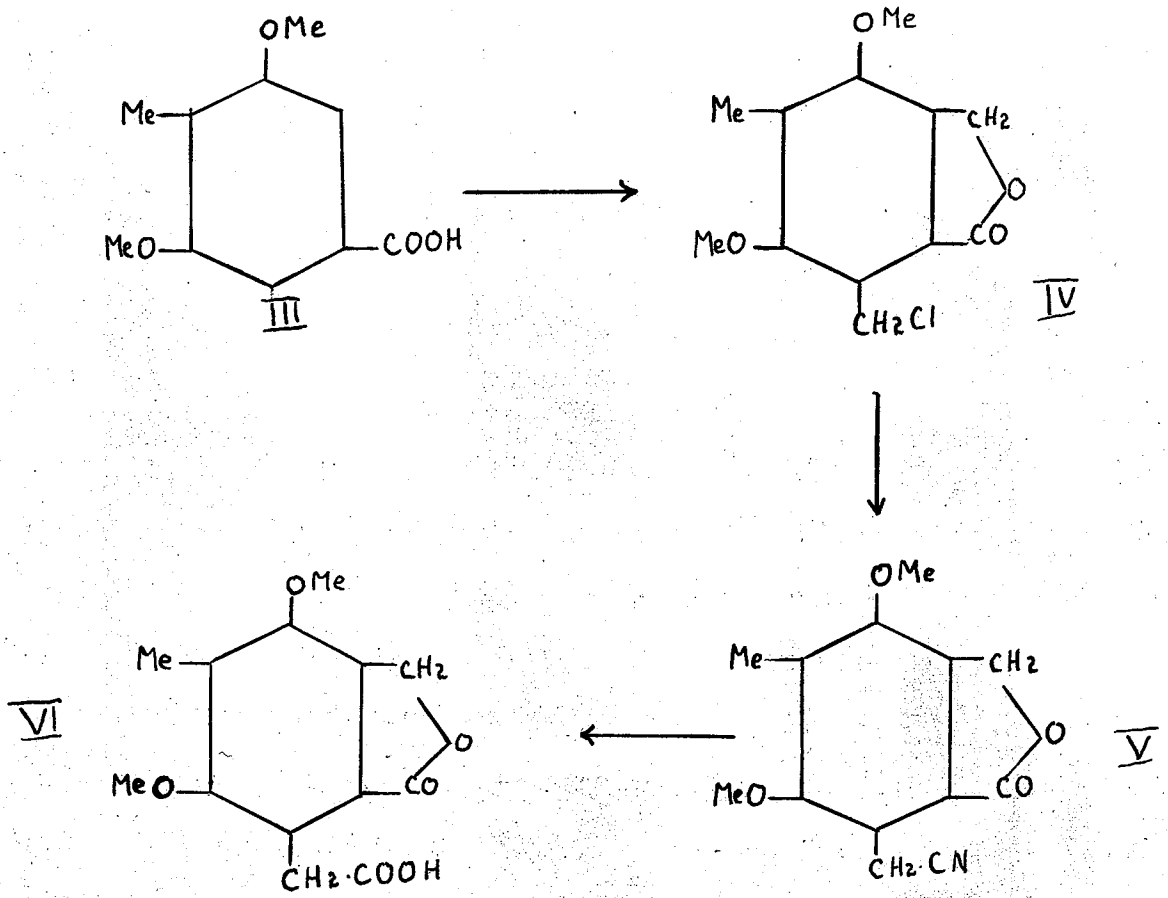


II

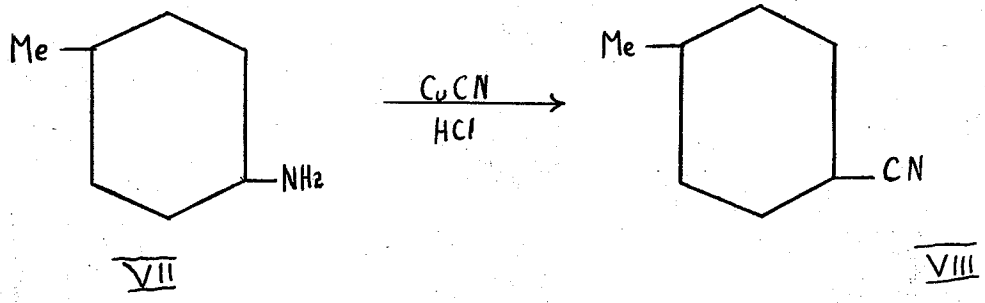
Piperonylic acid was recovered unchanged in all cases but one. From the latter condensation a small quantity of a substance which melted at 138-40° was isolated. It was quite possible therefore, that this product was the expected phthalide.

The chlorinated product (IV) which Charlesworth and Robinson (3) obtained in the formaldehyde-hydrochloric acid condensation with 3;5-dimethoxy-p-toluic acid (III) was later studied by Cameron (2). The latter's conclusions regarding the characteristics of the compound was based merely on a single chlorine analysis of questionable value, and theoretical considerations.

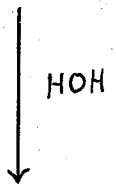
Accordingly, a closer investigation of this substance appeared desirable. It was hoped that the chlorocompound could be converted to a phenylacetic acid (VI) through a nitrile (V) in a similar series to that attained by Yan (31) with 5-methoxy-p-toluic acid.

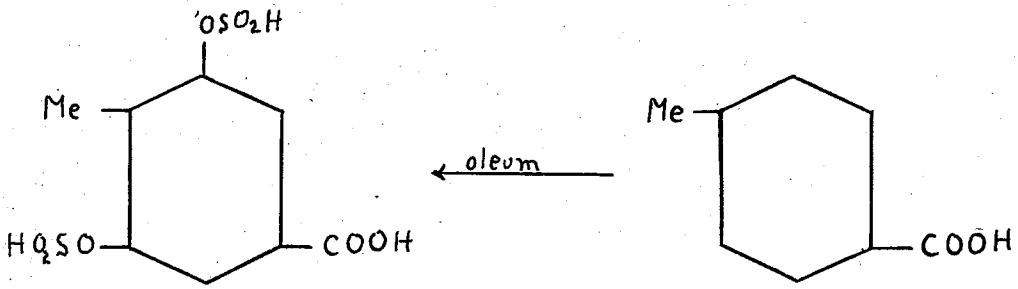


Although (IV) was obtained in a very pure form, the yield was too small to carry it through the next stages. Due to the poor yields obtained in the last two steps of the preparation of the acid (III), it was difficult to obtain appreciable amounts of this product for the condensations. The long and tedious process involved the preparation of p-toluic acid (IX) from p-toluidine (VII) through the nitrile (VIII); the subsequent sulfonation of (IX) to the sulfonic acid (X) which upon fusion with potassium hydroxide, gave 3:5-dihydroxy-p-toluic acid (XI). The latter substance was finally methylated to produce (III).

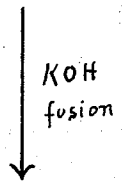


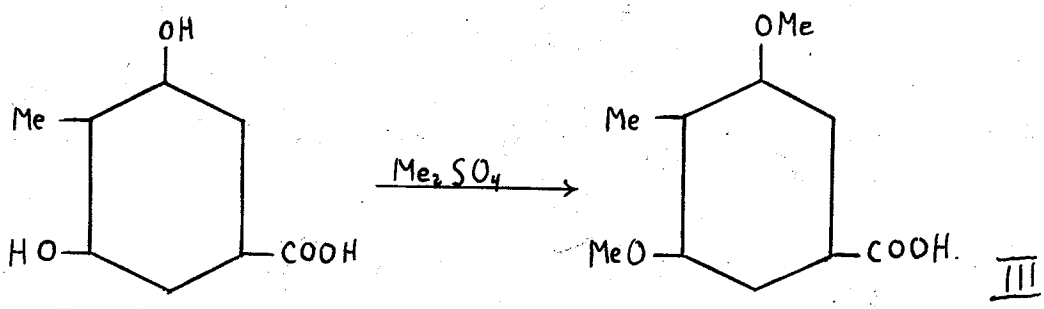
VII VIII





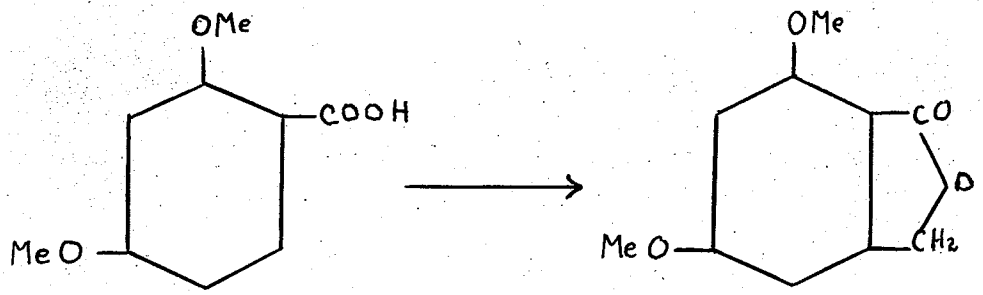
X IX





XI III

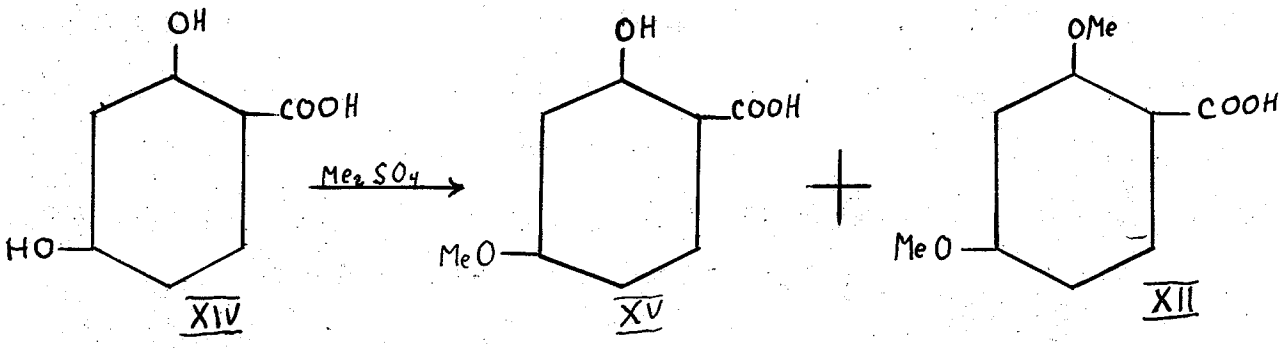
Thus far the reactions discussed, concerned the use of hydrochloric acid as one of the condensing reagents. To study the effect of hydrobromic and hydriodic acids in these condensations, the first substance selected was 2:4-dimethoxybenzoic acid (XII) from which Rennie (23) reportedly obtained 2:4-dimethoxybenzoic phthalide (XIII) in a formaldehyde-hydrochloric acid condensation.



