ACTION OF ALKALINE REAGENTS ON A HIGHLY PHENYLATED KETOLACTONE

The Action of Alkaline Reagents
on
A Highly Phenylated Ketolactone.

A Thesis

by

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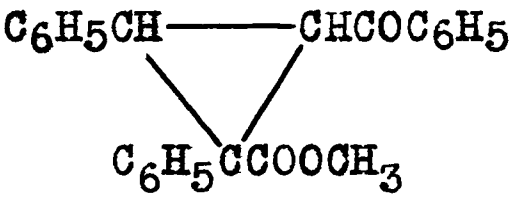
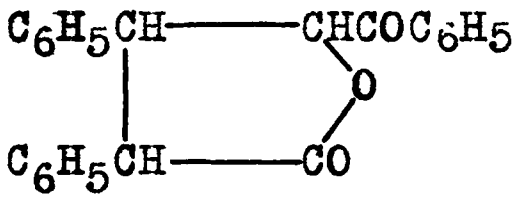
The author acknowledges with gratitude the assistance and encouragement tendered him by Dr. C. F. H. Allen.

Historical Introduction

With a view to securing an unknown highly substituted cyclopropane ketoester (I), Massey (1) in this laboratory carried out a series of reactions based on the work of previous investigators, and obtained a substance having the correct analysis and showing some of the expected properties. In certain respects, however, abnormalities were observed, and from the evidence marshalled in this thesis it must be concluded that the substance is actually α,β-diphenyl-γ-benzoylbutyrolactone (II).



I

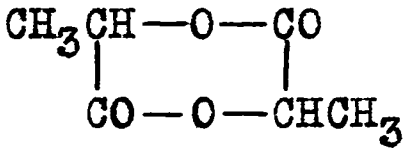


II

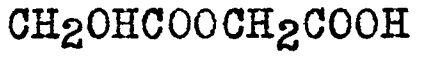
Since the method of preparation of this lactone is not a usual one, and on account of its unexpected chemical behaviour with alkaline reagents, a historical review is given as a background. This first portion of the thesis deals with the reactions by which lactones are formed and their chemical properties, special emphasis being laid upon the action of alkaline reagents.

In its simplest form lactonization may be considered to be a reaction of intramolecular esterification between the functional groups, hydroxyl and carboxyl, which are simultaneously present in the same molecule. The rela-

tive positions in space of these interacting groups determines the course and ease of the reaction. In the simplest class, the alpha-hydroxyacids, lactonization would require the formation of a three-membered ring containing oxygen. Apparently a more stable configuration is a six-membered ring containing two oxygen atoms, and we find that lactic acid on heating gives a lactide (III). In the case of the first member of the series, glycollic acid, the reaction stops before ring closure occurs.



III



IV

Likewise, dehydration of beta-hydroxyacids does not lead to the formation of a ring of small dimensions; here the elements of water are lost to form an α,β-unsaturated acid rather than a beta-lactone. Even if the acid is substituted and does not contain α-hydrogen atoms, it still resists lactonization and forms an open chain polymer (2).

Gamma-hydroxyacids, on the other hand, react in a so-called "normal" manner, and easily pass over into the corresponding lactones. Indeed, the lactone configuration is usually the stable one, and lactones are the substances isolated on acidification of the salts of the hydroxyacids.

The conditions are reversed in the case of delta-

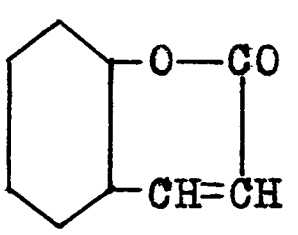
lactones, the corresponding acid being the stable configuration (3).

Among the epsilon-hydroxyacids we have the first appearance of a new phenomenon, and it is one which becomes of increasing importance as the distance between the hydroxyl and carboxyl groups increases. Among the alpha-and beta-hydroxyacids the observed disinclination to form lactones may be due to the instability of small rings in comparison with those containing five and six members; among the omega-hydroxyacids this disinclination has a simple mechanical reason, the increasing distance between groups and the great flexibility of the chain decreases the chance of the functional groups becoming coplanar, as they must do in order to react. To an increasing degree the reacting group finds itself nearer the functional groups of other molecules, and so the formation of open-chain polymers becomes the rule. There are but few cases (4,5) of an epsilon-hydroxy-acid cyclicising as the result of heat treatment.

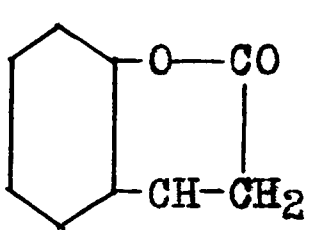
Without exception the higher omega-hydroxyacids yield polyesters on distillation, (6,7).

Among aromatic compounds the distinction between the classes of acids is by no means so clearly drawn, and we notice dissimilarities even among isomeric forms of the same compound. Thus the cis-isomer of coumaric acid spontaneously loses water to form the delta-lactone, coumarin (V), while the trans-isomer does not (8). Further, hydro-

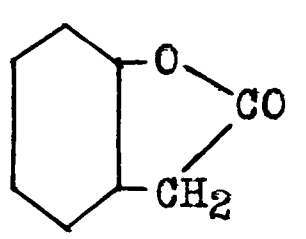
coumarin (VI), which is also a delta-lactone, is under no circumstances formed spontaneously, and, peculiarly enough, ketohydro-coumarone (VII), a gamma-lactone, likewise is not so formed. Even the relative positions of the reacting groups may act as the controlling factor; coumarin in which the carboxyl group is attached to the aliphatic side chain is stable; iso-coumarin (VIII) in which it is attached to the aromatic ring is unstable (9).



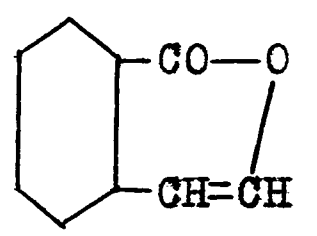
V



VI



VII



VIII

Many external factors exert an influence upon the ease of lactonization in any case. Certain of these may be under the control of the experimenter. Unlike esterification between an alcohol and an acid, lactonization is a monomolecular reaction and should be independent, therefore, of concentration. However, there is usually co-existent with lactonization the competing reaction of polymerization and this is bimolecular. Velocity measurements would necessarily reflect both these reactions.

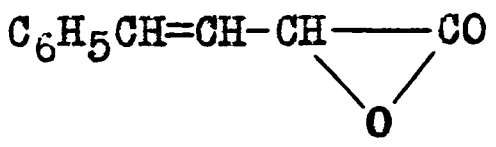
Lactonization parallels bimolecular esterification in its reaction to the presence of hydrogen ions, both processes being catalysed by them, though the careful work

of Taylor and Close (10) has shown that in the former case, there is not a strict proportionality between cause and effect. Like esterification, too, the linking of the hydroxyl group, whether primary, secondary, or tertiary, determines the velocity of lactonization. For instance, δ-methyl valerolactone is formed with greater ease than α-methyl valerolactone (11).

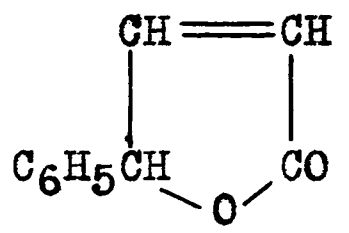
This thesis is not concerned with the stability of lactone rings, and so but slight attention will be given to the subject. Yet it should be noticed that only among the lower members does a superficial observation of the ease of reaction give any idea of the stability of the product. It is true that the gamma-lactones are in general the most stable and they seem to be formed with the greatest ease. Among the omega-lactones, the rings, when once formed are very stable, yet apparently their synthesis is difficult.

Methods of Formation of Saturated Lactones.

As an apparent exception to the rule that lactones, other than gamma and delta ones, cannot be formed by a dehydration of the corresponding acids, Tiemann (12) has described a substance obtained from phenyl-α-hydroxycrotonic acid by the action of acetic anhydride as an alpha lactone (IX). Molecular weight measurements indicated that it was not a lactide. It might well appear to have been an unsaturated γ-phenylbutyrolactone (X). It is now generally



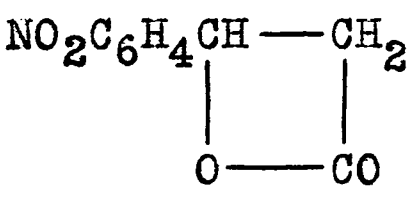
IX



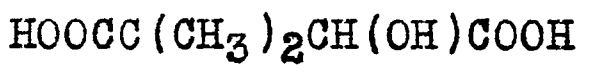
X

agreed that the formation of an alpha-lactone would be a rare phenomenon indeed.

Beta-hydroxyacids likewise cannot be dehydrated to lactones. Halogen acids, however, have been successfully used as starting materials. Einhorn, the first to prepare a beta-lactone, synthesized o-nitrophenyl-propiolactone (XI) from the corresponding beta-bromoacid by the action of sodium carbonate (13). Baeyer and Villiger (14) used silver oxide upon the halogen derivatives of as.-dimethylmalic (XII)

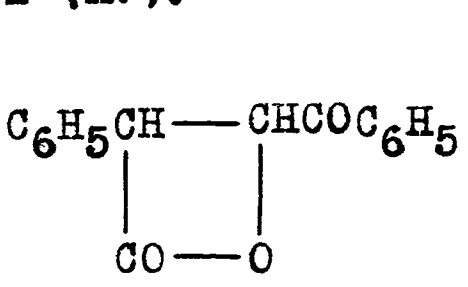


XI

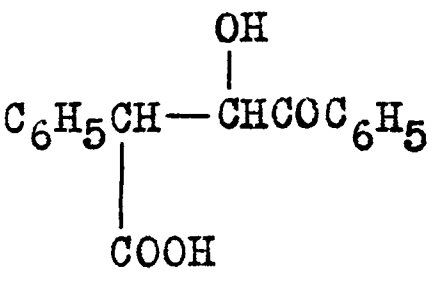


XII

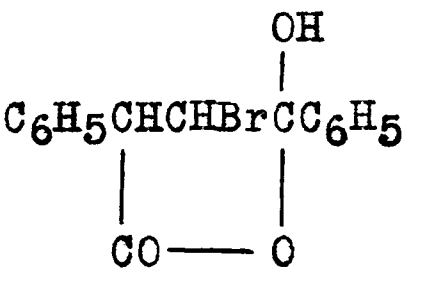
and other acids. The probable course of these reactions is the formation of a salt followed by elimination of the metal halide. The latter process has also been accomplished by Johannson (15) by means of silver nitrate. Theoretically, beta-bromoacids could react with bases to give rise to three types of products, beta-lactones, beta-hydroxyacids and alpha, beta-unsaturated acids. Using the high melting isomer of β-bromophenylbenzoylpropionic acid, Kohler and his co-workers (16) found that the corresponding lactone (XIII) and hydroxy acid (XIV) only were formed on treatment with dilute aqueas solutions of weak bases. Using strong alkalies in dilute solution, hydroxy ketones and polymers appeared as secondary products. The use of acetic anhydride (17) led to the production of an acetate of the gamma-lactol (XV).



XIII

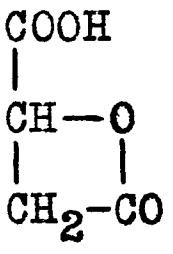


XIV

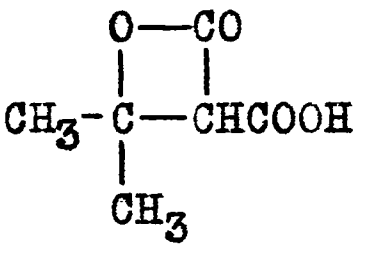


XV

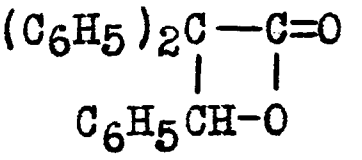
It is noteworthy that the sodium salt of bromo-succinic acid yielded the beta-lactone (XVI) and not the theoretically possible alpha-lactone (18).



XVI



XVII



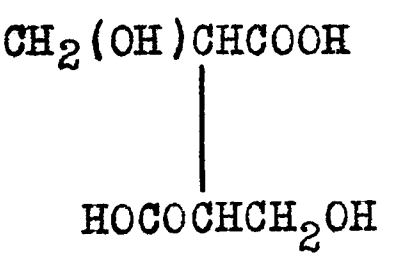
XVIII

Beta-lactones can also be effectively synthesized by condensation reactions. Malonic acid has been condensed with acetone by the action of acetic anhydride (XVII) (19), and it is characteristic of ketenes that they form beta-lactones with carbonyl compounds (XVIII) (20).

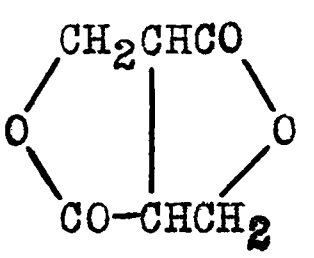
Certain general methods of synthesis can be used for the preparation of both gamma-and delta-lactones. Such are given below.

The lactonization of a gamma-hydroxyacid is usually a reaction which proceeds spontaneously, acidification of the salt of the acid leading directly to the lactone. In the case of delta-hydroxyacids dehydration usually requires heating or the use of special reagents.

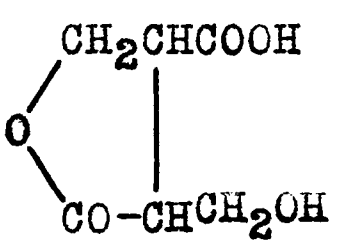
As would be expected polyhydroxy acids, such as mucic, saccharic, etc. form both lactonic acids and di-lactones. The interesting sym.-dimethylolsuccinic acid (XIX) has been studied by Michael (21).



XIX



XX



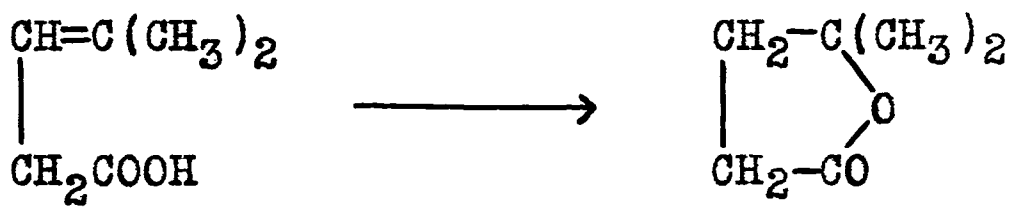
XXI

Such an acid contains two asymmetric carbon atoms and exists in two forms. If the dilactone (XX) corresponding to it was boiled with two equivalents of alkali, approximately equal quantities of the stereoisomeric disodium salts were obtained. One on acidification gave the original dilactone, and the other gave the monohydroxy-γ-lactonic acid (XXI). That such was the case was due to an interchange of the COONa group with the hydrogen atom attached to the same asymmetric carbon atom, with the result that the carboxyl and methylol groups of the corresponding acid were no longer coplanar, and so could not lactonize.

Halogen acids are also the source of lactones, the formation of a ring being the result of loss of HX brought about by distillation, or boiling with water or alkaline reagents. The course of the reaction in the latter case is uncertain; there may or may not be an intermediate formation of a hydroxy acid.

Lactone formation by the removal of hydrogen or alkyl halides from halogen ketoacids and esters will be treated at some length in a later section.

Geissler and Fittig (22) were the first to use unsaturated acids as a source of lactones and prepared isocapriolactone (XXII) by distilling pyroterebic acid. Water, hydrogen bromide, or 50% sulphuric acid are also effective cyclicising reagents.



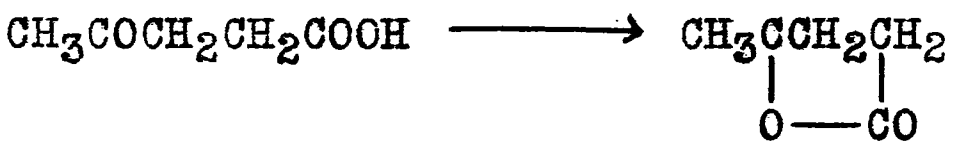
XXII

As a result of an extended investigation of this type of synthesis Fittig came to the conclusion that only β,γ- and γ,δ-unsaturated acids gave lactones. However, Fichter (23) and others have shown that if the chain is branched at the beta-carbon, α,β-unsaturated acids also react in this way. Linstead (24) has found that with these acids isomerization to the beta, gamma-form is a necessary precursor for lactonization, and, to illustrate this, has pointed out that 60% sulphuric acid, which is a satisfactory reagent for the lactonization of β,γ-n-hexenoic acid, is quite without effect on the α,β-isomer, but if it is diluted to 50% strength reaction occurs.

A process of self-addition appears to be a simple and adequate explanation of the mechanism of the cyclisation, for it may take place with remarkable ease, in some cases even in the solid state.

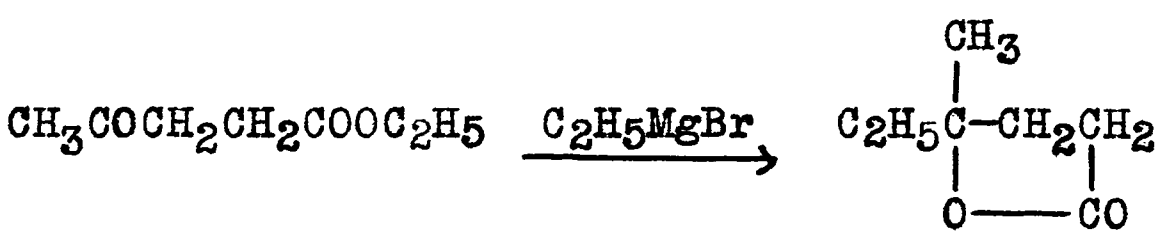
Among synthetic methods which may be used for the preparation of both gamma- and delta-lactones the last to be mentioned here is the reduction of aldehydo and ketonic acids by a reagent such as sodium amalgam; the corresponding hydroxy acids are formed as intermediates.

As an example one may cite the reduction of levulinic acid to δ-valerolactone.



Reduction of ketonic acids is a general reaction for the preparation of gamma-lactones; in a more specialized manner the reduction of the anhydride and chlorides of dicarboxylic acids, both aliphatic and aromatic, can serve for the preparation of such compounds (25, 26). The reduction of chlorides to lactones is of historic importance. By that means Saytzeff (27), in 1873, first prepared a lactone by the reduction of succinyl chloride. Nascent, or catalytic, hydrogen can be successfully used for these reactions.

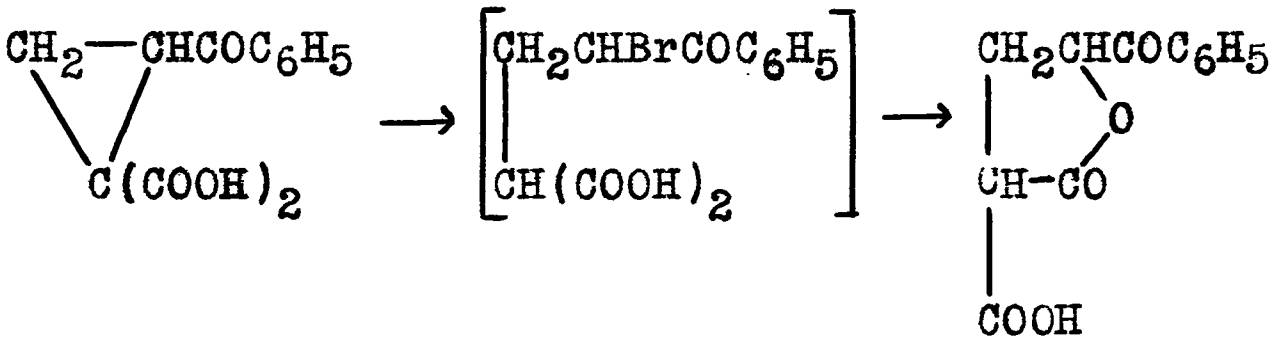
The Grignard reaction has been used for the synthesis of lactones, ketonic esters being acted upon by organomagnesium compounds. As an example Grignard (28) prepared α-methyl-α-ethylbutyrolactone in 35% yields by the action of ethylmagnesium bromide on ethyl levulinate (XXIII).



XXIII

Of theoretical interest is the action of hydrogen bromide upon the cyclopropane diacid (XXIV). Hydrogen bromide in acetic acid yields an oil which, on standing,

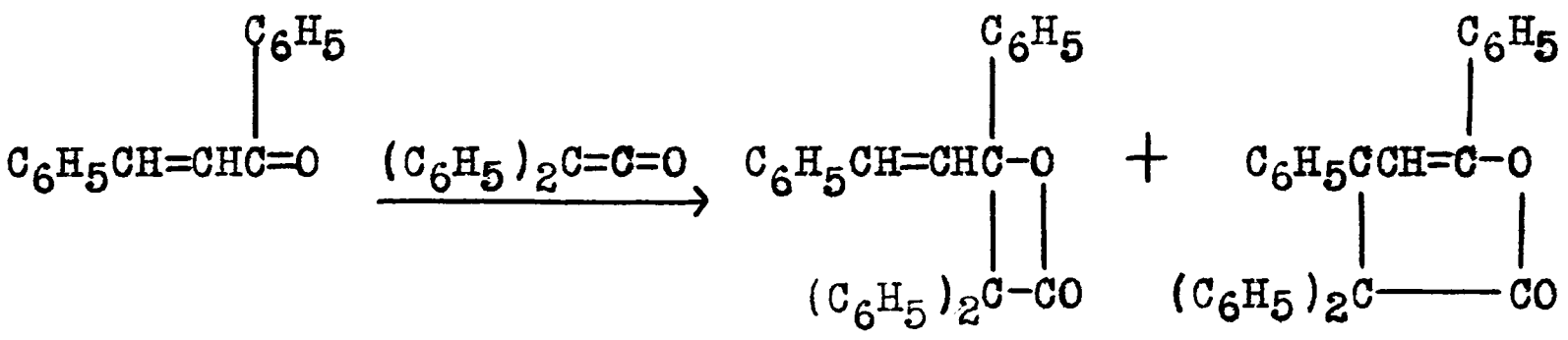
spontaneously loses hydrogen bromide to form the lactone (XXV) (29).



XXIV XXV

There can be no doubt that the main constituent of the oils is a γ-bromoketonic acid.

A ketene can react in two ways with an α,β-unsaturated aldehyde or ketone. With benzalacetophenone, (XXVI) for instance, diphenylketene adds 1,2 to the carbonyl group to form the beta-lactone (XXVII) and also 1,4 to the conjugated system, to form the delta-lactone (XXVIII).

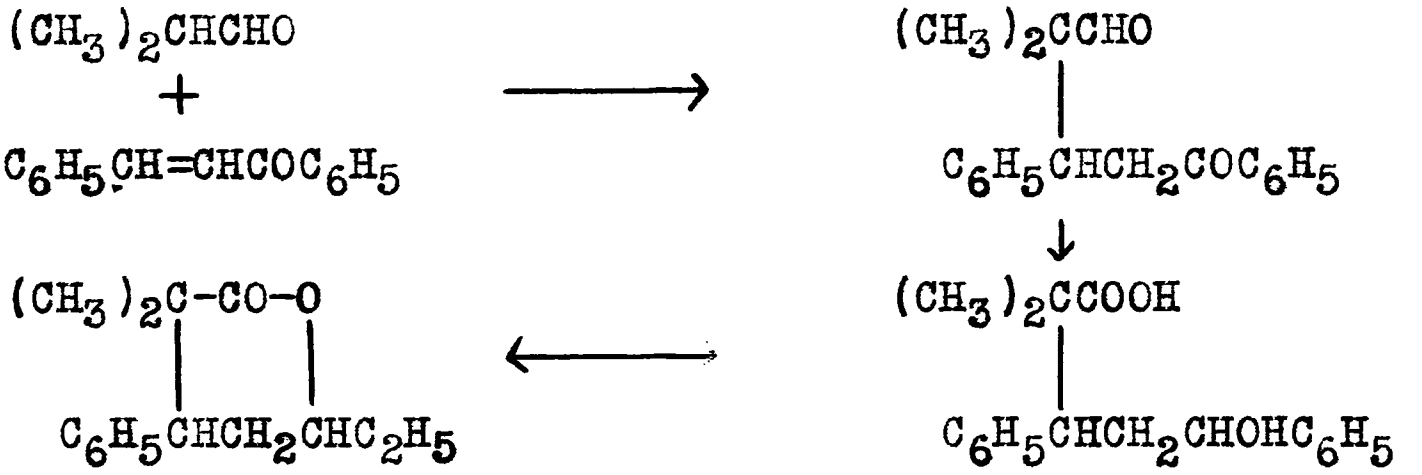


XXVI XXVII XXVIII

This reaction has been extensively studied by Staudinger (30).

An interesting method of synthesis of delta-lactones is that developed by Meerwein (31). As is well

known, under the action of alcoholates aliphatic aldehydes containing at least one alpha-H atom condense with α,β-unsaturated aldehydes and ketones. In the presence of the same condensing agent the 1, 5-dialdehydes and ketone-aldehydes thus formed undergo an internal Cannizzaro reaction, and are converted into the isomeric delta-lactones. The yields are stated to be quite satisfactory. The steps in a typical synthesis are set out below.



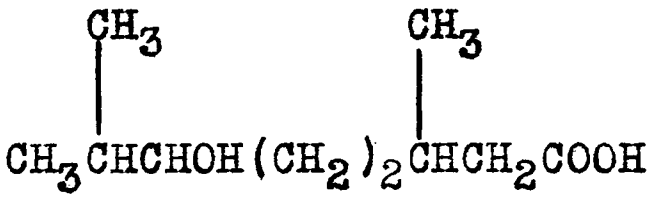
In recent years the preparation of macrocyclic compounds has been extensively studied by Ruzicka, Stoll, Zieger, Carothers and others. Carothers (32), in a concise theoretical treatment of the subject, has pointed out that rings of 3 and 4 atoms have very large strains due to the deflection of valencies, those of 5 atoms are strainless, most of those of 6 atoms are strained, and to this is due their easy polymerization. With Stoll, he comes to the rather unexpected conclusion that larger rings are strained, not because of any distortion of valencies but because of

the mutual repulsion of the non-linked peripheral atoms. He explains the apparent high stability of Ruzicka's macrocyclic paraffins and ketones by the fact that these compounds present no easy point of attack. Other large rings, especially anhydrides, reveal their condition of internal strain by polymerizing.

