REACTIONS OF GAMMA
KETONIC ESTERS

CERTAIN REACTIONS OF GAMMA KETONIC ESTERS

A Thesis

by

Gordon F. Frame

Submitted to the Faculty of Graduate Studies and Research of McGill University, in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

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SOME REACTIONS OF GAMMA KETONIC ESTERS

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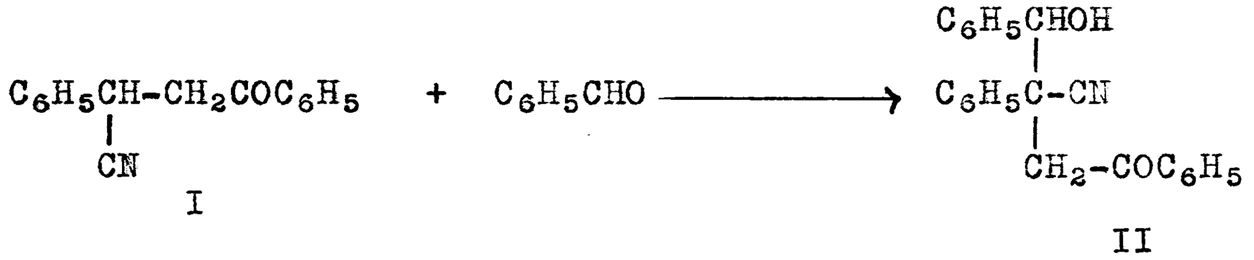
A Summary.

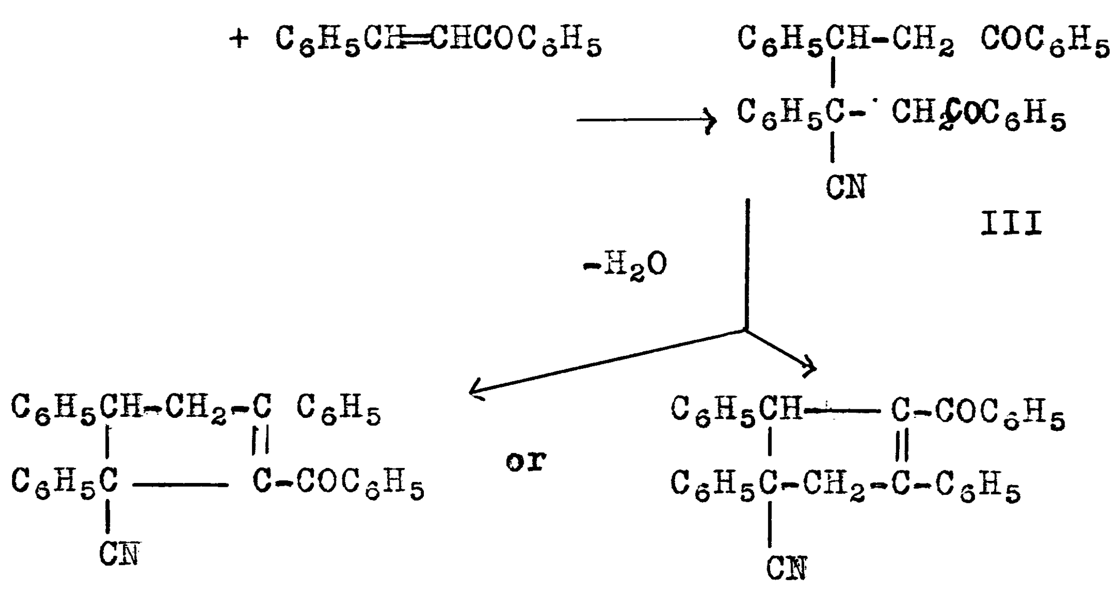
The gamma ketonic ester, methyl α-phenyl-β-p- chlorbenzoyl propionate, has been prepared and condensed with benzaldehyde to form an unsaturated lactone. This ester has also been condensed with piperonal to form an analogous product. Methyl α-phenyl -β-p-brombenzoyl propionate, and methyl α-phenyl -β-anisoyl propionate, when condensed with benzaldehyde and piperonal in a similar manner, formed unsaturated lactones of the same type. These unsaturated lactones have a tertiary hydroxyl group, and are therefore lactols. This hydroxyl group is comparable to that of triphenyl carbinol in most respects. The spontaneous closing of the ring on acidification is undoubtedly due to the increased branching of the chain, since the previous condensation products of this type that have been studied differ only in having one less phenyl group.

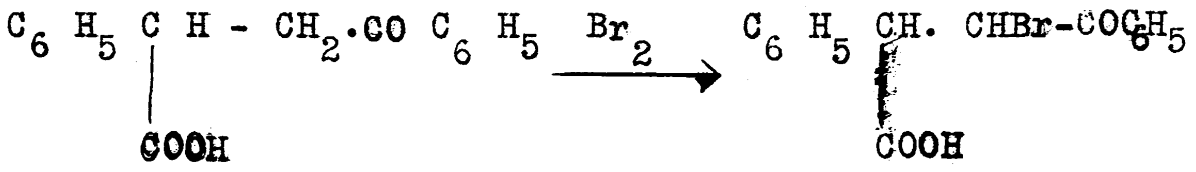
INDEX.

In a study of certain gamma ketonic nitriles, acids and esters, it has been found essential to determine whether the hydrogen in the alpha position to the ketone group is more or less active than the hydrogen alpha to the other unsaturated linkage. At present it is known (a) in the gamma ketonic nitrile (I) the hydrogen alpha to the cyano group is the more active, shown by the ease with which the nitrile adds to benzaldehyde (II) (1), and to benzalacetophenone (III) (2): (b) in the gamma ketonic acid (IV) the hydrogen alpha to the ketone group is more active, shown by its replacement on bromination (V) (3).


I

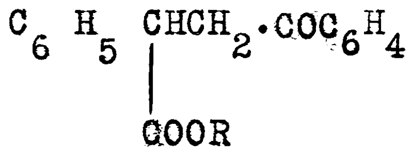
II


III



$$\underset{COOH}{C_6H_5CH}-CH_2.CO\,C_6H_5 \xrightarrow{Br_2} \underset{COOH}{C_6H_5CH}.\,CHBr-COC_6H_5$$

IV. V.



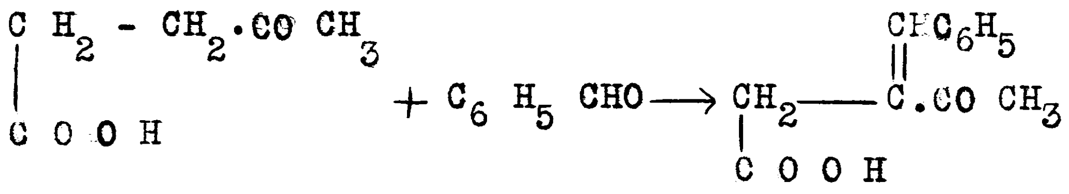
$$\underset{COOR}{C_6H_5CH}CH_2.COC_6H_4$$

VI.

The ketonic ester (VI) might be expected, a priori, to resemble the acid (IV), but it may not of necessity do so. Indeed it has been found that it yields an entirely unexpected product when condensed in the usual way with benzaldehyde. The primary object of this investigation has been to determine the structure of the products and so to learn how the reaction has taken place.

A search of the literature has revealed the following instances of reactions between aromatic aldehydes and γ-ketonic acids or esters.

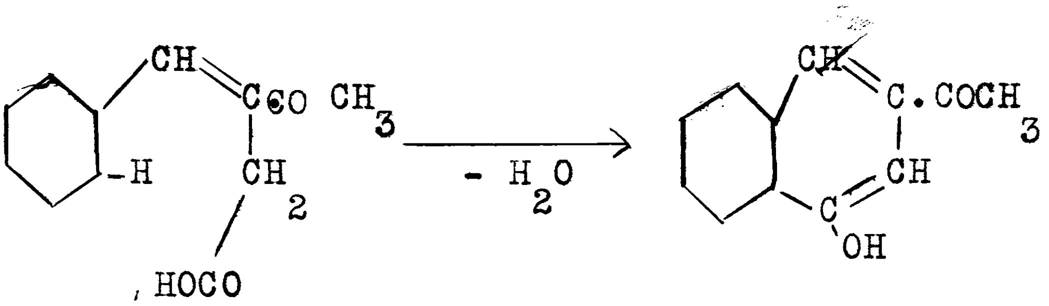
Erdmann (4) obtained β- benzal levulinic acid (VII) by refluxing levulinic acid with benzaldehyde in freshly fused sodium acetate.



$$\underset{COOH}{CH_2}-CH_2.CO\,CH_3 + C_6H_5CHO \longrightarrow \underset{COOH}{CH_2}-\overset{CHC_6H_5}{\overset{\|}{C}}.CO\,CH_3$$

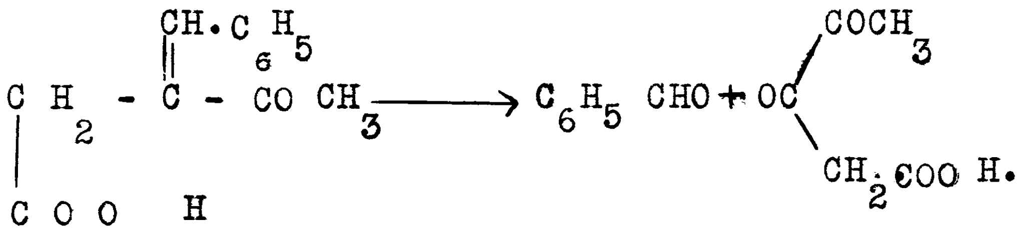
VII.

On distillation, 3 - aceto -1- naphthol (VIII) was formed, thus proving its structure.



VIII.

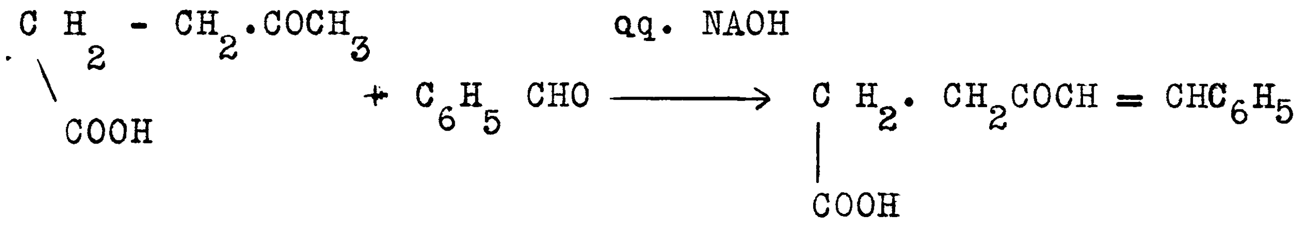
Harries (5) later confirmed its structure through ozonization, obtaining benzaldehyde and β-γ diketo butyric acid (IX).



$$\begin{matrix} & CH.C_6H_5 & \\ & \| & \\ CH_2 - & C - & CO\,CH_3 \\ | & & \\ COOH & & \end{matrix} \longrightarrow C_6H_5\,CHO + OC\begin{matrix} COCH_3 \\ CH_2COOH. \end{matrix}$$

IX.

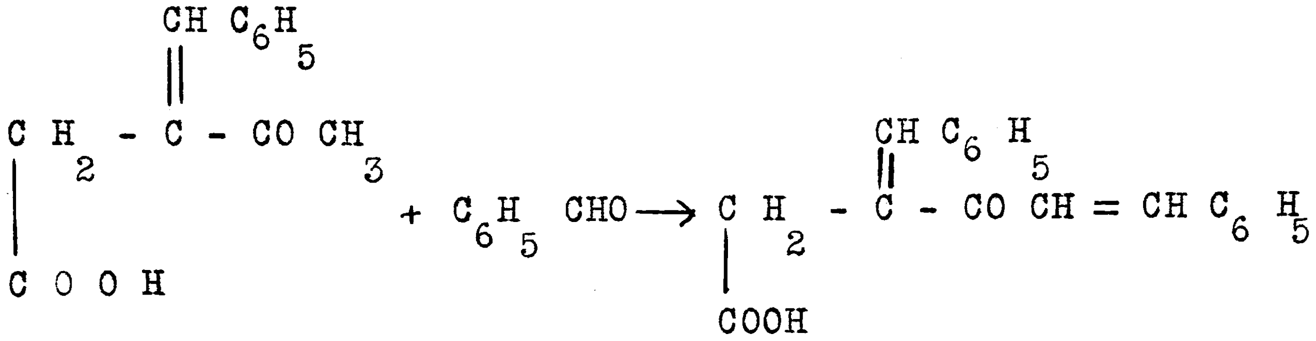
Erlenmeyer jun. (6) obtained δ-benzal levulinic acid (X) by heating levulinic acid with benzaldehyde in the presence of aqueous sodium hydroxide.



$$\begin{matrix} CH_2 - CH_2.COCH_3 \\ \backslash \\ COOH \end{matrix} + C_6H_5\,CHO \xrightarrow{aq.\ NAOH} \begin{matrix} CH_2.\ CH_2COCH = CHC_6H_5 \\ | \\ COOH \end{matrix}$$

X.

Erdmann (7) found that both β - and δ - benzal levulinic acids resulted from the condensation of levulinic acid with benzaldehyde, with either aqueous alkalies or mineral acids, as condensing agents. In the presence of aqueous alkali, β - benzal levulinic acid condensed further with benzaldehyde to form β - δ - dibenzal levulinic acid (XI).

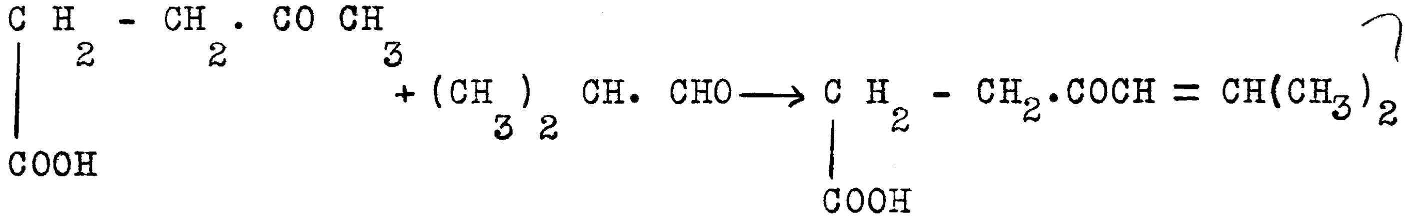


$$\begin{matrix}\mathrm{CH_2}-\overset{\displaystyle\mathrm{CH\,C_6H_5}}{\overset{\|}{\mathrm{C}}}-\mathrm{CO\,CH_3}\\ |\\ \mathrm{COOH}\end{matrix} + \mathrm{C_6H_5\,CHO} \longrightarrow \begin{matrix}\mathrm{CH_2}-\overset{\displaystyle\mathrm{CH\,C_6H_5}}{\overset{\|}{\mathrm{C}}}-\mathrm{CO\,CH=CH\,C_6H_5}\\ |\\ \mathrm{COOH}\end{matrix}$$

XI.