XII XIII

An attempt to reproduce the phthalide (XIII) by first using hydrochloric acid in the condensation, resulted in failure. Several condensations repeated with varying boiling periods produced the same result. Where Rennie obtained a product readily crystallized from absolute alcohol, the present reactions yielded a resin which was insoluble in the hot solvent. The resin which decomposed at 210-260°, could not be crystallized from any solvent.

In seeking an explanation for this apparent anomaly, the preparation of 2:4-dimethoxybenzoic acid (XII) must be considered. When 2:4-dihydroxybenzoic acid (XIV) was methylated by Graebe's method (9) (which Rennie employed), XII was not obtained alone, but a mixture of both 4-methoxy-2-hydroxybenzoic acid (XV) and 2:4-dimethoxybenzoic acid (XII) was produced.



Separation of XII from XV was found impossible and hence could not be used for the ensuing condensations. Since Rennie reported a lower melting point than that given for the pure acid (XII), it would indicate that he used the mixture for his experiments. An examination of Rennie's samples in this series, revealed that they gave ferric chloride reactions and were darkening on standing; this would indicate that they were of a phenolic nature. Such phenomena appeared to substantiate the presence of the hydroxy acid (XV) in these reactions.

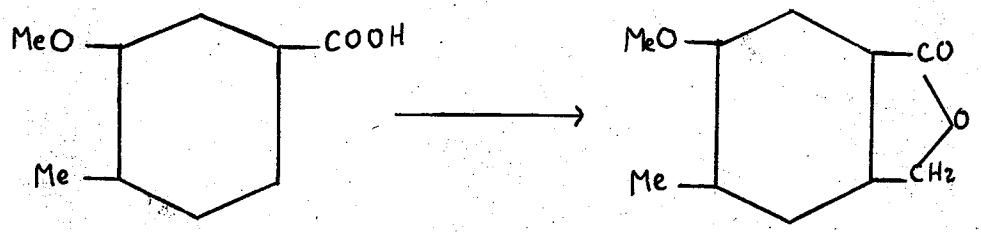
The resistance of the OH group ortho to COOH, to ordinary methylation processes, was previously demonstrated by Perkin (17). Consequently, after a careful search through the literature, an entirely different method for methylating 2:4-dihydroxybenzoic acid (XIV) was found (28). Production of XII by this method was obtained in very pure yields, non-contaminated by the monomethoxy acid.

As the pure acid yielded an insoluble resin in the condensations with formaldehyde and hydrochloric acid, it could then be inferred that the products obtained by Rennie (23) were due to the

influence of the monomethoxy acid (XV). Furthermore, none of these products had defined melting points, but merely decomposed at fairly high temperatures, suggesting a complex type of molecule rather than the simple phthalide (XIII).

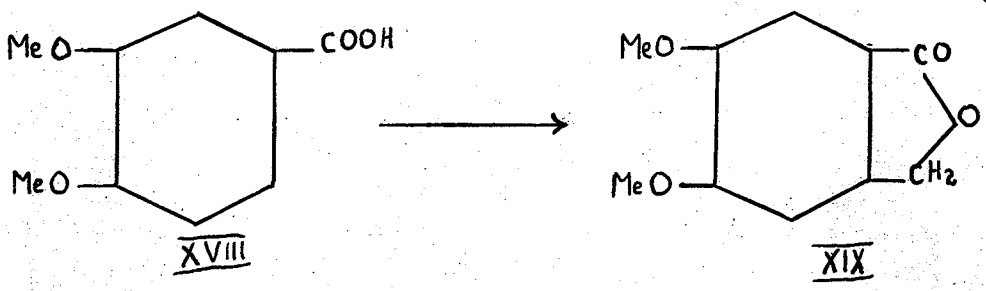
The peculiar position created by these condensations with respect to 2:4 - dimethoxybenzoic acid (XII), postponed the study with hydrobromic and hydriodic acid until further work will clarify the situation.

The first successful condensation with hydrobromic acid and formaldehyde, was obtained with 3-methoxy-p-toluic acid (XVI). Yan (31) had previously made the phthalide (XVII) of this acid in a formaldhyde-hydrochloric condensation. With the hydrobromic acid the same phthalide was produced. When hydriodic was used, the phthalide (XVII) again resulted in a similar condensation.



XVI XVII

Since veratric acid (XVIII) was the first to be studied with formaldehyde and hydrochloric acid, it was also selected for the condensations with the other halogen acids. Firstly, however, the acid was condensed with hydrochloric acid and formaldehyde in the same manner described by Perkin, Edwards, and Stoyle (18). As in their case, meconine (XIX) was produced.



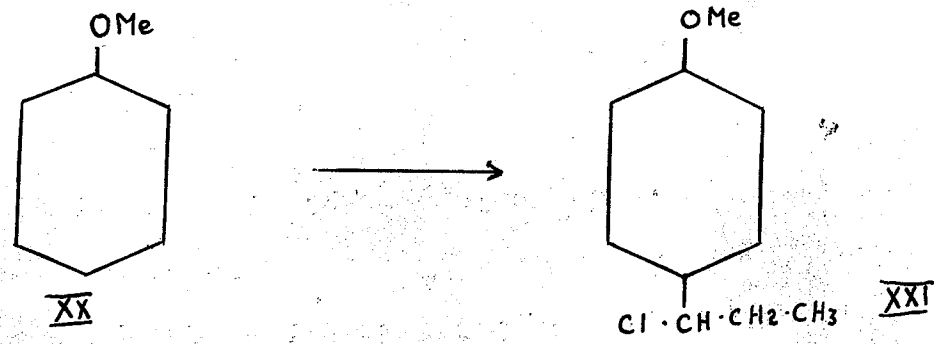
XVIII XIX

In subsequent condensations with hydrobromic and hydriodic acids respectively, veratric acid yielded meconine in both instances.

It is quite apparent from the condensations with hydrobromic and hydriodic acids, that the same product will be produced when these acids replace hydrochloric acid in the reactions with formaldehyde upon aromatic acids.

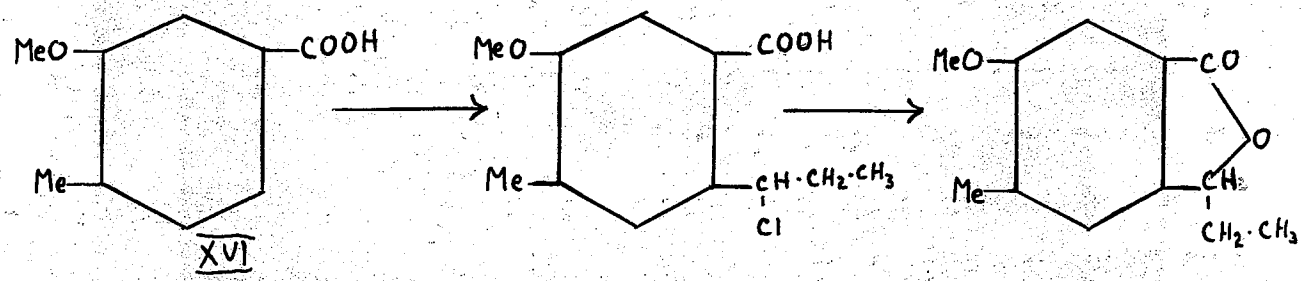
Inasmuch as the replacement of hydrochloric acid by the other halogen acids has proved successful in condensations with formaldehyde on aromatic acids, it was hoped that the use of other aldehydes in place of formaldehyde would be as equally successful. Since phthalides are the general type of products obtained in these reactions with aromatic acids, similar compounds would be expected with the higher aliphatic aldehydes.

The work of Quelet (20) and others with different aromatic compounds, has shown that the chlorine atom in the chloroalkyl radical of the higher aldehydes is attached to the carbon alpha to the ring nucleus. The chloropropylation of anisole (XX) is an example.



XX XXI

If a similar reaction could take place with an acid, an alkyl substituted phthalide would be expected. The course of the reaction with 3-methoxy-p-toluic acid would probably be as indicated below.



XVI

Unfortunately, attempted condensations with hydrochloric acid and acetaldehyde as well as propionaldehyde, on 3-methoxy-p-toluic acid (XVI) produced resinous substances from which the original acid (XVI) was recovered.

A blank run with hydrochloric acid and acetaldehyde resulted in formation of a resin after a short period of boiling. The same thing occurred with other higher aldehydes. When boiled alone for a great length of time the aldehydes remained unchanged. Obviously, the presence of the mineral acid induces polymerisation

of the aldehyde when heat is applied. As the condensations with aromatic acids require boiling the mixtures, reactions with the higher aliphatic aldehydes could not be expected under such conditions.

In reviewing the formation of phthalides from aromatic acids by condensations with formaldehyde and halogen acids, several factors must be considered. The most obvious point elucidated by this and previous investigations, is the importance of halogenmethylation ortho to the carboxyl group of the aromatic acid. Without such substitution of the halogenmethyl group, phthalide production is naturally impossible.

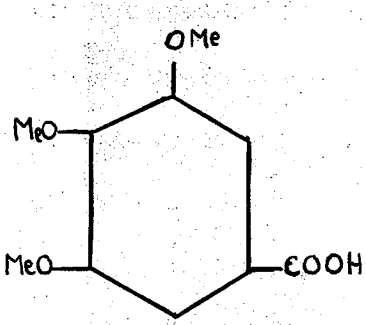
It follows, therefore, that the failure of certain aromatic acids to form phthalides (see Table I) can be linked with their resistance to halogenmethylation. Closer observation of these acids shows that nearly all have only a carboxyl group present or one more substituent group in the nucleus. This suggests that the carboxyl has an inhibiting effect on halogenmethylation. On the other hand, the acids which do form phthalides have at least two or more substituent groups such as CH_3 and OCH_3 in the ring. It would seem that these groups influence halogenmethylation and since there are two or more they overcome the inhibiting effect of the carboxyl group.

The latter suggestion is supported by the work of Quelet (19), Sommelet (25), Fuson and McKeever (8), and others, who found that similarly substituted hydrocarbons yielded chloromethyl derivatives. The influence of substituent groups has best been confirmed by Vavon, Bolle, and Calin (30). These men actually devised experiments by which they could measure the rate of halogenmethylation of various substituted aromatic compounds. Theyfound that the rate

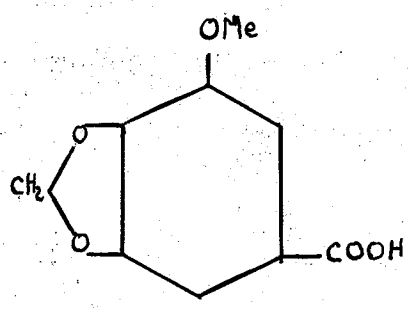
is increased by $-CH_3$, $-C_2H_5$, $-C_3H_7$, $-OCH_3$, and $-OC_3H_7$; and diminished by -Cl, -Br, -I, $-CH_2-Cl$, -COOH, $-NO_2$.