These considerations are reflected in the chemistry of lactones. In but a few cases has the preparation of an epsilon-lactone from simple distillation of the corresponding hydroxy acid been reported. ε-Hydroxycaprylic acid (XXIX) yields a small quantity of lactone on heating, but the acid (XXX) yields only undistillable residue (5). Baeyer and his co-workers (4) were able to prepare β-methyl-ε-isopropyl-ε-caprolactone by the vacuum distillation of 2,6-dimethyl-ε-hydroxycaprylic acid (XXXI).

$C_2H_5CHOH(CH_2)_4COOH$ XXIX

$C_2H_5CHOH(CH_2)_5COOH$ XXX



XXXI

Among the higher omega-hydroxyacids polymerization on heating is the rule. This has been the experience Chuit and Hausser (6) who synthesized and studied the dehydration of the entire series of acids, $HO(CH_2)_7COOH$ to

$HO(CH_2)_{20}COOH$, and of Lycan and Adams (7) and Carothers, (33) who carefully investigated the esterification of omega-hydroxydecanoic acid. In these experiments it is noted that we have the operation of two effects, both tending to the formation of open-chain polyesters rather than macrocylic lactones. One is the small probability of intramolecular reaction due to the great distance between reacting groups and the other is the slight tendency to form a molecule which would be under strain.

Using the principle of Ruggli, that high dilution favors intramolecular reaction, Stoll (34) has succeeded in preparing lactones from 14 and 15 carbon atom hydroxy-acids by a simple esterification reaction in yields as high as 93%.

Carothers (35) has shown that if the linear polyesters of carbonic and oxalic acids are distilled <u>in vacuo</u> under special conditions they are depolymerized to monomeric and dimeric macrocyclic esters. In the carbonate series dimers are formed almost exclusively with chains of unit length 7 to 12, monomers with chains of length greater than 14. Using special catalysts, he has since applied this method to the depolymerization of the esters of malonic acid and the higher acids of the series (36).

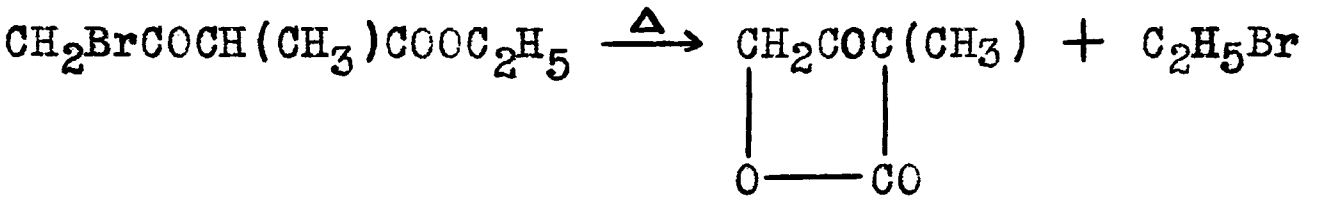
The use of permonosulphuric (Caro's) acid, has been of unique value in the preparation of ε-and higher

lactones. Baeyer and Villiger (37) were the first to apply it, oxidizing menthone to β-methyl-ε-isopropyl-ε-caprolactone in one operation. It has found its greatest application at the hands of Ruzicka and his co-workers in recent times (38). Using multimembered cyclic ketones, obtained by heating the thorium salts of dibasic acids, he synthesized lactones containing 13-17 carbon atoms. For instance, "exaltone", cyclopentadecanone was converted into the lactone, "exaltolide".

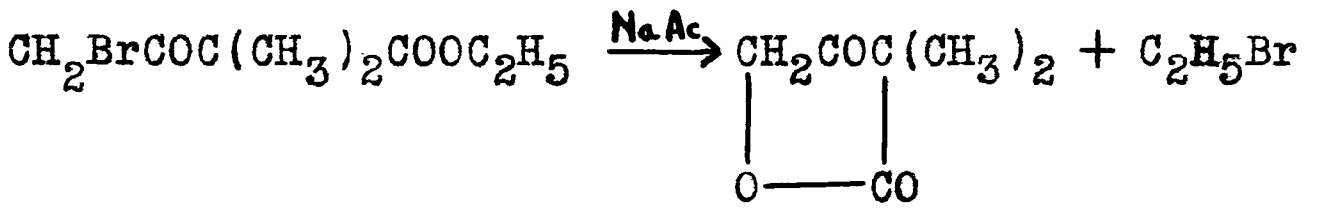
Kirschbaum (39) has isolated an unsaturated lactone, ambrettolide, from musk-seed oil. It could be saponified to 7-hexadecene-16-olic-1-acid, but, in accordance with the general rule, this acid cannot be reconverted into the lactone by heating. The lactone, however, could be prepared by heating the corresponding bromoacid with silver oxide.

The action of heat or alkaline reagents upon gamma-halogen acids and esters, processes which act in such a way as to remove hydrogen halides or alkyl halides, may lead to the formation of either gamma-lactones, or cyclopropane derivatives. Because of their intimate relationship to the subject of this thesis, these processes will be considered at some length.

By heating α-methylbromoacetoacetic ester (XXXII) Michael (40) showed that the elements of ethyl bromide were split off and a lactone ring was closed. Using the α,α-dimethyl ester (XXXIII), Conrad (41) caused the same reaction to occur by the action of sodium acetate.

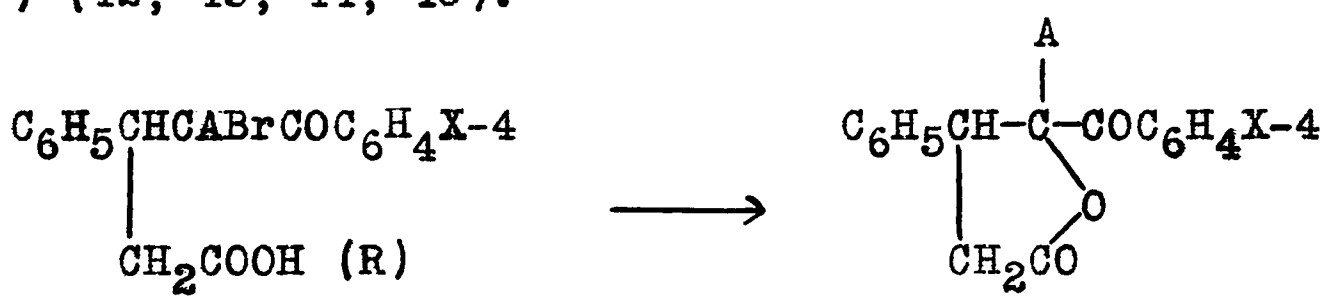


XXXII



XXXIII

On bromination, β-phenyl-δ-benzoylbutyric acid and its esters gave two isomeric γ-monobromides (XXXIV). Pyrolysis of the bromoacid or treatment of the acids or esters with dimethylaniline or aqueous sodium carbonate formed the corresponding β-phenyl-δ-benzoyl-γ-butyrolactones (XXXV) (42, 43, 44, 45).



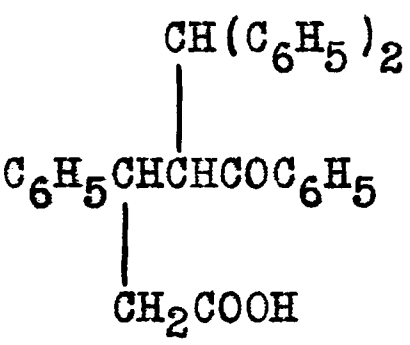
XXXIV XXXV

A = H, CH_3, X = H, Br, OCH_3

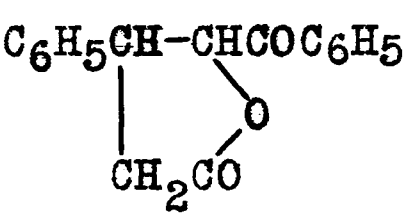
In the cases where the pyrolysis of the bromo-esters has been studied, it has been shown that they did not give a butyrolactone on heating (46). These appear to be exceptions to the rule.

A rather remarkable reaction has recently been observed by Kohler and Peterson (47). On the bromination

of β-phenyl-γ-(diphenylmethyl)-γ-benzoylbutyric acid (XXXVI), the diphenylmethyl group was replaced by bromine and the endproduct of the reaction was β-phenyl-γ-benzoyl-γ-butyrolactone (XXXVII).



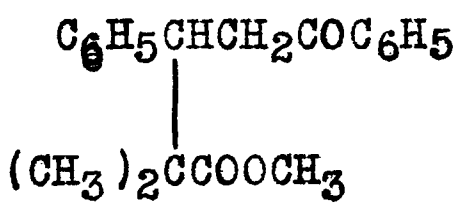
XXXVI



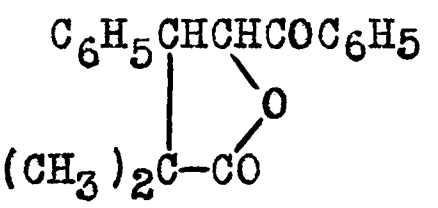
XXXVII

The preparation of α-methyl-β-phenyl-γ-benzoyl-butyric acid has been reported by Kohler and his co-workers (48). In a later paper (46), it is stated that the γ-bromo derivative of its methyl ester does not evolve methyl bromide on heating and form a lactone, though experimental details are lacking.

Interesting results were observed on the bromination of methyl α-α-dimethyl-β-phenyl-γ-benzoylbutyrate (XXXVIII).



XXXVIII



XXXIX

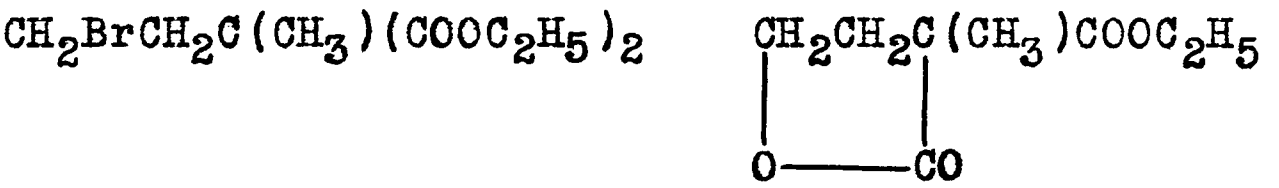
If the bromination was carried out in carbontetrachloride or chloroform a low-melting γ-bromoester was obtained.

Some of this spontaneously lost methyl bromide and gave two isomeric gamma-lactones (XXXIX). If the temperature was allowed to rise during the reaction the yield of the bromo-ester was diminished and that of the lactones increased (49).

Methyl α-cyano-β-phenyl-γ-benzoylbutyrate and its γ-p-chlorobenzoyl homologue were brominated in chloroform to produce alpha-bromoesters and a trace of alpha,gamma-dibromo compounds. On heating the former, hydrogen bromide was lost, with the formation of cyclopropane derivatives (50).

Among the gamma-bromo derivatives of malonic acid the formation of cyclopropanes appears for the first time.

By heating the ethyl ester of methyl-β-bromoethyl-malonic acid (XL) the lactone (XLI) was formed.

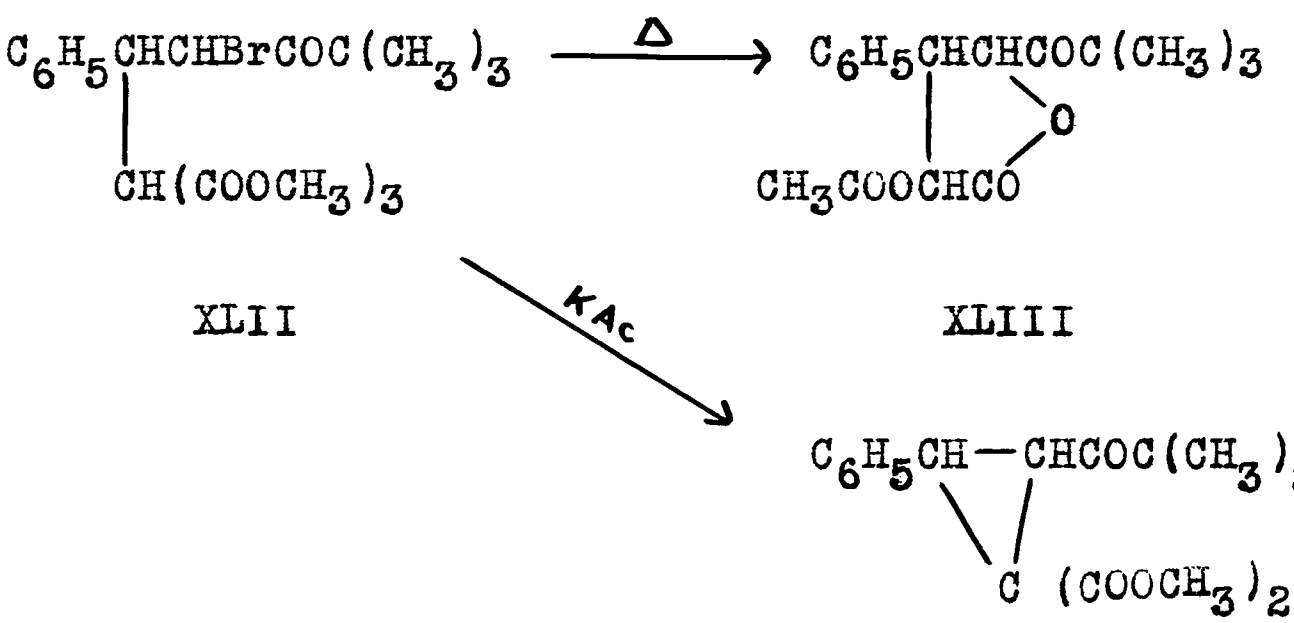


XL XLI

The β-chloro homologue, however, lost the elements of hydrogen chloride in adjacent positions and gave an unsaturated malonic ester. By treatment with barium hydroxide both were converted into the barium salt of the lactone acid (51). Isoamyl-β-chloroethylmalonic ester also acts in an anomalous manner. It was only decomposed a negligible amount on

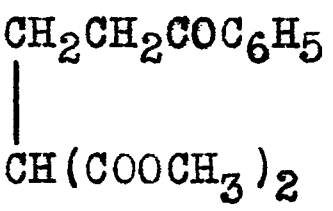
distillation, while the β-bromo homologue was decomposed to the lactone even at pressures as low as 3 mm. (52).

Bromination of methyl α-phenyl-β-pivalylethyl malonate in carbon tetrachloride yielded two isomeric gamma-bromoesters (XLII). Pyrolysis of the lower melting one resulted in the loss of methyl bromide and the formation of the butyrolactone (XLIII). Treatment of either ester with alcoholates or potassium acetate produced the cyclopropane (XLIV) (53).

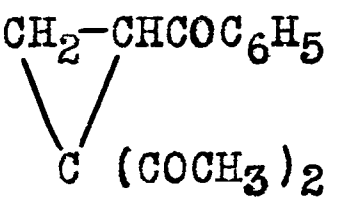


XLII XLIII XLIV

Bromination products of methyl β-benzoylethyl-malonate (XLV) have not been isolated, due to their oily nature, but these oils on treatment with potassium acetate were converted to a cyclopropane (XLVI) (29).

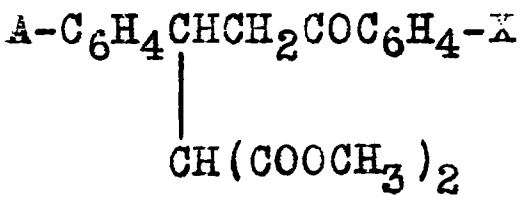


XLV



XLVI

On bromination the beta-substitution products of dimethyl ɣ-benzoylethylmalonate (XLVII) yielded either gamma-bromoesters, or mixtures of the alpha- and gamma-isomers. Many substances, such as amines, alcoholates, potassium acetate, acting on either of these isomers, gave a cyclopropane derivative. Lactones were produced by the pyrolysis of the gamma-isomers only (46, 54, 55, 56).

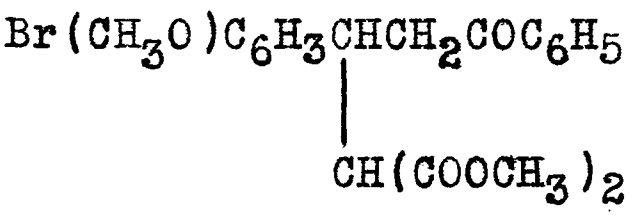


A = H, NO_2,

X = H, Br, OCH_3,

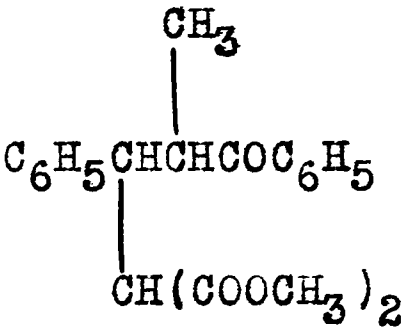
XLVII

Dimethyl β-(3,4-bromomethoxy-phenyl)-ɣ-benzoyl-ethylmalonate (XLVIII) yielded only oily products on bromination, of which the largest proportion apparently were gamma-bromo derivatives, for by the action of magnesium methylate or potassium acetate they gave a good yield of the corresponding cyclopropane (57).

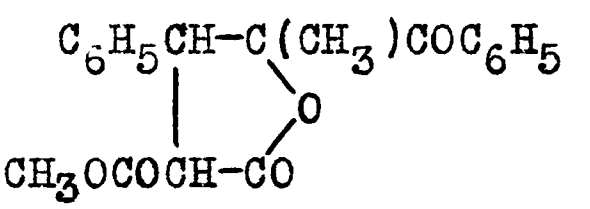


XLVIII

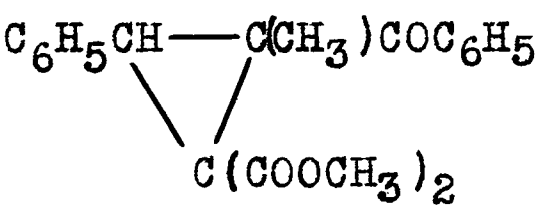
Dimethyl β-phenyl-γ-benzoylpropylmalonate (XLIX) brominated to give an oily product from which one solid could be separated in 30% yields. This was a gamma-bromo-ester, the heating of which produced the lactone (L) but treatment with magnesium methylate or potassium acetate gave the cyclopropane (LI) (45).



XLIX



L



LI

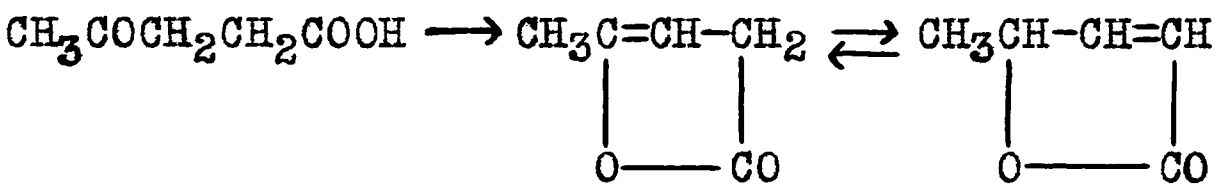
According to Kohler (46), by heating the gamma-bromo derivative of dimethyl α-methyl-β-phenyl-γ-benzoylethyl-malonate the lactonic ester is prepared in 90% yields.

It will be seen from the foregoing review that

in a large number of cases pyrolysis of gamma-bromo derivatives of ketobutyric acids and esters yields lactones, and almost invariably is this the case on treatment with alkaline reagents. On the other hand, gamma-bromo malonic esters yield lactones on pyrolysis and cyclopropanes with alkaline reagents.

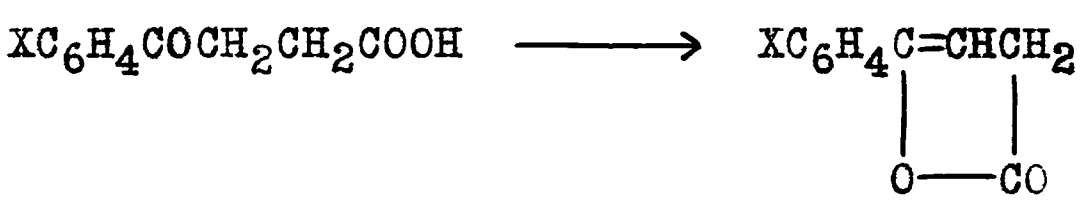
Unsaturated Lactones.

Unsaturated lactones in which the unsaturation lies within the lactone ring are best prepared by removing the elements of water from the enolic form of a keto acid. Theoretically, using a gamma-keto-acid, one would expect to secure an β,γ-unsaturated lactone, but Thiele (58) has shown that the more stable α,β-form is obtained by isomerization.

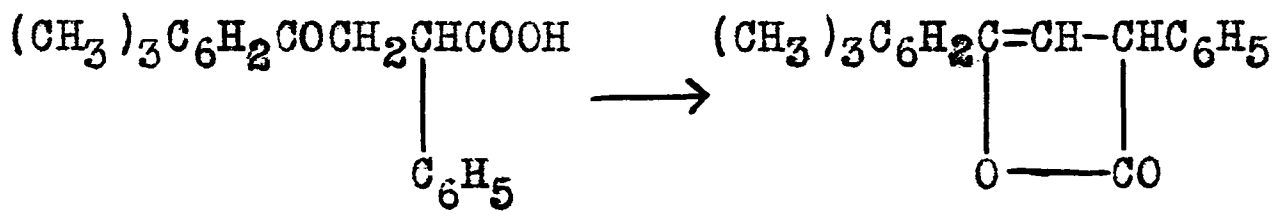


The same isomerization of a beta, gamma-lactone can be carried out by means of alkaline reagents such as ammonia, methylamine, etc.

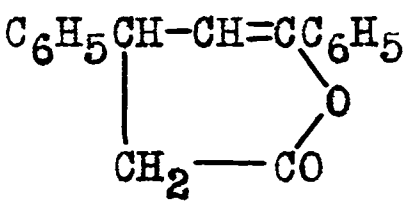
A similar lactonization in many cases results from the action of acetyl chloride on β-aroyl propionic acids. All which have been studied, except the mesitoyl homologue, gave unsaturated lactones thus



The mesitoyl homologue gave an enol acetate. In the α-acyl-β-aroyl series the formation of some type of dimer appeared to be the rule though the mesitoyl homologue was again an exception forming a crotonolactone in addition.



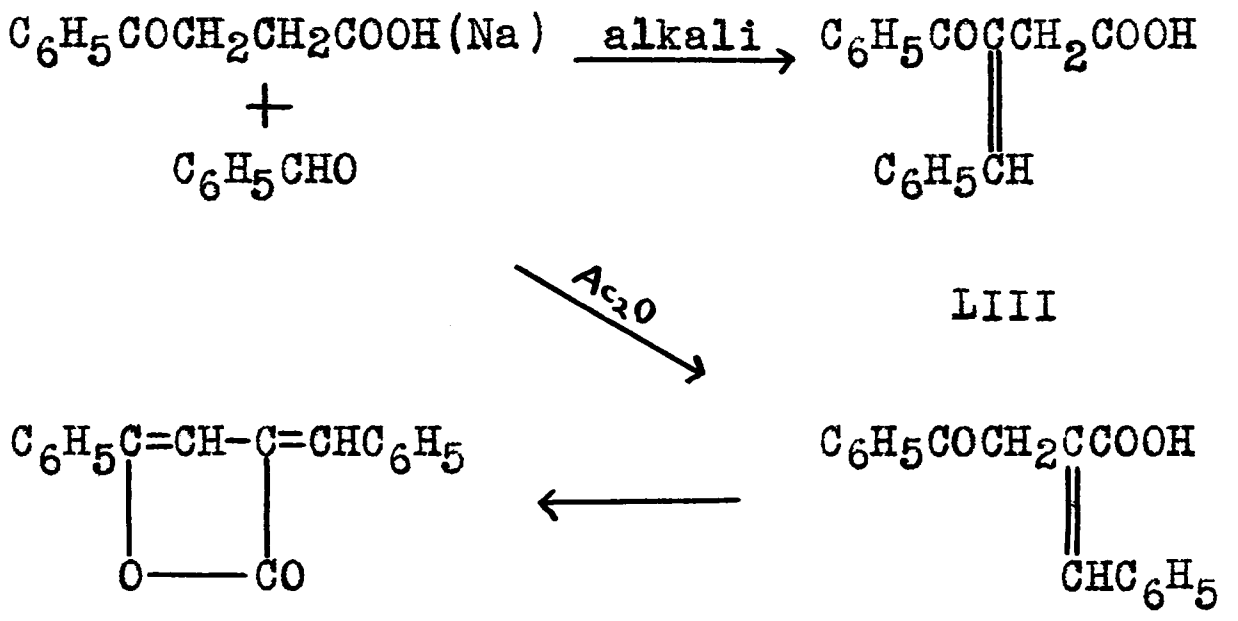
Barat (59) has stated that he obtained a lactone from β-phenyl-γ-benzoylbutyric acid by the action of acetyl chloride, but this has not been confirmed. The lactone (LII) has been prepared from this acid by the action of acetic anhydride, however (60).