δ [m - chlorbenzal] levulinic acid (ibid) was also prepared in a similar manner.

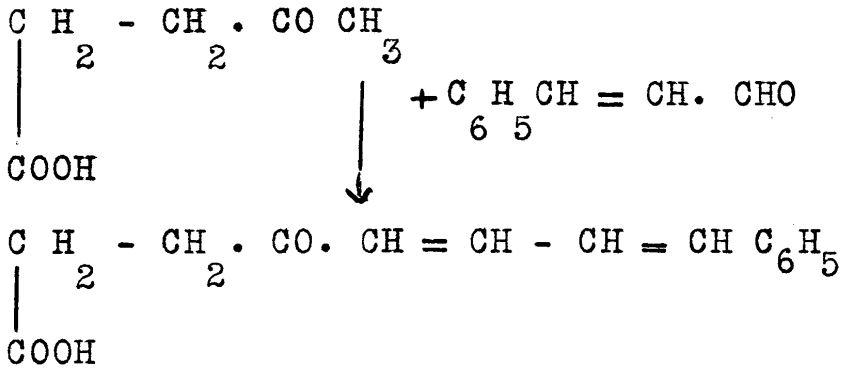
Isobutylidene levulinic acid (XII) was prepared by the condensation of levulinic acid with isobutyraldehyde in the presence of a 10% solution of sodium hydroxide (8).



$$\begin{matrix}\mathrm{CH_2-CH_2\,.\,CO\,CH_3}\\ |\\ \mathrm{COOH}\end{matrix} + \mathrm{(CH_3)_2\,CH.\,CHO} \longrightarrow \begin{matrix}\mathrm{CH_2-CH_2.COCH=CH(CH_3)_2}\\ |\\ \mathrm{COOH}\end{matrix}$$

XII.

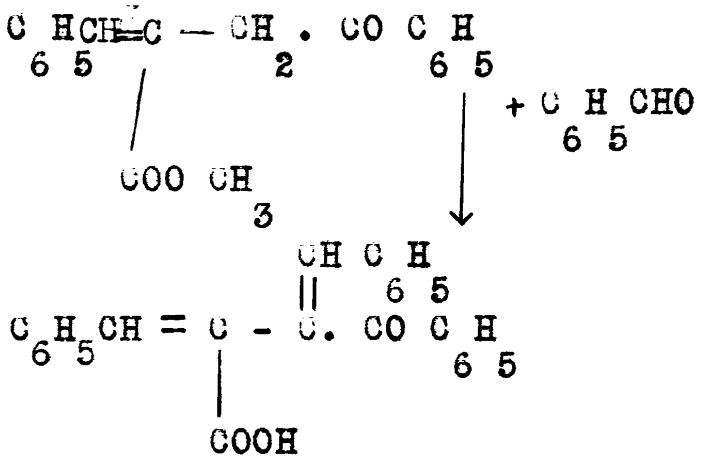
Rupe and Speiser (9) obtained δ cinnamal levulinic acid (XIII) by heating levulinic acid with cinnamic aldehyde to 150° in the presence of a few drops of pyridine.



$$\begin{matrix}\mathrm{CH_2-CH_2\,.\,CO\,CH_3}\\ |\\ \mathrm{COOH}\end{matrix} \xrightarrow{+\mathrm{C_6H_5\,CH=CH.\,CHO}} \begin{matrix}\mathrm{CH_2-CH_2\,.\,CO.\,CH=CH-CH=CH\,C_6H_5}\\ |\\ \mathrm{COOH}\end{matrix}$$

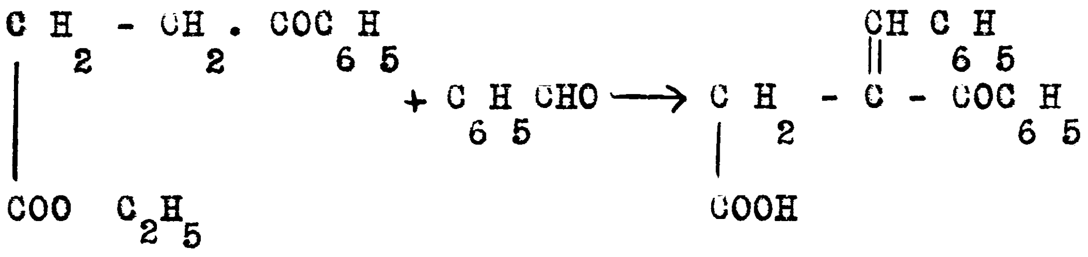
XIII.

α,β Dibenzal -β- benzoyl propionic acid (XIV) was formed when the methyl ester of - α benzal -β- benzoyl propionic acid was condensed with benzaldehyde in the presence of alcoholic potassium hydroxide solution in the cold (10).



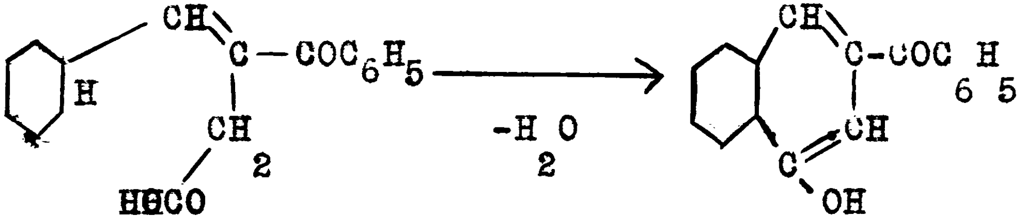
XIV.

Borsche (11a) obtained β-benzal β-benzoyl propionic acid (XV) by condensing the ethyl ester of β-benzoyl propionic acid with benzaldehyde in alcoholic solution (96%) with sodium methylate as the condensing agent.



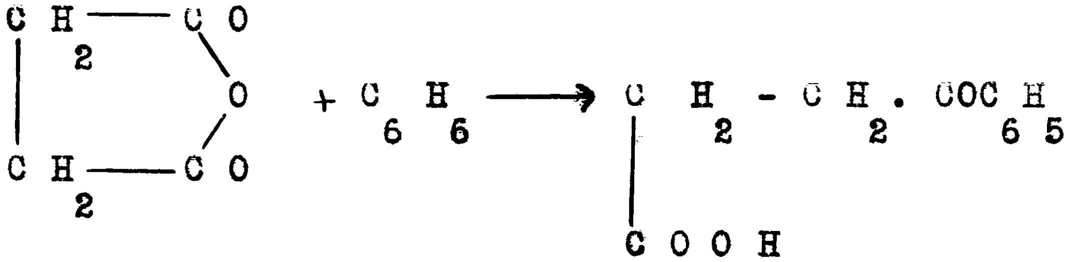
XV.

On heating this acid, -3- benzoyl naphthol (XVI) was formed with loss of water, thus proving its structure.



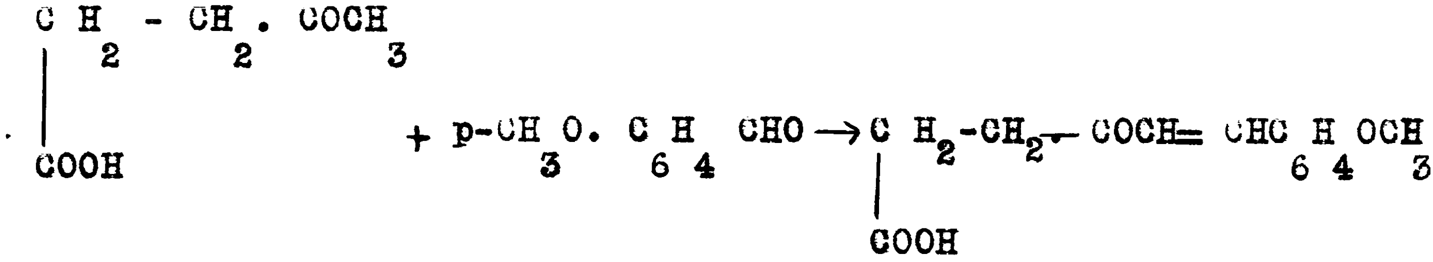
XVI.

He also condensed the sodium salts of several γ - ketonic acids with aromatic aldehydes to form β-γ unsaturated lactones. His starting materials were β-benzoyl propionic acid (XVII), β[p- toloyl] propionic acid, and δ- anisal levulinic acid (XVIII). The two former were prepared by heating benzene or toluene with succinic anhydride in the presence of aluminium chloride.



XVII.

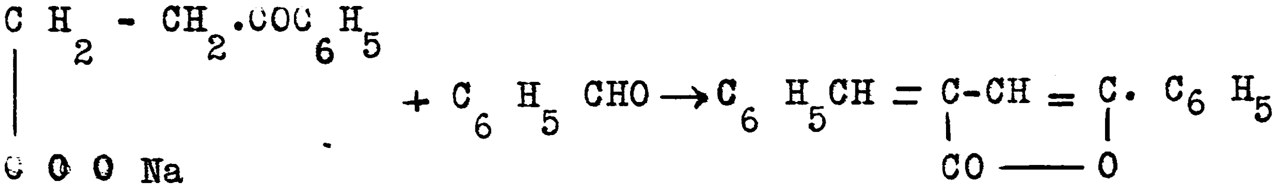
δ- Anisal levulinic acid was obtained by the condensation of levulinic acid with anisaldehyde in an alcohol medium, in the presence of dilute sodium hydroxide solution.



$$CH_2(COOH)\text{-}CH_2.COCH_3 + p\text{-}CH_3O.C_6H_4CHO \rightarrow CH_2(COOH)\text{-}CH_2\text{-}COCH{=}CHC_6H_4OCH_3$$

XVIII.

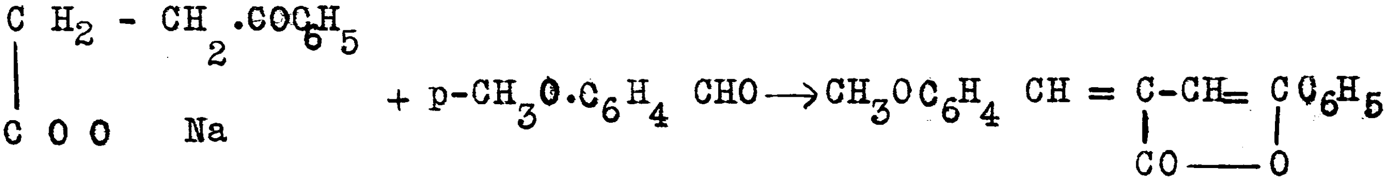
1-Benzal -3- phenyl crotonlactone (XIX) was the result of the condensation of the sodium salt of β- benzoyl propionic acid with benzaldehyde. In this reaction, as in all subsequent reactions described in this section, acetic anhydride was the condensing agent; the γ- ketonic acids were in the form of their sodium salts.



$$\begin{array}{l}CH_2-CH_2.COC_6H_5\\ |\\ COONa\end{array} + C_6H_5CHO \rightarrow C_6H_5CH=\begin{array}{l}C-CH=C\cdot C_6H_5\\ |\qquad\quad\;\; |\\ CO\text{——}O\end{array}$$

XIX.

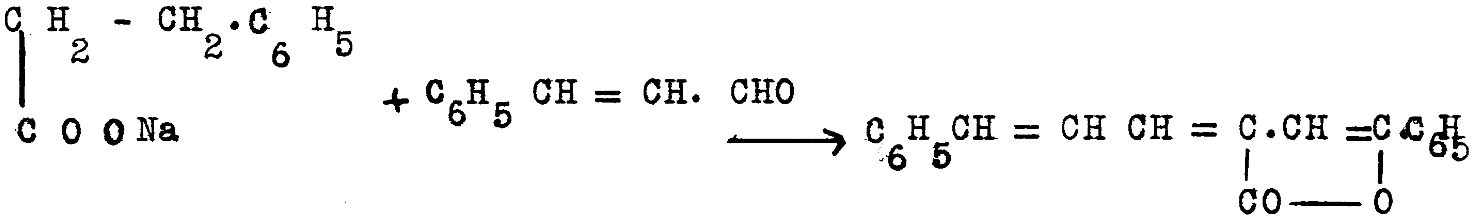
From benzoyl propionic acid and anisaldehyde, the analogous 1- anisal -3- phenyl crotonlactone (XX), resulted.



$$\begin{array}{l}CH_2-CH_2.COC_6H_5\\ |\\ COONa\end{array} + p\text{-}CH_3O.C_6H_4CHO \rightarrow CH_3OC_6H_4CH=\begin{array}{l}C-CH=CC_6H_5\\ |\qquad\quad\;\; |\\ CO\text{——}O\end{array}$$

XX.

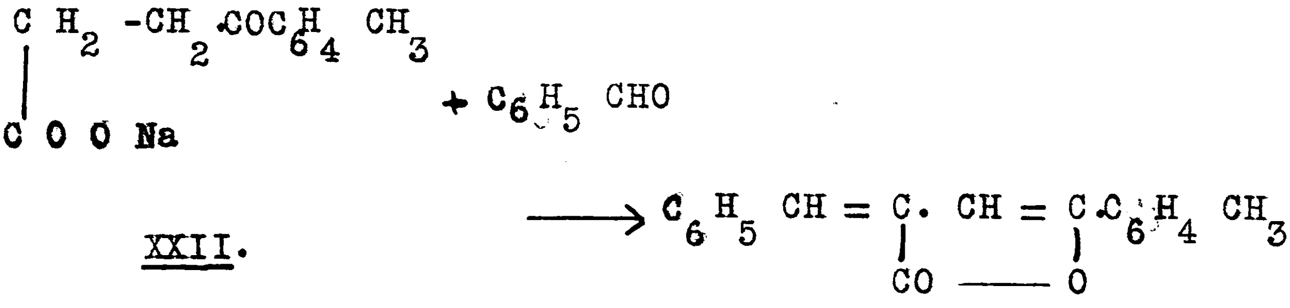
With cinnamic aldehyde, benzoyl propionic acid formed 1- cinnamal -3- phenyl crotonlactone (XXI)



$$\begin{array}{l}CH_2-CH_2.C_6H_5\\ |\\ COONa\end{array} + C_6H_5CH=CH.CHO \longrightarrow C_6H_5CH=CH\,CH=\begin{array}{l}C.CH=C.C_6H_5\\ |\qquad\quad\;\; |\\ CO\text{——}O\end{array}$$

XXI.

p-Toloyl propionic acid (XXII) combined with benzaldehyde to form 1- benzal -3- toloyl-crotonlactone (XXIII).

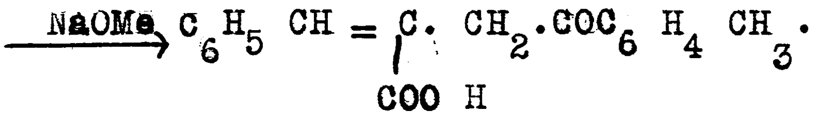


$$\begin{array}{l}CH_2-CH_2.COC_6H_4CH_3\\ |\\ COONa\end{array} + C_6H_5CHO \longrightarrow C_6H_5CH=\begin{array}{l}C.\;CH=C.C_6H_4CH_3\\ |\qquad\quad\;\; |\\ CO\text{——}O\end{array}$$

XXII.