On the basis of these deductions it seems inexplicable that 2:4-dimethoxybenzoic acid and piperonylic acid should behave negatively, as found in this investigation. Indications that piperonylic acid does form a phthalide has already been pointed out (c.f. p.13). It may be assumed for the present, therefore, that a further study of these acids may evolve the necessary experimental conditions for successful condensations.

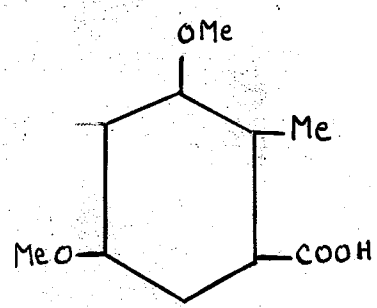
Although the normal phthalide appears most frequently, several acids produce only the chloromethylphthalide or both. Cameron (2) suggested that only those acids which have a CH_3 or OCH_3 group in the 3:5 or 3:4:5 position, will produce the halogenated product. This assumption appears valid for 3:5-dimethoxy-p-toluic (III), trimethylgallic (XXII), and myristicinic acids (XXIII). Contrary to this idea, however, 3:5-dimethoxy-p-toluic acid (XXIV) does not produce a chlorocompound.



XXII



XXIII



XXIV

The importance of experimental conditions in producing the chloromethylphthalide has been emphasized by the work of King and King (12). It will be recalled (p.9) that these men were able to make the normal phthalide or the chlorinated compound of trimethyl gallic acid by merely altering the quantity of hydrochloric acid.

If the mode of reaction described by King and King for the isolation of the chloromethylphthalide is general, then it should be possible to obtain the simple phthalide from all acids yielding a chloroproduct if experimental conditions are properly controlled.

Since halogenmethylation is essential for phthalide formation, then the phthalides obtained from condensations with hydrobromic and hydriodic acids must have come through the bromomethylation and iodomethylation of the nucleus. In all probability the aromatic acids that give chloromethylphthalides would produce the corresponding bromo- and iodo- derivatives if condensed with hydrobromic and hydriodic acids respectively.

The introduction of halogenalkyl groups into an aromatic acid by the use of higher aliphatic aldehydes can only be accomplished, when some means for prevention of polymerisation of the aldehyde has been devised.

EXPERIMENTAL SECTION

I. CONDENSATIONS WITH FORMALDEHYDE AND HYDROCHLORIC ACID

1. Piperonylic acid.

(a) Preparation of piperonylic acid.

The method described by Kostanecki and Tambor (13) for the preparation of veratric acid was employed. Piperonal (20 gm.) was refluxed with bromine in potassium hydroxide solution (20 gm.) for one hour on the sandbath. The solution was filtered and sodium bisulphite added to the filtrate which was then acidified. The acid (20 gm.), which precipitated as a white powder, was filtered, washed with warm water, and dried. Recrystallization from alcohol afforded a pure specimen, melting at 227°.

(b) Condensation of piperonylic acid.

Piperonylic acid (2 gm.) was boiled for 12 hours on the water bath with formaldehyde (15 c.c.) and hydrochloric acid (12 c.c.). The solid, which did not go into solution, was filtered off after cooling. This residue melted at 210° indicating that it was unchanged piperonylic acid; recrystallization of the substance followed by a mixed melting point determination, confirmed this fact. The filtrate was diluted with water and well-shaken, upon which, the emulsion that was formed, cleared, leaving resinous material on the sides of the flask. The solution was filtered and allowed to stand. After several days, a white crystalline substance settled out in minute quantities. With a few crystallizations from hot water, the product melted at 138-40°.

Several more condensations were carried out, using acetic and

phosphoric acids alternately, as catalysts. Although the boiling periods varied in each case, the low-melting substance obtained in the first condensation, was not isolated.

2. 3:5-Dimethoxy-p-toluic acid.

(a) Preparation of 3:5-dihydroxy-p-toluic acid.

Employing the method of Asahino and Asano (1), only comparatively poor yields of 3:5-dihydroxy-p-toluic acid could be obtained. p-Toluic acid was prepared from p-toluidine in a Sandmeyer reaction through the nitrile, as described by Cohen (4). Sulphonation of this acid was accomplished with a mixture of 60% and 20% oleum; the resulting sulphonic acid was converted to the potassium salt through its barium salt.

The potassium salt (65 gm.) was fused with potassium hydroxide (300 gm.) at 250-270° for 45 minutes. The melt was dissolved in water, acidified with hydrochloric acid, and extracted thoroughly with ether. Following evaporation of the ether, the residue was treated with warm water which dissolved the phenolic acid and left an insoluble substance. The aqueous solution was saturated with common salt and extracted with ether; evaporation of the solvent left a brownish-colored substance (8 gm.), melting at 245-248°. Due to the small yield, several runs were necessary to obtain sufficient material for the methylation process.

(b) Preparation of 3:5-dimethoxy-p-toluic acid.

3:5-Dihydroxy-p-toluic acid (17.5 gm.) was dissolved in 20% sodium hydroxide solution (250 c.c.), and dimethyl sulphate (75 c.c.) was added in three portions in an atmosphere of propane.

On shaking and cooling the solution for ½ hour, orange-yellow crystals of the sodium salt separated out; after which, the mixture was boiled under reflux for one hour to hydrolyse excess methyl sulphate. When cooled, the solution was acidified with hydrochloric acid which precipitated a cream-colored substance. The dimethoxy acid was filtered, washed with water, and crystallized from ethyl acetate in snow-white needles (8 gm.) which melted at 212°.

(c) Chloromethylphthalide of 3:5-dimethoxy-p-toluic acid.

The dimethoxy acid (3.5 gm.) was boiled on the water bath with formaldehyde (10 c.c.) and hydrochloric acid (6c.c.). During the heating period, small amounts of the aldehyde and mineral acid were added to replace any that may have been lost by boiling. Evidence of a reaction, was the formation of a dark brown resinous material, which floated on the surface of the solution; this was filtered while still warm, at the end of 1½ hours. The resin was taken up with alcohol from which a white, insoluble substance melting at 248-50°, was separated. Since this was a non-chlorinated product, it was of no interest in the present experiment, and hence, not analysed. The alcoholic filtrate yielded more of this substance.

When the original filtrate cooled, a crystalline material which proved to be the chlorinated compound, precipitated out. Several crystallizations from ethyl acetate, produced glistening white needles, melting at 130-1°. A semi-micro analysis for chlorine was obtained by a method described by Sucharda and Bobranski in "Semi-micro Methods for the Elementary Analysis Of

Organic Compounds".

Analysis

Calculated for $C_{12}H_{13}O_4Cl$: Cl, 13.84

Found : Cl, 13.62

3. 2:4-Dimethoxybenzoic acid

(a) Preparation of 2:4-dihydroxybenzoic acid.

A similar procedure as outlined by Nierenstein and Clibbens (15), was employed for this preparation.

Resorcinol (100 gm.), sodium bicarbonate (500 gm.), and water (1200 gm.) were refluxed together for 3 hours, while a steady stream of carbon dioxide was passed through the solution. The solution was cooled, acidified with hydrochloric acid, and the thick curdy precipitate immediately filtered and washed with small amounts of water. When crystallized from hot water, the aqueous solution was rapidly cooled, precipitating the acid in fine faintly colored crystals (55 gm.) which melted at 210°. Ethereal extracts of the original filtrate, yielded very small quantities of the acid.

(b) Preparation of 2:4-dimethoxybenzoic acid.

Since the ordinary methylation process used in the preparation of 3:5-dimethoxy-p-toluic acid failed, the method described by Tambor (28), was employed.

To a hot alcoholic solution of 2:4-dihydroxybenzoic acid (50 gm.), sodium hydroxide (24 gm. in 90 c.c. of water) and dimethyl sulphate (56 c.c.) were added slowly from tap-funnels. The addition was made alternately, beginning with sodium hydroxide and at the same time the mixture was well-shaken. The solution was heated for a short period, following which, exactly the same amount

of alkali and methyl sulphate was added once more to the boiling solution. Boiling was continued for a little while longer to hydrolyse any unchanged methyl sulphate and any ester that may have formed. The solution was diluted, acidified, and the resulting precipitate filtered off. Crystallization from dilute alcohol yielded snow-white needles (45 gm.) melting at 107-8°; Tambor's product melted at 108°.

(c) Condensation of 2:4-dimethoxybenzoic acid.

When the dimethoxybenzoic acid (3 gm.) was heated for a few minutes on the water bath with formaldehyde (15 c.c.) and concentrated hydrochloric acid (15 c.c.), the solution began to froth. The boiling was continued for ½ hour during which time the solid took on a resinous appearance, while the solution remained an amber color. On filtration, the greyish-green residue (3 gm.) failed to crystallize from any solvent. A melting point determination on the crude product showed that it decomposed at 210-265°. No substance was thrown out from the filtrate on addition of water.

Several condensations repeated with various heating periods, merely produced the same result.

4. Veratric acid.

(a) Preparation of veratric aldehyde.

The aldehyde was obtained in very good yields with the method described by Johnson and Stevenson (11). By methylating vanillin (50 gm.) with dimethyl sulphate (40 c.c.) and potassium hydroxide (30 gm. in 50c.c. water), a very pure product (48 gm.) which melted at 44-45° was obtained.

(b) Preparation of veratric acid.

Kostanecki and Tambor's method (13) which has already been described in connection with piperonylic acid, was employed in this preparation. Veratric acid (8.5 gm.) was obtained from the veratric aldehyde (10 gm.) in such pure form (melting point, 180°), that crystallization was unnecessary.

(c) Phthalide of veratric acid

The condensation of veratric acid was carried out in exactly the same way described by Perkin, Edwards, and Stoyle (18).

Veratric acid (3 gm.), formaldehyde (4 c.c.), and hydrochloric acid (12 c.c.) were heated for 12 hours on the water bath; after an hour's heating the solution became quite dark. On completion of the reaction, the solution was rapidly cooled, diluted with water to form an emulsion which was shaken until a clear solution appeared, leaving tarry material on the sides of the flask. The solution was immediately filtered and allowed to stand; after some time a brownish substance slowly precipitated. The crude material was crystallized from water yielding the phthalide, meconine, in white needles (1.4 gm.) which melted at 156-7°. Perkin, Edwards, and Stoyle give m.p. 157° for their product.