LII

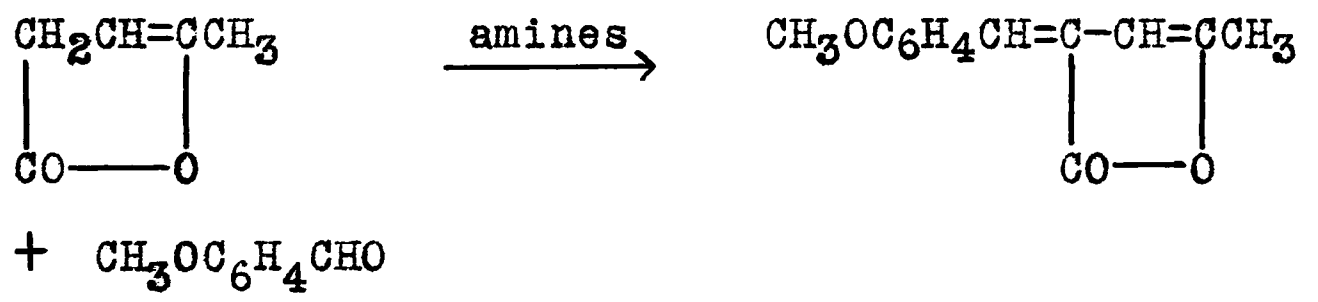
Acetic anhydride has been widely used to prepare lactones from ketonic acids in this manner.

It is of interest to note that lactonization may accompany certain types of condensation. Under the action of alkaline condensing agents, benzoylpropionic acid and benzaldehyde form the simple benzal derivative (LIII), but if acetic anhydride is used as the condensing reagent with the sodium salt of the acid, simultaneous condensation and lactonization occur with the formation of α-benzal-γ-phenyl-crotonolactone (LIV) (61). This is typical of a large number of reactions.

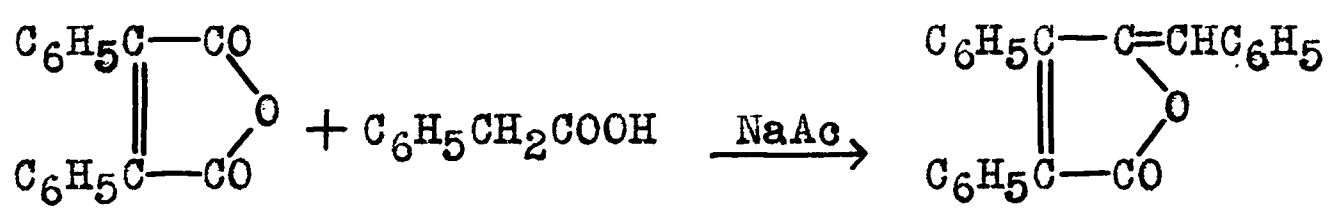


LIV

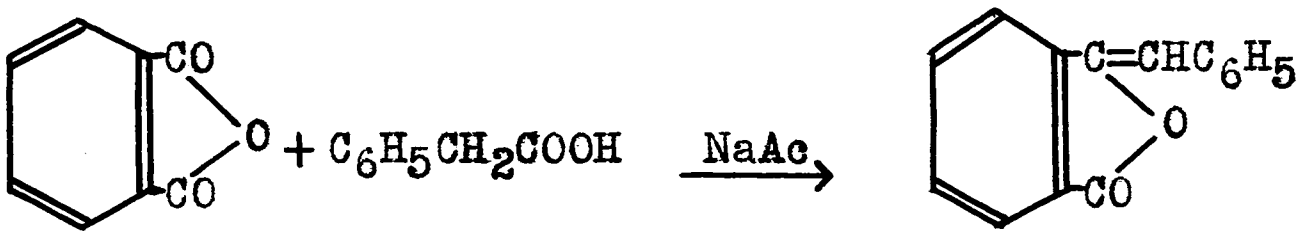
Lactones which are at once unsaturated within the ring and within a side-chain attached to it may be synthesized by condensations of aldehydes with β,γ-unsaturated lactones or from phenyl acetic acid and the anhydrides of unsaturated or aromatic dicarboxylic acids. Representative examples of such reactions are given below



Reference 62.



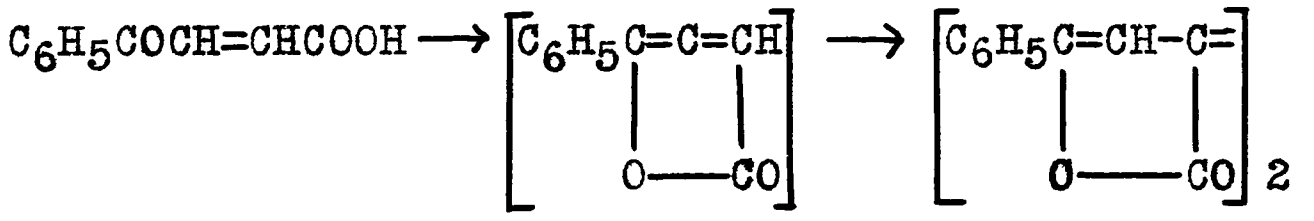
Reference 63. LXXVII



Reference 64.

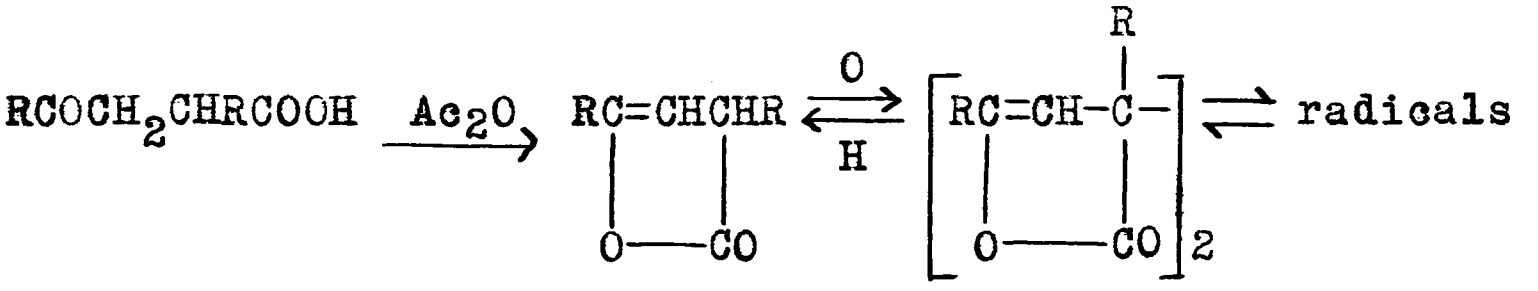
The properties of such compounds are of especial interest to this thesis and will be discussed in another section. However, it may be mentioned here that the unsaturated lactone (LXXVII) was reported to add a molecule of water to the extra-annular double bond on alkali fusion. As will be shown in the Experimental Part, such a drastic reaction is unnecessary - by simple solution in sodium hydroxide and acidification the water addition compound, a lactol, may be obtained. Since the water is easily split off, the crystallization is troublesome; the isolation after alkali fusion was probably fortuitious.

If β-benzoylacrylic acid (LV) is dehydrated with acetic anhydride a brilliantly coloured compound is obtained, known as a Pechmann dye. The constitution of such "dyes" has been the subject of study for many years, but it is now generally believed that they are trans-dilactones of the type (LVI) (65).



LV LVI

Pummerer (66) obtained a somewhat similar compound by the dehydration of α-tolyl-γ-toloylpropionic acid (LVII). The dilactone (LVIII) has the property of dissociating into green radicals.

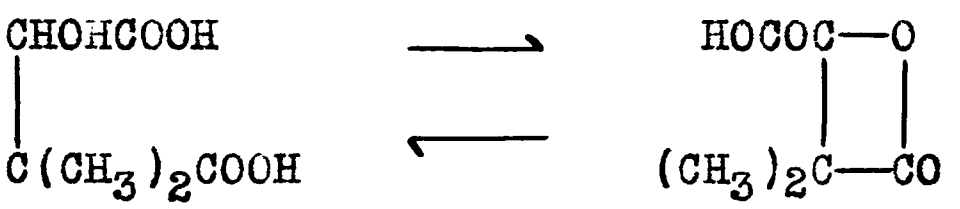


LVII LVIII

Reactions of Lactones.

Hydrolysis.

Though beta-lactones cannot be formed from the corresponding hydroxy acids by the splitting off of water, in aqueous solution they readily form these same acids and on evaporation are again obtained. The beta-lactone of as.-dimethylmalic acid serves as a good example (14).



Gamma-lactones are stable in aqueous media. However, in the presence of hydrogen ions an equilibrium, usually far over on the lactone side, is rapidly reached, and by the action of strong alkalies the salts of the corresponding hydroxy acids are prepared.

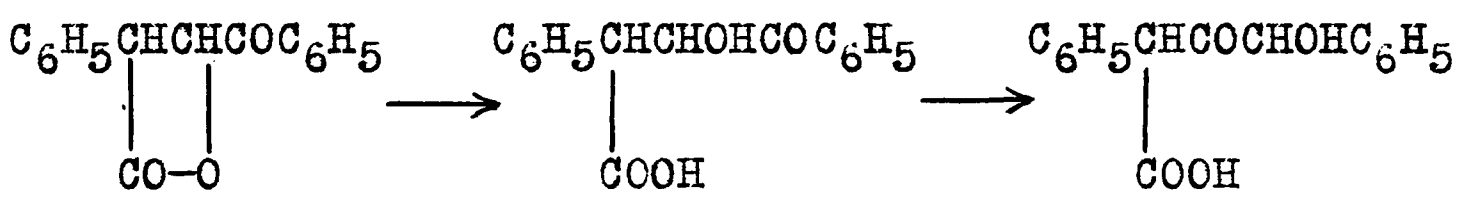
The delta-lactones are much less stable than the gamma-ones. For instance, under comparable conditions δ-caprolactone is in equilibrium with 35% of the hydroxy acid and γ-valerolactone with 6.6% (48). Like beta-lactones epsilon-lactones are completely hydrolysed in the presence of water. The macrocyclic esters containing 13-17 carbon atoms are oils stable to water.

Beta, γ - and γ, δ - unsaturated lactones yield the salts of γ-ketonic acids by hydrolysis with bases.

Concentrated halogen acids act upon lactones to

form halogen-containing acids; in the presence of alcohols the corresponding esters are prepared.

In general, strong bases form the salts of hydroxy lactones with saturated lactones; in the case of gamma-lactones the reaction is reversed by acidification. In certain special cases other changes may occur at the same time. Thus Michael (21) has noticed that if the dilactone of sym.-dimethylolsuccinic acid is boiled with two equivalents of alkali racemization occurs to the extent of about 50%, products from acidification being the original dilactone and a lactonic acid. Kohler and his co-workers (16,68) were able to show that on treatment with aqueous solution of weak bases α-phenyl-β-benzoylpropiolactone (LIX) gave two hydroxy acids (LX, LXI) one of which arose from the interchange of hydroxyl and carbonyl groups.



LIX LX LXI

One of the properties of sodium alcoholates, though not a very general one, is to form alkoxyl salts with lactones.

H. Meyer (69) has made an extensive study of the action of ammonia on a large number of beta-, gamma-, and delta-lactones. Obviously, in general, there can be but two products from the interaction of ammonia and a lactone.

By opening the lactone ring and addition of ammonia to the ends of the chain a hydroxy amide is formed, and this may lose water to produce a lactam#. In no case has there been reported the formation of an amino acid by such a reaction. Meyer has formulated rules which govern the two possible reactions; it is apparent that the nature of the hydroxy group of the hydrolysed lactone is the controlling factor.

1. If the hydroxyl is tertiary or secondary and adjoins an ethylenic linkage, as in enols, a lactam is formed.

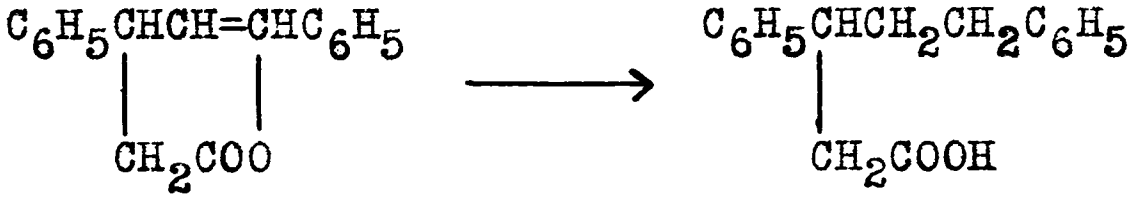
2. If the hydroxyl is primary, secondary (not adjacent to a double bond), or phenolic, a hydroxy amide is formed.

At high temperatures gamma-lactones form gamma-cyano acids with potassium cyanide (71).

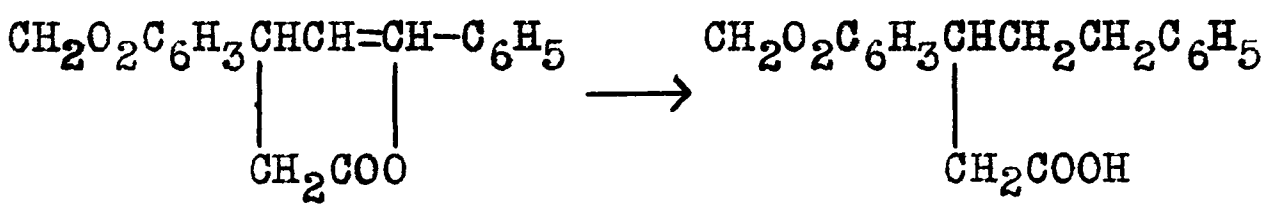
Hilditch's statement (70), that "Ammonia...is never known to rupture the ring system," of lactones, is obviously incorrect.

Reduction.

There have been but few studies of the catalytic reduction of lactones. Mannich and Butz (72) stated that, operating in acetone with palladized charcoal, the lactones of δ-hydroxy-β,δ-diphenyl-γ-pentenoic acid (LXII) and of β-methylenedioxyphenyl-δ-phenyl-γ-pentenoic acid (LXIV) smoothly took up two equivalents of hydrogen and formed the monobasic acids β,δ-diphenyl valeric (LXIII) and β-methylenedioxyphenyl-δ-phenylvaleric acids (LXV).



LXII LXIII

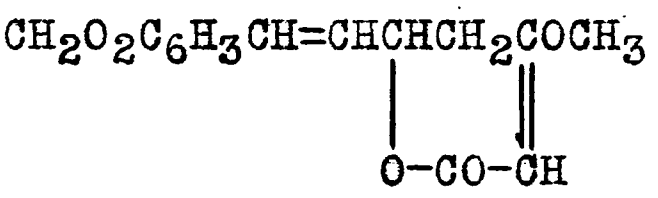


LXIV LXV

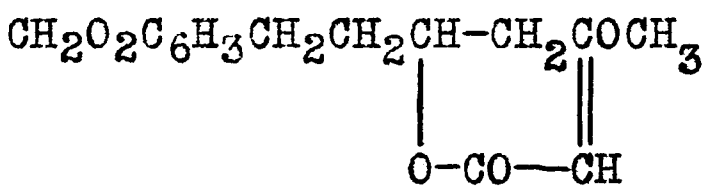
If the hydrogenation is interrupted after one equivalent has been absorbed products are obtained which are not homogeneous. Apparently they consist largely of saturated lactones. The lactone of β-phenyl-δ-methyl-γ-pentenoic acid, unexpectedly, cannot be reduced.

Borsche and Peitsch (73) have reported on the catalytic dehydrogenation of methysticin (LXVI), a natural

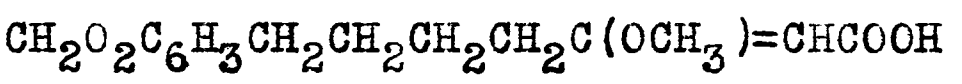
lactone occurring in kawa root. With one equivalent of hydrogen methysticin is converted to dihydromethysticin (LXVII) together with some tetrahydromethysticinic acid. With two equivalents of hydrogen there is a quantitative preparation of the tetrahydro acid (LXVIII). Further hydrogenation leads to a hexahydro acid.



LXVI



LXVII



LXVIII

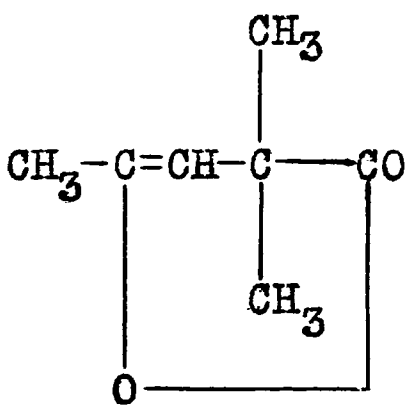
Each step in the hydrogenation is marked by a sharp decrease in the reaction rate.

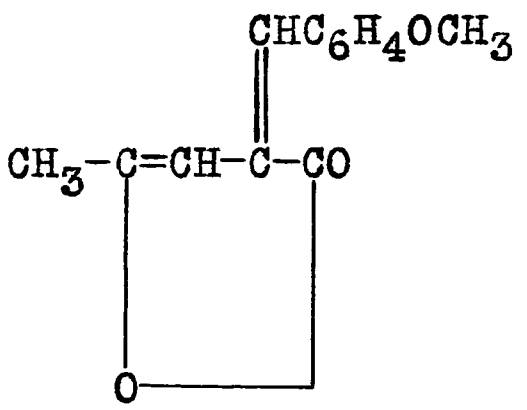
From a very careful investigation of the rates of hydrogenation of unsaturated lactones, Jacobs and Scott (74) have deduced the following rule, namely, "that whenever a substance containing a lactone group and double bond is rapidly hydrogenated to the saturated desoxyacid without a definite break at the 1-mol. stage with the formation of the saturated lactone, it may be supposed that the substance is the lactone of an enolized oxo-acid". Beta,γ-angelica-lactone is reduced in 15 minutes to valeric acid; α,β-angelica-

lactone is reduced in 75 minutes to γ-valerolactone together with a little valeric acid, the appearance of the latter being due to preformation of the β,γ-isomer. Similar results are obtained with α,α-dimethyl homologue, but here there is no acid formation with α,β-isomer since isomerization is impossible.

In a second paper (75) they studied the effect of beta-substitution. β-Methyl-β,γ-angelicalactone yields 70% acid and 30% saturated lactone, the α,α,β-trimethyl homologue 50% acid and some lactone. It is evident that beta-substitution acts to diminish hydrogenation to acids.

A striking difference was noted between α,α-dimethyl-β,γ-angelicalactone (LXIX) and its anisal homologue.

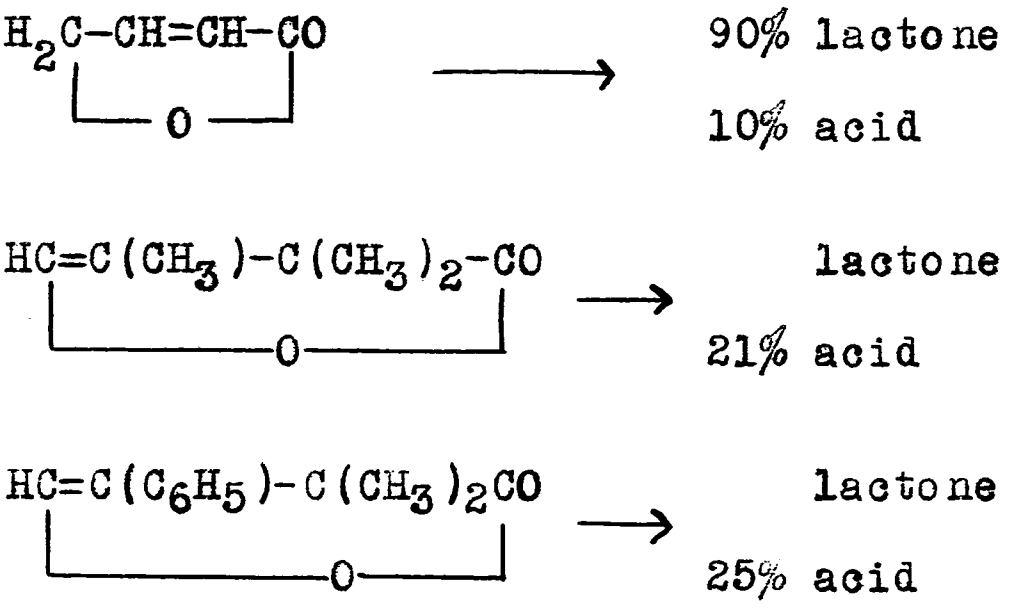




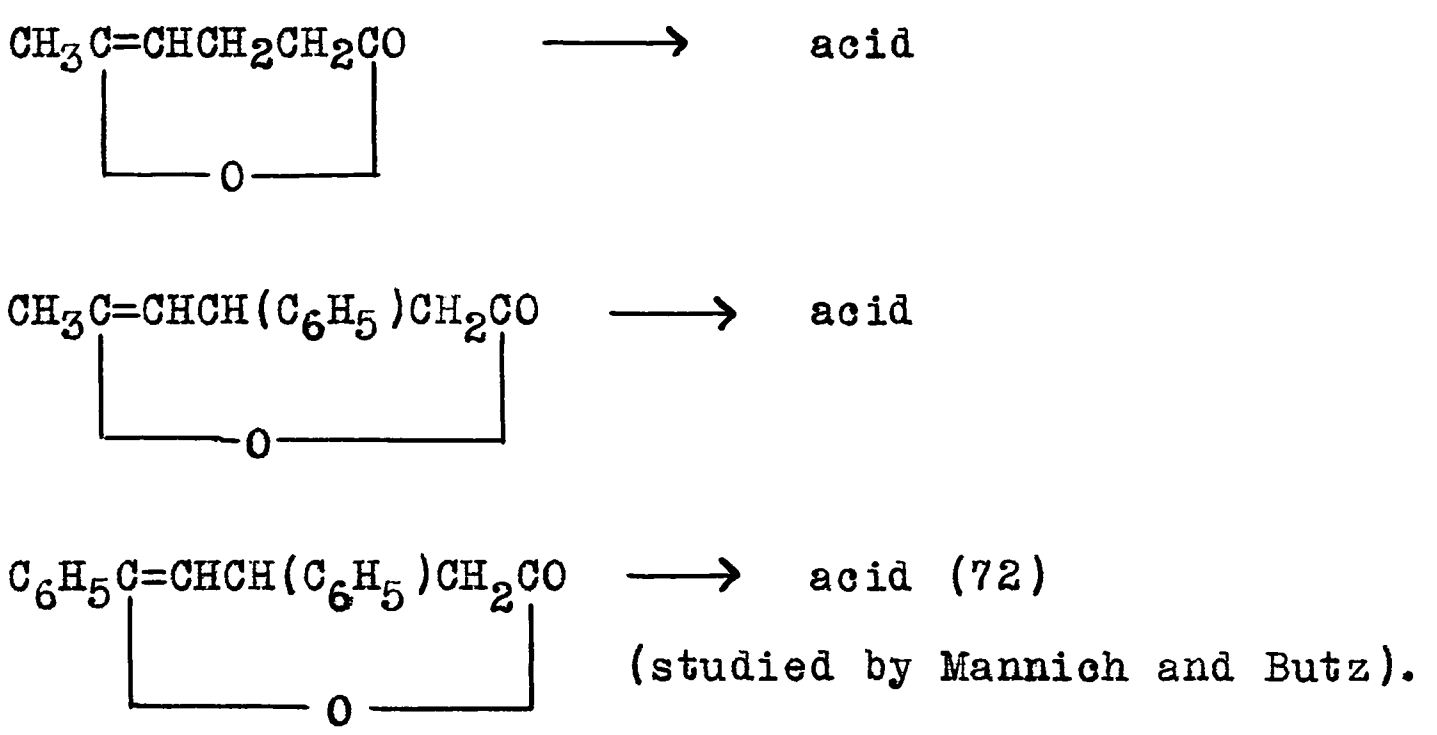
LXIX

A saturated acid was the product of the former, a lactone, together with some acid, of the latter.

The following lactones of γ-aldehydo acids were investigated.



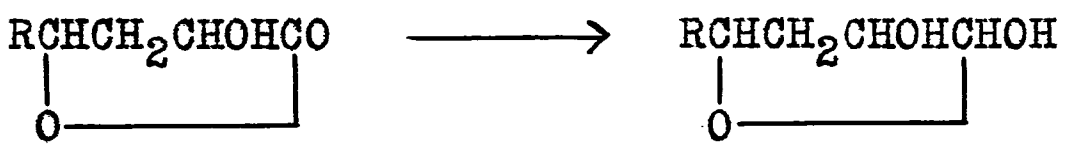
Jacobs pointed out that although beta-substitution tends to inhibit acid formation, with delta-lactones this effect may be nullified by the fact that they are in general more easily opened than gamma-lactones. That this is so is made evident by a consideration of the following reactions.



Hydriodic acid and red phosphorus reduce lactones to the corresponding fatty acids.

Normally lactones are reduced by sodium and alcohol to glycols. A method of preparation of lactones

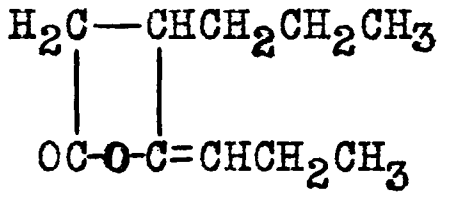
consists in the reduction of the anhydrides of dicarboxylic acids, a large proportion of glycols being formed at the same time (76). ∝,ɣ-Dihydroxy-ɣ-lactones and hexonic lactones react similarily with sodium amalgam, being reduced to the ∝,ɣ-dihydroxyaldehyde (77).



Oxidation.

The behaviour of lactones on oxidation varies with the type of substitution of the lactone ring. Oxidation of lactones, which are disubstituted on the gamma-carbon atom, attacks one of these substituents. Socalled primary and tertiary lactones are usually completely broken up.

Studies of the action of ozone upon lactones are very rare. The complex beta-lactone (LXX) on treatment with ozone in chloroform yielded propionic acid and propylmaleic anhydride (78).