XXIII.

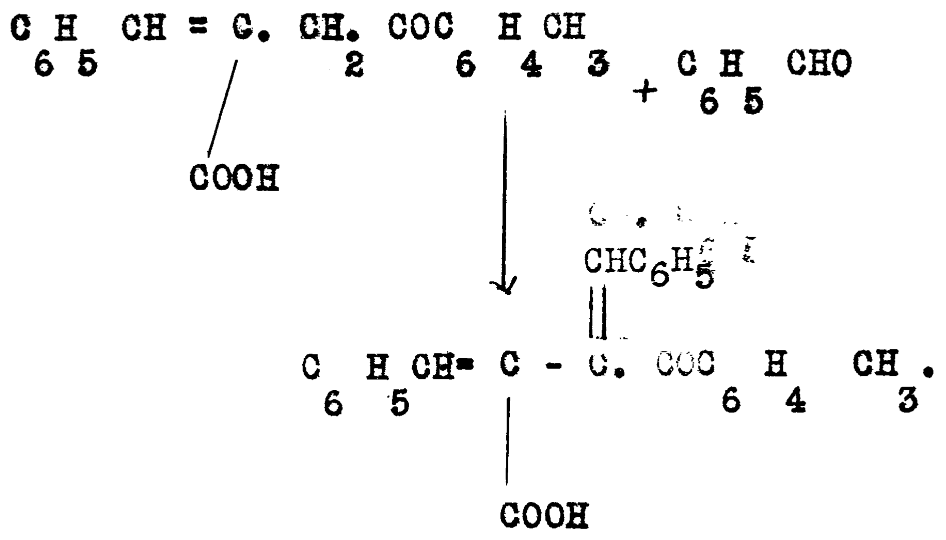
The latter lactone was hydrolysed with sodium methylate to form α- benzal -β- toloyl propionic acid (XXIV).



$$\xrightarrow{NaOMe} C_6H_5CH=\underset{\displaystyle COOH}{C}.\;CH_2.COC_6H_4CH_3.$$

XXIV.

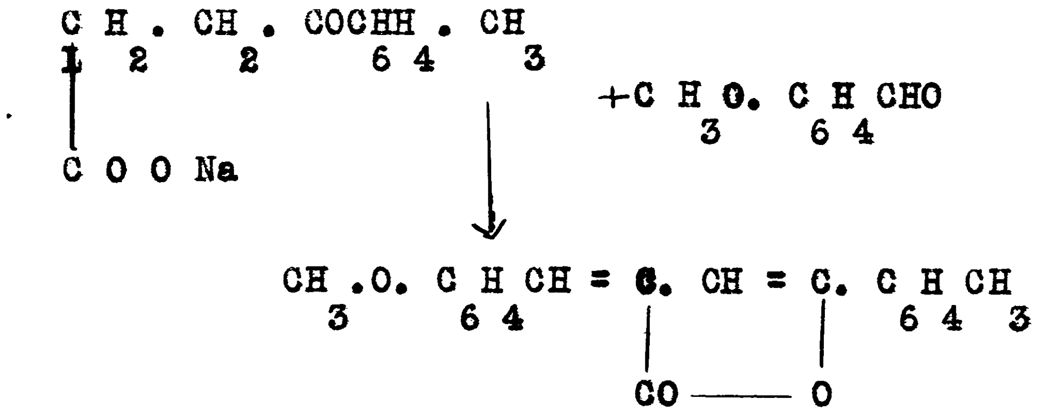
This acid was condensed with benzaldehyde in the presence of sodium ethylate in alcohol, to form α,β dibenzal β- toloyl propionic acid (XXV).



$$C_6H_5CH=C(COOH).CH_2.COC_6H_4CH_3 + C_6H_5CHO \rightarrow C_6H_5CH=C(COOH)-C(=CHC_6H_5).COC_6H_4CH_3$$

XXV

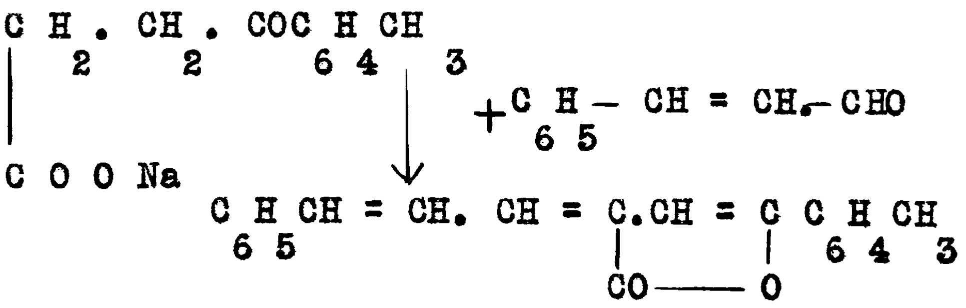
From β-toloyl propionic acid and anisaldehyde, 1-anisal -3- toloyl crotonlactone (XXV1) was formed.



$$CH_2(COONa).CH_2.COC_6H_4.CH_3 + CH_3O.C_6H_4CHO \rightarrow CH_3.O.C_6H_4CH=C.CH=C.C_6H_4CH_3 \; (CO—O)$$

XXV1.

With cinnamic aldehyde, the analagous 1- cinnamal -3- toloyl crotonlactone (XXV11) resulted.

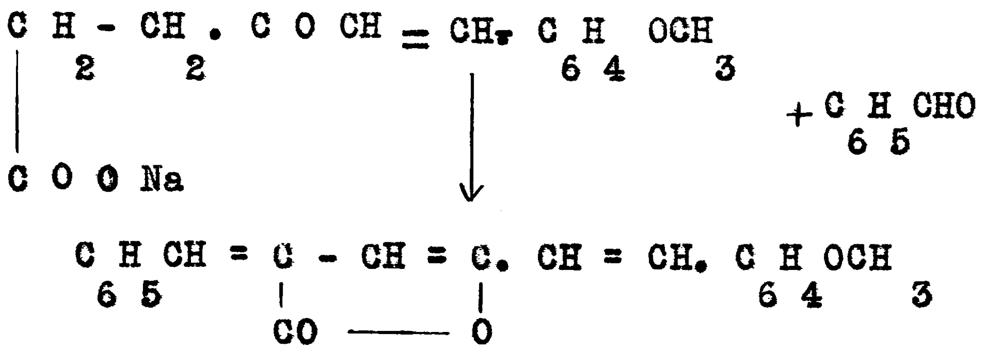


$$CH_2(COONa).CH_2.COC_6H_4CH_3 + C_6H_5-CH=CH.-CHO \rightarrow C_6H_5CH=CH.CH=C.CH=C\,C_6H_4CH_3 \; (CO—O)$$

XXV11

The lactone ring of the latter compound was opened with sodium methylate to form the methyl ester of α-cinnamal-β-toloyl propionic acid. From this ester, a phenyl hydrazone and a semi carbazide were made in acid solution.

δ- Anisal levulinic acid condensed with benzaldehyde to form 1- benzal -4- anisal angelicalactone (XXV111).

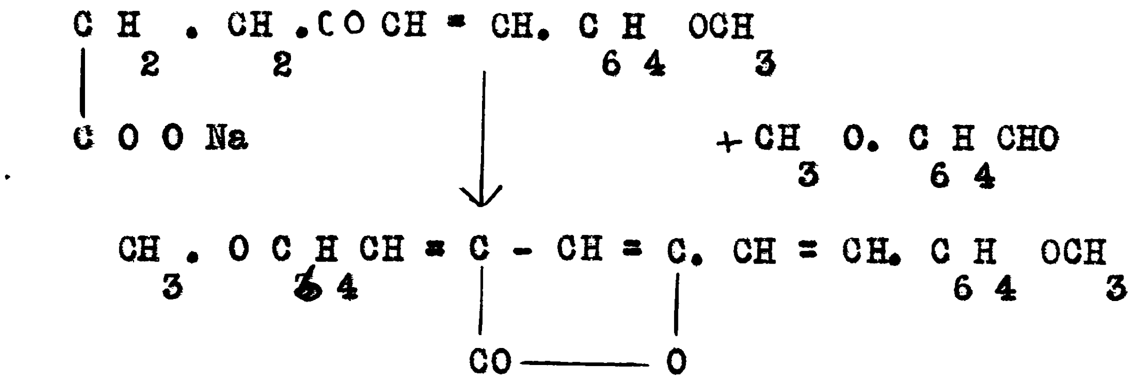


$$\begin{array}{l} CH_2-CH_2.COCH=CH.C_6H_4OCH_3 \\ | \\ COONa \end{array} + C_6H_5CHO \longrightarrow$$

$$C_6H_5CH=\underset{\underset{CO\text{———}}{|}}{C}-CH=\underset{\underset{O}{|}}{C}.CH=CH.C_6H_4OCH_3$$

XXVIII

With anisaldehyde, 1.4 dianisal angelicalactone (XXIX) resulted.

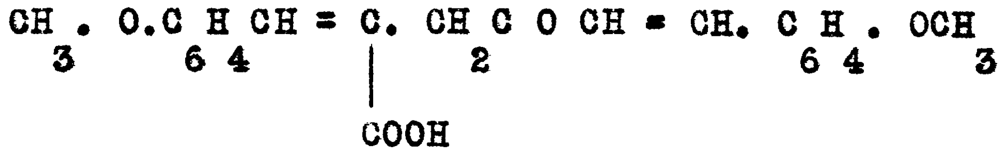


$$\begin{array}{l} CH_2.CH_2.COCH=CH.C_6H_4OCH_3 \\ | \\ COONa \end{array} + CH_3O.C_6H_4CHO \longrightarrow$$

$$CH_3.OC_6H_4CH=\underset{\underset{CO\text{———}}{|}}{C}-CH=\underset{\underset{O}{|}}{C}.CH=CH.C_6H_4OCH_3$$

XXIX

The latter lactone was hydrolysed to α,β-dianisal levulinic acid (XXX) with aqueous sodium carbonate.

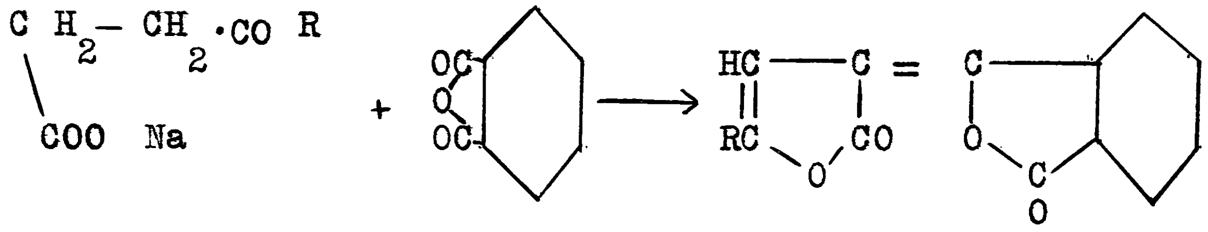


$$CH_3.O.C_6H_4CH=\underset{\underset{COOH}{|}}{C}.CH_2COCH=CH.C_6H_4.OCH_3$$

XXX.

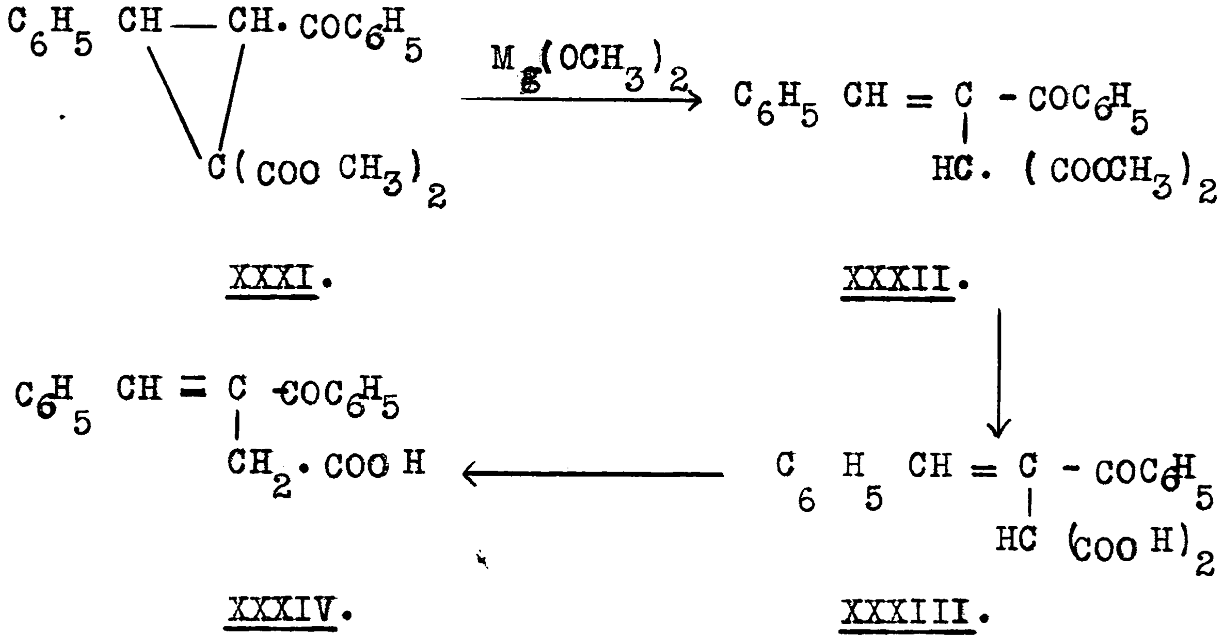
This acid formed a phenyl hydrazone in acid solution.

Borsche (11b) also condensed these same γ-ketonic acids with phthalic anhydride in the presence of acetic anhydride. The product isolated in each case was a dilactone having the structure given below.



$R = C_6H_5, p\text{-}CH_3\cdot C_6H_4, p\text{-}CH_3O\cdot C_6H_4\ CH = CH\text{-}$

Kohler and Conant (12a) treated methyl 2-phenyl -3-benzoyl cyclopropane dicarboxylate (XXXI) with magnesium methylate to obtain methyl β- benzoyl -γ- phenyl vinyl malonate (XXXII); the corresponding dibasic acid (XXXIII) obtained on hydrolysis was heated to form β- benzal -β-benzoyl propionic acid (XXXIV).



XXXI.