It was found that the heating period may be reduced to 2½ hours on the water bath and 1 hour over the wire gauze, to produce the same result.

II. CONDENSATIONS WITH FORMALDEHYDE AND HYDROBROMIC ACID

1. Phthalide of veratric acid.

Veratric acid (3 gm.) was condensed with formaldehyde (15 c.c.) and hydrobromic acid (15 c.c.) in a similar manner to that employed with hydrochloric acid. The mixture in this case was boiled on the water bath for 2½ hours and 15 minutes on the wire gauze. The procedure followed from this point, was exactly the same as the previous case. Here again, a brown crystalline powder was obtained from the solution. On crystallization from water, white needles (1 gm.) were obtained, which melted at 156-7°.

A mixed melting point with the product from the hydrochloric acid condensation, gave 156°. Therefore, both products were the same i.e. the phthalide, meconine.

2. 3-Methoxy-p-toluic acid.

(a) Preparation of 3-methoxy-p-toluic acid.

Sulphonation of p-toluic acid (95 gm.) by 15% oleum (25 c.c.) according tothe directions of Meldrum and Perkin (14), yielded the desired 3-mono-sulphonic acid (100 gm.) in pure form. The acid melted at 240-1°.

The alkali fusion was carried out at 270° for 10 minutes and at 285° for 10 minutes; the 3-hydroxy-p-toluic acid obtained, was crystallized from water in fine white needles (60 gm.), melting at 208°.

Methylation of the hydroxy acid (45 gm.) was accomplished by the method employed with 3:5-dihydroxy-p-toluic acid, the resulting

3-methoxy-p-toluic acid was obtained in pure white needles (42 gm.) after crystallization from acetic acid. The pure product melted at 157°.

(b) Phthalide of 3-methoxy-p-toluic acid.

The mono-methoxy acid (3.5 gm.) was heated for 2½ hours on the steam bath with concentrated hydrobromic acid (15 c.c. of 48%) and formaldehyde (10 c.c.). During this period an extra 2 c.c. of the aldehyde and mineral acid were added. On cooling, a crystalline material (3.3 gm.) settled out; crystallization from dilute alcohol yielded white prisms (2.25 gm.) that melted at 143°. A mixed melting point with the known phthalide, synthesized with hydrochloric acid, proved it to be the same product.

III. CONDENSATIONS WITH FORMALDEHYDE AND HYDRIODIC ACID

1. Phthalide of veratric acid

The condensation of veratric acid (3 gm.) with formaldehyde (10 c.c.) and hydriodic acid (15 c.c. of 50%) was carried out with a little more difficulty than in the previous reactions. In this case a longer heating period (5 hours) on the water bath was necessary. The brownish product which separated as in the previous cases, was washed with sodium bisulphite and crystallized from water in faintly colored crystals which melted at 156°. Mixed melting point determinations with the meconine obtained from both the hydrobromic and hydrochloric acid condensations established this product to be the same substance.

2. Phthalide of 3-methoxy-p-toluic acid.

3-Methoxy-p-toluic acid (3.5 gm.) was boiled with formaldehyde (10 c.c.) and hydriodic acid (15 c.c. sp. gr. 1.7) for 2 hours on the water bath. The substance produced was triturated with sodium thiosulphate and then with sodium bisulphite to remove iodine. After washing with warm water the substance was recrystallized from alcohol and water; several crystallizations were necessary before the product was obtained in glistening white needles which melted at 142-3°. Mixed melting point determinations with the phthalides obtained in the other condensations with 3-methoxy-p-toluic acid gave 142°. This confirmed the synthesis of the same phthalide as produced in the other two cases.

IV. CONDENSATIONS WITH HIGHER ALDEHYDES AND HYDROCHLORIC ACID

1. Condensation of 3-methoxy-p-toluic acid and paraldehyde.

The methoxy acid (3.5 gm.) was heated with paraldehyde (12 c.c.) and hydrochloric acid (7 c.c.) on the water bath. Solution of the solid began to take place slowly after 15 minutes; within ½ hour the solution became very dark and viscous; at the end of an hour the heating was stopped, and the solution allowed to cool. The black resin, produced in the reaction, was filtered and washed with water. Alcohol treatment merely separated unchanged 3-methoxy-p-toluic acid. The addition of water to the filtrate yielded more of the unchanged acid.

Several blank runs with paraldehyde and hydrochloric acid produced resinous substances in each case. Various modifications in

the heating period, and the introduction of different catalytic agents, did not prevent the polymerisation of the aldehyde.

Similar condensations were attempted with propionaldehyde and butyraldehyde, but in all experiments only the resinous material was obtained.

SUMMARY

1. Condensations of piperonylic acid with formaldehyde and hydrochloric acid alone, and in the presence of acetic and phosphoric acids, yielded the unchanged aromatic acid in all but one case. In this instance, a low-melting substance which may be the phthalide, was isolated.

2. Analytical data on the chloroproduct obtained from the formaldehyde-hydrochloric acid condensation of 3:5-dimethoxy-p-toluic acid, agreed with the structure of the chloromethylphthalide.

3. 2:4-Dimethoxybenzoic acid gave only a greenish-grey resinous material when condensed with formaldehyde and hydrochloric acid. As a result, it has been shown that Rennie's product from a similar condensation with this aromatic acid, may not be the phthalide. The merits of Rennie's series have been critically discussed.

4. The normal phthalides of both 3-methoxy-p-toluic acid and veratric acid have been produced in separate condensations with hydrochloric, hydrobromic, and hydriodic acids.

5. It has been concluded that chloromethylation, iodomethylation, and bromomethylation, precede phthalide formation in hydrochloric, hydriodic, and hydrobromic acid condensations, respectively.

6. Polymerisation of the higher aliphatic aldehydes by the action of hydrochloric acid at high temperatures, has been found to prevent successful condensations with aromatic acids.

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PART II

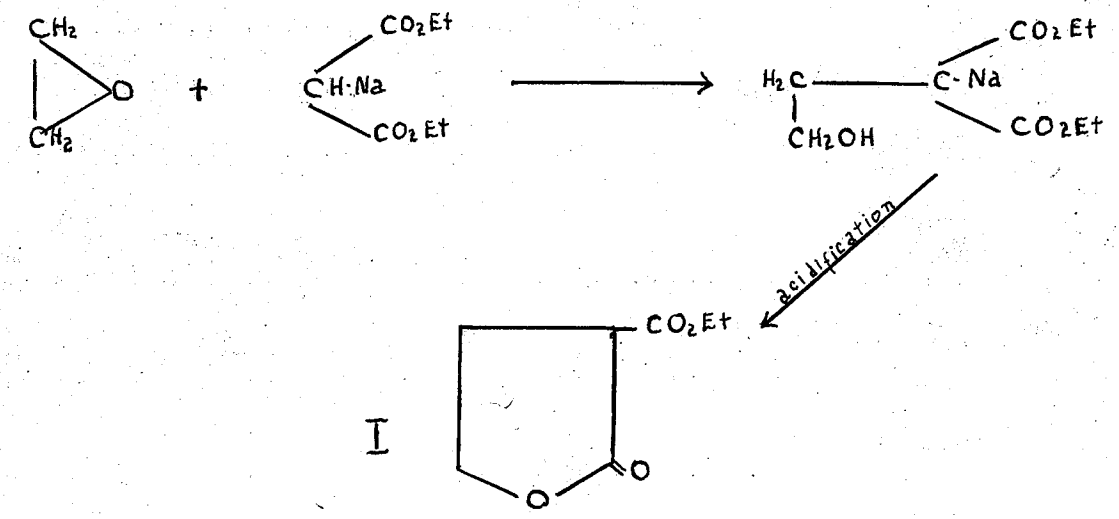
SYNTHESIS OF ∝-ETHANOLGLUTARIC ACID LACTONE AND RELATED SUBSTANCES

SYNTHESIS OF α-ETHANOLGLUTARIC ACID LACTONE AND RELATED SUBSTANCES

INTRODUCTION

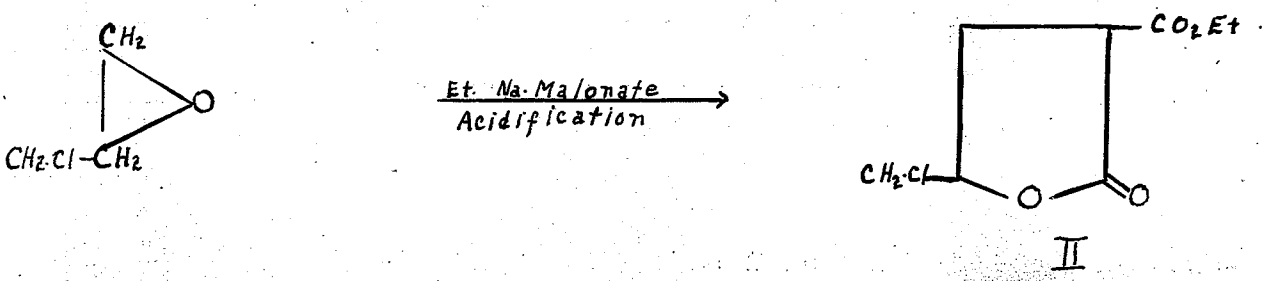
The study of 2-ketocyclohexylsuccinic acid and related substances by Alexander (1), suggested that some aspects of the problem should be further investigated. Consequently, the syntheses of certain γ-lactones of 4-hydroxybutyric acid involving the use of ethylene and propylene oxides, were undertaken in the present work.

This type of lactone has been made by Traube and Lehmann (19) who condensed ethylene oxide with ethyl sodiomalonate to produce a sodio-derivative which on acidification, resulted in the butyric lactone (I).



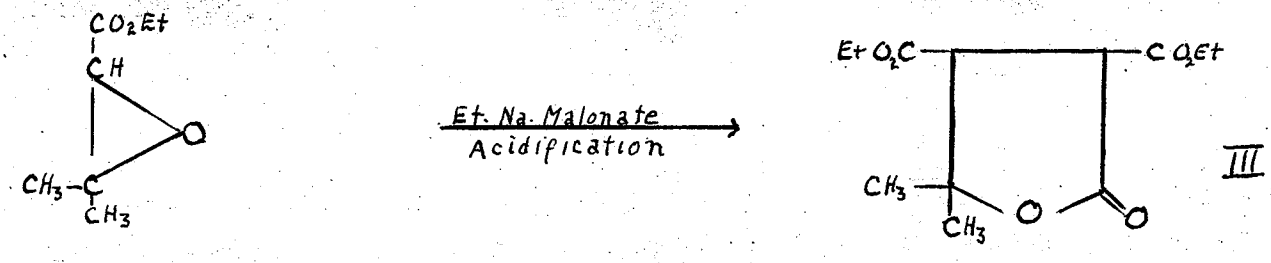
I

In a similar manner, they obtained the lactone (II) from the epichlorohydrin of ethylene oxide (20).