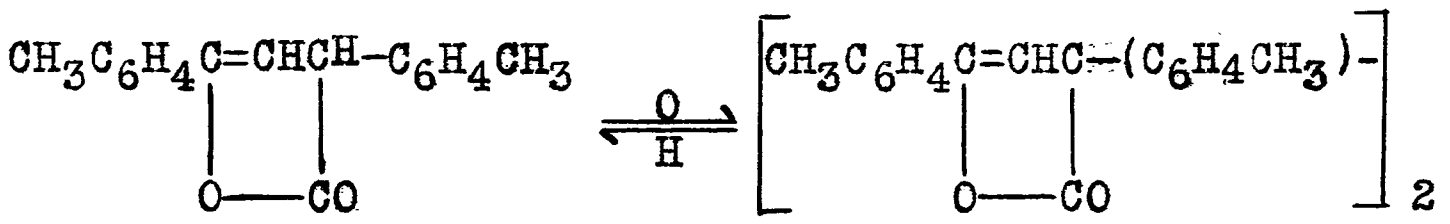


LXX

Thiele has studied the effect of potassium permanganate upon unsaturated lactones. He found that α,β-angelicalactone was oxidized to the lactone of α,β,γ-trihydroxyvaleric acid, whereas an analogous reaction did not occur with the β,γ-isomer (79).

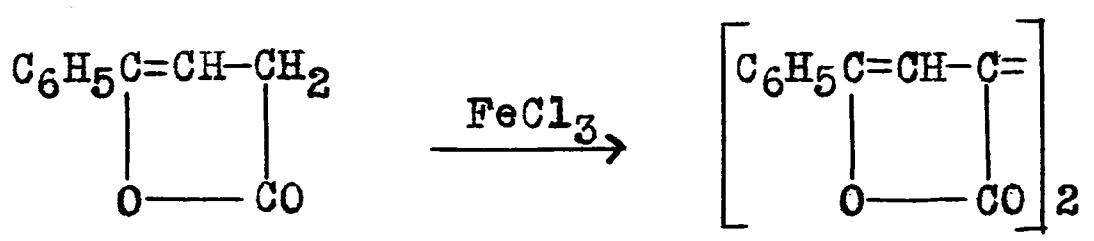
It is evident from the work of Pummerer (66) that under special conditions oxidation may lead to the doubling-up of two lactone molecules. Thus he found that the lactone (LXXI) was converted into the dilactone (LVIII) by a dehydrogenation reaction under the influence of atmospheric oxygen, bromine, or ferric chloride. The reverse hydrogenation could

only be brought about by the Clemmensen method.



LXXI LVIII

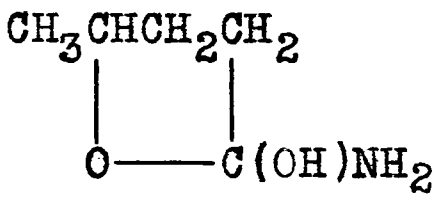
If the monolactone is not substituted in the alpha position, under the influence of ferric chloride it is dehydrogenated and coupled by a double bond. Kugel (80) thus converted phenylcrotolactone (LXXII) into the cis-dilactone (LVI)



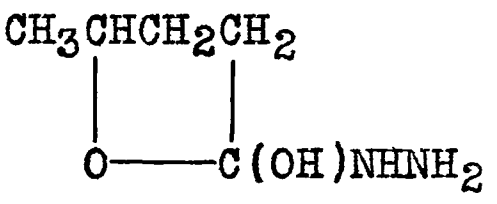
LXXII LVI

Condensation.

Many examples of condensations of ammonia, hydrazine, and derivatives of hydrazine with the carbonyl group of lactones have been reported. Such condensations do not involve ring opening. Thus Neugebauer (81) has reported that γ-valerolactone reacts with alcoholic ammonia to form a substance of the structure (LXXIII), and Blaise (82) has stated that hydrazine forms (LXXIV).



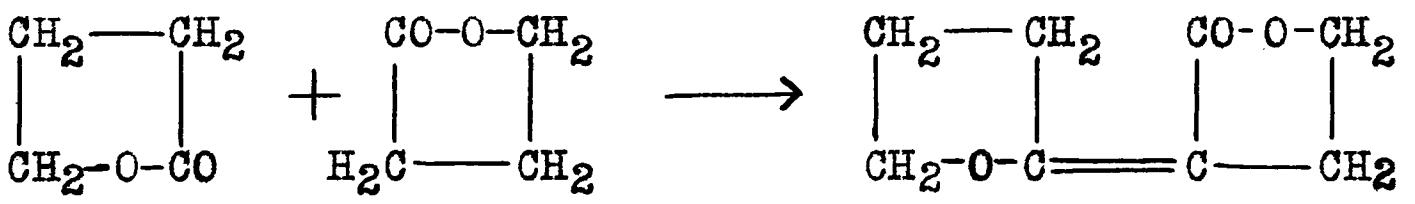
LXXIII



LXXIV

The former is unstable to heat and the latter to acids. The evidence is not convincing; it would appear that an open-chain formula would be more acceptable for substances of this type.

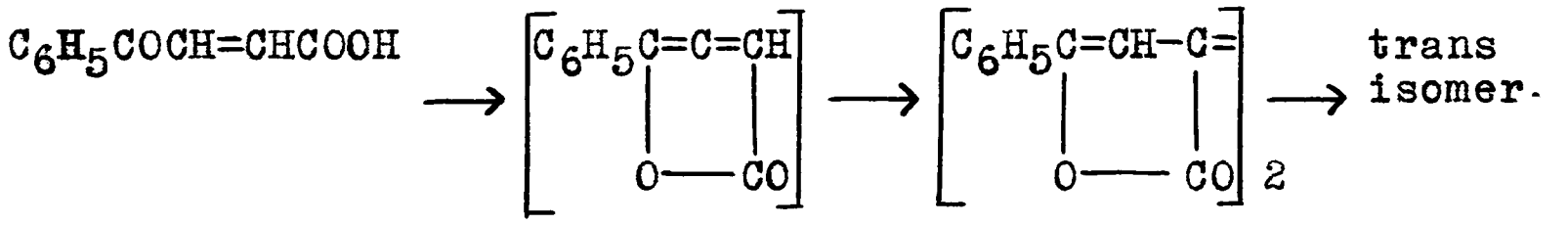
Under the combined influence of heat and sodium methylate, condensation of a different type occurs, being a condensation between two molecules of gamma-lactone and a simultaneous elimination of water.



LXXV

By boiling γ-butyrolactone or its γ-substitution products with alcoholic sodium methylate solution and acidifying the sodium derivatives which separated a substance of the type (LXXV) was obtained, together with γ-methoxybutyric acid (83).

An interesting type of polymerization occurs on dehydration of β-benzoylacrylic acid (LV) and results in the formation of the trans-lactone (LVI). Bogert and Ritter (65) have postulated that the mechanism of the reaction is the formation of an intermediate allene lactone (LXXVI) which undergoes a bimolecular condensation immediately.

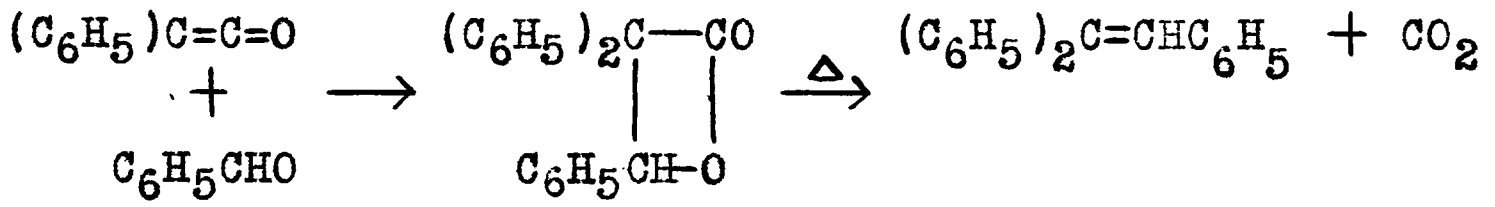


LV LXXVI cis isomer LVI

This seems extremely improbable; no cyclic allenes are known. Further, from an examination of conventional models, such a structure is incapable of existence.

Pyrolysis.

Heat treatment of lactones may lead to a variety of products. The beta-lactone ring on pyrolysis splits off carbon dioxide and forms an unsaturated compound (20).



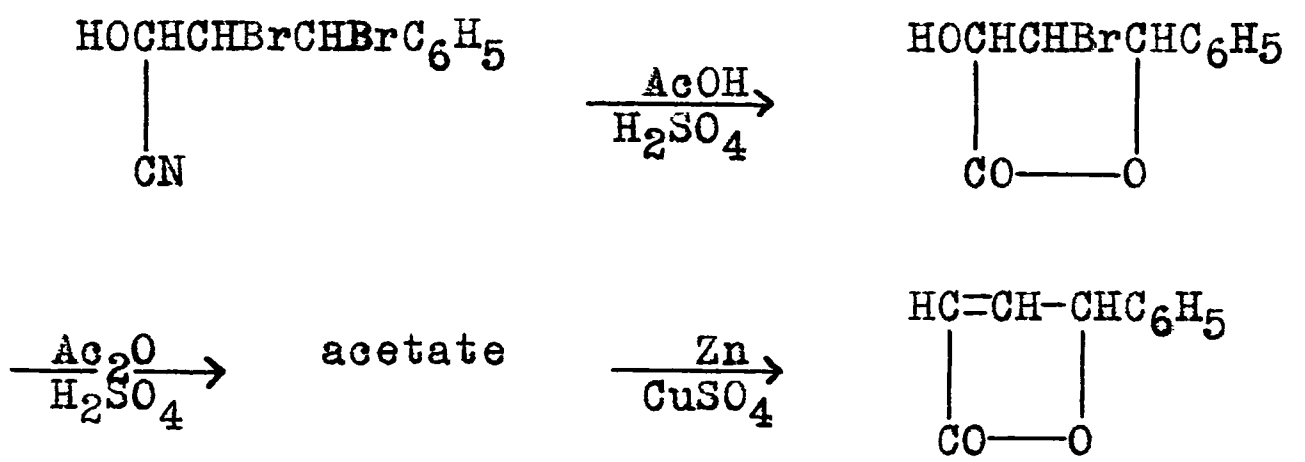
In general gamma-lactones are so stable that they can be distilled unchanged.

Delta-lactones possess the unique property of undergoing spontaneous reversible polymerization. Thus δ-valerolactone, which is a mobile liquid, slowly changes into a solid polymer on standing, and can be regenerated from it on heating. This phenomenon has been noted among other 6-membered lactones and is probably a general property (84).

Recently Carothers (35) has shown that the macrocyclic esters may likewise be polymerized, though the reaction requires the use of elevated temperatures and catalysts such as potassium carbonate.

Miscellaneous Reactions.

Thiele (85) has made an extensive study of the isomerism of unsaturated lactones. He prepared β,γ-unsaturated crotolactone by the simple operation of removing water from benzoyl-propionic acid through the agency of acetic anhydride. The synthesis of the alpha, beta-isomer was somewhat more complicated. It is outlined below

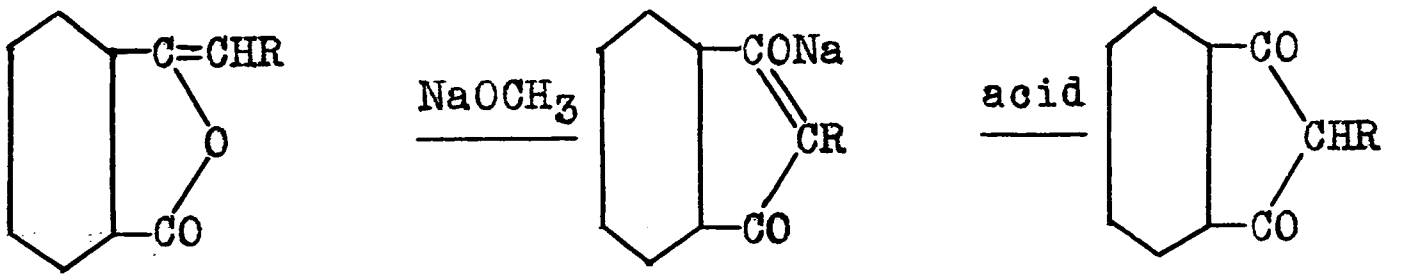


The alpha, beta-isomer could be changed into the beta, gamma- one by the action of acetic anhydride; the reverse process proceeded under the influence of fairly strong amines, such as ammonia, methyl amine, etc. Weak amines, such as aniline and pyridine were of no value.

The action of organometallic compounds upon lactones has not received much attention. In the aliphatic series of lactones, zinc alkyls act in the manner of sodium methylate and form condensates of the type, dibutolactone (86). They are without effect upon aromatic lactones such as phthalide. With methyl magnesium bromide, butyrolactone yielded α,α-dimethyltetramethylene glycol (87).

1,3-Indandiones, (1,3-diketohydrindenes).

Although the 1,3-indandiones are not lactones, nevertheless they merit attention in this thesis because their monosubstitution products are analogous to a new unsaturated diketone found in our work; they are easily synthesized from certain unsaturated lactones by the action of sodium methylate. Thus Nathanson (88) has shown that if the lactones of the type (LXXVII) were treated with sodium methylate, or, less satisfactorily, alcoholic sodium hydroxide, they were converted into the indandiones (LXVIII).



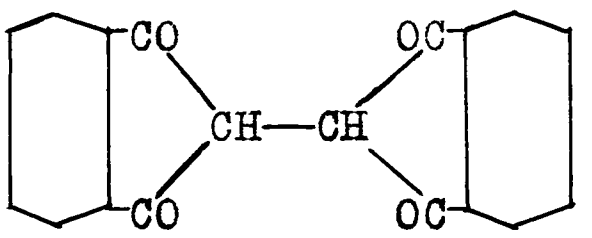
LXXVII LXXVIII

R= aliphatic or aromatic radical.

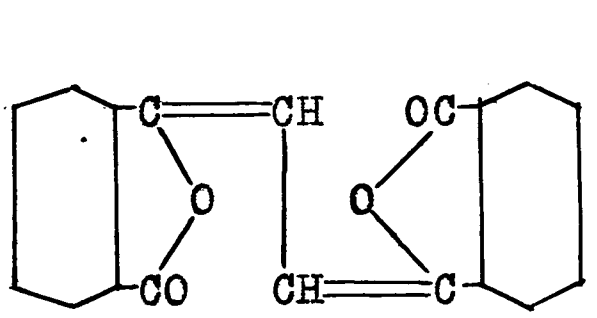
It is interesting to note that the 2-phenyl derivative can be prepared from the acid (LXXIX) by the action of alcoholic potassium hydroxide. The yields are poor (ibid.).

LXXIX

A perfectly analogous reaction occurred when the R component acted as a bridge between two lactones; thus ethinediphthalide (LXXX) was converted into bisdiketohydrindene (LXXXI). Gabriel (89) has shown that isoethinediphthalide (LXXXII) is also a product of the reaction.

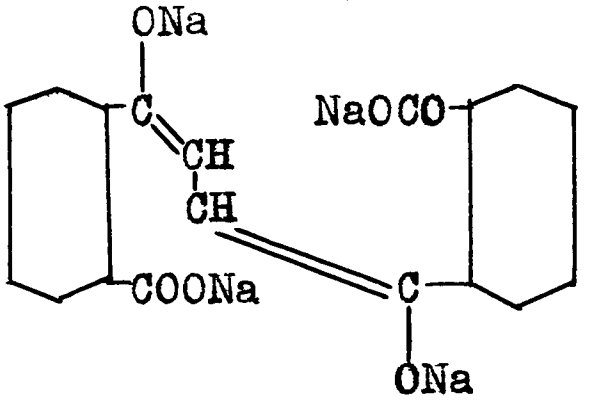


LXXXI

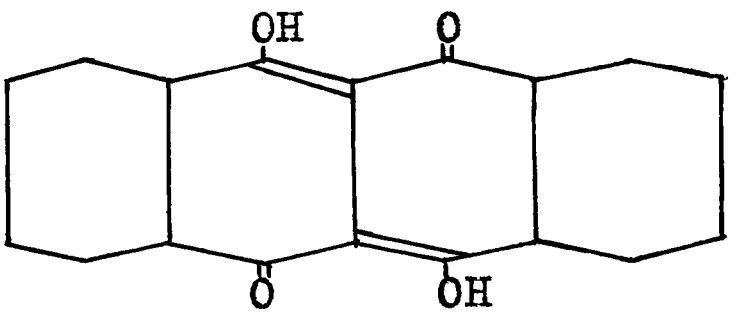


LXXX

$NaOCH_3$

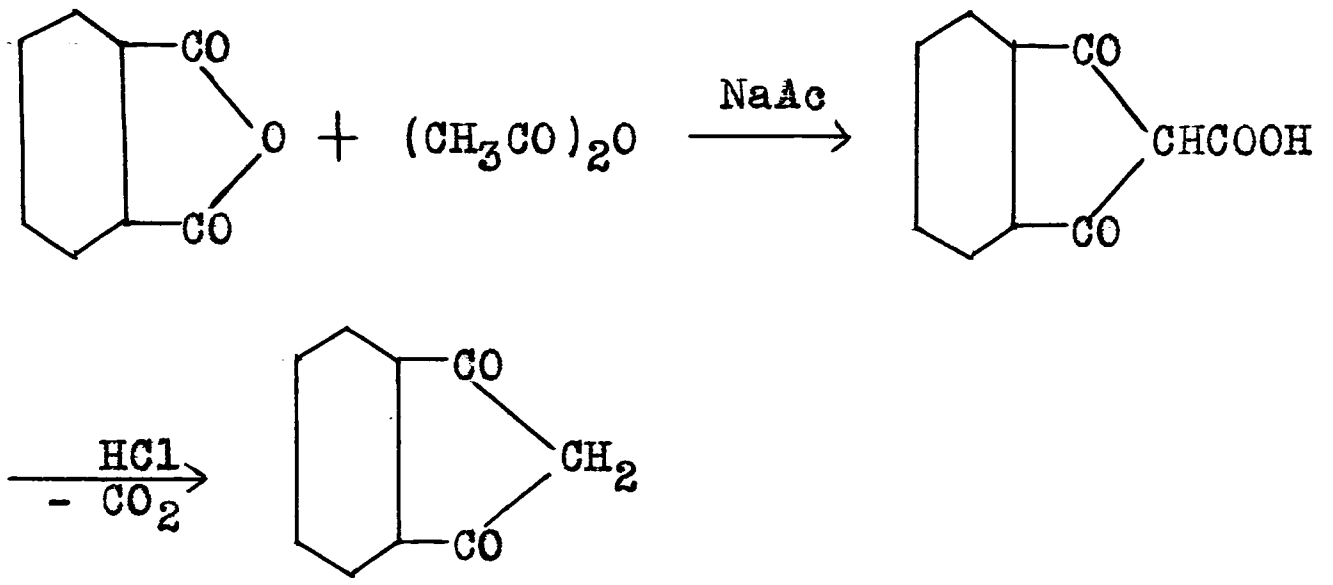


LXXXV



LXXXII

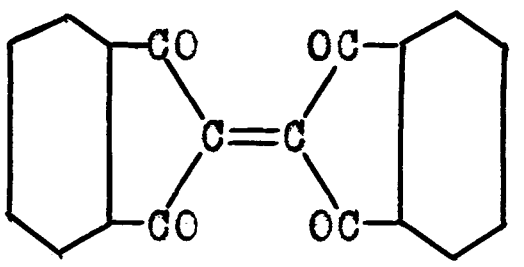
1,3-Indandione itself has been prepared by Gabriel (90) by the following reaction



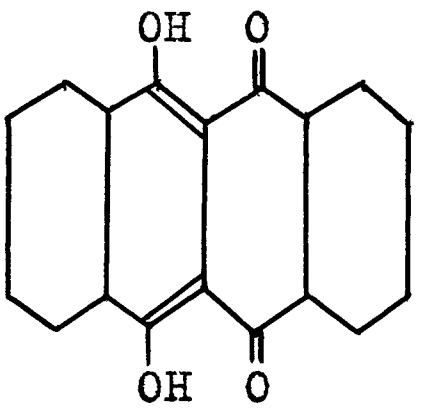
These substances are 1,3-diketones and exhibit most of their characteristic properties, as well as others peculiar to the ring system. Thus, although they are colorless (and give no colour with ferric chloride), they dissolve in bases and give highly coloured enolates. The latter may be alkylated or acylated in the usual manner.

The unsubstituted dione shows some slight differences from the monosubstituted homologues. Thus on boiling with water or dilute alkalies or acids it was converted into anhydrobisdiketohydrindene (LXXXIII). This is an oxidation reaction analogous to the formation of Pechmann dyes. The same result was achieved by prolonged heating at a temperature just below its melting point, or by treatment of (LXXXI) with an alkaline solution of hydrogen peroxide. Oxidation by potassium persulphate in alkaline solution produced 9,10-dihydrooxynaphthacenequinone (LXXXIV). The mechanism was probably dimerization resulting from oxidation, followed by addition and loss of water from the intermediate (LXXXV). formed. Indandione reacted with chloroform in the presence

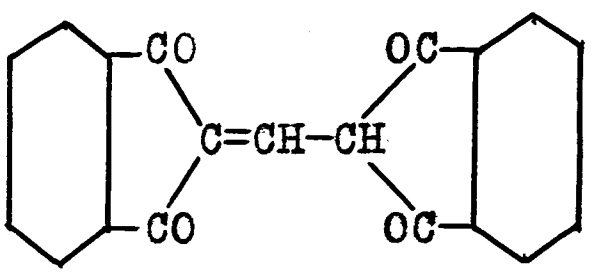
of sodium methylate to form (LXXXVI).



LXXXIII



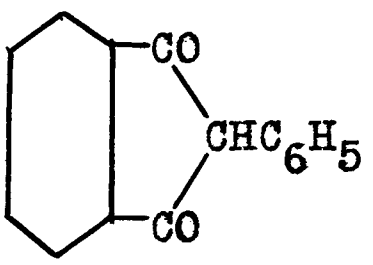
LXXXIV



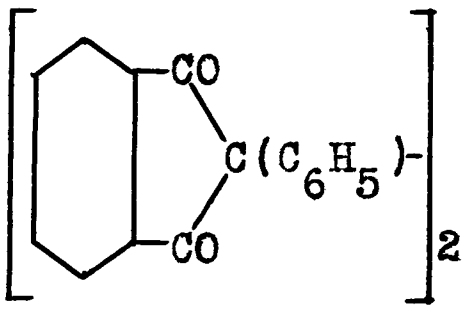
LXXXVI

In its mode of condensation with aldehydes and ketones, it was a typical 1,3-diketone.

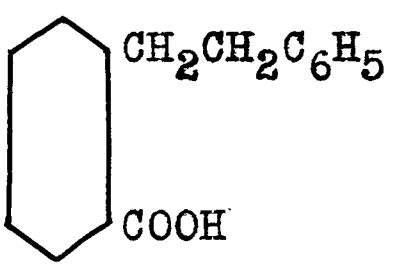
The reactions of 2-phenyl-1,3-indandione (LXXXVII) are typical of the monosubstitution products.



LXXXVII



LXXXVIII



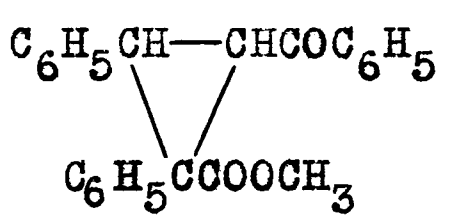
LXXXIX

It dissolved in alkalies to form a red enolate; well-defined copper and silver derivatives were prepared. Concentrated sulphuric acid gave rise to a blue colour. Potassium persulphate in alkaline solution (89) or fuming nitric acid (88) dimerized the compound to (LXXXVIII). Reduction by hydriodic acid in a sealed tube yielded the acid (LXXXIX). The 2-halogen derivatives were obtained by direct action of the halogen in a solvent; the 2-acyl derivatives were cleaved by

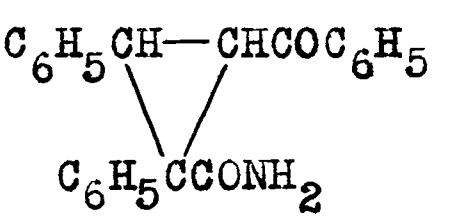
bromine, giving a dibromoindandione and an aroic acid (91). The 2-alkyl derivatives were synthesized by the action of alkyl halides on the sodium derivative. The compound formed a dioxime and a monophenylhydrazone.

Theoretical Discussion.

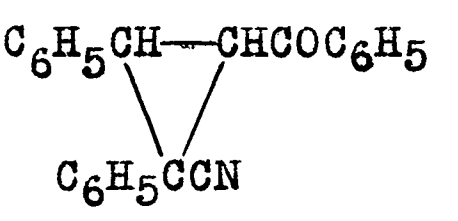
With a view to securing the highly substituted cyclopropane ketoester (I) and comparing its behaviour with the usual ring opening reagents, the synthetic reactions customarily employed for this purpose were carried out, and a substance having the correct analysis was obtained (1). This new compound was believed to be the desired derivative since it could be converted into a known cyclopropane nitrile (XCI) by way of the amide (XC), and by its behaviour with reducing agents.