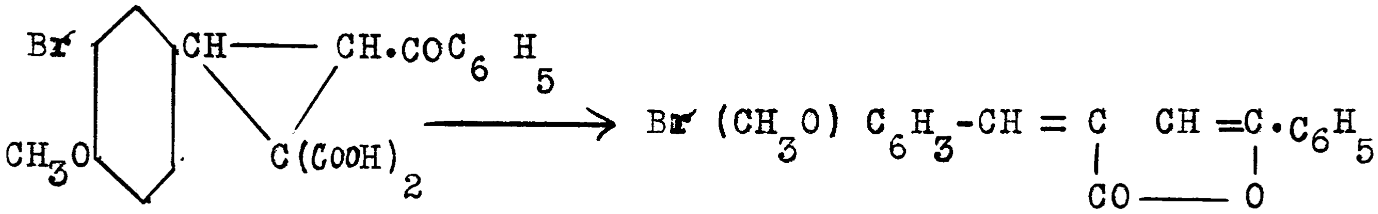
XXXII.

XXXIV.

XXXIII.

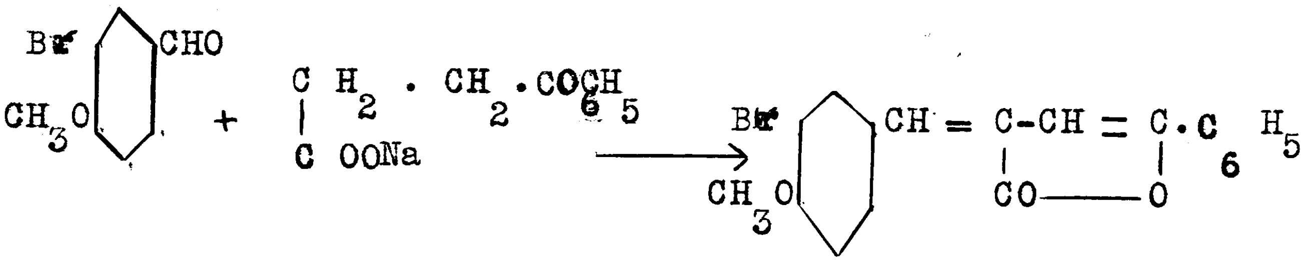
The structure of (XXXIV) was confirmed by a synthesis following the directions of Borsche. (loc. cit.) .

The same authors (12b) obtained a lactone (XXXV) analagous to those synthesized by Borsche by treating the cyclopropane diacid (XXXVI) with phosphorus pentachloride in chloroform solution.

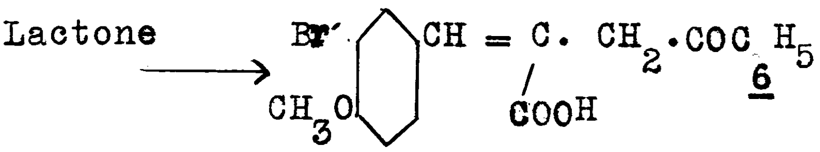


XXXVI. XXXV.

Its structure was proved by a synthesis from β- benzoyl propionic acid and -3- brom anisic aldehyde in the presence of acetic anhydride.

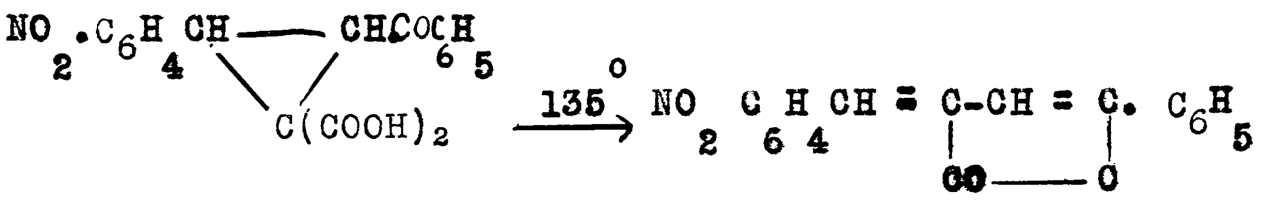


This lactone was hydrolysed by strong bases to α-(3,4- Bromomethoxy-benzal) - β- benzoyl propionic acid (XXXVII).



XXXVII.

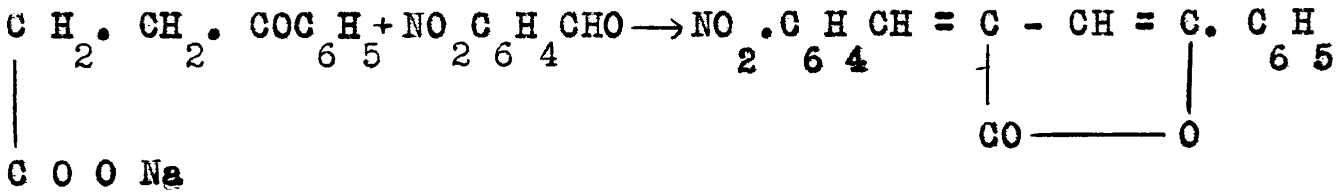
Kohler, Hill and Bigelow (13) obtained α- (3-nitrobenz) -γ- phenyl crotonlactone (XXXVIII) on heating 2-(3-nitrophenyl) -3- benzoyl cyclopropane diacid (XXXIX) to 135°.



$$NO_2\cdot C_6H_4CH\overset{C(COOH)_2}{-}CHCOC_6H_5 \xrightarrow{135^\circ} NO_2C_6H_4CH=\underset{CO\text{———}O}{C-CH=C}\cdot C_6H_5$$

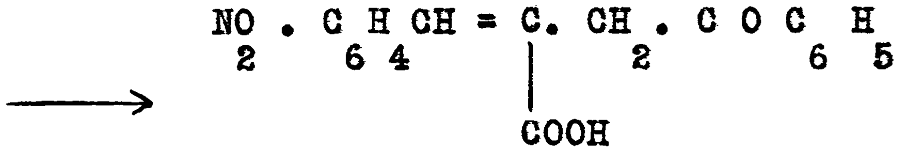
XXXIX XXXVIII

Its structure was proved by a synthesis from benzoyl propionic acid and meta nitro benzaldehyde.



$$\underset{COONa}{CH_2}\cdot CH_2\cdot COC_6H_5+NO_2C_6H_4CHO\rightarrow NO_2\cdot C_6H_4CH=\underset{CO\text{———}O}{C-CH=C}\cdot C_6H_5$$

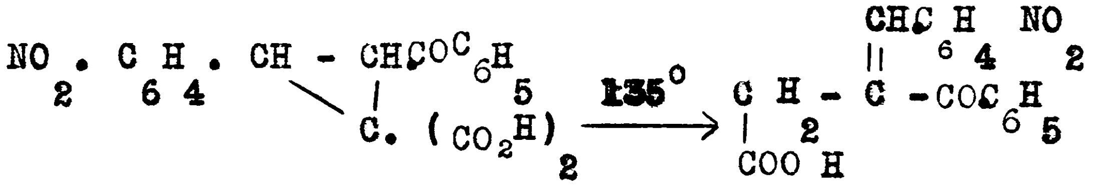
This lactone goes over very easily to, α-(m.-nitro benzal) β- benzoyl propionic acid. (XL)



$$\longrightarrow NO_2\cdot C_6H_4CH=\underset{COOH}{C}\cdot CH_2\cdot COC_6H_5$$

(XL)

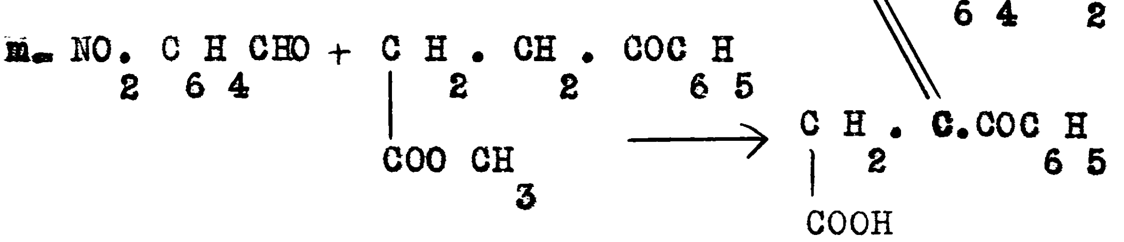
An additional pyrolysis product of the above mentioned cyclopropane diacid, was β-[3-nitro] benzal β-benzoyl propionic acid (XL1).



$$NO_2\cdot C_6H_4\cdot CH-\underset{C\cdot(CO_2H)_2}{CHCOC_6H_5}\xrightarrow{135^\circ}\underset{COOH}{CH_2}-\overset{CHC_6H_4NO_2}{\overset{\|}{C}}-COC_6H_5$$

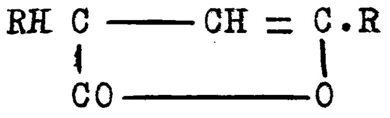
XL1

Its structure was proved by synthesis from meta nitrobenzaldehyde and the methyl ester of benzoyl propion~~ate~~ic acid, in absolute alcohol in the presence of sodium ethylate as condensing agent.

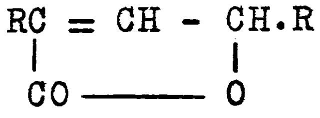


$$m\text{-}NO_2C_6H_4CHO+\underset{COOCH_3}{CH_2}\cdot CH_2\cdot COC_6H_5\longrightarrow\underset{COOH}{CH_2}\cdot\overset{CH\cdot C_6H_4NO_2\ m.}{\overset{\|}{C}}\cdot COC_6H_5$$

Thiele and his co-workers have shown that γ- ketonic acids having the β- position unsubstituted, lose water easily in the presence of a dehydrating agent such as acetic anhydride, to form unsaturated lactones. Two series of unsaturated γ- lactones are known, depending on the position of the double bond within the lactone ring. One is β-γ , and the other ,α-β unsaturated.

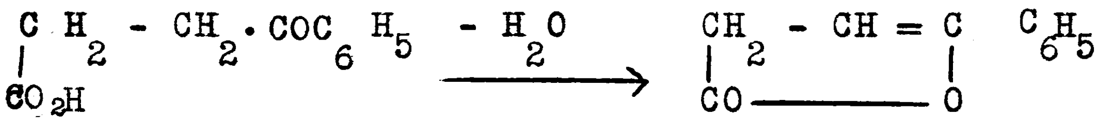


β-γ unsaturated.



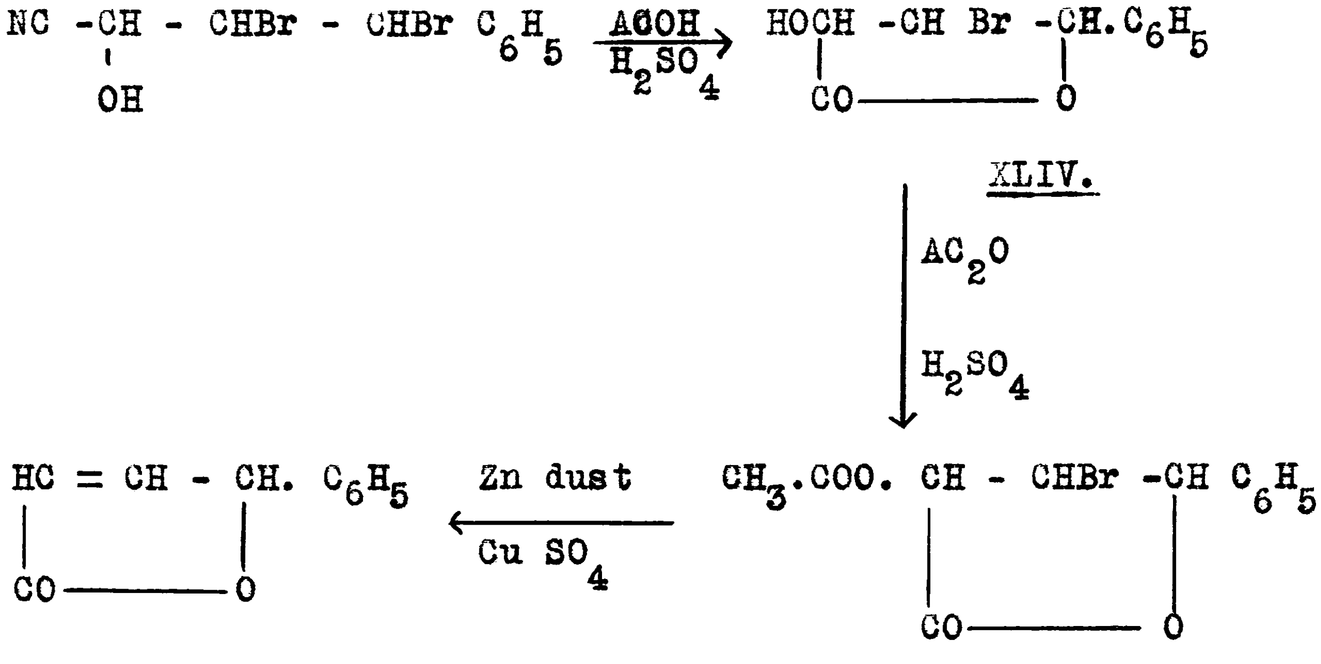
α-β unsaturated.

Thiele and Sulzberger (14) found that when acetic anhydride acted on benzoyl propionic acid, the β-γ unsaturated phenyl crotonlactone (XLII) was formed.



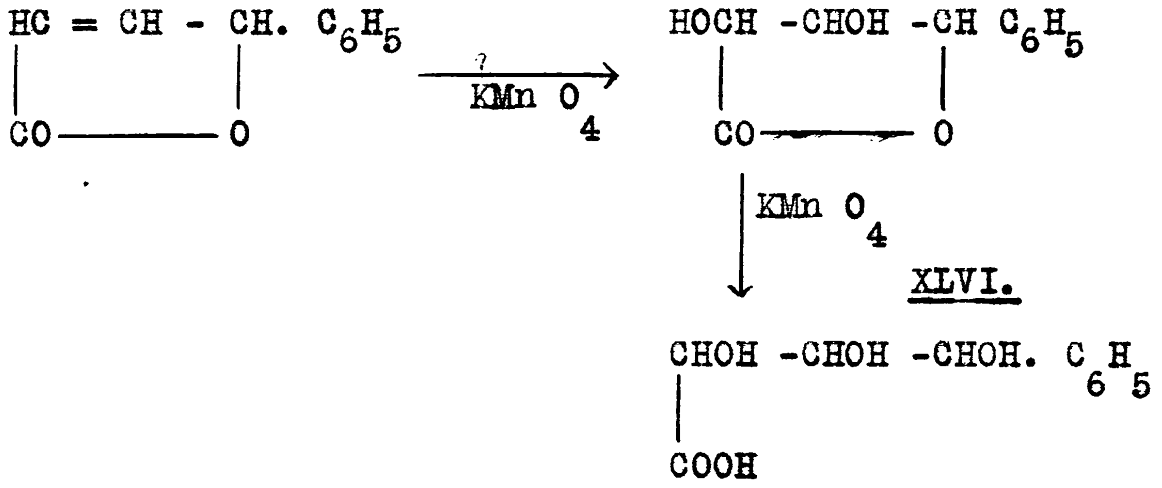
XLII.