II

A successful synthesis of terebic acid (III) was accomplished by Haller and Blanc (12) in a similar reaction with ethyl β-β-dimethyl glycidate.

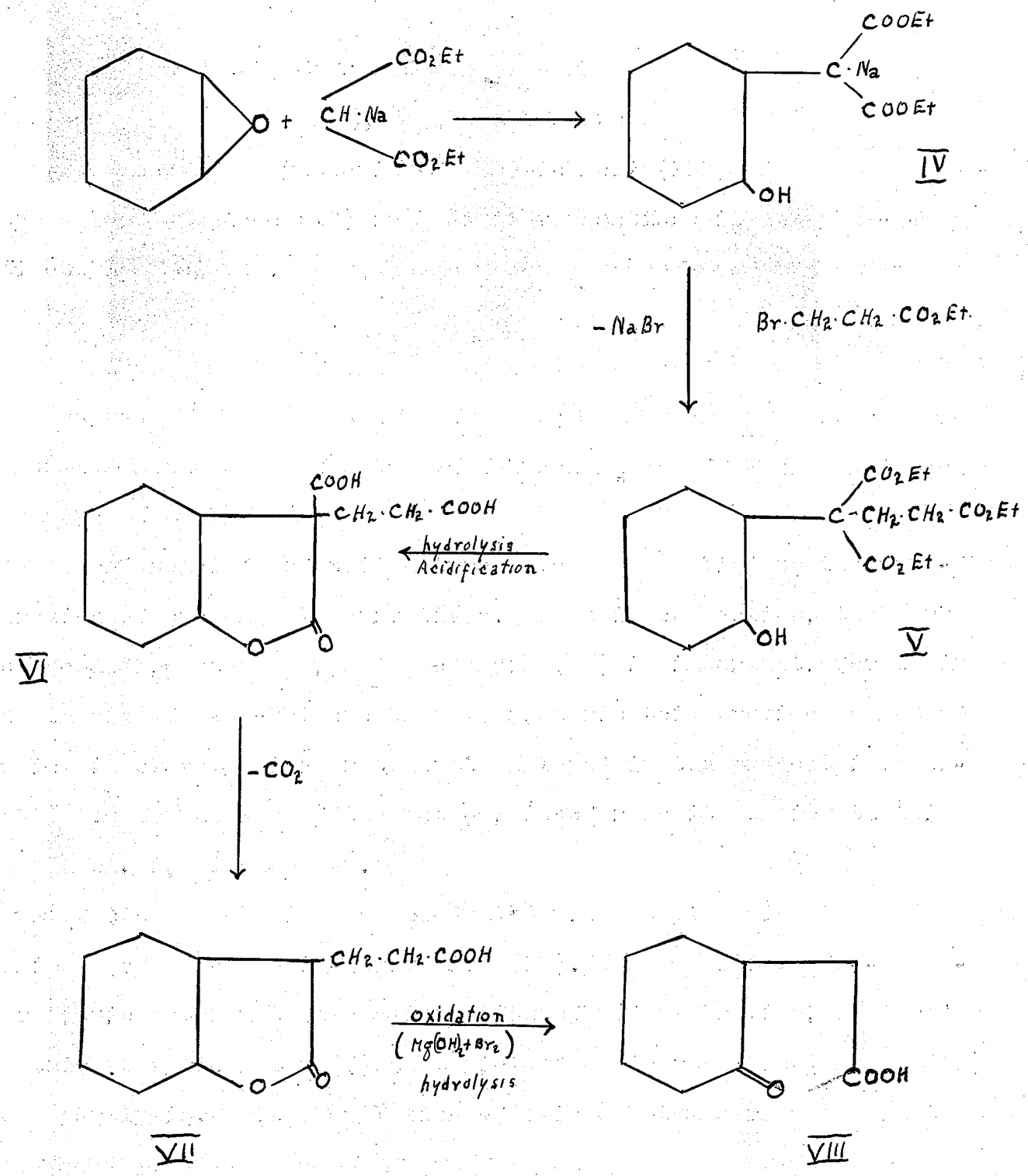


III

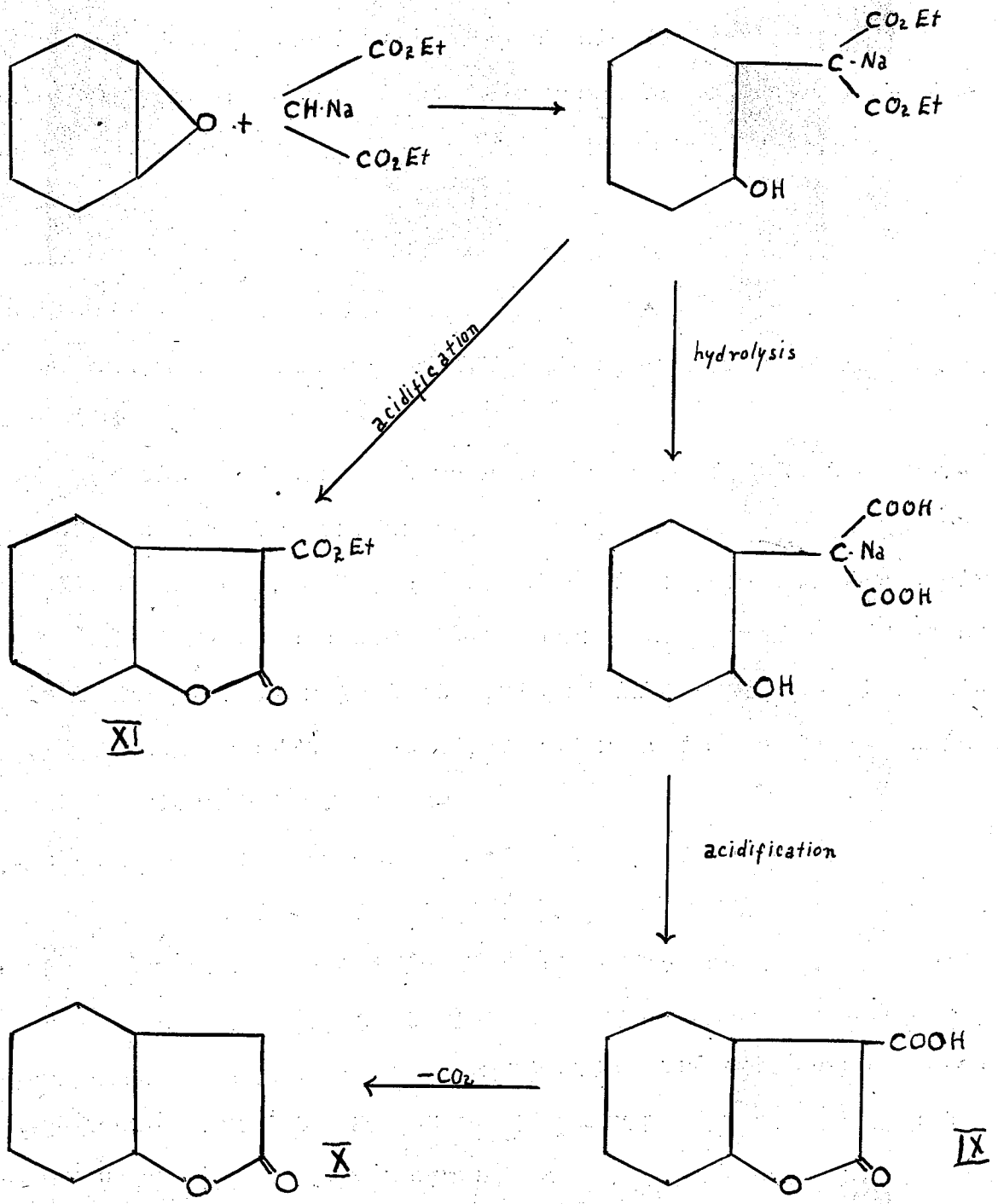
Condensations of this nature have been applied to the preparation of cyclohexyl derivatives. In this connection, the work of Kendall, Osterberg, and MacKenzie (15) is important, for their synthesis of α-(2-ketocyclohexyl) glutaric acid provides a method which is closely similar to that employed in the present investigation. An outline of the method, insofar as it applies to this research, is given below.

Cyclohexene oxide was condensed with ethyl sodiomalonate which gave a new sodio-derivative (IV). The addition of β-bromopropionic ester with the elimination of sodium bromide, produced a tricarboxylic ester (V) that yielded a dicarboxylic lactone (VI) on hydrolysis. Decarboxylation of this substance resulted in the

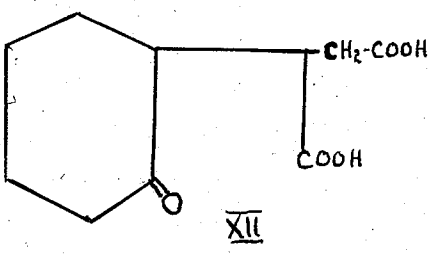
glutaric acid lactone (VII). Oxidation and hydrolysis of the lactone gave ∝-2-ketocyclohexylglutaric acid(VIII).



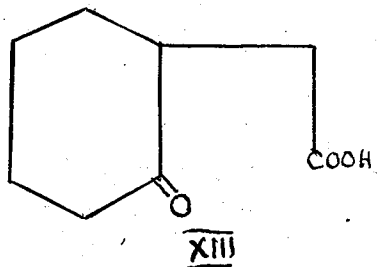
Prior to Kendall's publication, Coffey (8) had condensed cyclohexene oxide with ethyl sodiomalonate, but hydrolysed the new sodio-derivative without further condensation; this was followed by acidification and decarboxylation of the resulting acid lactone (IX) to give cyclohexanolacetic acid lactone (X).



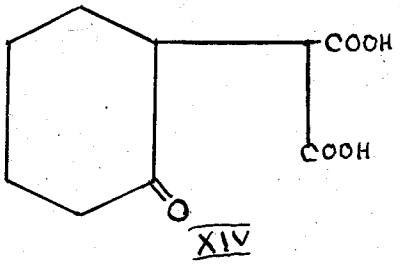
Later, Charlesworth (5) carried out similar syntheses whereby he confirmed the preparation of 2-ketocylohexylglutaric acid by Kendall, Osterberg, and MacKenzie ; and more recently McCrae, Charlesworth, and Alexander (16) have extended this method to a synthesis of 2-ketocyclohexylsuccinic acid (XII), 2-ketocyclohexylacetic acid (XIII), and 2-ketocyclohexylmalonic acid (XIV). The latter two substances were obtained from Coffey's ester lactone (XI) of cyclohexanolacetic acid.