I



XC



XCI

However, the action of basic reagents gave rise to a considerable variety of products which could not be reconciled with the ester formula (I), nor was a methoxyl group detected in a Zeisel determination, and it was eventually found that the substance was a lactone (II). Although very sensitive to bases, it was soluble in sodium hydroxide and recovered unchanged on immediate acidification. It formed derivatives showing the presence of a carbonyl group. Since it gave the known ketoacids (XCII) on reduction, the same chain was

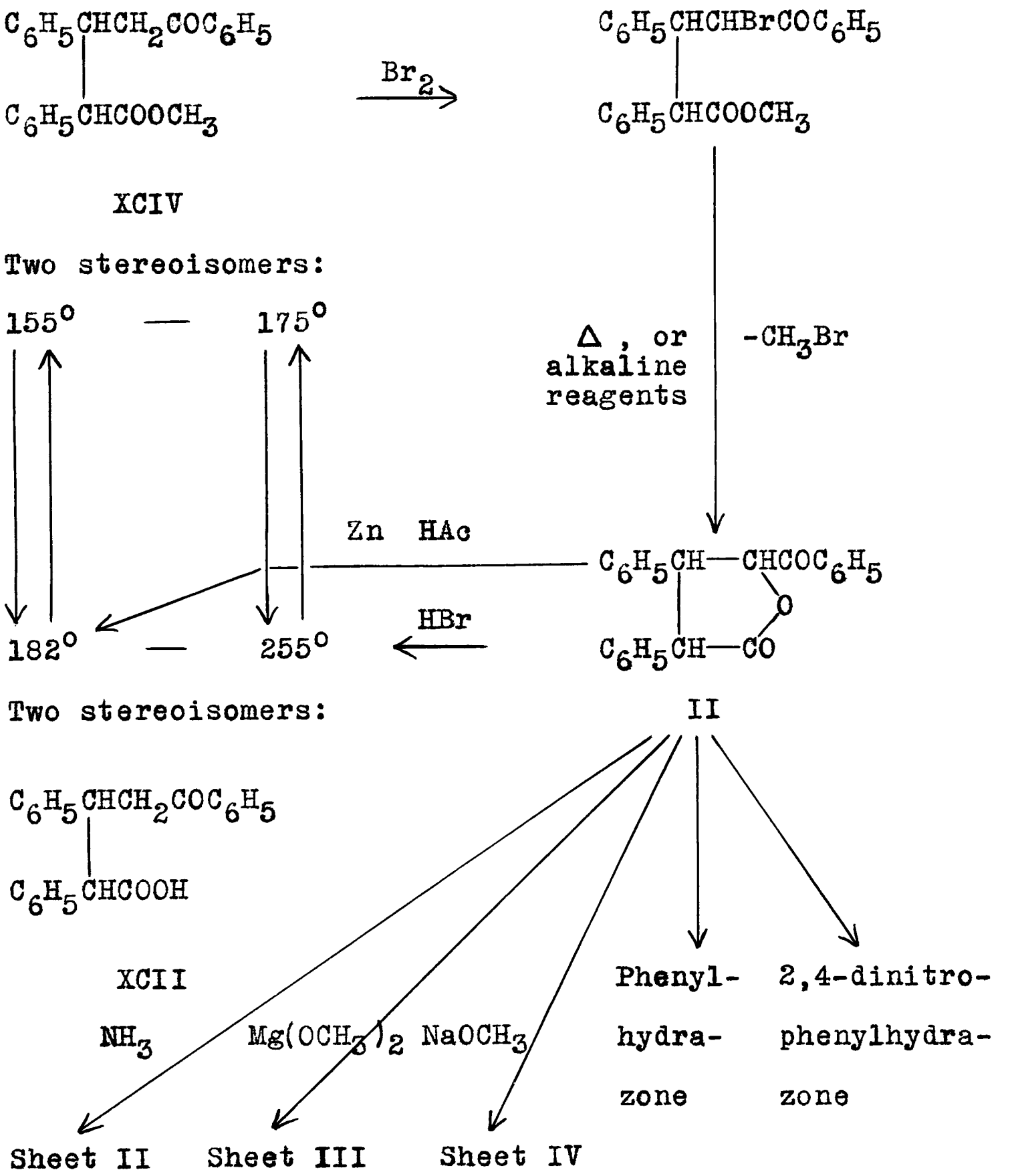
present as in the starting material. These reactions are collected in Sheet I. The relation between the open-chain acids and esters is known from the work of Avery (92).

The methods of formation, heating alone, or in solution in the presence of potassium acetate, dimethyl-aniline, pyridine, etc., are analogous to certain similar cases in the literature and were considered on pages 16-19. They involve a loss of methyl bromide; in this instance, the process is an easy one since it takes place even in an acetic acid solution.

When a suspension of the lactone in absolute methyl alcohol is saturated with ammonia it gives a new unstable substance, formed by the addition of ammonia. The latter is evolved at the melting point or removed by recrystallization from acetic acid, or by refluxing with phosphorus pentoxide in xylene. It appears, therefore, that the substance is an open-chain hydroxyamide (XCIII) in which the elements of ammonia are loosely bound, since there is little or no tendency to close a lactone ring by the elimination of water. The open-chain formula is preferred to any other kind on account of the fact that the elements of water can be eliminated to yield a known cyclopropane derivative.

Sheet I.

Preparation and Summarized Reactions of ∝,β-Diphenyl-γ-benzoylbutyrolactone.

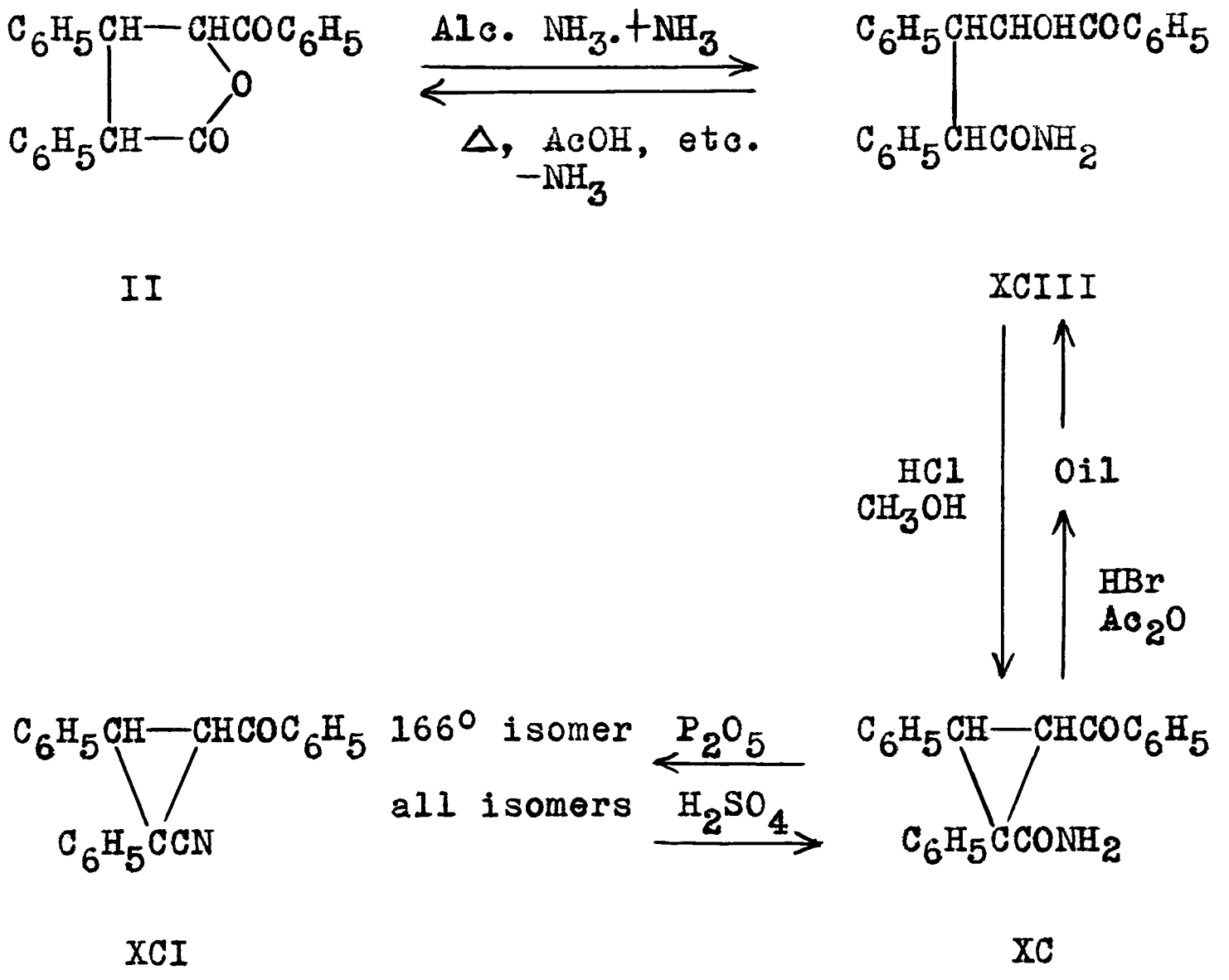


When a solution of the new substance in methyl alcohol is saturated with anhydrous hydrogen chloride it is transformed into the known cyclopropane amide (XC), which Boyer (93) had obtained from all three stereoisomeric forms of the cyclopropane nitrile (XCI) by the action of sulphuric acid. Boyer showed that one of the stereoisomeric forms of the nitrile was regenerated by phosphorus pentoxide, making it seem probable that the cyclopropane ring had not been opened by the sulphuric acid. Massey found that the reverse reaction, opening of the cyclopropane ring to give the open-chain hydroxyamide, could be brought about by the use of hydrogen bromide in acetic anhydride. Presumably, an acetate is the primary product, for the oil formed only slowly changed into the solid amide. Traces of the latter were also noted in the residues from treatment of the cyclic nitrile (XCI) with sulphuric acid. These observations have been confirmed.

The foregoing relationships are set out in Sheet II.

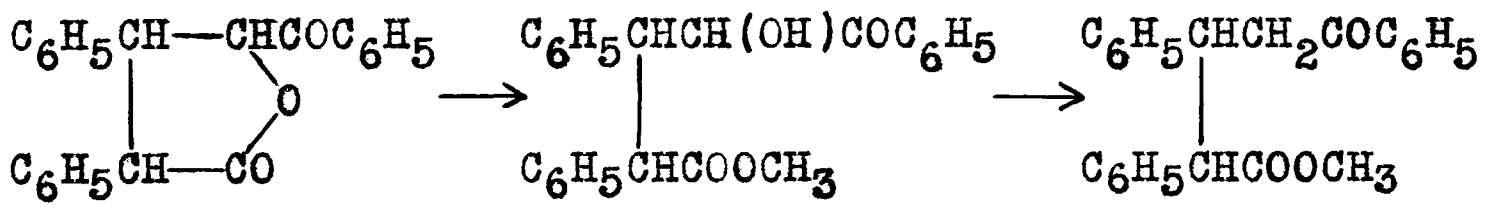
Sheet II.

Reactions of the Butyrolactone with Ammonia.



From a preliminary investigation of the many products resulting from the action of sodium methylate upon the butyrolactone it appeared advisable to avoid complications due to the presence of water by first determining the effect of magnesium methylate.

When an alcoholic solution of magnesium methylate was allowed to act upon the lactone for lengths of time varying from one half to one hour, followed by acidification, an oily yellow solid was obtained. By trituration with ether this was separated into a white solid and a yellow oil. After separation from the small amount of unchanged lactone and purification the white solid, which amounted to 20-30% of the starting material, was found to be one of the two isomeric forms of α,β-diphenyl-γ-benzoylbutyrate (XCIV). This is best accounted for by the opening of the lactone ring and the addition of methyl alcohol to the ends of the chain, with subsequent reduction of the gamma-hydroxyl group, thus



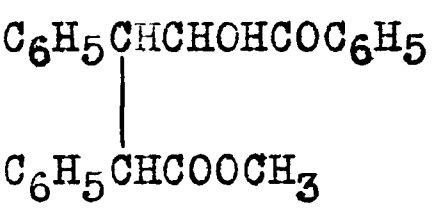
II XCV XCIV

On standing the ether-soluble oil slowly deposited a white crystalline solid A, m.p. 174°, and on more prolonged standing a solid B, m.p. 117°. Both solids appear to be addition products of the lactone and methyl alcohol, and

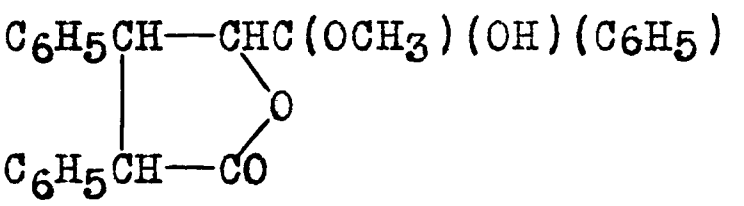
were reconverted into the lactone by pyrolysis, A at its melting point and B at temperatures not less than 180°. The methyl alcohol evolved from a sample of A was collected at a low temperature and identified as its 3,5-dinitrobenzoate.

With sodium methylate both compounds gave a variety of ill-defined products, the only one which could be identified being the original lactone. Magnesium methylate, however, brought about the conversion of B into A, indicating that they were probably stereoisomers.

There are two possibilities. The methyl alcohol could add to the lactone by opening of the ring and addition to the ends of the chain to form the hydroxyester (XCV), (which already has been suggested as an intermediate in the formation of the open-chain ketoester), or by addition to the carbonyl group to form the hemiacetal (XCVI).



XCV

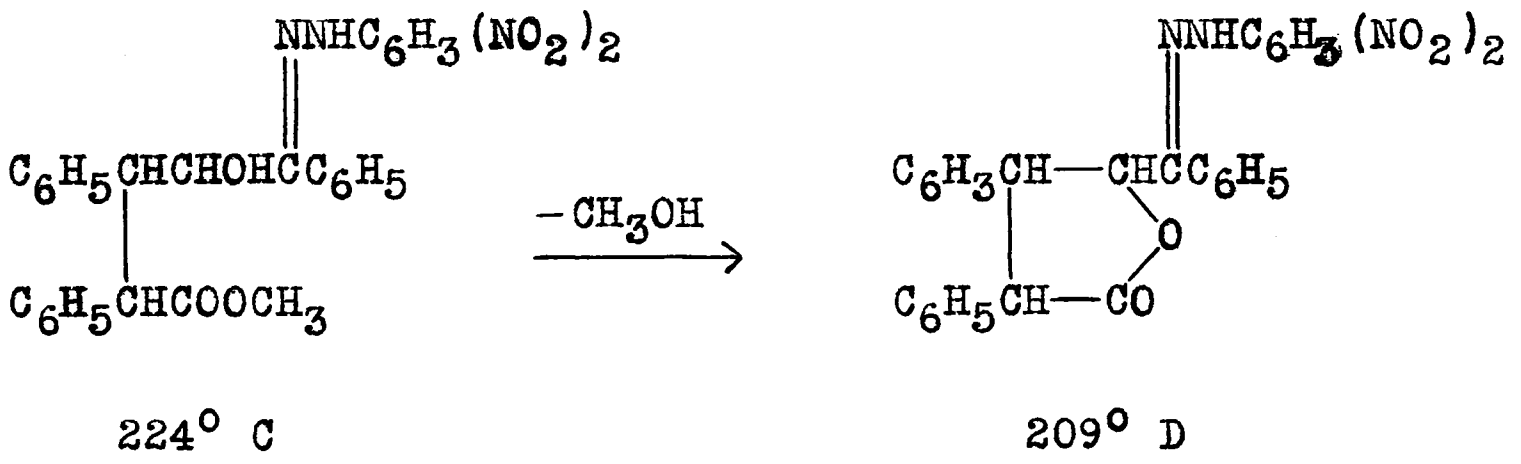


XCVI

The hemiacetal formula was excluded for both substances by the formation of carbonyl derivatives and of acetates, and the non-formation of an acetal under appropriate conditions.

When a 2,4-dinitrophenylhydrazone was prepared in the usual was, using methyl alcohol and a trace of hydro-

chloric acid, A gave two hydrazones, C (brilliant red needles), and, on further standing, D (an orange solid). By a mixed melting point D was proved to be the dinitrophenylhydrazone of the original lactone. The substance B gave as its only product the latter hydrazone, D. At first sight it might seem that these were geometrical isomers as described in certain instances by Bredereck (94), but analysis distinguished between them. Further, although derivative D could not be converted into C, the reverse process resulted from refluxing with methyl alcohol containing a little hydrochloric acid. The net result was the elimination of a molecule of methyl alcohol, and the relation between the two derivatives became clear.



224° C 209° D

In an attempt to reverse the hydrazone formation, D was refluxed with benzaldehyde in methyl alcohol containing hydrochloric acid; a small amount of C was obtained.

The oily portion, obtained by treatment of the lactone with magnesium methylate and apparently freed from all solid material by numerous washings with ether-petroleum ether mixture during many months, was further studied in an attempt to identify other reaction products. The oils in ether solution were extracted successively with sodium carbonate, sodium bicarbonate, and sodium hydroxide solutions. The sodium hydroxide washings only deposited an oily solid on acidification; this amounted to about 3% of the total oil. On separation from adhering oil and crystallization from methyl alcohol it was found to be the high-melting form of the ketoacid (XCII), corresponding to the ketoester (175°) already separated. It is a question whether this acid is a primary product of the reaction or results from the action of the sodium hydroxide on the ketoester still remaining in the oil. Its non-appearance in the bicarbonate and carbonate washings substantiates the latter view.

After evaporation of the ether, the neutral oils were steam-distilled, and a small amount of benzaldehyde was detected in the distillate as the dinitrophenylhydrazone. From the oils remaining in the distillation flask the dinitrophenylhydrazone of the original lactone was obtained.

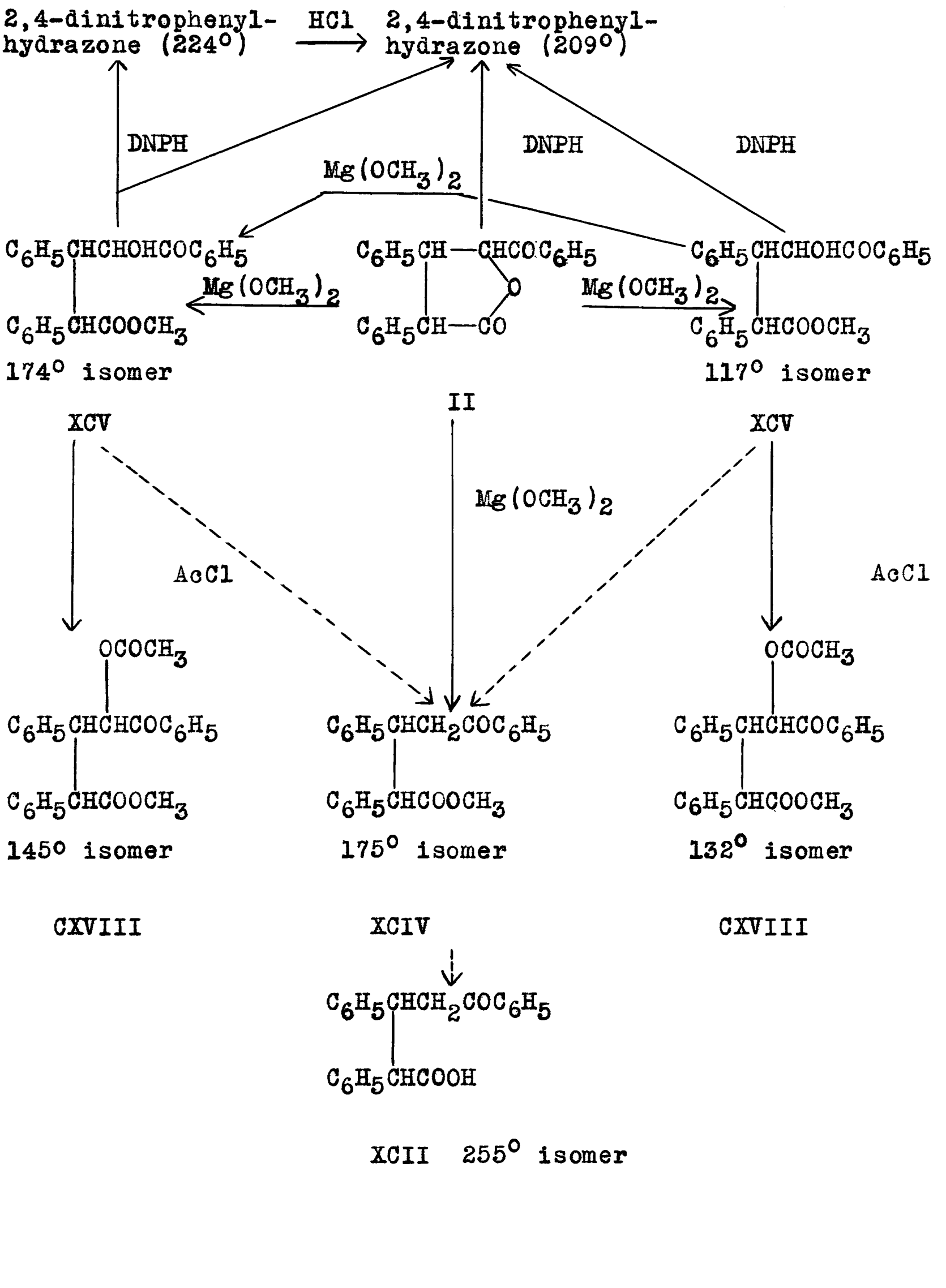
It is obvious that the high-melting ketoester and acid, which make up the largest proportion of the ether-insoluble solids, arise in the reaction products by a reduction reaction. This will be discussed in the next

section.

The course of the reaction of magnesium methylate upon the butyrolactone is given on Sheet III

Sheet III.

Reactions of the Butyrolactone with Magnesium Methylate.



The action of sodium methylate upon the lactone is more complex than that of the magnesium compound. An explanation of the presence of such products as have been isolated is not difficult if one bears in mind that traces of water are always present in the reaction mixture.

It was the custom to shake the cold alcoholic solution of sodium methylate with the lactone until solution was complete; this required from seven to ten hours. After acidification, and trituration with alcohol a brilliant yellow compound, $C_{23}H_{16}O_2$, was obtained (XCVII), amounting to about 35% of the starting material. This substance was the principle product of the reaction and is described in the next section in detail.

The remainder of the reaction product was a thick viscous yellow oil, from which small amounts of unchanged starting material separated during several months' standing. A chloroform solution of the oil was systematically extracted with sodium bicarbonate, potassium carbonate, copper acetate and sodium hydroxide, and the following substances separated- there was nothing in the potassium carbonate and copper acetate extracts.

1. from the sodium bicarbonate: 255° ketoacid (under certain conditions) (XCII), and diphenylmaleic anhydride (XCVIII),
2. from the sodium hydroxide: high-melting isomer of diphenylsuccinic acid (XCIX),
3. from the water wash of the chloroform solution, after the

sodium hydroxide extraction: the lactone (C) and a quantity of oils, soluble in sodium hydroxide but insoluble in sodium bicarbonate,

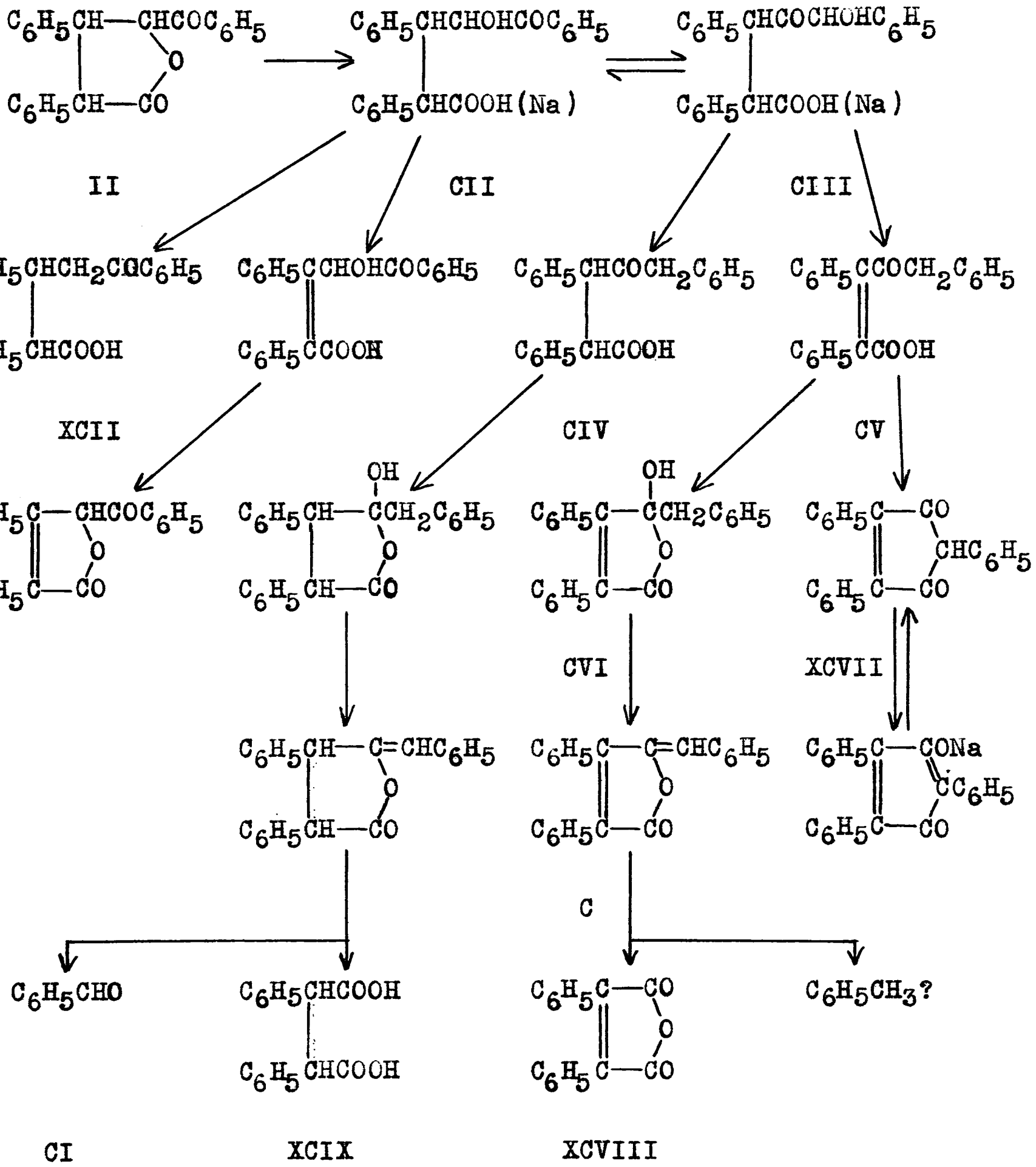
4. from a steam distillation of the residual oil: benzaldehyde (CI).