The isomeric α-β unsaturated lactone (XLIII) was obtained in the following manner. The dibromide of cinnamic aldehyde cyanhydrin was heated with a mixture of acetic and sulphuric acids and water for some hours to form phenyl bromhydroxybutyrolactone (XLIV). The acetate (XLV) of this hydroxy compound was obtained by treatment with acetic anhydride and a trace of sulphuric acid. This acetate, in the presence of zinc dust and copper sulphate, was reduced to α-β unsaturated phenyl crotonlactone.



XLIV. XLIII. XLV.

On oxidation with potassium permanganate in water solution, the corresponding dihydroxy saturated lactone (XLVI) was formed, which was further oxidized to the tri hydroxy acid (XLVII). Its structure was thus proved.

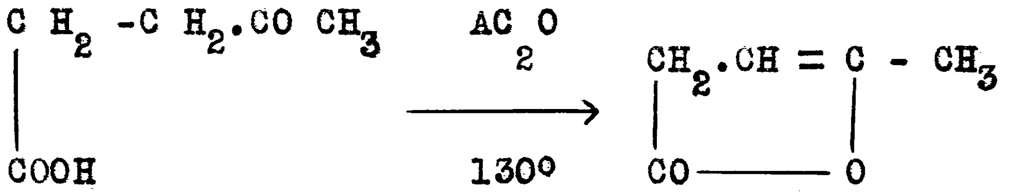


XLVI. XLVII.

Both unsaturated lactones were hydrolysed by alcoholic potassium hydroxide to benzoyl propionic acid.

The β-γ unsaturated lactones were found to be converted to the α-β form, by treating with such alkaline reagents as ammonia, methyl- , diethyl - trimethyl - , triethyl-amines, and piperidine; neutral reacting amines such as aniline and pyridine did not effect this rearrangement.

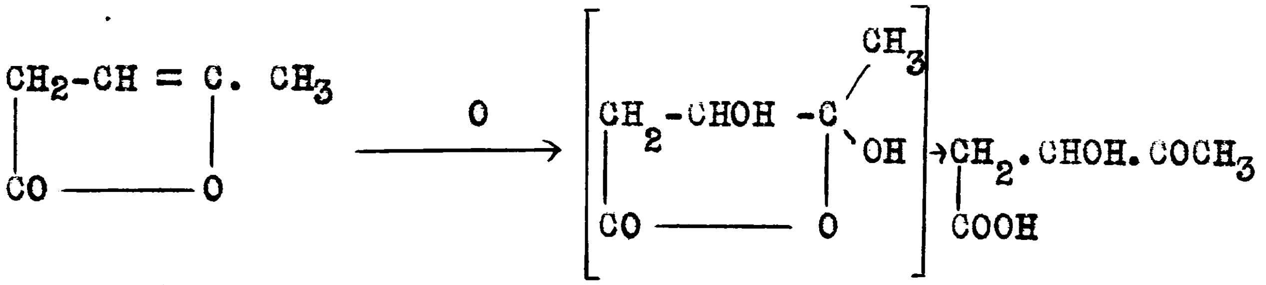
Thiele, Tischbein, and Lossow (15) obtained β-γ unsaturated angelicalactone (XLVIII) by heating levulinic acid with acetic anhydride at 130° for some hours.



XLVIII.

An intermediate product, acetyl levulinic acid, was obtained in this reaction, but a discussion of it is reserved for a later section. On oxidation of this unsaturated lactone, β-hydroxy levulinic acid (XLVIX) was obtained.

The course of the oxidation is represented:



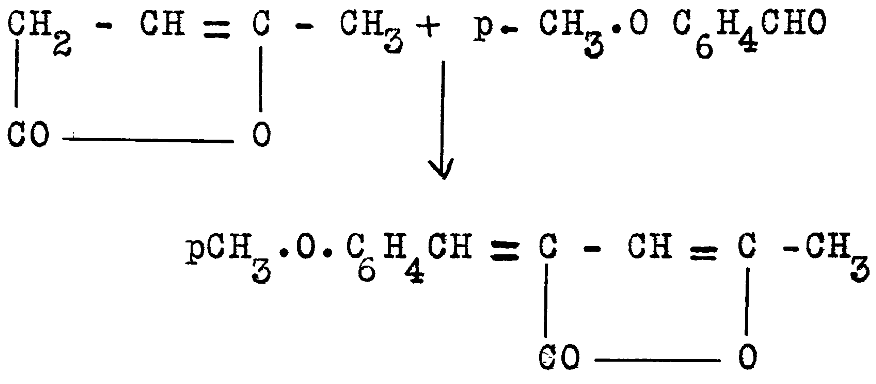
L.

XLVIX.

The hydroxylactone was not obtained; if formed, it must have gone over easily to the ketonic acid.

α-β-unsaturated angelicalactone was prepared from the isomeric β-γ-substance, by treatment with triethyl amine.

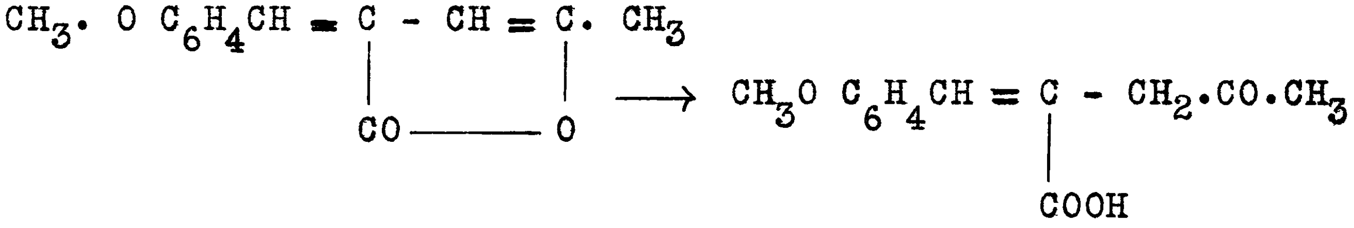
On condensation of β-γ unsaturated angelicalactone, with anisaldehyde in the presence of diethyl amine (ibid) the corresponding anisal lactone (LI) was formed.



$$\begin{array}{l}\begin{array}{llll}\text{CH}_2 & -\ \text{CH} = & \text{C} & -\ \text{CH}_3 + p\text{-}\ \text{CH}_3\text{.O C}_6\text{H}_4\text{CHO}\\ | & & | & \\ \text{CO} & \text{———} & \text{O} & \end{array}\\ \qquad\qquad\downarrow \\ \begin{array}{lllll} p\text{CH}_3\text{.O.C}_6\text{H}_4\text{CH} = & \text{C} & -\ \text{CH} = & \text{C} & -\text{CH}_3\\ & | & & | & \\ & \text{CO} & \text{———} & \text{O} & \end{array}\end{array}$$

LI.

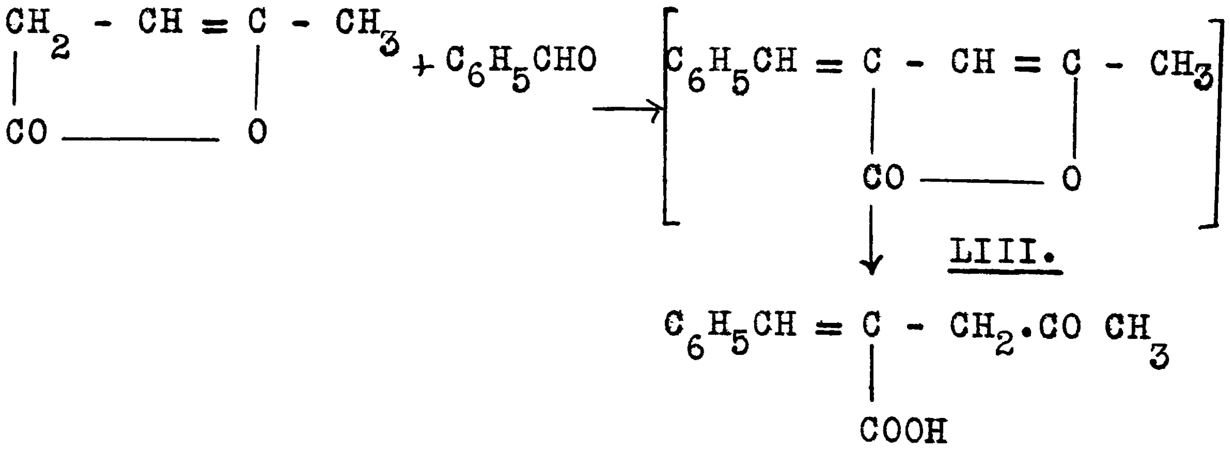
This condensation also took place with aniline and ammonium acetate as condensing agents, but the yields were smaller. On hydrolysis with aqueous sodium carbonate this substance yielded α-anisal levulinic acid (LII).



$$\begin{array}{lllll}\text{CH}_3\text{. O C}_6\text{H}_4\text{CH} = & \text{C} & -\ \text{CH} = & \text{C.} & \text{CH}_3\\ & | & & | & \\ & \text{CO} & \text{———} & \text{O} & \end{array} \longrightarrow \begin{array}{ll}\text{CH}_3\text{O C}_6\text{H}_4\text{CH} = & \text{C} - \text{CH}_2\text{.CO.CH}_3\\ & | \\ & \text{COOH}\end{array}$$

LII.

When the β-γ unsaturated lactone was condensed with benzaldehyde in the presence of diethylamine, the analagous benzal angelicalactone (LIII) was not isolated, but after hydrolysis with sodium carbonate, α- benzal levulinic acid (LIV) was obtained.

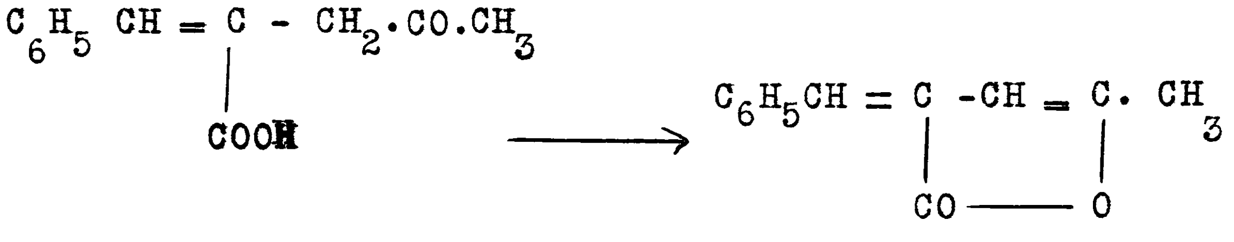


$$\begin{array}{l}\begin{array}{llll}\text{CH}_2 & -\ \text{CH} = & \text{C} & -\ \text{CH}_3\\ | & & | & \\ \text{CO} & \text{———} & \text{O} & \end{array} + \text{C}_6\text{H}_5\text{CHO} \longrightarrow \left[\begin{array}{lllll}\text{C}_6\text{H}_5\text{CH} = & \text{C} & -\ \text{CH} = & \text{C} & -\ \text{CH}_3\\ & | & & | & \\ & \text{CO} & \text{———} & \text{O} & \end{array}\right]\\ \qquad\qquad\qquad\qquad\qquad\downarrow \\ \qquad\qquad\qquad\qquad\begin{array}{ll}\text{C}_6\text{H}_5\text{CH} = & \text{C} - \text{CH}_2\text{.CO CH}_3\\ & | \\ & \text{COOH}\end{array}\end{array}$$

LIII.

LIV.

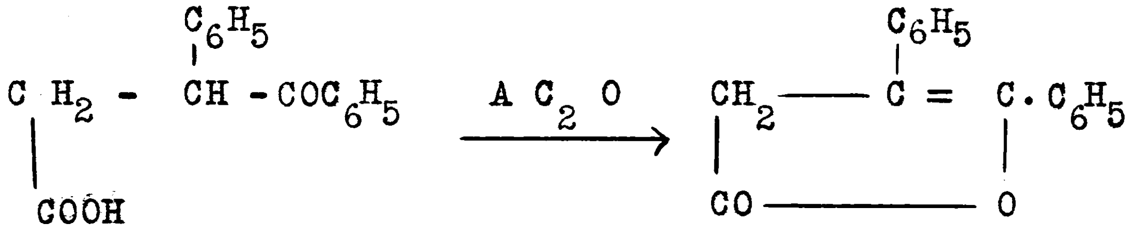
When α-benzal levulinic acid was treated with acetic anhydride and a trace of sulphuric acid, a yellow lactone was obtained, to which the structure (LV) was ascribed by the authors, although this has not been proved.



LV.

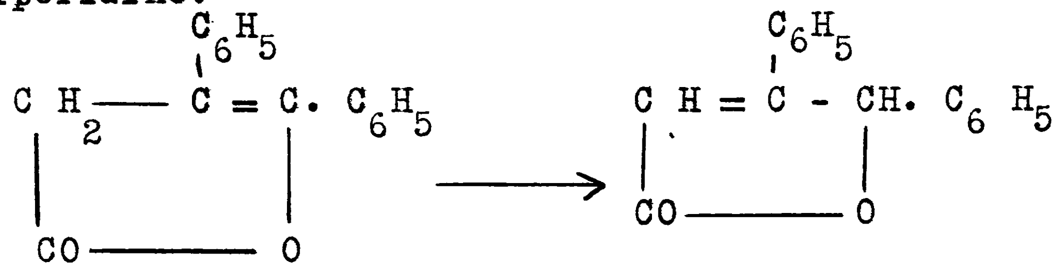
No condensation occurred when the α-β unsaturated angelicalactone was treated with aldehydes in the presence of a non-rearranging base such as aniline; when an "alkaline reacting base" such as diethyl or triethyl amine, was used as the condensing agents, anisal angelicalactone was obtained, with anisaldehyde.

Thiele and Straus (16a) treated β- phenyl -β- benzoyl propionic acid with acetic anhydride and a trace of sulphuric acid, to obtain β-γ unsaturated diphenyl crotonlactone (LVI).



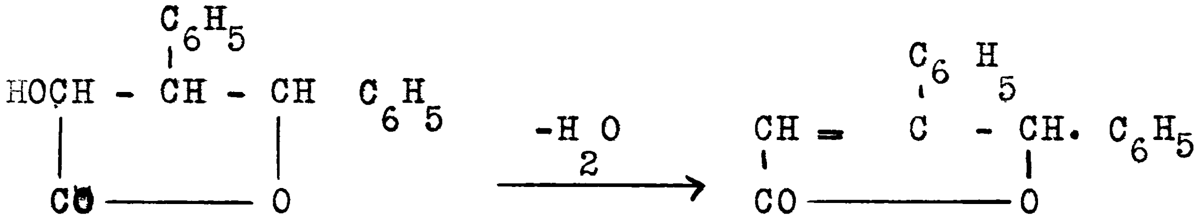
LVI.

The isomeric α-β- unsaturated diphenyl crotonlactone (LVII) was obtained by heating the β-γ substance with piperidine.