XII



XIII

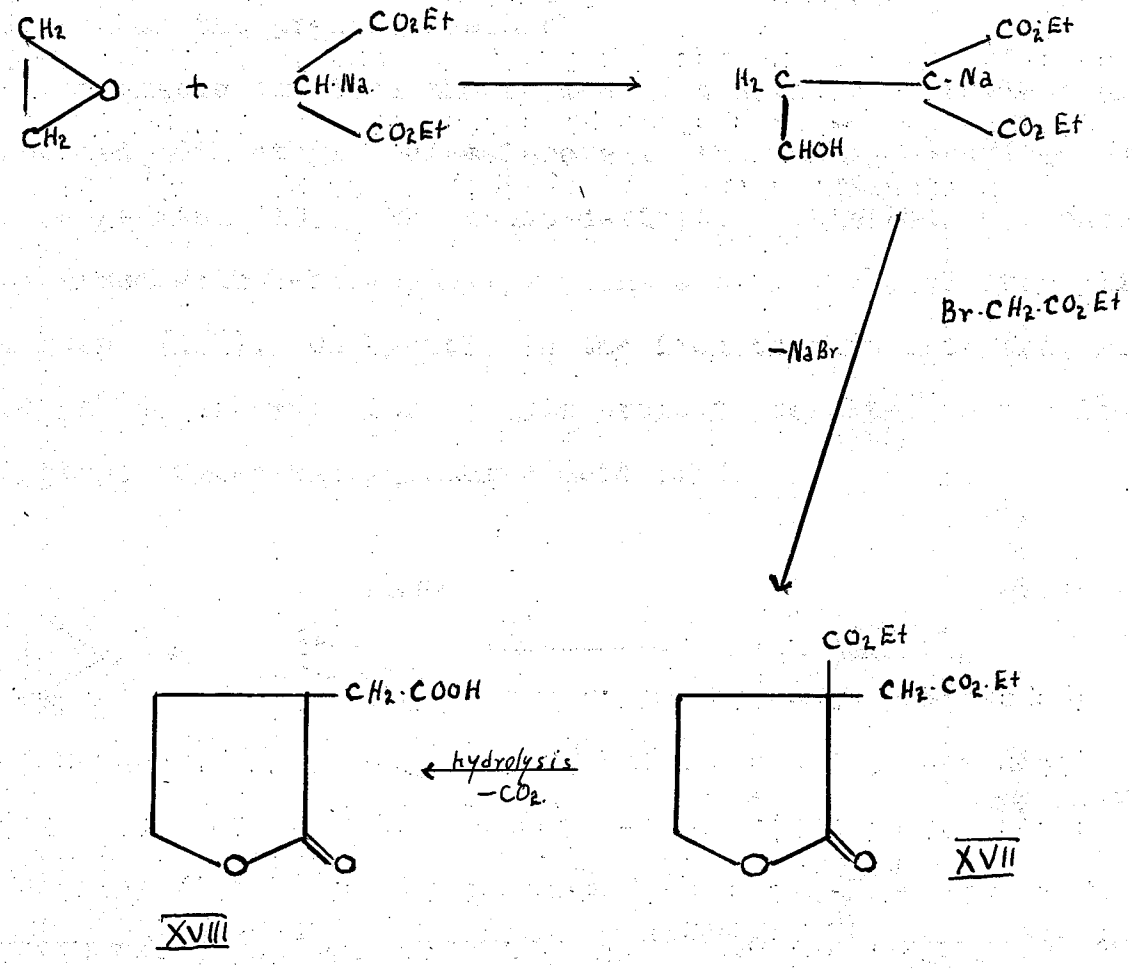


XIV

Previously, Chuang and Ma (9), Chatterjee (7), and Ghosh (11) had prepared 2-ketocyclohexylacetic acid by different methods, but in no case was the product obtained, as pure as that prepared by McCrae, Charlesworth, and Alexander. Recently, Charlesworth, McCrae, and MacFarlane (6) have confirmed the structure of the 2-ketocyclohexyl acids by independent methods.

The application of Kendall's (15) and Coffey's (8) methods of syntheses to ethylene and propylene oxides, was attempted by Archibald (2). However, lack of sufficient experimental evidence and analytical data left Archibald's results in doubt. Subsequently, Alexander (1) continued this investigation with which he had partial success.

Alexander definitely accomplished the synthesis of ∝-ethanolsuccinic acid lactone (XVIII) in the following manner. By condensing ethylene oxide with ethyl sodiomalonate, the usual sodio-derivative was obtained. β-Bromoacetic ester was added to this sodio-compound to produce the ester lactone (XVII) which was subjected to a hydrolysis, followed by decarboxylation that resulted in the lactone of ∝-ethanolsuccinic acid.

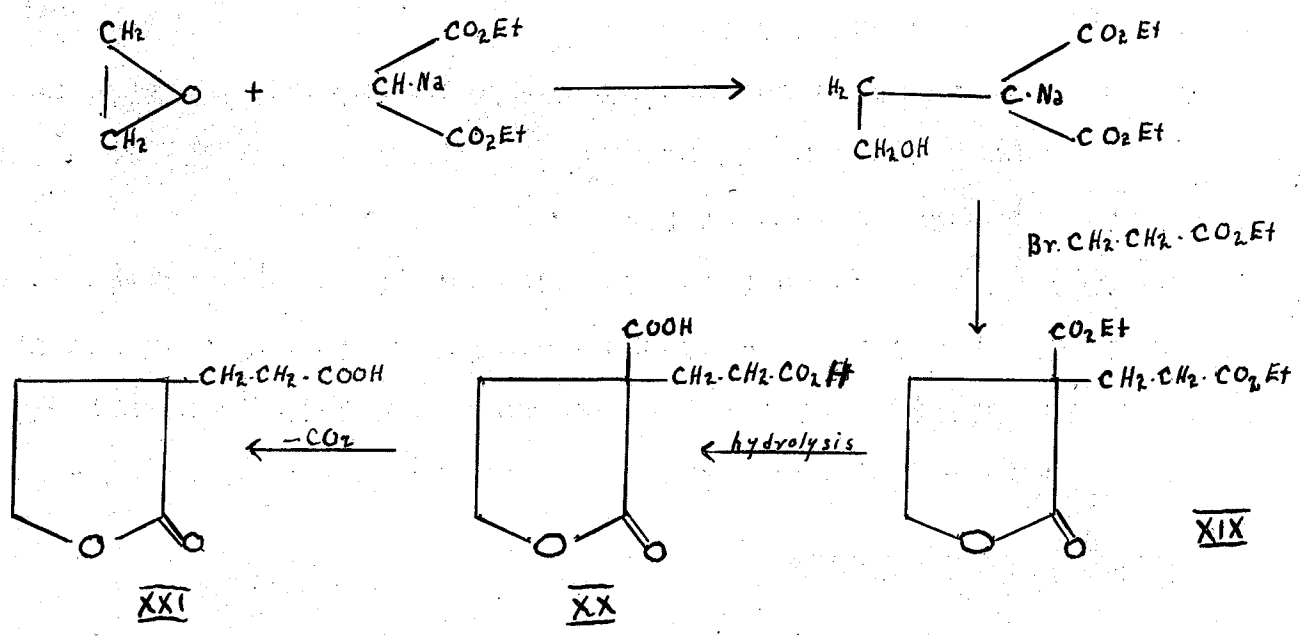


DISCUSSION OF RESULTS

Archibald (2) attempted to synthesize the lactone of ∝-ethanolglutaric acid in a similar manner that Kendall, Osterberg, and MacKenzie (15), obtained 2-ketocyclohexylglutaric acid. However, Archibald failed to achieve his purpose, since no analytical data of his product was made available.

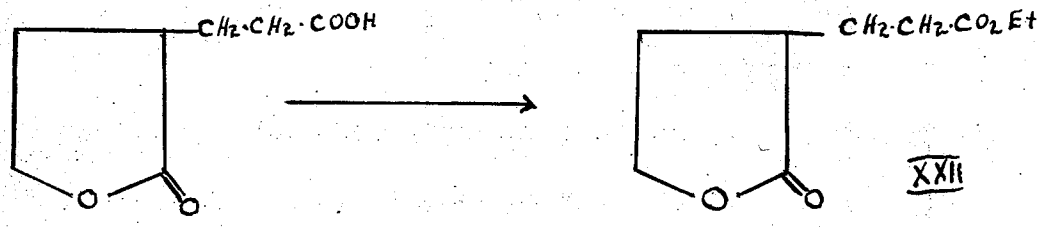
Later, a further effort was made by Alexander (1) to obtain the compound, but he too was unable to report any definite results. A re-investigation of this synthesis has been satisfactorily accomplished in the present research.

The synthesis involved the following reactions. Ethylene oxide was condensed with ethyl sodiomalonate in the manner described by Traube and Lehmann (19). The sodio-derivative obtained, was once more condensed with β-bromoethylpropionate to yield a dicarboxylic ester lactone (XIX). On hydrolysis the dicarboxylic acid (XX) was isolated and decarboxylation of this product, resulted in the desired lactone of ∝-ethanolglutaric acid (XXI).



In Archibald's (2) attempted synthesis, he reported the isolation of the diester (XIX) for which he apparently obtained a good analysis. Although Archibald gave a slightly higher boiling point (204-206°/15 mm.) for this compound than that obtained in the present work (200-1°/15 mm.), the acid lactone (XXI) which he presumably derived from the ester (XIX) had a very wide boiling range (170-185°/11 mm.). The obvious impurity of this substance rendered it useless for analysis.

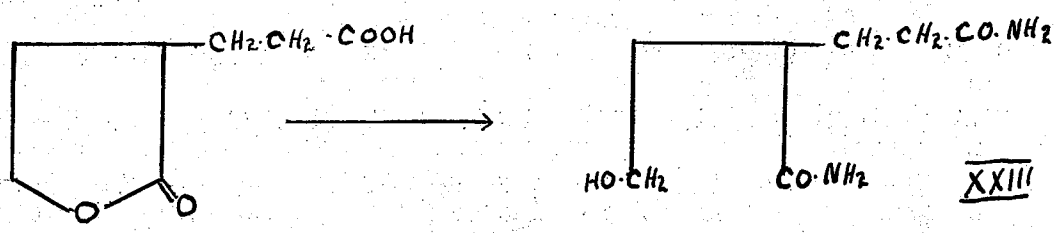
Alexander (1) does not report the separation of this ester(XIX), but hydrolysed directly without distillation, followed by acidification and immediate decarboxylation. Like Archibald, Alexander also obtained the acid lactone (XXI) with a wide boiling range (174-187°/14 mm.); as a result, Alexander was unable to analyse his product. However, Alexander converted the substance (XXI) to the ethyl ester (XXII), but though he apparently obtained a pure product (164-6°/8 mm.), his analysis did not agree with the calculated value.