The remainder of the oil resisted further separation and identification.

The formation of the reaction products and their interrelation is shown in Sheet IV.

Sheet IV.

Reaction of the Butyrolactone with Sodium Methylate.



It is obvious that all of these substances are secondary and later products of the reaction. It is equally obvious that the first thing that happens is the formation of the sodium salt of the acid (CII). In a series of papers, described in the introduction (p. 30), Kohler has shown that in the case of simpler substances, alpha-hydroxyketones are both isomerized and reduced by alkalies. If applied to the present reaction, a portion of the hydroxyketone (CII) may be considered to rearrange to (CIII); each of these may then give a distinct series of degradation products.

In the series starting with (CII), the reduction product (XCII) was isolated; the necessary hydrogen could have come from the dehydrogenation of the secondary alcohol to a ketone or to an unsaturated hydroxy compound. No trace of anything corresponding to either was found, but it may have been the constituent of the residual oil which was lactonic in nature -- insoluble in sodium bicarbonate, soluble in sodium hydroxide.

In the series starting with (CIII), the corresponding substances are represented by (CIV) and (CV). The diphenylsuccinic acid found is probably the final product of the degradation of (CIV). The unsaturated lactone (C), yellow diketone (CVII), and diphenylmaleic anhydride undoubtedly arose from (CV). The benzaldehyde is a hydrolytic product of uncertain origin. The unsaturated lactone (C) was found to be identical with benzaldiphenylmaleide synthesized

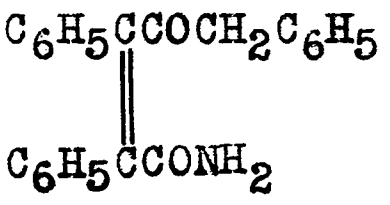
as reported in the literature (63).

The unsaturated lactol (CVI) was doubtless formed, but on account of its tendency to lose water was not isolated in the complex oily mixture. As mentioned on p. 27, it is only necessary to dissolve the lactone in alkali and the lactol can be isolated on acidification, using the proper technique (Experimental Part). A new synthesis of lactone and lactol is described later.

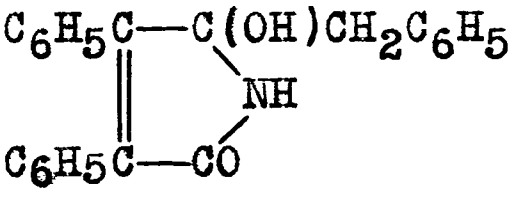
Reactions of the Unsaturated Lactone.

The other reactions of the unsaturated lactone (C) which are of interest are summarized in Sheet V.

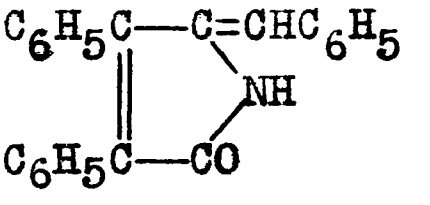
Heating in a sealed tube with ammonia gave rise to an open-chain ketamide (CVII) and the lactam (CVIII)(101). The lactam was unchanged by prolonged heating with alcoholic hydrogen chloride in a sealed tube. These served not only as reference compounds, but were of interest because they were obtained from a similar treatment of the yellow diketone.



CVII



CIX



CVIII

In view of recent analogous cases (95), it seems probable that (CVII) should have a cyclic structure (CIX).

Reduction by hydriodic acid (96) gave a lactone with a saturated sidechain (CX); zinc in acetic acid was observed to act in a similar manner.

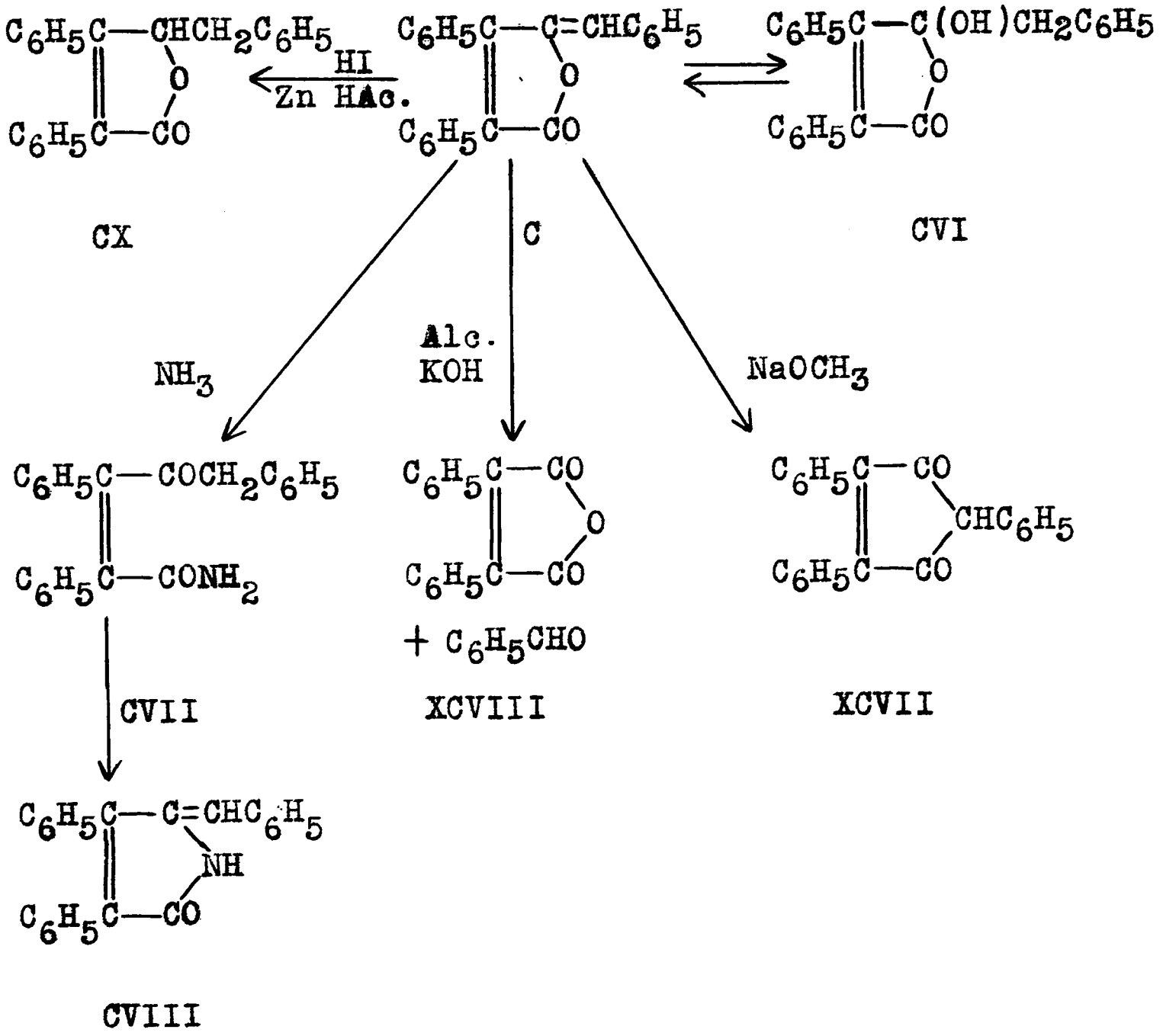
The presence of alkalies was found to bring about several reactions. The formation of the unsaturated lactol (CVI) has already been mentioned. On boiling for a short time in sodium methylate, or a longer time with sodium ethylate or alcoholic potassium hydroxide, the yellow diketone was formed. The nature of the change is considered under the discussion of the latter. Very prolonged boiling

with alcoholic alkali brings about a scission of the maleide with the production of diphenylmaleic anhydride together with a trace of benzaldehyde. Another possible product of the scission is toluene; its presence could not be detected. The occurrence of the anhydride in the oils is now accounted for. Cohn (97) claimed to have got the lactol by this procedure.

In the Grignard "machine", the lactone showed two additions, as was expected.

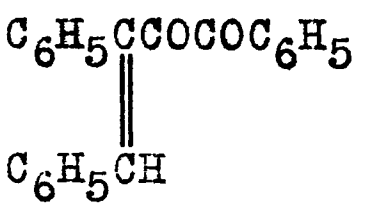
Sheet V.

Reactions of the Lactone.

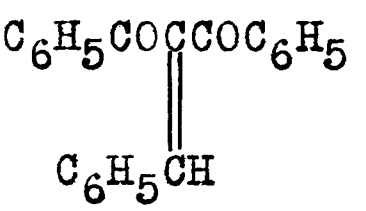


The Diketone, $C_{23}H_{16}O_2$:

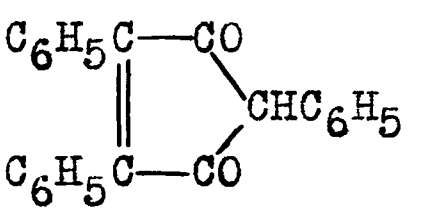
It proved most difficult to reconcile the reactions, and to determine the structure of this yellow substance. A search of the literature revealed no substance having the same properties. The possible structures that could arise are given below;



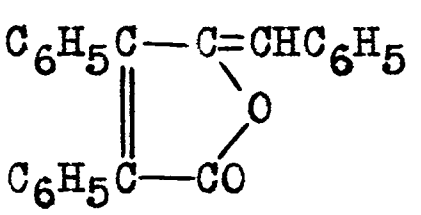
A



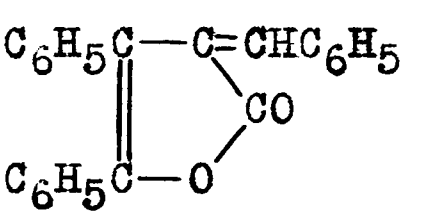
B



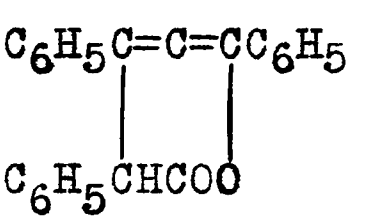
XCVII



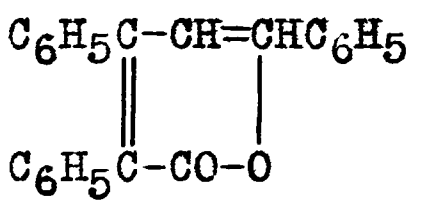
C



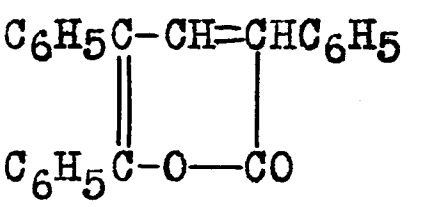
C'



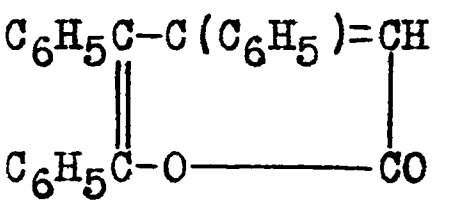
H



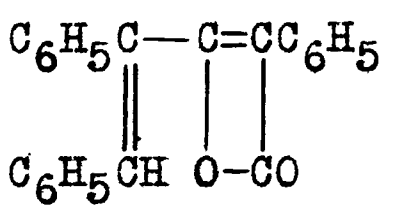
D



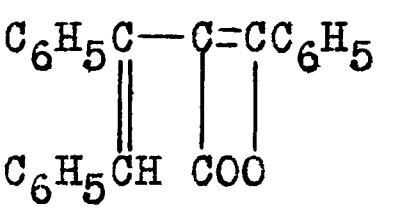
E



I



F



G

The substances represented by C, C' and I are known and are not the same. The yellow substance does not give a quinoxaline; this probably excludes A. In the Grignard "machine" it shows an immediate evolution of gas, corresponding to one

active hydrogen and (slowly) two additions. This observation excludes all possibilities except XCVII and the less likely H.

The yellow compound gave no colour with ferric chloride, nor did it form a copper derivative when an ethereal solution was shaken with copper acetate. It was insoluble in aqueous solutions of sodium carbonate and sodium hydroxide, but in the presence of alcohol it dissolved in the latter reagent to form a very deep purple solution, and was quantitatively recovered unchanged on acidification. The alkaline solution was relatively stable to boiling. It slowly formed a mono-2,4-dinitrophenylhydrazone, thus resembling other beta-diketones. In chloroform solution it did not decolorize bromine. However, potassium permanganate was instantly decolorized, the sole products of the reaction being benzaldehyde and benzoic acid. Chromic acid gave as a principle product a bimolecular yellow amorphous solid, together with some benzoic acid, while selenium dioxide in

---

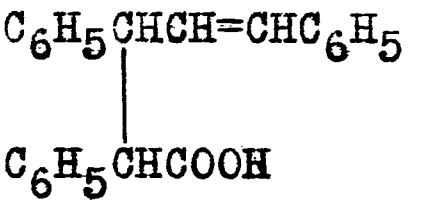
Lactones with Grignard reagent show no active hydrogen and two additions (98,99,p. 65), whereas 1,3-diketones that have a substituent on the middle carbon atom are cleaved with the consumption of two moles of reagent (100) as is made apparent in the "machine" by slow addition. No allenic lactones are known, but neither have any cyclopentendiones been reported.

dioxane gave only the bimolecular product. The latter also resulted from prolonged heating in the air above the melting point and in high boiling solvents. Treatment with ozone yielded no useful substance. By a special procedure which tended to keep the reaction mixture slightly basic, and using 30% hydrogen peroxide, a deep yellow compound was obtained in 60% yields.

Nothing helpful was learned from the action of acids. The compound was recovered unchanged from a methyl alcohol solution saturated with hydrogen chloride, and from glacial acetic acid. Concentrated sulphuric acid formed a deep red solution, but there was no reaction at room temperature; after heating at 100° for two hours there were isolated unchanged starting material, benzaldehyde, and the bimolecular product. Refluxing with 50% nitric acid gave p-nitrobenzoic acid.

Reduction reactions, however, were of more assistance. The use of zinc in acetic acid, or of hydriodic acid and red phosphorus, gave the same unsaturated acid which decolorized bromine and potassium permanganate instantly. Oxidation gave benzoic acid (benzaldehyde could be detected as a primary product by careful manipulation) and diphenylsuccinic acid. Therefore, the acid is α,β-diphenyl-γ-benzalbutyric (CXI) and the chain is present as in the original lactone (II). This shows that there has been no deep-seated rearrangement involving shifts of phenyl or carboxyl

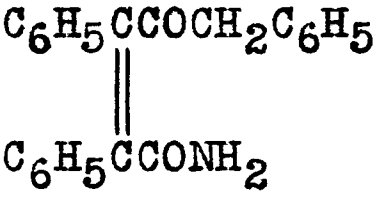
groups, and excludes any substance having a different chain.



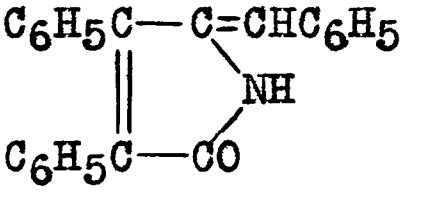
CXI

Catalytic reduction also gave an unsaturated acid (CXIa) apparently an isomer of the one obtained by reduction with nascent hydrogen.

On heating with alcoholic ammonia in a sealed tube, two known nitrogen-containing compounds were produced (CVII, CVIII).



CVII



CVIII

They were synthesized as directed in the literature (101) and their identity assured by careful comparison. This again shows there has been no shift of groups along the chain.

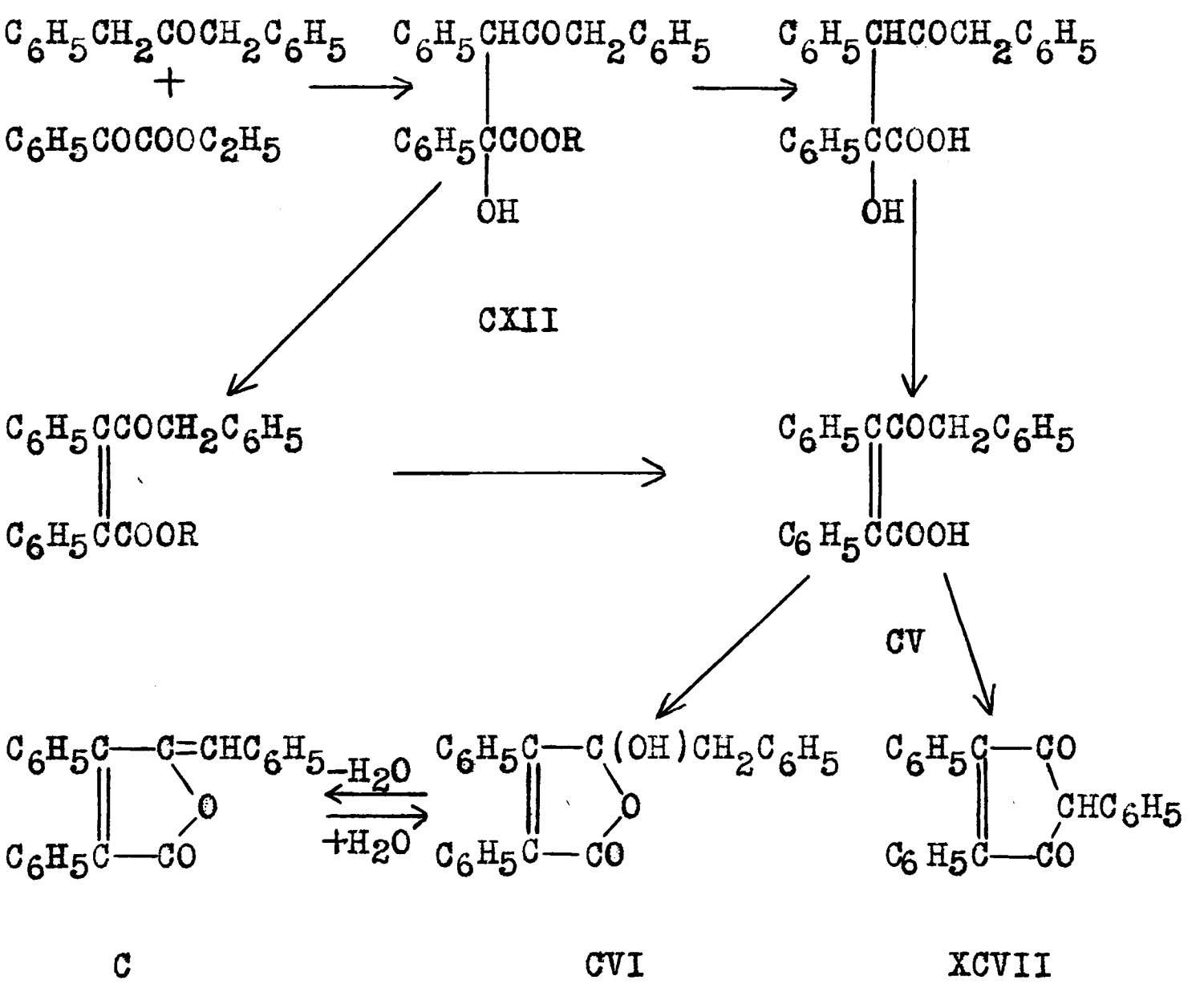
Having reached the conclusion that the substance, $C_{23}H_{16}O_2$, must be the cyclic diketone, an independent synthesis was attempted. This not only gave the desired diketone, but showed its relation to the whole problem. When dibenzylketone and ethyl benzoylformate were condensed in the presence of one equivalent of sodium ethylate a 27% yield of the

lactone (C) was obtained, but if sodium methylate was used as the condensing agent the yellow diketone was detected by the purple colour of the enolate in the reaction mixture and isolated on acidification. Finally, refluxing the lactone with alcoholic sodium methylate gave a quantitative yield of the yellow compound.

The relationship between the compounds is summarized in Sheet VI.

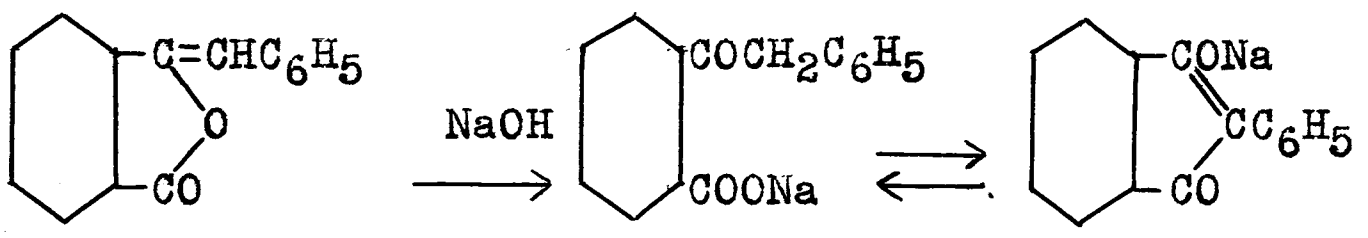
Sheet VI

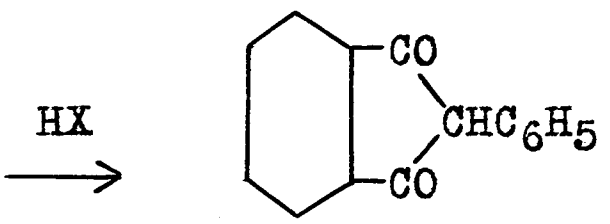
Synthesis of the Lactone and Diketone



These reactions indicate clearly that the ketoacid (CV) is the true intermediate product. Whether water is eliminated via the lactole, which would lead to the lactone (readily isolated on account of its slight solubility) or is eliminated to give the enolate of the diketone depends upon operating conditions.

An analogous case has been described in the Introduction; benzalphthalide is converted into the 2-phenyl-indandione-1,3 by alkalies.





LXXXVII

In both cases the reaction runs to the right owing to the formation of the sodium enolate of the diketone which is removed as a component of the equilibrium. It must be an equilibrium in the present instance also, otherwise the action of ammonia on both maleide and diketone could not give rise to the same lactam.

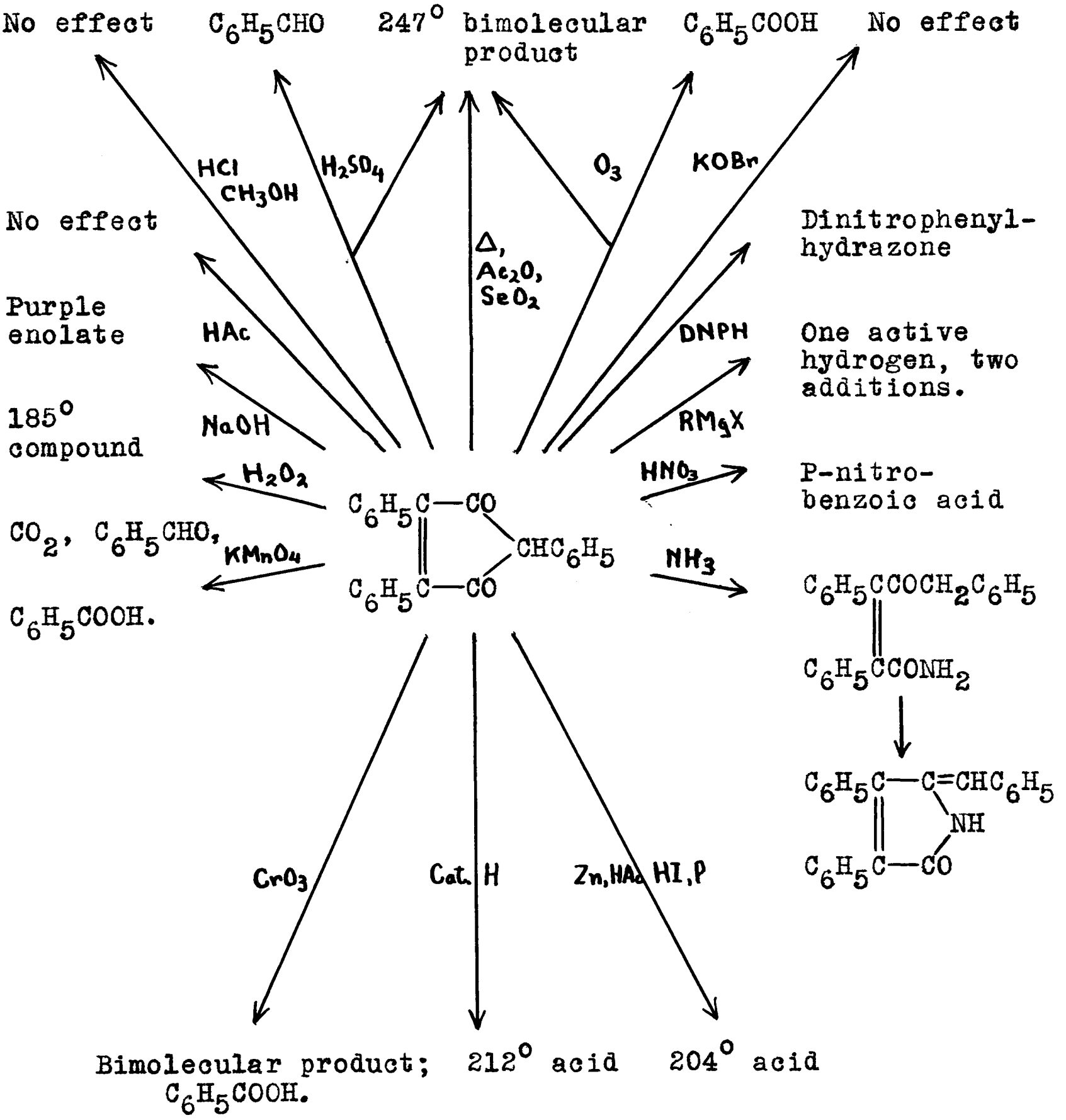
If a trace of sodium alcoholate at room temperature, or piperidine, was used as catalyst, a high yield of the primary addition product (CXII) was obtained. In the

Grignard "machine" it added two equivalents of the reagent with the evolution of one equivalent of gas; with acetyl chloride it formed an acetate, but only an intractable gum could be obtained after treatment with acetic anhydride. Superficially, it appeared not to be an intermediate in the formation of either the unsaturated lactone or the cyclic diketone, for it could not be changed into them by the action of alcoholates.