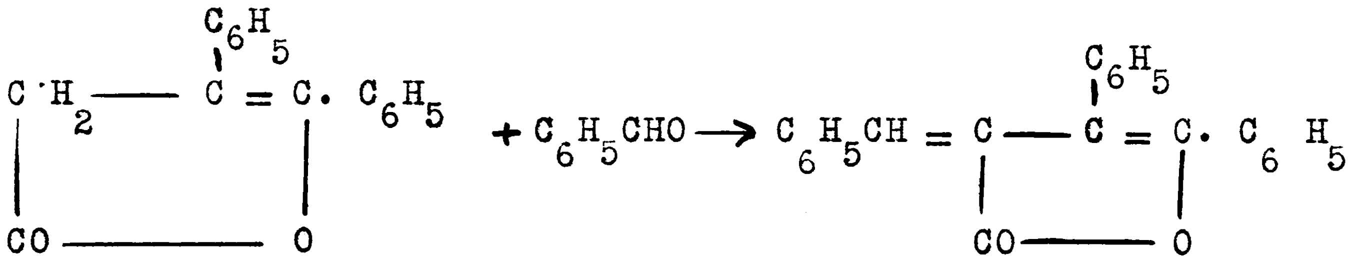


LVII.

Erlenmeyer and Lux (17) have proved the structure of the latter by its formation from diphenyl hydroxybutyrolactone by loss of water.

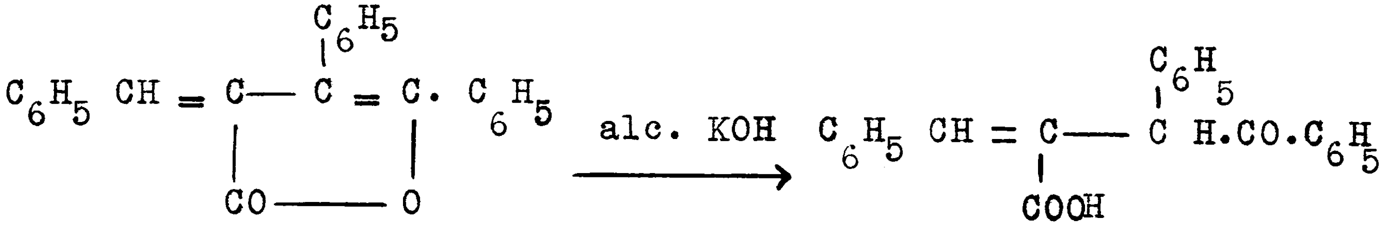


The β-γ unsaturated lactone was condensed with benzaldehyde in the presence of aniline to form benzal diphenyl crotonlactone (LVIII).



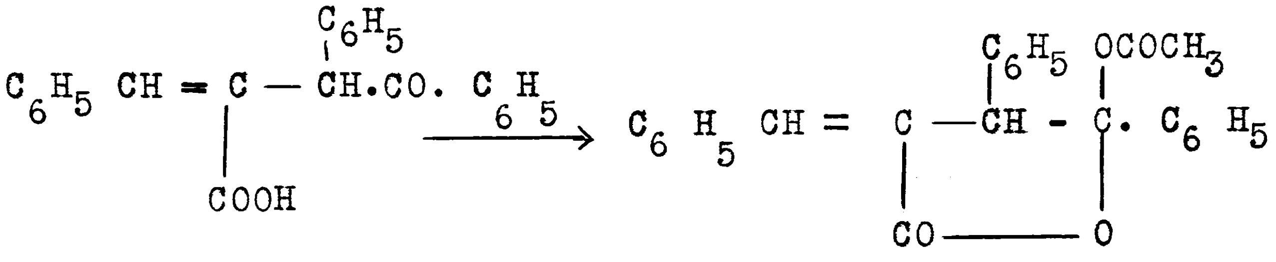
LVIII.

The latter substance was hydrolysed with alcoholic potassium hydroxide to α-benzal-β-phenyl-β- benzoyl propionic acid. (LVIX).



LVIX.

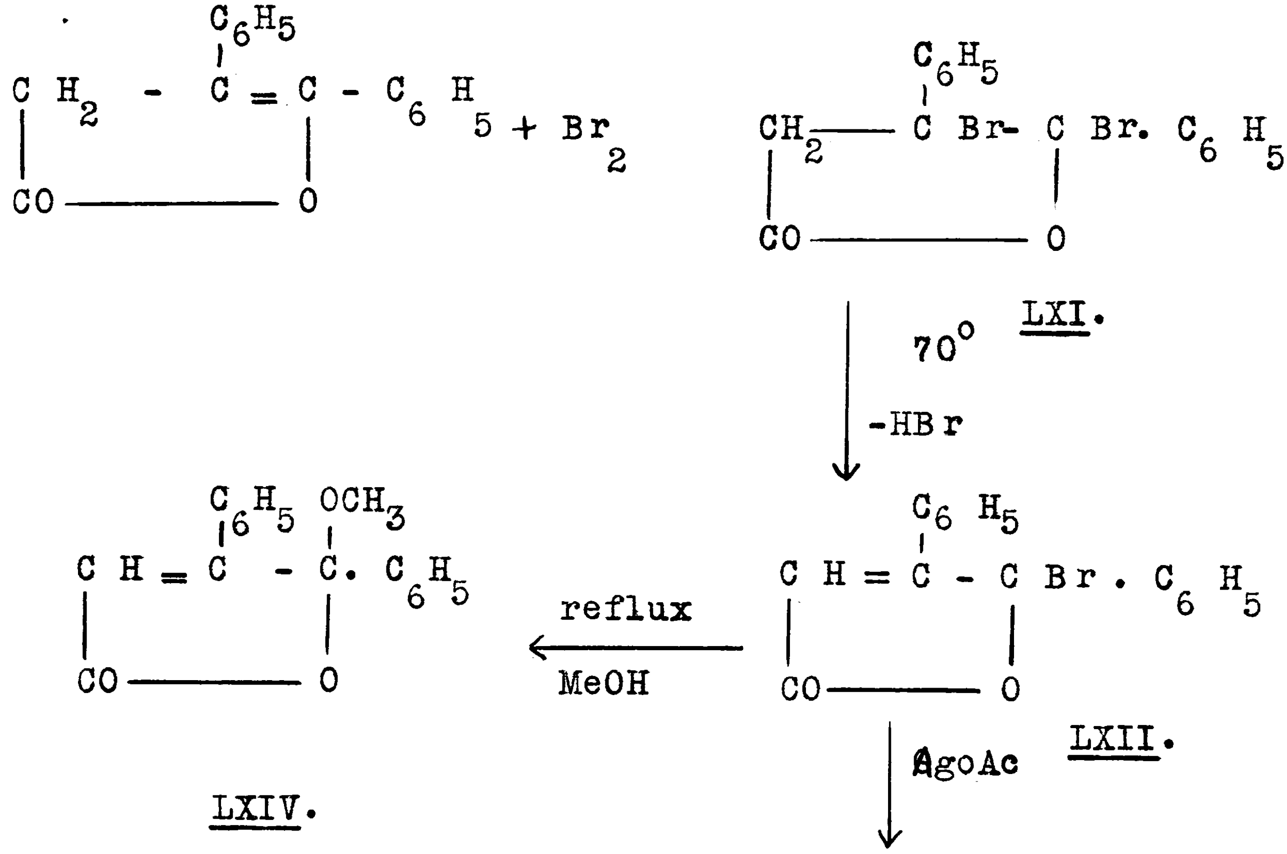
When this unsaturated acid was treated with acetic anhydride in the presence of a little sulphuric acid it formed an acetate of an isomeric cyclic form (LX).

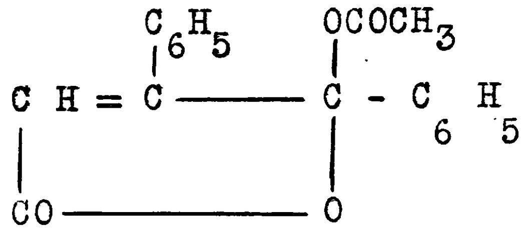


LX.

The methyl ester was formed thru the silver salt, and could not be made by refluxing the acid in alcohol in the presence of a mineral acid.

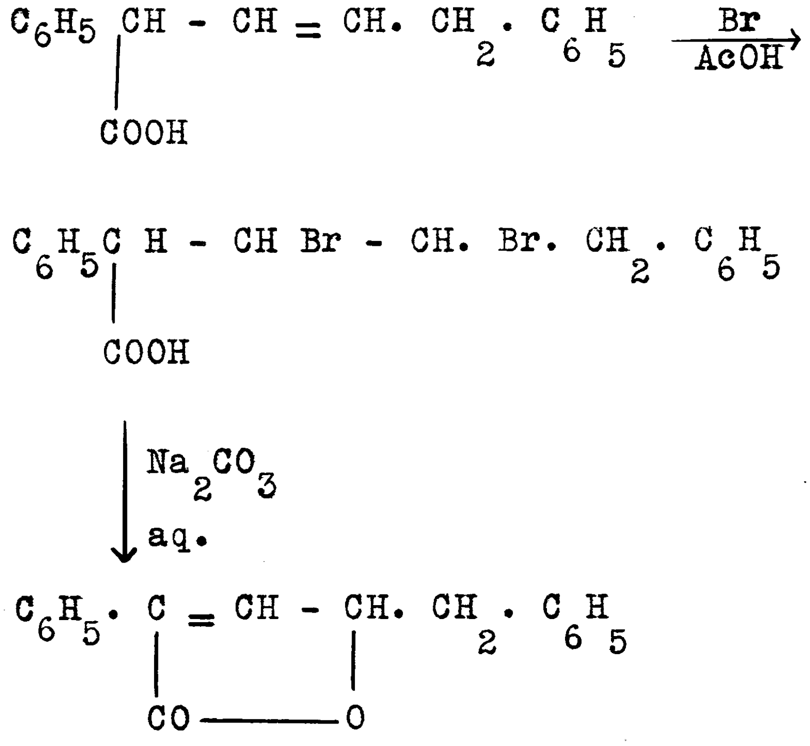
The β-γ unsaturated diphenyl crotonlactone was further treated with bromine and gave the saturated dibromide (LXI); this on heating to 70° lost hydrobromic acid with the formation of the unsaturated monobromide (LXII). The latter on treatment with silver acetate in absolute ether yielded the acetate derivative (LXIII) and on refluxing in methyl alcohol, the ether (LXIV).





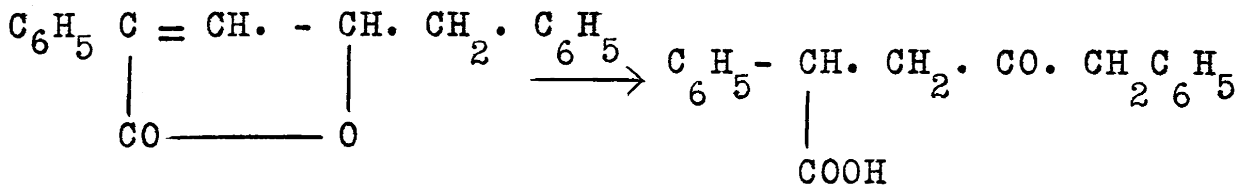
LXIII

α-β unsaturated benzyl phenyl crotonlactone (LXV) was prepared by Thiele and Straus (16b), by treating the dibromide of diphenyl pentenic acid with sodium carbonate solution.



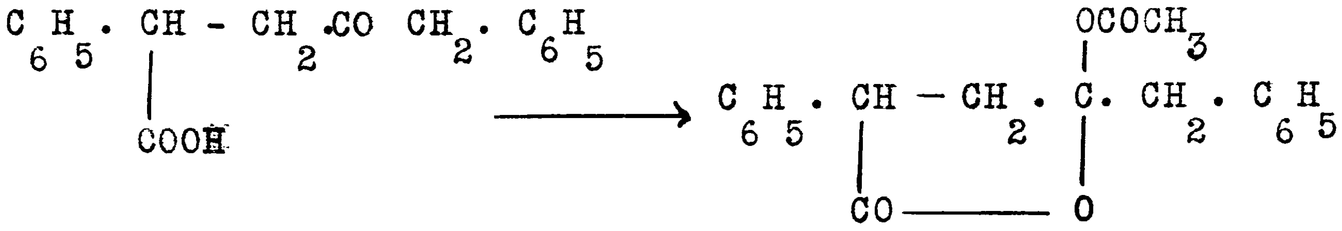
LXV.

This was hydrolysed with alcoholic potassium hydroxide to α-phenyl -β- phenacetyl propionic acid (LXVI)



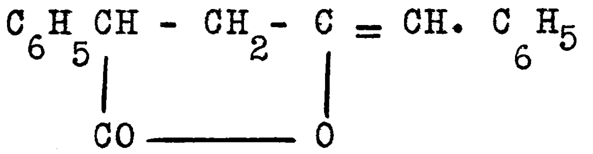
LXVI.

When this γ-ketonic acid was treated with excess acetic anhydride in the presence of a trace of sulphuric acid, an acetate (LXVII) was formed.



$$\underset{\displaystyle COOH}{C_6H_5.\,CH} - CH_2.CO\;CH_2.\,C_6H_5 \longrightarrow C_6H_5.\,\underset{\displaystyle CO\text{———}}{CH} - CH_2.\,\overset{\displaystyle OCOCH_3}{\underset{\displaystyle O}{C}}.\,CH_2.\,C_6H_5$$

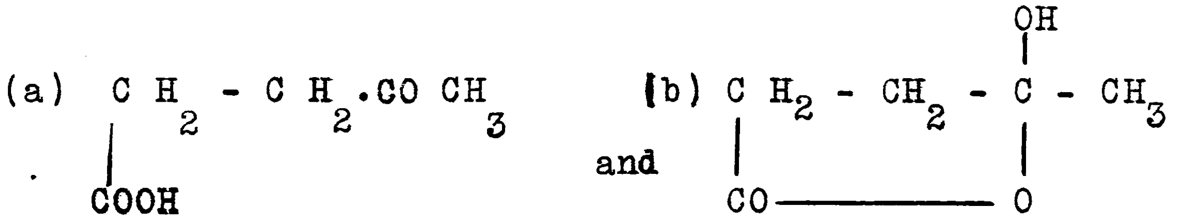
LXVII



$$C_6H_5\underset{\displaystyle CO\text{———}}{CH} - CH_2 - \underset{\displaystyle O}{C} = CH.\,C_6H_5$$

The unsaturated lactone, $C_6H_5CH - CH_2 - C = CH.\,C_6H_5$, was also formed in much smaller quantity.

Some keto and aldehyde acids have the property of reacting in either of two forms (a) as the open chain keto form, (b) as the closed chain hydroxy lactone form. For example, levulinic acid, the simplest γ-ketonic acid, reacts in both forms given below.