XXI XXII

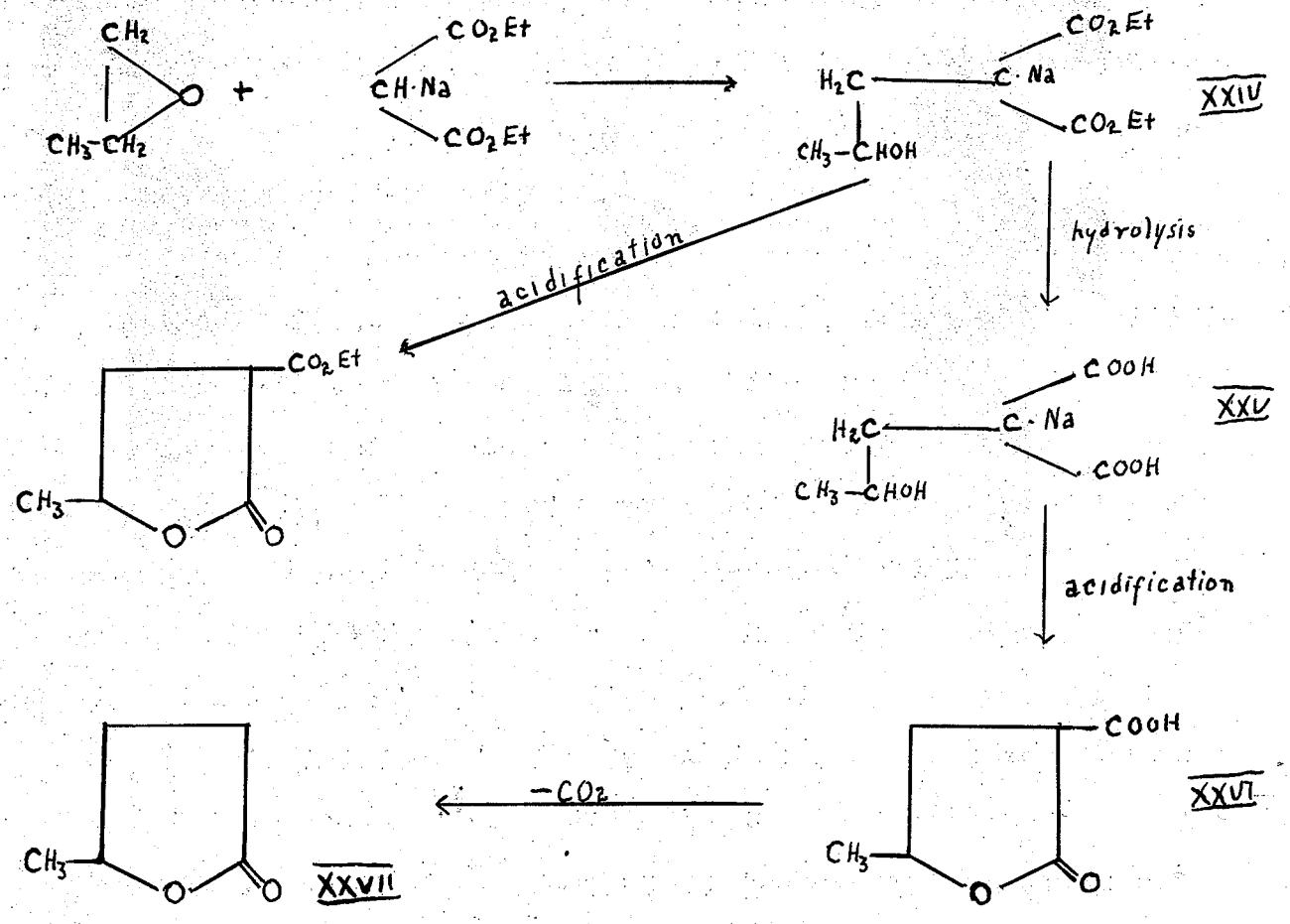
It has already been mentioned that the diester (XIX) separated in the present synthesis, was obtained in pure form. Following hydrolysis of this compound, certain modifications in the method were employed, which enabled the isolation of the intermediate dicarboxylic acid (XX) in a very pure state. This compound had not been previously reported by either Archibald or Alexander.

Decarboxylation of this intermediate acid yielded a viscous oil which distilled at 217-219°/12 mm. The high boiling point with its narrow range, when compared with the products obtained by Archibald and Alexander, indicates that neither of these men had obtained the desired acid lactone (XXI). Furthermore, the substance obtained in this investigation, solidified, a phenomenon which did not occur in the previous cases. This is the first instance where the isolation of ∝-ethanolglutaric acid lactone (XXI) has been definitely reported. An attempt is being made to obtain the amide (XXIII) of this lactone.



By a method similar to that employed by Coffey (8), it was possible to accomplish the synthesis of the lactone of 4-hydroxyvaleric acid (valerolactone) (XXVII). The early part of the synthesis was very similar to that used in the preparation of ∝-ethanolglutaric acid lactone. Propylene oxide was condensed with ethyl sodiomalonate producing a new sodio-derivative (XXIV). This compound

was subjected to a hydrolysis, the resulting product (XXV) then being acidified to yield a carboxylic acid lactone (XXVI); decarboxylation of this product gave valerolactone (XXVII).

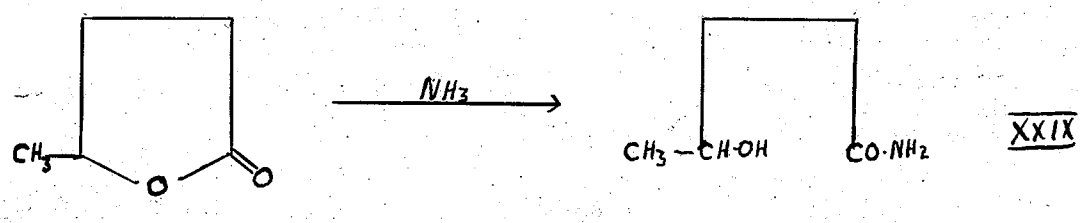


Alexander had also attempted to synthesize the valerolactone, but failed to obtain any analytical data on his substance. He did, however, try to isolate some intermediate substances which would indicate the plausibility of such a synthesis. Alexander (1) reported the barium salt of XXV, giving an analysis in fairly close agreement with the formula. In isolating this substance, Alexander employed ammonia to wash the product; this seemed rather unusual

for barium hydroxide would precipitate and contaminate the organic salt. Under these circumstances, analytical results would be questionable.

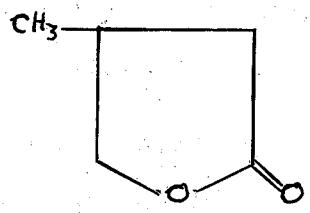
By acidifying the sodio-derivative (XXIV) before hydrolysing, Alexander presumably obtained the ester lactone (XXVIII). However, analysis of this compound did not agree with the requirements of the proposed formula. Thus, Alexander's attempted synthesis is unacceptable.

Further proof that valerolactone had been synthesized in the present work, was obtained by converting the lactone (XXVII) to the amide (XXIX). The solid amide produced, agreed with the melting point given by Boorman and Linstead (4) and Neugebauer (17) who had previously made this amide.



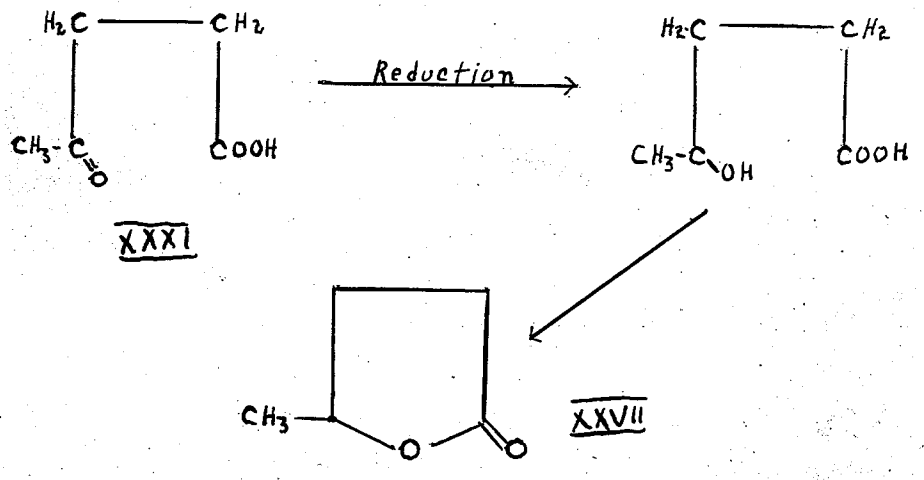
XXIX

The possibility that the isovaleric lactone (XXX) was the product obtained in the synthesis, could of course be eliminated, if the methyl group was definitely fixed in the γ position.

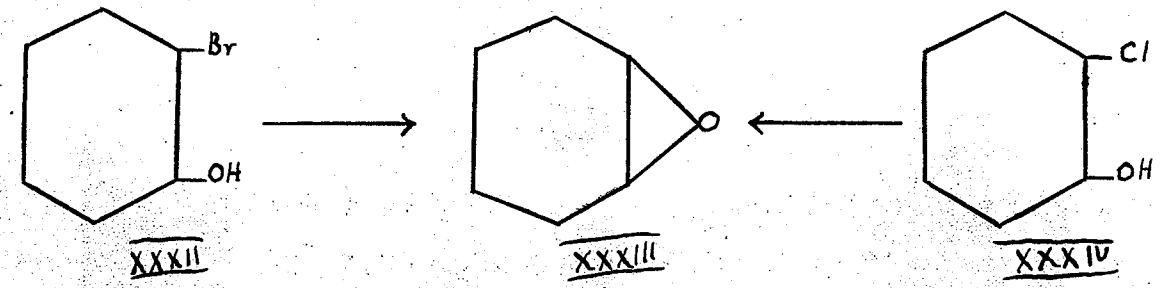


XXX

Both Neugebauer and Boorman and Linstead made their lactone by the reduction of levulinic acid (XXXI), as first described by Wolff (21). In this case only the normal lactone (XXVII) would be possible; and since the amide from the present synthesis was the same as that of the other men, it must have been produced from the same lactone. This, therefore, would confirm the synthesis of the normal valerolactone and not its isomer, in the present investigation.