The reactions of the triphenylcyclopentenedione are collected together in Sheet VII.

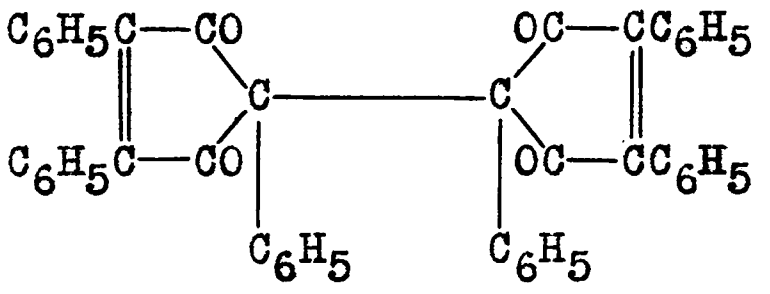
Sheet VII.

Reactions of Triphenylcyclopentenedione



The 247° Oxidation Product, $C_{46}H_{30}O_4$:

It was found that the cyclic diketone on heating in the air, in high boiling solvents, or by treatment with mild oxidizing reagents gave rise to an amorphous yellow compound. A molecular weight determination indicated that the substance was a dimer of the diketone. By analogy with the bisindandiones (p. 46 Introduction) this is a similar substance, and is accordingly represented by (CXIII).



CXIII

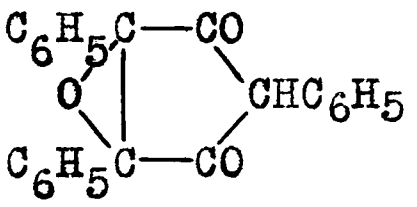
The observed fact that our compound decomposed with evolution of a gas at its melting point is not entirely consistent with the assigned structure. All attempts to identify the gas were unsuccessful.

The Substance Resulting from the Action of Hydrogen Peroxide.

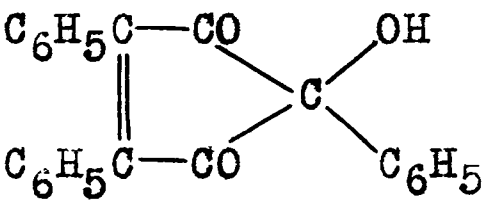
A structure cannot be assigned at this time with certainty to this substance. It is a pale yellow compound analysing for the empirical formula of $C_{23}H_{16}O_3$, or the addition of one oxygen atom to the cyclic diketone. A molecular weight determination indicated that it was monomolecular. It dissolved in aqueous sodium hydroxide to form a deep yellow solution. It did not decolorize bromine nor

did it form a dinitrophenylhydrazone. By refluxing with acetyl chloride, or less satisfactorily with acetic anhydride, it was converted into a new yellow compound. The analysis of the latter did not correspond to an acetate structure or a dehydration product.

From a consideration of the work of previous investigators there appear to be two possible structures for the hydrogen peroxide product (CXIV, CXV).

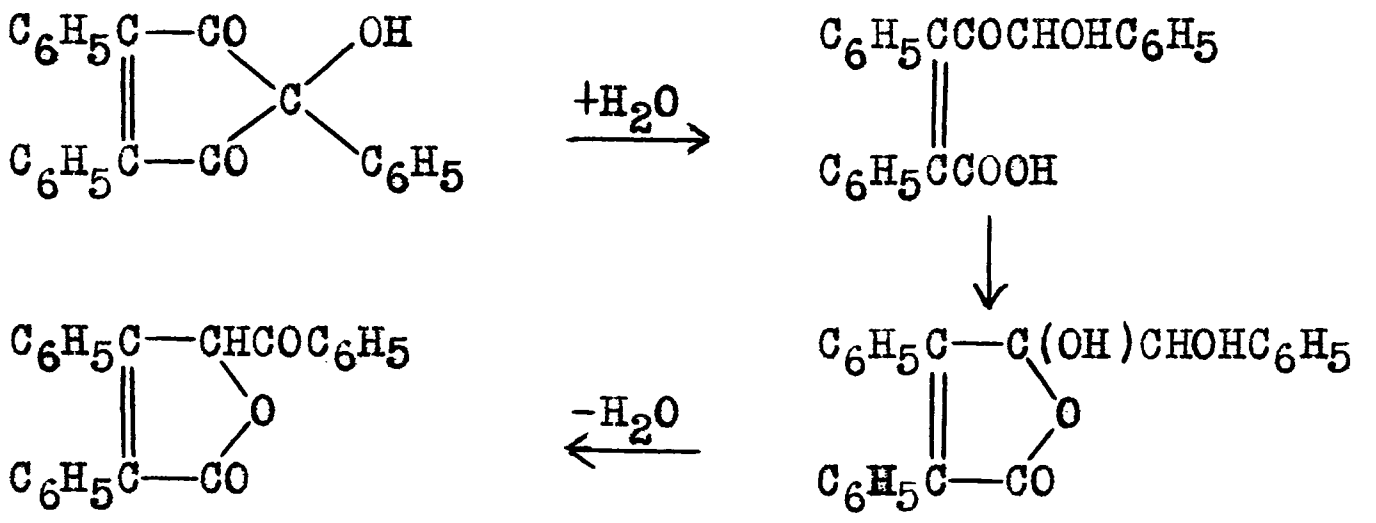


CXIV

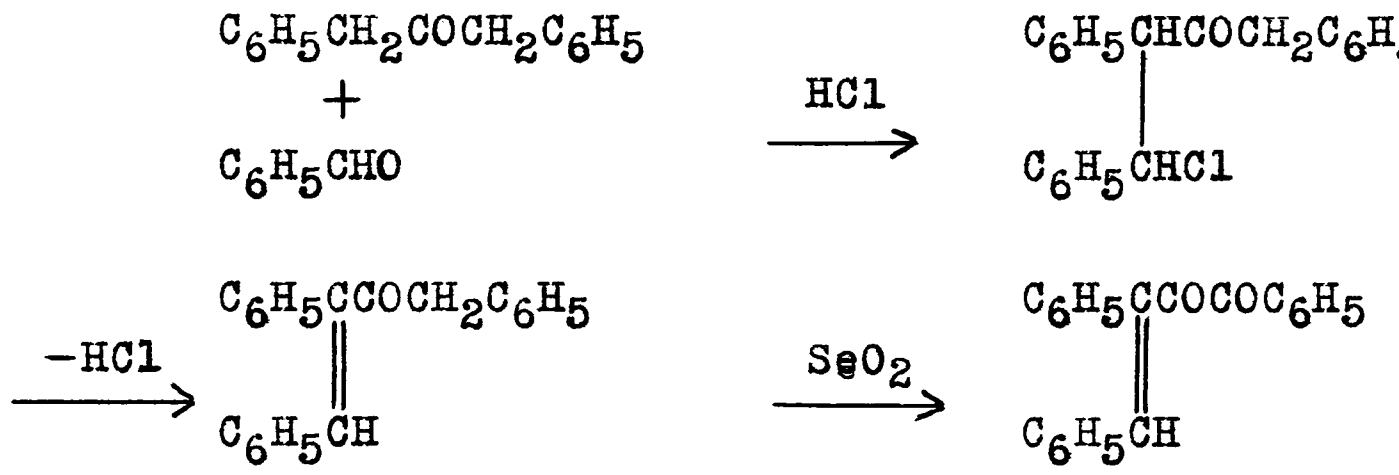


CXV

The existence of such a peroxide structure has been well substantiated by the work of Wertz (102) and of Treibs (103). However, such a substance would still possess the characteristic property of a 1,3-diketone to form a highly coloured enolate; our compound forms no such enolate in the presence of alkalies. The structure (CXV) appears to be more likely (104), but this type of compound is known to undergo a series of reactions involving ring opening and disruption of the molecule. Some possibilities are outlined below.



At one time it seemed possible that the yellow diketone might be the substance (CXVI); a synthesis of this compound was devised according to the following outline.



CXVII CXVI

There are two substances described in the literature to which the structure (CXVII) has been assigned, though never definitely substantiated (103). We have obtained both isomers, but neither gave a yellow compound by the action of selenium dioxide (any 1,2-diketone would be yellow). The high melting form gave a white oxidation product that formed a derivative with o-phenylenediamine; further it was oxidized to a substance, m.p. 172°, which, however, was not

the expected ∝-phenylcinnamic acid. Since these compounds gave no promise of being of assistance to the present problem, they were not further investigated.

Experimental

I. Preparation of α,β-diphenyl-γ-benzoylbutyrolactone and its derivatives.

A. Methyl α,β-diphenyl-γ-benzoylbutyrate (XCIV).

This substance can exist in two stereoisomeric forms. Massey (1) has shown that by using sodium methylate as condensing agent the change from the lower to the higher melting isomer is catalysed and a good yield of the latter obtained. If the butyrate is to be used for the preparation of the butyrolactone the relative proportion of the two isomers present is of no importance; both give γ-bromoesters on bromination.

The preparation of the higher melting isomer was carried out in the following manner: the condensing agent was prepared by dissolving 37.5 g. of sodium in 650 cc. of absolute methyl alcohol and was added to a solution of 339 g. of crude benzalacetophenone and 245 g. of methyl phenylacetate in 326 cc. of absolute methyl alcohol in a 3-l. flask under a reflux condenser. After the heat of reaction had subsided, the mixture was vigorously shaken until a white precipitate separated. After standing for one hour, the mixture was acidified with 150 cc. of glacial acetic acid, the mass well broken up, filtered, sucked dry and washed with a little cold methyl alcohol. The crude material was crystallized from benzene, the hot saturated solution being decanted away from any solid material. The

weight of the pure, higher melting isomer, m.p. 175°, was 475 g., yield 81%. The insoluble residues contained about 81 g. of acidic material.

Anal. Calcd. for $C_{24}H_{22}O_3$: OCH_3, 8.7. Found: 8.2.

B. Bromination of methyl α,β-diphenyl-γ-benzoylbutyrate.

The starting material was either the pure 175° isomer or the mixed ketoesters. In either case it was essential to use material that had been recrystallized in order to get rid of the acid, and to diminish the quantity of oily byproducts.

Seventy grams of the ester were suspended in 400 cc. of carbon tetrachloride contained in a 1-l. Erlenmeyer flask and 32 g. (11 cc.) of bromine were added in small amounts, the reaction being started by the addition of a trace of acetone and catalysed by sunlight. After the addition of the bromine the mixture was heated to boiling until the rapid evolution of hydrogen bromide ceased. The solid in some cases went into solution at this point but was redeposited by a more complete removal of hydrogen bromide. The solid was filtered by suction and washed with methyl alcohol to give a product of satisfactory purity, m.p. 146°, weight 50 g. This was a mixture containing a high percentage of the 145° gamma-bromoester.

Anal. Calcd. for $C_{24}H_{21}O_3Br$: OCH_3, 7.1. Found: 6.7.

C. α,β-Diphenyl-γ-benzoylbutyrolactone.

The starting material was freed from oils, if necessary, by recrystallization from acetic acid.

(a) Preparation.

A solution of 20 g. of the bromoester and 20 g. of potassium acetate in 100 cc. of glacial acetic acid was refluxed in a 250 cc. r.b. flask for two hours. Bumping occurred due to the deposition of potassium bromide but never became serious. While still hot the product was poured into 500 cc. of water and allowed to stand overnight. The solid masses were broken up, filtered by suction, and washed thoroughly with water, and, after drying, crystallized by pouring a hot saturated chloroform solution into two volumes of methyl alcohol. The white crystalline solid melted at 155°, weight 10 g., yield 62%. The mother liquors gave 2.5 g. of a solid, evidently a mixture melting at 122°, which it was found impossible to separate.

Anal. Calcd. for $C_{23}H_{18}O_3$: C, 80.7; H, 5.0. Found: C, 81.4; H, 5.0.

A methoxyl determination was negative.

(b) Pyrolysis of Methyl α,β-diphenyl-γ-bromo-γ-benzoylbutyrate.

An accurately weighed sample of the 172° bromoester, weight about 0.05 g., was pyrolysed at 180-200°C. in the reaction flask of a Zeisel apparatus (Clark's modification). The methyl bromide evolved was measured by the

gravimetric method; an 80% yield was observed.

Weight of beaker and sample	0.8866 g.
Weight of beaker	0.8366 g.
Weight of sample	0.0500 g. ≡ 0.0092 g. Br
Weight of micro-crucible and AgBr	4.4077 g.
Weight of micro-crucible	4.3903 g.
Weight of AgBr	0.0174 g. ≡ 0.0074 g. Br

(c) 2,4-Dinitrophenylhydrazone.

To a boiling saturated solution of the butyrolactone in 15 cc. of methyl alcohol, an excess of 2,4-dinitrophenylhydrazine was added, and then 3-4 drops of concentrated hydrochloric acid. On standing, brilliant yellow leaflets of the hydrazone separated, m.p. 209-10°.

Anal. Calcd. for $C_{29}H_{22}O_6N_4$: N, 10.7. Found: N, 10.5.

(d) Action of Bromine.

Five grams of the lactone were dissolved in 15 cc. of carbon tetrachloride and 2.5 g. (1 equivalent) of bromine added. In order to start the reaction a drop or two of acetone was added. On prolonged refluxing, there appeared to be some evolution of hydrogen bromide, and the colour faded from red to yellow. On working up the reaction product there was obtained some two grams of unchanged starting material, one half gram of a white solid, m.p. 198-200° with decomposition, and the remainder as an oil. It dissolved in

aqueous potassium carbonate, but did not decolorize potassium permanganate.

II Action of Ammonia on the Butyrolactone:

α,β-Diphenyl-γ-hydroxy-γ-benzoylbutyric amide (XCIII).

A suspension of 10 g. of the lactone in 125 cc. of absolute ethyl alcohol was saturated in the cold with anhydrous ammonia. Some heat was developed and most of the solid went into solution. The supernatant liquid was poured off and allowed to stand in a stoppered flask overnight. The crop of fine needles was filtered off and washed with ethyl alcohol, m.p. 202° with decomposition; the yield was almost quantitative. The product could be crystallized from ethyl alcohol unchanged.

Anal. Calcd. for $C_{23}H_{21}O_3N$: C, 76.8; H, 5.8; N, 3.9.
Found: C, 76.0, 76.1; H, 5.5, 5.5; N, 3.7.

Elimination of Ammonia from the Hydroxyamide.

Ammonia was eliminated from the hydroxyamide and the butyrolactone reformed by any of the following processes: heating of the solid to 205° for five minutes, recrystallizing from glacial acetic acid, or refluxing for one half hour with an equal weight of phosphorus pentoxide in xylene.

1,3-Diphenyl-1-carbamyl-2-benzoylcyclopropane (XC).

One gram of the above hydroxyamide was suspended in methyl alcohol and saturated with anhydrous hydrogen chloride. The dark viscous solution was allowed to stand

overnight. The oil obtained on evaporation was triturated with ether and the solid obtained crystallized from methyl alcohol containing a little chloroform, m.p. 180°. A mixed melting point showed it to be identical with the amide obtained by Boyer (93) by the action of sulphuric acid on the cyclopropane nitrile (XCI).

III Action of Magnesium methylate on the Butyrolactone.

A solution of magnesium methylate was prepared by adding slowly 5 g. of magnesium to 80 cc. of anhydrous methyl alcohol (dried by distillation from magnesium methylate) in a 250-cc. flask fitted with a condenser. It was found advantageous to cool the mixture efficiently during the addition of the metal.

The solution thus prepared was shaken for one hour at room temperature with 25 g. of the lactone. The deep yellow suspension was poured over 400 g. of cracked ice and 25 cc. of concentrated hydrochloric acid. After the ice was completely melted, the pale yellow oily solid was broken up, filtered by suction, and thoroughly washed with water. The oil was separated into a white solid and a yellow oil by trituration with ether. The solid, containing much inorganic material, was extracted with boiling acetone and gave 5-7 g. of a white crystalline material, m.p. 175°. A mixed melting point with the 175° ketoester (XCIV) proved them to be identical.

The ether-soluble oil on standing for a few days

deposited a solid which was separated by trituration with a 1:1 mixture of ether and Skelly-solve B. After purification by crystallization from methyl alcohol, 1 g. of a white crystalline solid, m.p. 174°, resulted.

On longer standing 8 g. of another white substance could be separated, which, on purification, melted at 117°.

It was noticed that if the length of time that the magnesium methylate was allowed to act upon the lactone was decreased a larger amount of solid separated, it separated more rapidly, and was made up principally of the 117° isomer, while if the length of reaction time was increased a smaller amount separated slowly and was principally the 174° isomer.

Anal. Calcd. for $C_{24}H_{22}O_4$: C, 77.0; H, 7.9; OCH_3, 8.3. Found: C, 76.8, 76.6; H, 7.8, 7.8; OCH_3, 7.7, 7.6, (174° isomer); C, 76.6, 76.6; H, 7.6, 7.7; OCH_3, 7.7, 7.9, (117° isomer).

Action of Magnesium methylate on the 117° Isomer.

A solution of magnesium methylate, prepared by the addition of 0.2 g. of magnesium to 5 cc. of absolute methyl alcohol, was added to one gram of the 117° isomer and the mixture shaken for fifteen minutes in the cold. The mixture became deep orange in colour and the solid dissolved almost completely. The product was poured into 20 cc. of ice water containing 1 cc. of concentrated hydrochloric acid, the solid broken up, filtered by suction, and washed thoroughly with water. The solid was freed from inorganic material by

washing with ether, which after several hours standing was triturated with methyl alcohol. A solid was obtained which on crystallization from methyl alcohol-acetone proved to be the 174° isomer. A second treatment yielded unchanged starting material.

The residual oils (reaction of magnesium methylate and butyrolactone) from which no more solid separated after many months standing was dissolved in ether and shaken with aqueous solutions of sodium bicarbonate, sodium carbonate, and sodium hydroxide. Only the sodium hydroxide solution gave a precipitate on acidification; it weighed 0.3 g. It was crystallized from methyl alcohol; m.p. 251°. A mixed melting point proved it to be the 255° ketoacid (XCII), corresponding to the 175° ketoester.

The neutral oils were steam distilled and from the distillate there was obtained the 2,4-dinitrophenyl-hydrazone of benzaldehyde. From the oil remaining in the distilling flask the dinitrophenylhydrazone of the butyro-lactone was prepared.

Action of Sodium methylate on the Hydroxyesters.

One gram of the 174° isomer was dissolved in 25 cc. of boiling methyl alcohol, the solution cooled and 1 cc. of sodium methylate solution (8 g. sodium in 100 cc. of alcohol) added. The mixture, after standing for one half hour, was

acidified with 1 cc. of glacial acetic acid, evaporated to a small volume, and the white crystalline solid filtered out by suction. The solid was washed with ether and then with water; on crystallization from methyl alcohol-acetone it gave 0.55 g. of unchanged starting material and 0.2 g. of the butyrolactone. The remainder was oil.

Under similar conditions the 117° isomer likewise was partially converted into the butyrolactone.

Pyrolysis of the Methyl α,β-diphenyl-γ-hydroxy-γ-benzoyl-butyrates.

Five grams of the 174° isomer was heated at 180-90° for an hour in an apparatus which permitted of the sweeping out of the gas evolved by a slow stream of dry air and of its condensation in a U-tube maintained at a low temperature. The condensate was identified as methyl alcohol by the preparation of the 3,5-dinitrobenzoate, m.p. 105-6°. Trituration of the glass remaining in the pyrolysis vessel with ether gave a solid which was shown to be the lactone (II).

The 117° isomer could not be pyrolysed at its melting point. However, at a temperature of 190° it likewise eliminated methyl alcohol and reformed the butyrolactone.

Dinitrophenylhydrazones.

One half gram of the 174° isomer was dissolved in 25 cc. of boiling methyl alcohol, 2,4-dinitrophenylhydrazine added to saturation, and the solution acidified with a few

drops of hydrochloric acid. On standing for some time in the cold a quantity of brilliant red rods separated, m.p. 224°. Anal. Cald. for $C_{30}H_{26}O_7N_4$: N, 10.1. Found: N, 10.0, 9.9. On heating or otherwise disturbing the filtrate a yellow voluminous precipitate deposited. It was identified as the dinitrophenylhydrazone of the butyrolactone (II).

Under similar conditions, the 117° isomer gave only the dinitrophenylhydrazone of the butyrolactone.

Elimination of Alcohol from the 224° Dinitrophenylhydrazone.

A small amount of the hydrazone was refluxed for several hours in 10 cc. of methyl alcohol containing a few drops of hydrochloric acid. On cooling, the starting material was first deposited and then the hydrazone of the butyrolactone. When chloroform was substituted for the methyl alcohol as solvent, the conversion was complete.

Attempted Preparation of a Hemi-acetal of the Butyrolactone.

(a) One gram of the butyrolactone was dissolved in 15 cc. of methyl alcohol, 0.2 g. of anhydrous copper sulphate added, and the mixture refluxed for four hours. On cooling 0.65 g. of unchanged starting material crystallized; it was found impossible to detect a substance, other than unchanged starting material, in the filtrate.

(b) One gram of the butyrolactone was dissolved in 15 cc. of methyl alcohol, three drops of concentrated hydrochloric acid added, and the mixture refluxed for twelve hours. Unchanged starting material was recovered on cooling.

Acetates (CXVIII) of the α,β-diphenyl-γ-hydroxy-γ-benzoyl-butyrates.

One half gram of the ester (174°) was dissolved in a minimum amount of acetyl chloride, allowed to stand overnight, and evaporated to dryness. The residue, twice recrystallized from methyl alcohol, separated as rods, m.p. 145°.

Anal. Calcd. for $C_{26}H_{24}O_5$: C, 75.0; H, 5.8; OCH_3, 14.9.
Found: C, 74.8, 74.7; H, 5.8, 5.9; OCH_3, 14.9.

Operating under similar conditions with the lower melting isomer, unchanged starting material was recovered, but if the acetyl chloride solution was refluxed for four hours, and the residue obtained on evaporation was recrystallized from methyl alcohol there was obtained white rosettes of crystals, m.p. 132°.

Action of HCl on the Methyl α,β-diphenyl-γ-hydroxy-γ-benzoyl-butyrates.

One gram of the 174° isomer was dissolved in a minimum amount of boiling methyl alcohol, 1 cc. of concentrated hydrochloric acid added and the solution allowed to crystallize; unchanged starting material was obtained. However, if the solution was refluxed for one hour before crystallization there was obtained, together with unchanged starting material, a substance melting at 151°. A mixed melting point showed that it was not the original butyrolactone (II).

The 117° isomer on crystallization from a methyl alcohol solution containing a little hydrochloric acid gave a substance melting at 142°.

These compounds were not further investigated, but were probably some of the eight possible stereoisomers.

Action of Sodium methylate on Oils from treatment of the Butyrolactone with Magnesium methylate.

Eleven grams of oil obtained from the action of magnesium methylate in the usual manner and freed as far as possible from all solid material were dissolved in 75 cc. of anhydrous methyl alcohol. A solution of 2 g. of sodium in 50 cc. of methyl alcohol was added, the mixture allowed to stand for two hours and then poured over cracked ice containing 12 cc. of concentrated hydrochloric acid. After one week's standing the oils were freed from solid by trituration with a 1:1 misture of ether-Skelly solve B. The solid, m.p. 170-90°, (0.35 g.) was crystallized from methyl alcohol to yield a small amount of 175° ketoester (XCIV) and an acid melting at 208-9°. Further amounts of the latter substance were obtained by washing the oils with aqueous sodium bicarbonate. This acid was not the acid (CXI) obtained by the action of nascent hydrogen on the diketone, nor the acid (CXIa) obtained by its catalytic reduction. On methylation it was converted into a neutral substance, m.p. 219°.

IV Action of Sodium methylate on the Butyrolactone.

To a suspension of 20 g. of the butyrolactone in

200 cc. of absolute methyl alcohol was added a sodium methylate solution (4 g. sodium in 100 cc. of alcohol), and the mixture shaken for ten hours, when solution was complete. The dark brown product was poured, with constant stirring, in 200 cc. of water containing 10 cc. of glacial acetic acid. After standing overnight the semi-solid yellow mass was filtered out, dried, and triturated with cold methyl alcohol. The brilliant yellow crystalline solid so obtained was filtered and crystallized from a 2:1 mixture of methyl alcohol and chloroform. The substance weighed 6.5 g. (yield 32%) and melted at 166°.

Anal. Calcd. for $C_{23}H_{16}O_2$: C, 85.2; H, 4.9. Found: C, 85.6, 85.3; H, 5.0, 5.1 (micro); C, 85.4; H, 5.3 (semi-micro). A methoxyl determination was negative.

The alcohol-soluble oils on standing deposited 1.5 g. of a solid which could be separated by trituration with 1:1 mixture of ether-Skelly solve B. It was identified as unchanged starting material by a mixed melting point.

The oils, freed as far as possible from all solid material, were dissolved in chloroform and washed successively with a saturated aqueous solution of sodium bicarbonate, and with a 10% solution of potassium carbonate, and with a 5% solution of sodium hydroxide. On acidification there was obtained from the bicarbonate solution 0.1 g. of diphenylmaleic anhydride but from the carbonate only a trace of oily material.

On washing the chloroform solution with sodium hydroxide the former became coloured a brilliant green and the latter a deep orange. This orange colour was very persistent and the extraction was not continued until it no longer appeared in the hydroxide solution. The combined sodium hydroxide washings were acidified and 0.1 g. of diphenylsuccinic acid (235° isomer) obtained.