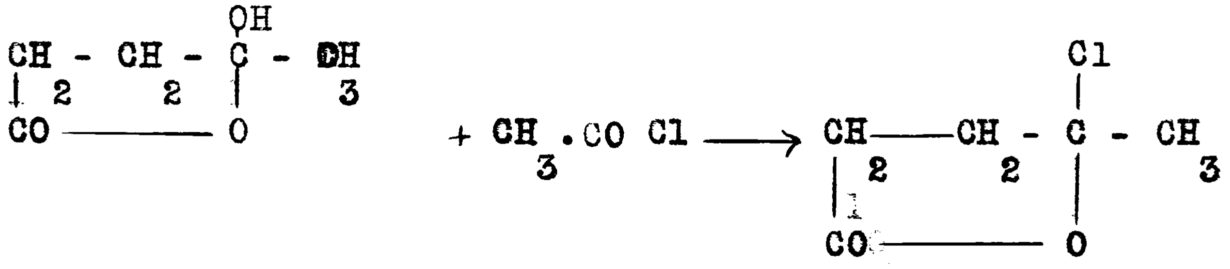
$$\text{(a)}\;\underset{\displaystyle COOH}{CH_2} - CH_2.CO\,CH_3 \quad\text{and}\quad \text{(b)}\;\underset{\displaystyle CO\text{———}}{CH_2} - CH_2 - \overset{\displaystyle OH}{\underset{\displaystyle O}{C}} - CH_3$$

Open chain keto form Hydroxy lactone.

A survey of the compounds showing this behaviour is presented here.

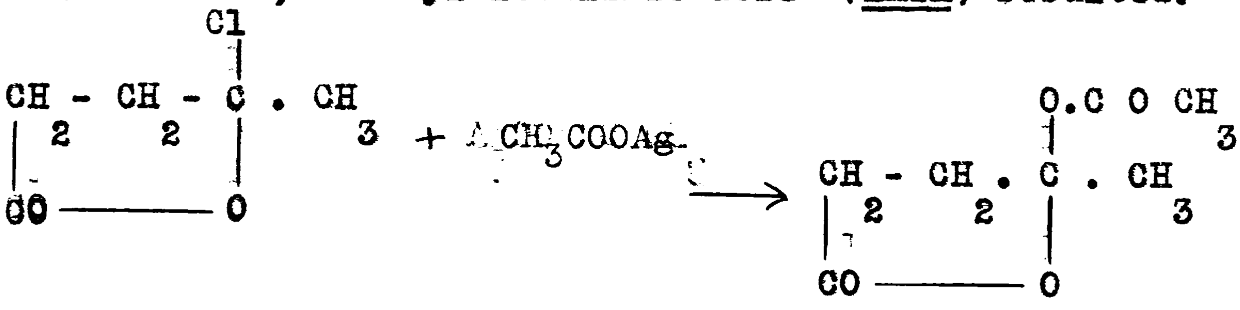
As evidence in favour of the open chain form of levulinic acid E. Fischer (18) prepared a phenyl hydrazone with phenyl hydrazine acetate. Muller (19) formed an oxime with hydroxylamine in sodium carbonate solution. A semi carbazone (20) resulted by the action of semi carbazide in the presence of potassium acetate. The formation of these derivatives was taken to indicate the presence of a free carbonyl group. Conrad (21) obtained the ethyl ester by refluxing levulinic acid in alcohol in the presence of sulphuric acid. A silver salt was obtained by Grote, Kehrer, and Tollens (22), and this on treatment with methyl iodide yeilded the methyl ester.

In favor of the hydroxy lactone form (b), Bredt (23) obtained a chloride (LXV111) when an excess of acetyl chloride reacted with levulinic acid in the cold.



LXV111

When this chloride was treated with silver acetate in absolute ether, "acetyl levulinic acid" (LXIX) resulted.

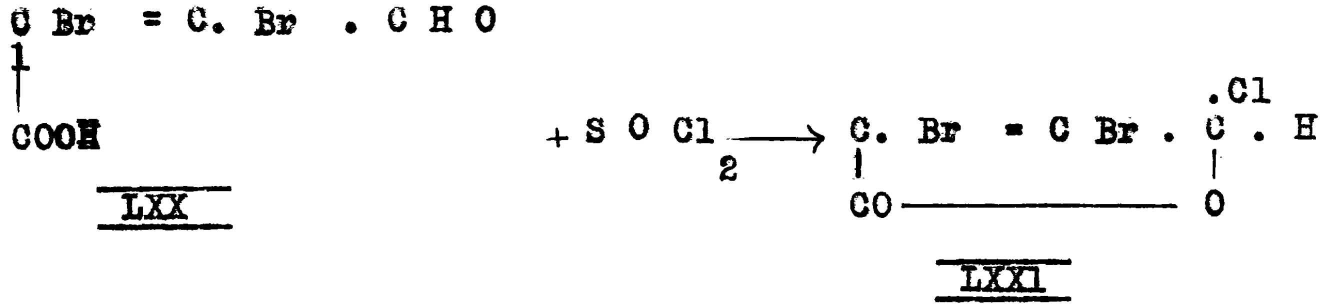


LXIX

On treatment of levulinic acid with acetic anhydride (ibid) at room temperature, the same crystalline acetyl levulinic acid was formed. As mentioned previously, Thiele, Tischbein, and Lossow (loc. cit) later obtained this compound in the same manner.

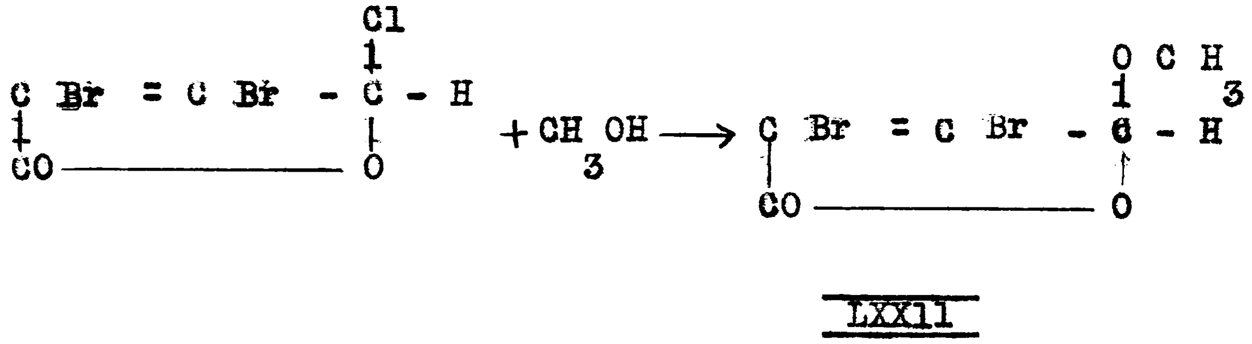
Dibrom mucic acid (LXX) exhibits the same kind of tantomerism.

H. Meyer (24) obtained an oily chloride (LXXl) when this acid was treated with thionyl chloride at 50°.


LXX

LXXl

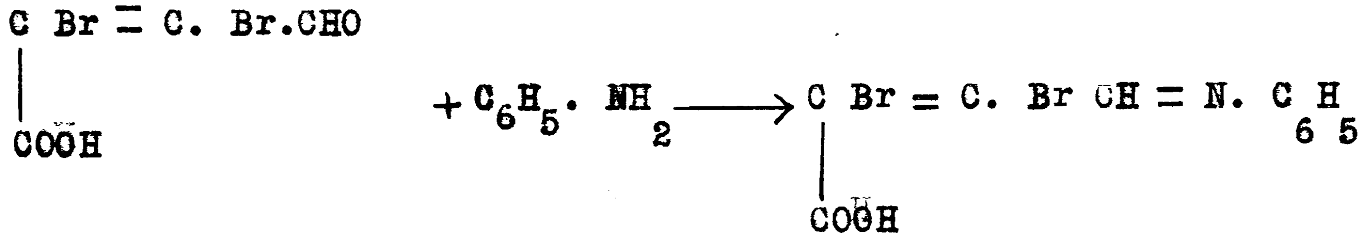
When this chloride (oil) was refluxed for an hour in methyl alcohol, a methyl ether, or pseudo methyl ester (LXXll) resulted.


LXXll

Its structure was proved by a methoxyl determination, and by its failure to form an oxime.

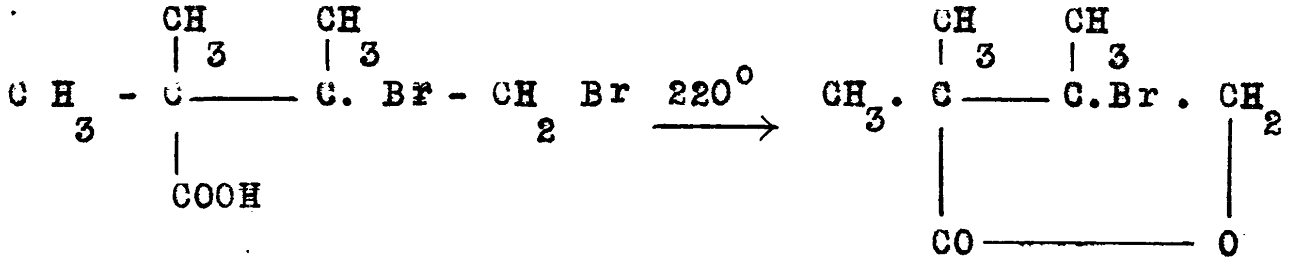
Hill (25a) obtained a bromide by heating the acid with bromine in the presence of water to 150°. On refluxing in ethyl alcohol, the pseudo ethyl ester was obtained.

Hill and Cornelison (25b) later formed an oxime of dibrom mucic acid by refluxing with hydroxylamine in alkaline solution. Simonis (26) proved the presence of the aldehydic function by treatment of the acid with primary amines to form anils. With aniline this acid readily formed anil dibrom mucic acid (LXXIII).

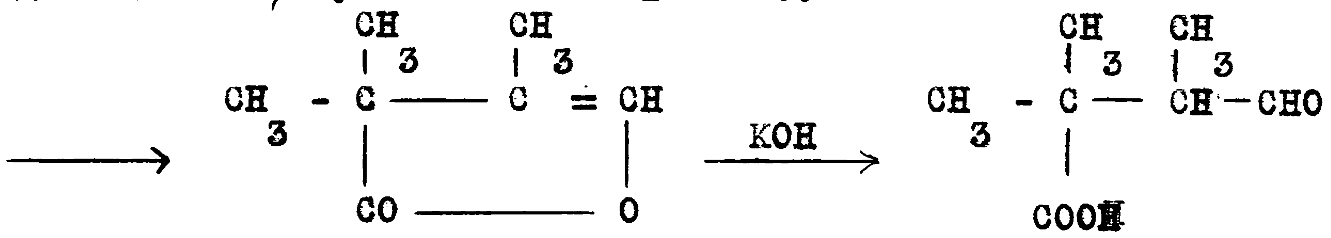


LXXIII

Another γ- aldehydic acid, α,α,β- trimethyl β-formyl propionic acid (LXXIV) was found by Blaise and Courtot (27) to exist in the hydroxy lactone form. This acid was obtained by heating α,α,β-trimethyl -β-γ -dibrom butyric acid to form a β-γ unsaturated lactone (LXXV) which was hydrolysed with alkali to give the desired product.

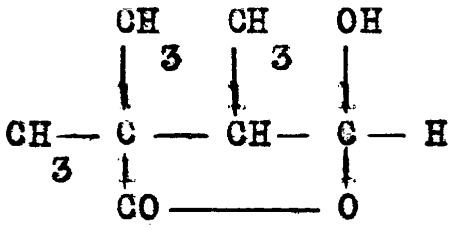


This saturated lactone was heated further with quinoline to form the β- γ unsaturated lactone.

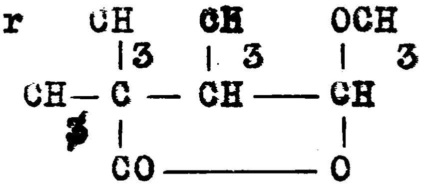


LXXV. LXXIV.

This acid did not dissolve in alkali carbonate solution, nor decolorize Schiff's reagent, thus indicating the absence of a free carboxyl group, and aldehyde function. The presence of a hydroxyl group was proved by the formation of an acetate with acetic anhydride, and of a phenyl urethane with phenylisocyanate. The presence of a lactone chain was indicated by molecular volume measurements. It must then have the closed chain structure.

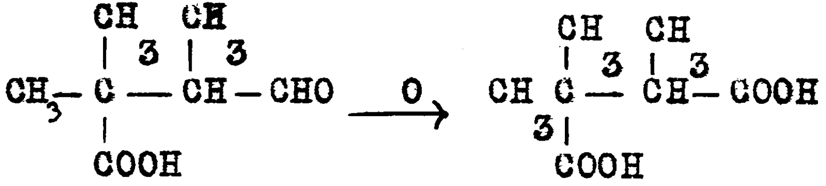


Refluxed in alcohol in the presence of a little sulphuric acid the pseudo ester was formed



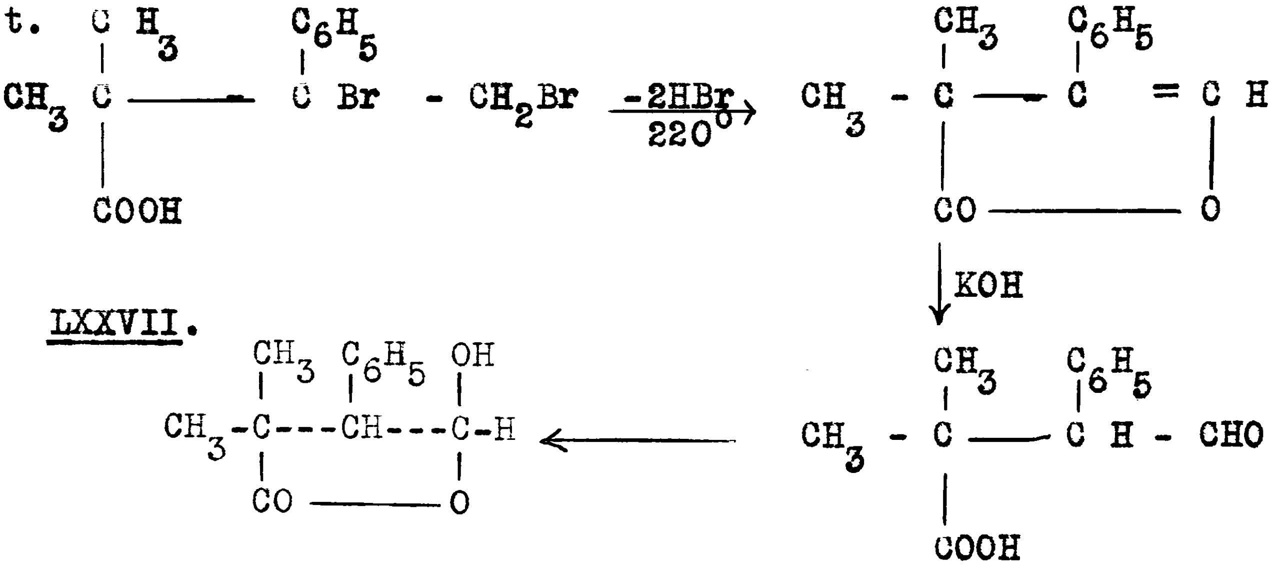
The lactone ring was easily broken however, for the substance formed an oxime, semi carbazone, and phenyl hydrazone, with suitable reagents in alkaline solution.