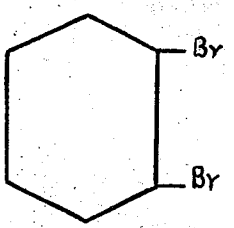
An interesting point that arose during the course of the research, concerned the preparation of cyclohexene oxide (XXXIII) from o-bromocyclohexanol (XXXII). The use of cyclohexene oxide in syntheses such as employed in this work, has already been discussed. Kendall and his co-workers (15) and also McCrae, Charlesworth, and Alexander (16), made use of this compound. In all these cases, the oxide was prepared from the chlorohydrin (XXXIV)



XXXII XXXIII XXXIV

It was suggested that cyclohexene oxide could also be prepared from the bromohydrin in a similar way. Charlesworth (5) had previously prepared the bromohydrin from a monobromourea solution, but McCrae and Archibald (private communication), reported that the substance was dibromohexane (XXXV) and not the o-bromocyclohexanol; as a result, cyclohexene oxide would not be produced.

Contrary to McCrae and Archibald's assertion, bromohydrin was prepared from a monobromourea solution in the present work, and the synthesis of cyclohexene oxide in comparatively good yield, was successfully accomplished.



XXXV

EXPERIMENTAL SECTION

I. SYNTHESES INVOLVING ETHYLENE OXIDE

(a) Preparation of ethyl β-bromopropionate.

β-Bromopropionic acid was first prepared as described by Kendall and MacKenzie (14). This involved the action of 48% hydrobromic acid (490 c.c.) on ethylene cyanohydrin (100 gm.). The resulting acid was obtained in a fairly good yield (135 gm.). Esterification was accomplished by adding ethyl alcohol and a small quantity of sulfosalycilic acid (catalyst) to the β-bromopropionic acid in a carbon tetrachloride solution, and the mixture subjected to the conditions outlined by Kendall. The ester obtained (150 gm.), boiled at 73.5°/17mm. (Kendall gives 60-65°/15 mm.).

(b) Lactone of α-carboxy-α-ethanolglutaric acid.

Sodium (17.5 gm.) was dissolved in absolute alcohol (285 c.c.) followed by the addition of ethyl malonate (125 gm.). To the ethyl sodiomalonate which was precipitated, ethylene oxide (35 gm.) was added in the cold. The mixture was well-shaken for a prolonged period during which it was occasionally cooled in ice. When most of the solid seemed to go into solution, a new sodio-derivative suddenly precipitated in a solid mass. As this precipitate appeared with evolution of heat, it was necessary to keep the flask well-cooled to avoid decomposition of the new compound. The mixture was allowed to stand overnight to complete the reaction of any unchanged materials. More absolute alcohol (150 c.c.) was put in, followed by the slow addition of β-bromopropionic ester. On prolonged shaking, the mixture became quite warm and at the same time sodium bromide was precipitated.

On completion of this reaction, the mixture was distilled up to 87° to eliminate excess alcohol. The addition of water to the remaining mixture, dissolved the sodium bromide and an oily layer appeared at the top of the aqueous portion. The oil was separated and the aqueous layer extracted with ether, after which the ethereal solution was added to the rest of the oil and dried with anhydrous sodium sulphate. Upon evaporation of the ether, the remaining oil was distilled under reduced pressure.

Fraction 1. -- 130°/15 mm. (45.6 gm.).
Fraction 2. 200-201°/14 mm. (71.6 gm.).
Fraction 3. 202-215°/14 mm. (16.0 gm.).

Fraction 2, was hydrolysed with 5N Sodium hydroxide (185 c.c.). After most of the alcohol was removed, the alkaline solution was distilled under reduced pressure to a comparatively small volume. The remaining solution was carefully acidified by passing in hydrochloric acid gas until the solution was acid to Congo red. During acidification there was a slight effervescence along with the precipitation of sodium chloride; the salt was immediately filtered and the filtrate allowed to stand. After a while, purewhite needle-like crystals were precipitated. The precipitate was taken up in ether to eliminate any inorganic salt that might be present and the ethereal solution dried over sodium sulphate. On further concentration of the filtrate more of this substance was obtained and treated in the same way.

A pure white material (30 gm.) melting at 125°, was obtained from the ethereal extract. Recrystallisation of a small quantity

yielded glistening white needles melting at 125° with evolution of carbon dioxide.

Analysis

Calculated for $C_8H_{10}O_6$: C, 47.52; H, 4.95

Found : C, 47.15; H, 4.87

(c) Lactone of ∝-ethanolglutaric acid

The lactone of ∝-carboxy-∝-ethanolglutaric acid (25 gm.) was decarboxylated on an oil bath at 160°. The remaining substance was distilled in two fractions under reduced pressure.

Fraction 1. 170-200°/12 mm. (6.2 gm.)

Fraction 2. 217-219°/12 mm. (10.1 gm.)

Fraction 2 was very viscous, making it necessary to distil through the side-arm of the distillation flask. Upon standing several days, the viscous oil solidified in snow-white needles which were thoroughly washed with petroleum ether. After drying, the substance melted at 51.5-53°.

Analysis

Calculated for $C_7H_{10}O_4$: C, 53.16; H, 6.33

Found : C, 53.00; H, 6.44

II. SYNTHESES INVOLVING PROPYLENE OXIDE

(a) Lactone of 4-hydroxyvaleric acid.

The method employed is similar to Coffey's (8) syntheses involving cyclohexene oxide. Malonic ester (144 gm.) was added to a solution of sodium ethylate obtained by dissolving sodium (20 gm.) in absolute alcohol (350 c.c.). The sodio-derivative which precipitated, was cooled in ice while propylene oxide (54 gm.) was run in. Continuous shaking caused the precipitate to dissolve, but after a while a new sodio-derivative settled out in a white solid mass and allowed to sit overnight.

The mixture was boiled under reflux with 5N sodium hydroxide for one hour, to hydrolyse the ester. As in the previous synthesis, the alcohol was removed and the alkaline solution distilled under reduced pressure to a small volume. The greater portion of this solution was carefully acidified with concentrated hydrochloric acid, during which time the evolution of carbon dioxide was definitely observed. The solution was extracted with ether and dried over anhydrous sodium sulphate. A pale yellow oil remained when the ether was evaporated.

An attempt to distil the oil failed as decarboxylation occurred during the distillation process. Consequently, the oil was completely decarboxylated at 160° on the oil bath. The substance remaining, was dissolved in ether and washed with sodium carbonate to eliminate any unchanged acid. The ethereal extract was then dried over sodium sulphate. On evaporation of the ether, the substance left behind, was subjected to a fractional distillation under

reduced pressure.

Fraction 1. -- 85°/13 mm. (2½ gm.).

Fraction 2. 85-95°/12 mm. (14 gm.).

Fraction 3. 95-103°/13 mm. (4½ gm.).

Fraction 2, was redistilled at 83-84°/12 mm. producing a clear, colorless oil (13.5 gm.). This boiling point agrees with the figure given in Heilbron (13) for valerolactone.

Analysis

Calculated for $C_5H_8O_2$: C, 60.0 ; H, 8.0

Found : C, 60.1 ; H, 7.7

(b) Amide of 4-hydroxyvaleric acid lactone.

Preparation of the amide involved a slight modification of the method employed by Boorman and Linstead (4).

The valerolactone (8 gm.) was dissolved in half its volume of aqueous ammonia (d. 880). The solution was then saturated with ammonia gas and allowed to stand twenty-four hours; at the end of this period, the solution was again saturated with ammonia and once more allowed to stand overnight. The viscous liquid was put in a vacuum dessicator until a white solid appeared; however, this was again saturated with ammonia gas, as some of the liquid was still present. When this was once more put into the dessicator the liquid turned completely solid. The new substance was thoroughly washed with ether and dried on a porous plate in the vacuum dessicator. After crystallization by slow evaporation of a saturated

chloroform solution, the pure white needles obtained, melted at 51.5°. Boorman and Linstead (4) give 51.5-2° and Neugebauer gives 50° for the melting point of this amide.

III. SYNTHESIS OF CYCLOHEXENE OXIDE

(a) Preparation of Monobromourea solution.

Urea (400 gm.), precipitated chalk (280 gm.) and water (250 c.c.) were placed in a flask equipped with a dropping funnel, mechanical stirrer, with mercury seal and outlet tube. The flask was cooled in ice and over a period of four hours, bromine (170 c.c.) was slowly added from the dropping funnel. When the reaction was over, more water was added (800 c.c.) and the excess chalk removed by filtration.

The strength of the solution was determined by titration with standard sodium thiosulphate. 1 c.c. of the monobromourea solution was diluted with water to which 10 c.c. of 1.8N potassium iodide solution was added, and the whole acidified with glacial acetic acid. This solution was immediately titrated.

1 c.c. solution was equivalent to 17.7 c.c. .1N sodium thiosulphate. The solution was 10.2% hypobromous acid and 1017 c.c was equivalent to 100 gm. cyclohexene.

(b) Preparation of o-bromocyclohexanol.

The method employed was similar to Detoeuf's (10) preparation of o-chlorocyclohexanol.

The monobromourea solution (1000 c.c.) previously prepared, was poured into a 5-litre flask along with ice (500 gm.), water (500 gm.), cyclohexene (100 gm.), and glacial acetic acid (80 gm.).

The mixture was well agitated for several hours until titration showed that no hypobromous acid was left. At the end of this time, a heavy oil layer settled to the bottom of the flask, and after separation, the oil (155 gm.) was dissolved in ether and dried over sodium sulphate. The ether was evaporated and the remaining oil distilled under reduced pressure. The fraction boiling between 100-105°/19 mm. was collected. The yield was 140 gm. or 70%.

The product obtained was not the dibromohexane, since the density of the latter was much higher (1.79) than the substance prepared here (1.437/15°). Bedos (3) gives the density of o-bromohexanol as 1.402/12° which agreed with the present figure.

(c) Preparation of cyclohexene oxide.

The method of Osterberg (18) was employed in this preparation. o-Bromocyclohexanol (50 gm.) was added to sodium hydroxide solution (12 gm. in 65 c.c. water), and stirred for two hours. At the end of this time the oily layer which rose to the top of the solution was separated. The substance was subjected to several distillations through a column, the final product (15 gm.) boiling at 129-30°; the yield could be improved if larger quantities were used, since the loss in the column was considerable.

The density of this product was .963 as compared with Beilstein's figure-- .975.

SUMMARY

1. The lactone of ∝-ethanolglutaric acid has been synthesized and the isolation of the intermediate ∝-carboxy-∝-ethanolglutaric acid lactone has been effected

2. The lactone of 4-hydroxyvaleric acid and its amide have been synthesized.

3. o-Bromocyclohexanol has been prepared by the action of a monobromourea solution on cyclohexene, and the constitution of the bromohydrin proved by its conversion to cyclohexene oxide.

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