The green chloroform solution was washed with water, during which operation the colour was transferred to the aqueous layer and the chloroform became yellow. On acidification of a test portion of the washings a large amount of pale yellow oil was deposited. This oil was soluble in aqueous sodium hydroxide, but from it no solid separated even on long standing and no derivative of an acid with p-bromophenacyl bromide could be prepared. The main portion of the washings were diluted and the solid, which separated on standing, filtered out and recrystallized from methyl alcohol to yield 0.1 g. of the unsaturated lactone (C).

From the chloroform layer, now freed from all acidic and water-soluble material, the solvent was distilled, and the residue (about 2 g.) steam distilled. From the oily portion of the distillate a small amount of the 2,4-dinitrophenylhydrazone of benzaldehyde was prepared. No hydrazone could be prepared from the oil remaining in the distilling flask.

V The Unsaturated Lactone (C).

(a) Preparation from diphenylmaleic anhydride.

To 50 g. of benzyl cyanide contained in an all-glass bromination apparatus equipt with a gas trap, and heated in an oil-bath at 180°, 67 g. of bromine were added slowly and at such a rate that there was a steady flow of gas. One hour sufficed for the addition but heating was continued for one half hour longer, or until no more hydrogen bromide was evolved. The black reaction mass was poured out while still hot into an evaporating dish, and on cooling broken up. The solid, with the residue in the reaction flask, was dissolved as far as possible in chloroform, filtered from undissolved solid and washed with water. The solvent was allowed to evaporate slowly and, from time to time, a total of 20 g. of a dark crystalline substance was filtered. It was washed free of tarry material with ethyl alcohol, dissolved in boiling alcohol with the aid of a little chloroform, decolorized with Nuchar and allowed to crystallize. The dicyanostilbene separated as lustrous, brown plates, m.p. 159°.

To a saturated boiling solution of 3.5 g. of dicyanostilbene in 150 cc. of ethyl alcohol, 3.5 g. of potassium hydroxide were added and the mixture refluxed for two hours. The alcohol was distilled off slowly and the residue baked on the waterbath for a few minutes. The solid was dissolved in water, acidified with hydrochloric acid,

the yellow precipitate filtered off and washed thoroughly with water. The diphenylmaleic anhydride, m.p. 154°, dissolved in alcohol to give a yellow solution with a green fluorescence.

An unsuccessful attempt was made to synthesize this substance by the action of sodium hypobromite upon diphenylcyclopentenone after the method of Japp and Lander (106). We found that both hypobromite and hypochlorite were without action upon this compound.

A mixture of 0.5 g. of diphenylmaleic anhydride, 0.4 g. of phenylacetic acid and 0.05 g. of freshly-fused sodium acetate was heated in an oil-bath at 200° and maintained at that temperature for one hour. Evolution of gas commenced at 180° and continued in diminishing amount to the end. The dark yellow melt was dissolved in ethyl alcohol with the aid of a little chloroform, decolorized with Nuchar and allowed to crystallize slowly. The α,β-diphenyl-γ-benzalcrotonolactone was obtained as light brown needles, m.p. 175°.

Reduction of the Unsaturated Lactone.

(a) By zinc and acetic acid.

One gram of the lactone was refluxed with zinc dust and glacial acetic for one hour. The colorless supernatant liquid was poured into a large excess of water, the white material filtered out, dried, and crystallized from methyl alcohol, m.p. 127°. This substance is α,β-diphenyl-γ-benzyl-

crotonolactone (CX).

(b) By hydriodic acid.

Two grams of the lactone and 1 g. of red phosphorus were intimately mixed and added to 15 cc. of constant-boiling hydriodic acid. The mixture was refluxed for two hours in an all-glass apparatus, cooled, and the clear liquid decanted from the tarry product. After washing with water the latter was boiled vigorously for one half hour with sodium bisulphite solution, cooled, and the tar filtered off and washed. It was extracted with several 10 cc. lots of boiling methyl alcohol, filtered free of phosphorus, and the solution concentrated. A fine-crystalline solid separated, m.p. 127-8°, weight 1.2 g. It proved to be identical with the substance obtained from the zinc reduction above.

Action of Alcoholic Potassium Hydroxide on the Lactone.

Two grams of the unsaturated lactone in 30 cc. of absolute ethyl alcohol containing 0.4 g. of KOH (one equivalent) were refluxed for twenty-four hours. At first the solution was dark brown in colour, but later an insoluble yellow solid separated, and the colour faded. The mixture was steam distilled. To the distillate, containing much alcohol, was added a glacial acetic acid solution of phenylhydrazine. On standing 0.05 g. of the hydrazone of benzaldehyde separated and was filtered out. Hydrochloric acid was added to the filtrate, which was then washed with ether. No toluene could be detected in the residue left after care-

ful evaporation of the ether washings.

From the mixture remaining in the distilling flask 0.8 g. of unchanged starting material were filtered. The clear filtrate was acidified with glacial acetic acid to yield 0.6 g. of diphenylmaleic anhydride.

Action of Ammonia.

Amide of β-phenacyl-α,β-diphenylacrylic acid (CVII).

One half gram of the lactone and 40 cc. of ethyl alcohol, saturated with ammonia at zero degrees, was heated for six hours at 100° in a sealed tube. When the clear solution was concentrated, a white finely crystalline solid separated, m.p. 199-201°, (decomp.). The yield was almost quantitative.

α,β-Diphenyl-γ-benzalcrotonolactam (CVIII).

By crystallization of the amide from glacial acetic acid the corresponding lactam (CVIII) was prepared, m.p. 241°. This substance was also detected, in some preparations, in the reaction product of ammonia on the unsaturated lactone.

In an attempt to reconvert it into the corresponding lactone the following treatment was carried out: A quantity of the lactam in ethyl alcohol, saturated with anhydrous hydrogen chloride at 0°, was heated in a sealed tube at 100° for six hours. Only unchanged starting material was recovered.

V Reactions of the Diketone (XCVII).

(a) Dinitrophenylhydrazone.

When a solution of the diketone and 2,4-dinitrophenylhydrazine in alcohol was acidified with a few drops of hydrochloric acid, no insoluble material separated as is usually the case. However, after refluxing and concentrating an orange solid separated. It was recrystallized from methyl alcohol and chloroform to give fine, brilliant orange needles, m.p. 235° C.

Anal. Calcd. for $C_{29}H_{20}O_5N_4$: N, 11.1. Found: N, 11.1, 11.1.

(b) Action of Alcoholic Ammonia.

A mixture of one gram of the diketone in 15 cc. of ethyl alcohol, saturated with ammonia at 0°, was heated in a sealed tube at 100° for six hours. The mixture, which was a deep purple colour at the beginning, became brown toward the end of the reaction. A quantity of light brown needles separated and was filtered out; they had a melting point of 241°, and were identified as α,β-diphenyl-γ-benzal-crotonolactam by a mixed melting point. The filtrate, after treatment with Nuchar, was separated into more of the 241° compound, and some β-phenacyl-α,β-diphenylacrylic amide, m.p. 198-200°, identified by a mixed melting point.

(c) Reduction of the Diketone.

By zinc and acetic acid:

Ten grams of the diketone was added to a mixture of 200 cc. of glacial acetic acid and 20 g. of zinc dust. The mixture was refluxed for one half hour, when the reaction was complete, as shown by the disappearance of the character-

istic yellow colour of the diketone. The hot supernatant liquid was filtered by suction into 400 cc. of cold water, the precipitate allowed to coagulate, then washed thoroughly with water and dried. The product was recrystallized from methyl alcohol to yield 9 g. of a white crystalline solid, m.p. 204-5°.

The compound was soluble in alkalies, and instantly decolorized permanganate in acetone, and bromine in chloroform. An attempt to make a 2,4-dinitrophenylhydrazone was unsuccessful.

By hydriodic acid:

An intimate mixture of 2 g. of the diketone and 1 g. of red phosphorus were added to 10 cc. of constant-boiling hydriodic acid, and refluxed for two hours in an all-glass apparatus. The mixture was cooled, the clear liquid decanted from the solid resin, and the latter boiled with two or three lots of sodium bisulphite solution during one half hour. On cooling the solid was filtered off, washed with water, and dried. The organic material was dissolved away from the red phosphorus with boiling methyl alcohol, the solution decolorized with Nuchar, and allowed to evaporate. On trituration of the residual oil with ether, brilliant white crystals separated, m.p. 204-5°. This product was identical with that obtained by reduction with zinc and acetic acid.

Anal. Calcd. for $C_{23}H_{20}O_2$: C, 84.1; H, 6.0. Mol. Wt. 328. Found: C, 83.9, 83.5; H, 5.8, 5.8, (1). Mol. Wt. 345.

Oxidation of α,β,δ-triphenyl-Δ3,4-valeric acid (CXI).

By chromic acid:

One gram of the acid was dissolved in 10 cc. of boiling glacial acetic acid, and to it was added dropwise a hot solution of 0.8 g. of chromic acid in 10 cc. of glacial acetic acid over a period of twenty minutes. The reaction mixture was poured not into an evaporating dish, 1.2 g. of concentrated sulphuric acid added (sufficient to convert all the chromium to the sulphate), and the mixture heated on a waterbath until freed of all acetic acid, loss by evaporation being made up by the addition of water. After cooling, the salt solution was poured off, the product broken up, washed and airdried. It was triturated with ether. The soluble material on evaporation of the ether was a clear yellow oil; it was dissolved in ethyl acetate and ethyl alcohol added to incipient cloudiness. By this means an ill-defined yellow amorphous solid was obtained, m.p. 175-85°.

The insoluble material, weighing about 0.3 g. was purified with difficulty. Crystallized in the above special manner it was deparated as a pale yellow amorphous solid, m.p. 230°. It was identified by a mixed melting point as the high-melting isomer of diphenylsuccinic acid.

By permanganate:

To one gram of the acid in 20 cc. of gently re-

fluxing acetone, 2.4 g. of finely-ground potassium permanganate (a slight excess) were added in small quantities so that the heat of reaction was sufficient to maintain the reflux. The reaction was carried out in a closed system, volatile products being swept out with a stream of nitrogen and passed through a solution of calcium hydroxide. During the reaction the deposition of only a trace of calcium carbonate was noticed.

The precipitated manganese dioxide was filtered out and washed repeatedly with acetone; the filtrate and washings were evaporated to dryness and baked a few minutes on the waterbath. The residue, which smelt strongly of benzaldehyde, was steam-distilled, the distillate being passed into a solution of phenylhydrazine. A small amount of the phenylhydrazone of benzaldehyde separated and was identified by a mixed melting point.

The residue remaining in the distilling flask was purified with difficulty. It was dissolved in methyl alcohol with the aid of a little chloroform, treated with Nuchar, and allowed to cool, a yellow amorphous solid separated, m.p. 225°. This was found to be the high-melting isomer of diphenylsuccinic acid.

(d) Oxidation of the Diketone.

1. By nitric acid:

One gram of the yellow diketone was refluxed with 50% nitric acid for three hours. On standing an oily solid

separated, and was filtered out. Attempts to obtain a crystalline solid from it by trituration with various solvents were unsuccessful. It was dissolved in ether and washed with an aqueous solution of sodium bicarbonate. On acidification of the latter, and crystallization of the precipitate with chloroform a small amount of pale yellow solid was obtained, m.p. 229-30°. It was identified as p-nitrobenzoic acid by means of a mixed melting point.

From the ether layer on evaporation was obtained a deep red oil. Attempts to form a phenylhydrazone, a bisulphite-addition compound, or a copper enolate were unsuccessful.

2. By sulphuric acid:

Five grams of the diketone were dissolved in 25 cc. of concentrated sulphuric acid to form a thick red solution, which was heated on a waterbath for two hours. It was allowed to cool and poured into 200 g. of chopped ice, and then steam distilled. From the distillate there was prepared 0.2 g. of the phenylhydrazone of benzaldehyde. The liquid in the distilling flask was freed from about 0.5 g. of unchanged starting material by filtering and then washing with ether, and the ether extracted with sodium bicarbonate. The only material which could be identified in the residue obtained on evaporation of the ether was the 247° oxidation product (CXIII).

3. By selenium dioxide.

To a solution of 0.4 g. of selenium dioxide in 15 cc. of boiling dioxane, 1.0 g. of the diketone was added and the solution refluxed for one and a half hours with stirring. The precipitated selenium was filtered and the filtrate poured into 100 cc. of water, ammonium chloride added to hasten coagulation and the product filtered. It was dissolved in mixed chloroform and methyl alcohol and crystallized as a yellow amorphous solid, m.p. 245°. A mixed melting point proved it to be identical with the product obtained by Massey (1) by chromic acid oxidation.

Anal. Calcd. for $C_{46}H_{30}O_4$: C, 85.6; H, 5.3; Mol. Wt. 646.
Found: C, 84.8, 85.0; H, 5.1, 5.1; Mol. Wt. 716.

The compound was recovered unchanged after standing for many hours in chloroform solution saturated with anhydrous hydrochloric acid.

4. By potassium hypobromite.

To a freshly prepared solution of potassium hypobromite, made by adding bromine to a 10% solution of potassium hydroxide until the orange colour just failed to be discharged, 5 cc. of methyl alcohol were added, as a wetting agent, and 0.5 g. of the diketone. The mixture was shaken for three to four hours and allowed to stand overnight. The insoluble material was filtered out and washed thoroughly with water to remove adhering hypobromite. Melting point of the insoluble material was 166° i.e. it was unchanged starting

material.

Oxidation by potassium permanganate or chromic acid was not attempted. Massey (1) reported that the former gave carbon dioxide, benzaldehyde, and benzoic acid, and the latter benzoic acid and the 247° compound (CXIII). We found that, operating in ethyl bromide, ozone gave traces of benzaldehyde, benzoic acid, and the 247° compound.

5. By hydrogen peroxide.

To a solution of 0.5 g. of the diketone in 15 cc. of acetone 10 cc. of 30% hydrogen peroxide at room temperature (containing 1/100 N acid) were added; a bright yellow precipitate of the diketone separated. A 10% solution of potassium hydroxide was added dropwise from a burette, each successive drop being added only after the incipient purple coloration was discharged by shaking. This required 0.3 cc. over a period of one hour. A deep yellow precipitate, weight 0.3 g., was filtered out. m.p. 185°. It was satisfactorily recrystallizedfrom methyl alcohol containing a little chloroform.

Anal. Calcd. for $C_{23}H_{16}O_3$: C, 81.2; H, 4.7; Mol. Wt., 340.
Found: C, 81.0, 81.2; H, 4.5, 4.5; Mol. Wt., 372.

The filtrate was slightly acid after decomposition of the hydrogen peroxide, but no further products could be separated.

The new substance dissolved in warm aqueous sodium hydroxide, it did not decolorize bromine, nor was it changed

by anhydrous hydrogen chloride, or glacial acetic acid. A 2,4-dinitrophenylhydrazone could not be prepared.

Action of Acetyl Chloride.

One gram of the compound was dissolved in 15 cc. of acetyl chloride. On evaporation a pale yellow crystalline solid separated. It crystallized from a mixture of methyl alcohol and chloroform in rosettes of crystals, m.p. 155°. A methoxyl determination was negative.

Anal. Cald. for an acetate, $C_{25}H_{18}O_4$: C, 78.6; H, 4.7.
Cald. for a dehydration product, $C_{23}H_{14}O_2$: C, 87.1; H, 4.3.
Found: C, 80.0, 79.8; H, 4.9, 4.8.

The same material was obtained, though less satisfactorily, by refluxing an acetic anhydride solution of the compound.

VI Syntheses from Dibenzylketone and Benzoylformic ester.

(a) The Unsaturated Lactone (C).

To a warm solution of 6.1 g. of dibenzylketone and 5. g. of ethyl benzoylformate in 15 cc. of absolute ethyl alcohol (dried over CaO), a fresh solution of sodium ethylate (0.6 g. of sodium in 15 cc. of absolute ethyl alcohol) was added and the solution refluxed for one hour. The mixture soon became deep yellow in colour, and after fifteen minutes a crystalline solid was deposited. At the completion of the reaction, the mixture was acidified with glacial acetic acid (colour of acid solution, yellow), cooled, and filtered. The pale yellow crystalline mass of lactone was washed with a little alcohol, m.p. 172°, weight

3.0 g. yield 27%. This substance in the crystalline state has a characteristic green tinge. It is best recrystallized from normal propyl alcohol.

In order to learn to what extent the lactone was converted into the diketone under the same operating conditions as were used for the original butyrolactone, 1 g. of the lactone was added to 15 cc. of absolute methyl alcohol containing 0.2 g. of sodium. The mixture slowly became purple; it was shaken for ten hours. The crystalline material was filtered out and washed with methyl alcohol, m.p. 173°, weight of unchanged lactone 0.65 g.

The purple filtrate was acidified with glacial acetic acid and allowed to stand. A yellow crystalline material separated, m.p. 166°, weight of diketone 0.15 g. On evaporation of the alcohol solution to dryness a pale yellow, oily residue was obtained. About 0.1 g. of the diketone was separated from it.

Thus under the conditions, 25% of the lactone was converted into the diketone.

(b) The Diketone (XCVII).

If the same quantities of ketone and ester were used as for the preparation of the lactone, but the sodium ethylate replaced by sodium methylate, the solution became purple on refluxing and no solid deposited. At the end of two hours the solution was acidified with glacial acetic

acid (purple colour changed to yellow) and diluted with water to incipient cloudiness. On cooling a deep yellow mass of triphenylcyclopentendione deposited. It was filtered out and crystallized from butyl ether, m.p. 165°. The yield was almost quantitative.

The compound was insoluble in phosphoric acid, unchanged by alcoholic hydrogen chloride, or by alkali fusion.

(c) The Lactol (CVI).

A solution of 6.1 g. of dibenzylketone, 5.0 g. of benzoylformic acid, and 30 cc. of absolute ethyl alcohol containing 0.6 g. of sodium were allowed to stand at room temperature for one hour. The gelatinous precipitate was filtered out and acidified with acetic acid to yield a pale yellow product, m.p. 167° with sintering. It separated from dilute acetic acid as a white substance, m.p. by "dip" method 181°.

By the following process it was converted into the lactone: A quantity of the substance was added to phosphorus oxychloride and the mixture warmed on a steambath to form a clear yellow solution. This was cooled, ice added, and decomposition completed by warming. The mixture was digested with alcohol on a steambath, cooled, and filtered; the melting point of the insoluble material was 163-4°. A mixed melting point showed this to be the lactone (C).

(d) The Primary Addition Product (CXII).

A solution of 6.1 g. of dibenzylketone, 5 g. of

ethyl benzoylformate, 0.5 g. of piperidine in 30 cc. of ethyl alcohol was refluxed for five hours. On cooling and agitation of the liquid 3.5 g. of a white crystalline material separated. Successive crops were obtained on evaporation; the yield was nearly quantitative. It was recrystallized from ethyl alcohol and separated as fine needles, m.p. 128°. It was obtained equally well by the use of a trace of sodium ethylate at room temperature.

Anal. Calcd. for $C_{25}H_{24}O_4$: C, 77.3; H, 6.2; OC_2H_5, 11.6. Found: C, 77.0, 69.9; H, 6.0, 6.1; OC_2H_5, 12.6.

This substance did not form the diketone on reaction with alcoholates, but gave light coloured oils, the odor of which resembled that of the components.

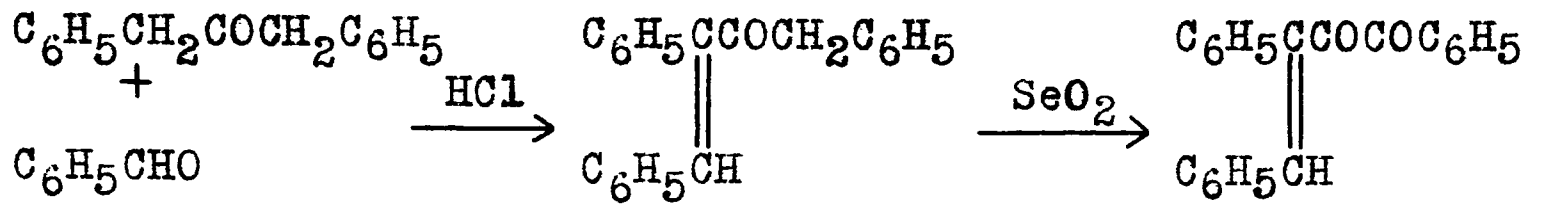
Action of Acetyl chloride.

One half gram of the above compound was refluxed for four hours with acetyl chloride. The residue left after evaporation proved to be very soluble in most solvents, but was satisfactorily recrystallized from methyl alcohol. The derivative formed melted at 101°, (mixed melting point with starting material, 90°).

Anal. Calcd. for $C_{26}H_{24}O_5$: C, 75.0; H, 5.8. Found: C, 75.1, 75.1; H, 6.0, 6.1.

VIII Phenyl ∝-phenylcinnamoyl diketone.

Attempted preparation from Benzaldibenzylketone.



A mixture of 10 g. of dibenzyl ketone and 12 g. of benzaldehyde was saturated with anhydrous hydrogen chloride. After standing for forty-eight hours, the solid reaction product was broken up, washed free of oils with methyl alcohol, and crystallized from mixed methyl alcohol and dioxane, m.p. of the ketone 165-6°, weight, 11 g. A further 3 g. were recovered from the filtrates. The yield of the benzaldibenzylketone was almost quantitative.

To solution of 3.75 g. of selenium dioxide in 20 cc. of boiling dioxane, 10 g. of the unsaturated ketone were added and refluxed with stirring for two hours. The reaction mixture was filtered from selenium and added slowly with stirring to 150 cc. of water. After standing for several hours the insoluble material was filtered, washed thoroughly with water and dried. On crystallization from mixed methyl alcohol and dioxane there was obtained 5.5 g. of a white crystalline solid, m.p. 200-201°.

Attempted Preparation of a Quinoxaline.

Seven tenths of a gram of o-phenylene diamine were dissolved in 15 cc. of a 2:1 mixture of methyl alcohol and dioxane, 1.4 g. of potassium acetate added and the mixture boiled. To the filtrate 0.5 g. of the supposed phenyl ∝-phenylcinnamoyl ketone were added and the solution cooled;

no quinoxaline separated but on concentrating and cooling a substance, in the form of white leaflets separated, m.p. 147-8°. It did not have the appearance of a typical quinoxaline.

Action of Sodium peroxide.

Two grams of sodium peroxide were added slowly to 10 cc. of ice water, followed by a solution of 1 g. of the supposed diketone in 10 cc. of methyl alcohol, and the mixture shaken for one and a half hours at room temperature. It was then poured into 75 cc. of water and the insoluble material filtered out; it proved to be unchanged starting material. On acidification of the filtrate a small amount of a solid was obtained, which crystallized from mixed methyl alcohol and dioxane as a brilliant white substance, m.p. 171-2°. A mixed melting point showed that it was not ∝-phenylcinnamic acid.

Action of Sodium Hypobromite.

A solution of sodium hypobromite was prepared by adding 2 g. of bromine to 10 cc. of 15 % NaOH, and to this was added 1 g. of the ketone. The mixture was mechanically stirred for three hours. On dilution, the material recovered was unchanged starting material.

Action of Bromine.

The ketone did not instantly decolorize a solution of bromine in carbon tetrachloride, nor was there any decolorization on standing in the sunlight for two hours.

Since none of these substances remotely resembled any compounds of interest to this thesis, they were not further investigated.

Dinitrophenylhydrazone of Ethyl Benzoylformate.

To 5 cc. of boiling ethyl alcohol, saturated with 2,4-dinitrophenylhydrazine, 1 cc. of ethyl benzoylformate and 2-3 drops of concentrated hydrochloric acid were added, and the solution concentrated to half its volume. On cooling fine orange needles of the hydrazone separated. The compound was effectively recrystallized from ethyl alcohol, m.p. 156°.

Summary.

1. By the action of heat, or alkaline reagents the gamma-bromoesters of α,β-diphenyl-γ-benzoylbutyric acid lose methyl bromide and yield α,β-diphenyl-γ-benzoylbutyrolactone.

2. The butyrolactone is converted by alcoholic ammonia into α,β-diphenyl-γ-hydroxy-γ-benzoylbutyric amide. In alcoholic hydrogen chloride the latter compound loses the elements of water to form 1,3-diphenyl-1-carbamyl-2-benzoylcyclopropane. Each reaction can be reversed by the use of appropriate reagents.

3. Magnesium methylate forms a variety of products from the butyrolactone, among which were isolated and identified α,β-diphenyl-γ-benzoylbutyric ester and two stereoisomeric methyl α,β-diphenyl-γ-hydroxy-γ-benzoylbutyrates. Of the latter the higher melting isomer forms a dinitrophenyl-hydrazone, both isomers give acetates, and new substances by the action of alcoholic hydrochloric acid. Magnesium methylate converts the lower isomer into the higher, and heating converts both into the butyrolactone.

4. The action of sodium methylate is more drastic and only secondary products may be isolated. These comprise--α,β-diphenyl-γ-benzoylbutyric acid, α,β-diphenyl-γ-benzalcrotonolactone, 2,4,5-triphenylcyclopentendione, diphenylmaleic anhydride, diphenylsuccinic acid, and benzaldehyde.

5. A new synthesis of α,β-diphenyl-γ-benzalcrotonolactone from dibenzylketone and benzoylformic ester is described.

6. The crotonolactone can be converted into the cyclopentendione by the action of alcoholates.

7. Both the crotonolactone and the diketone give the same products with ammonia--an open-chain ketamide and a lactam.

8. Reduction of the cyclopentenedione by zinc and acetic acid, or hydriodic acid gives an open-chain γ,δ-unsaturated acid, the structure of which was established by oxidation to diphenylsuccinic acid and benzaldehyde.

9. The diketone is believed to be the first of its type--a cyclopentendione not fused to a benzene ring. It shows a marked resemblance to the 1,3-indandiones.

10. Its behaviour with characteristic reagents was carefully determined. The most conspicuous property is the formation of a stable deep purple enolate.

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