The structure of the acid was proved by oxidation with chromic acid to form trimethyl succinic acid.



$$CH_3-\underset{COOH}{\overset{CH_3}{C}}-\overset{CH_3}{CH}-CHO \xrightarrow{O} CH_3\underset{COOH}{\overset{CH_3}{C}}-\overset{CH_3}{CH}-COOH$$

The same authors (ibid) found that γ-keto α,α-, dimethyl - β - phenyl butyric acid (LXXVI) had analegous properties. It was obtained by heating α,α - dimethyl β-phenyl, -β-γ-, dibrom butyric acid (LXXVII) with loss of hydrogen bromide to form an α-β unsaturated lactone, which on alkali hydrolysis, gave the desired product.

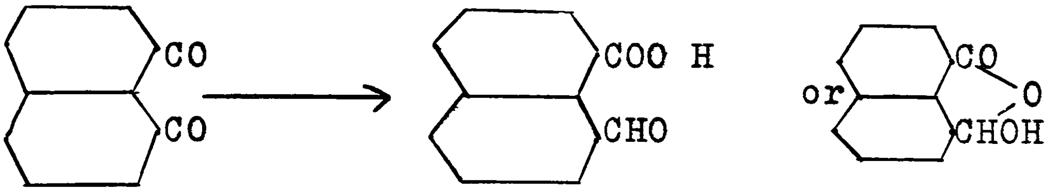


LXXVII.

LXXVI.

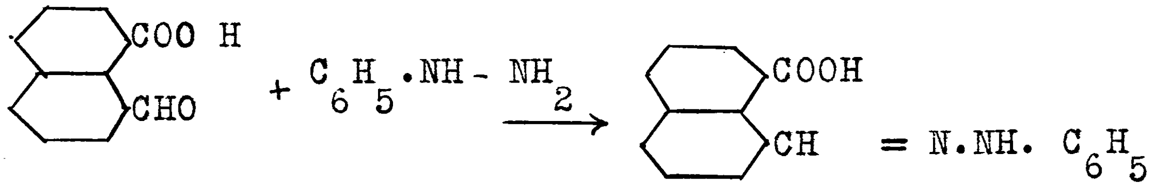
It formed a phenylurethane with phenylisocyanate, and an acetate with acetic anhydride; with hydroxylamine it gave an oxime, and with semi carbazide a semi carbazone. On oxidation with chromic acid, it gave dimethyl phenyl succinic acid.

There is some evidence that naphthaldehydic acid (LXXVIII) exists in the form of the hydroxy lactone. This substance was obtained by Graebe and Gfeller (28) in almost quantitative yield by heating acenaphthequinone to 150° with aq. potassium hydroxide.



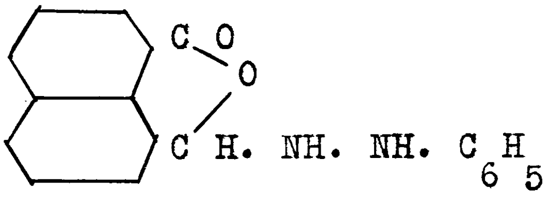
LXXVIII.

Alkali carbonates dissolved this substance in the cold. With one mole of phenyl hydrazine in neutral alcoholic solution, it formed either a hydrazone (LXXIX) or a hydroxynaphthalid (LXXX).



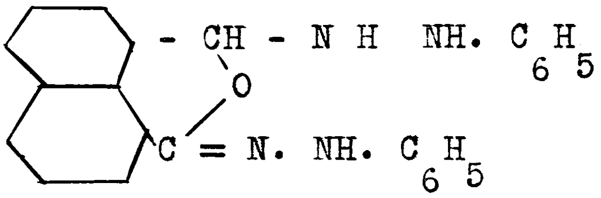
Hydrazone LXXIX

or

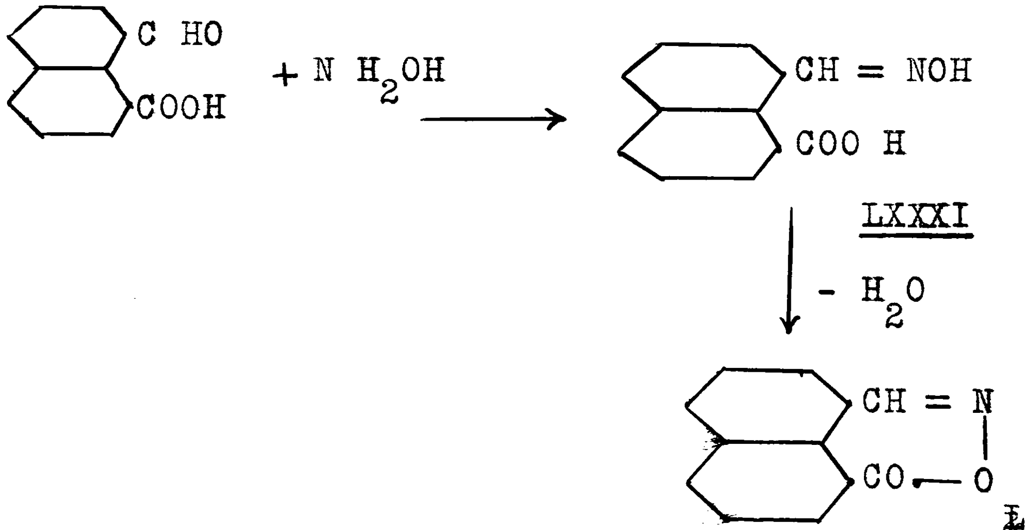


LXXX.

With two moles of phenyl hydrazine, a substance $C_{24}H_{20}ON_4$, was formed, to which the authors gave the structure:



In sodium carbonate solution, naphthaldehydic acid formed an oxime (LXXXI) with one mole of hydroxylamine. This oxime was unstable, and easily lost water to form the anhydride (LXXXII).

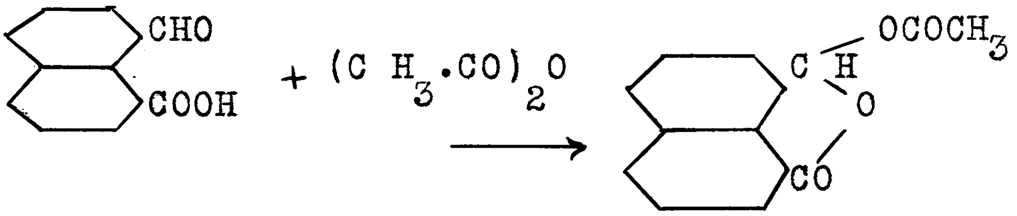


LXXXI

LXXXII

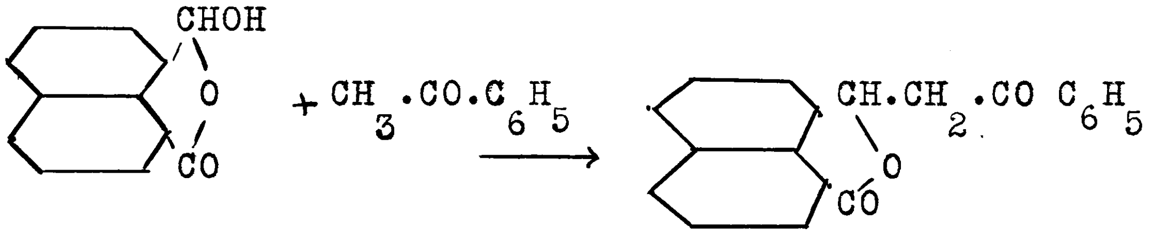
With two equivalents of hydroxylamine, a compound, $C_{12}H_{10}O_3N_2$, of unknown structure, resulted.

Naphthaldehydic acid was heated with acetic anhydride at 180° for three hours to form an acetate (LXXXIII).



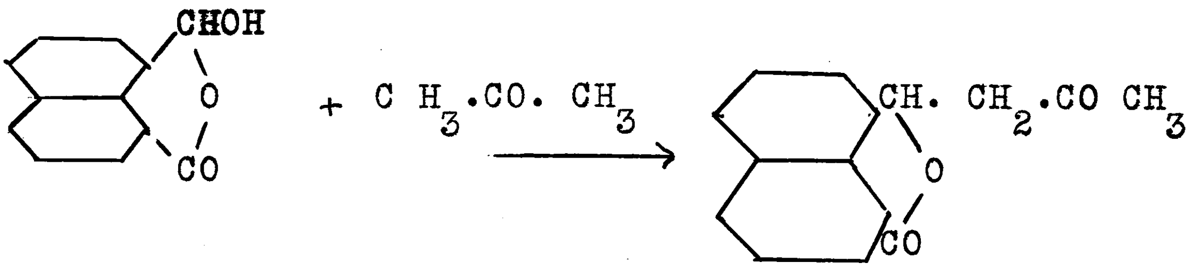
LXXXIII

Zink (29a) condensed naphthaldehydic acid with acetophenone in the presence of sodium hydroxide to obtain naphthalid methyl phenyl ketone (LXXXIV).

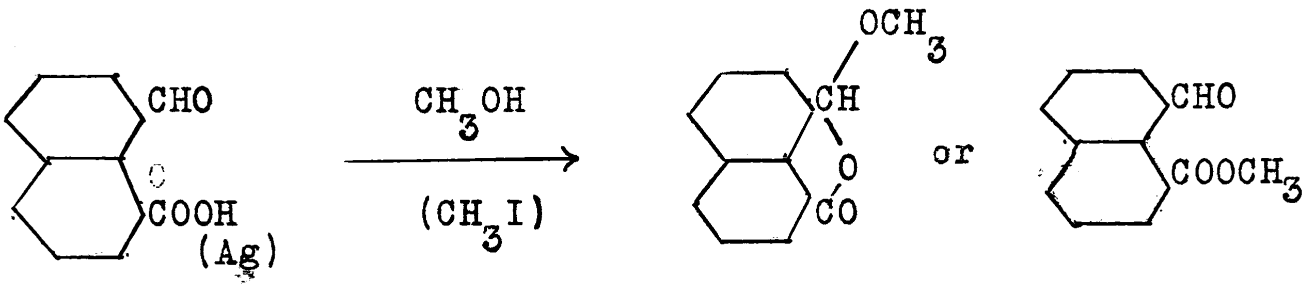


LXXXIV.

With acetone (ibid) an analogous product resulted.



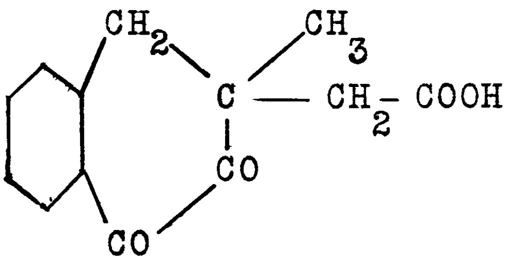
The same author (29b) obtained the same ester by refluxing naphthaldehydic acid in methyl alcohol in the presence of a little sulphuric acid, and by treating the silver salt of the acid with methyl iodide.



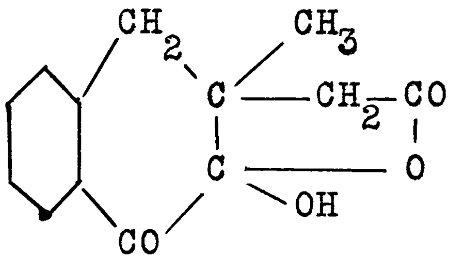
LXXXVI LXXXV.

He was unable to prove whether it was the true ester (LXXXV) or the pseudo ester (LXXXVI).

Kon, Stevenson, and Thorpe (30) have found a further example of this kind of tautomerism in the substance whose structure is represented below.



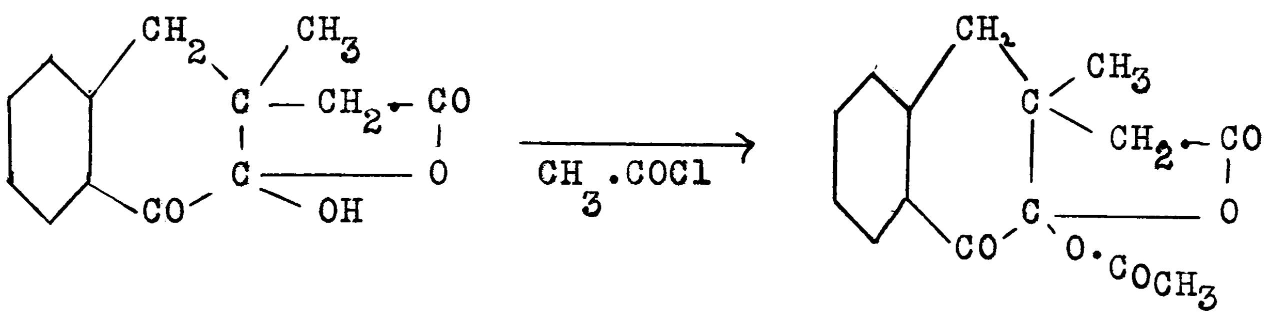
(a)



(b)

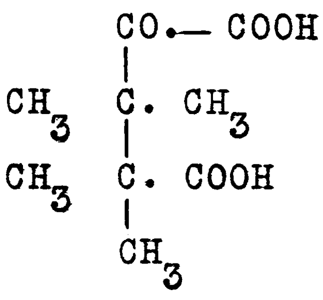
Structure (a) was proved by the formation of a quinoxaline when treated with O. phenylene diamine, which is the normal behaviour of a 1:2 diketone.

When refluxed with acetyl chloride, anacetate (LXXXVII) resulted, proving the presence of (b).

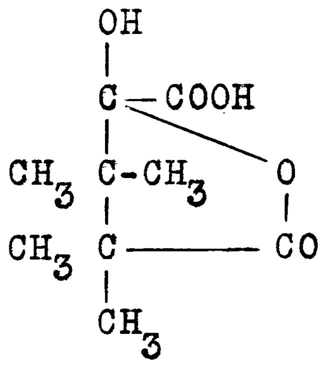


LXXXVII.

Rothstein and Shoppe (31) have investigated α-keto-$\beta,\beta,\gamma,\gamma$-tetramethyl glutaric acid, and found evidence of the two tantomeric forms:



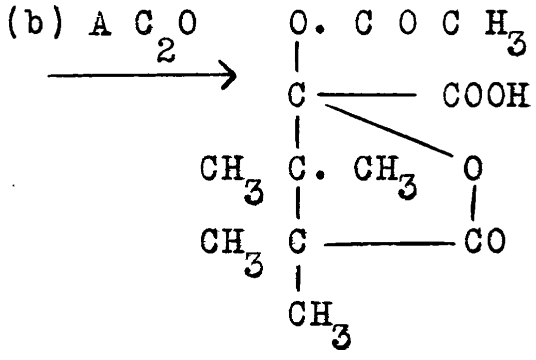
(a)



(b)

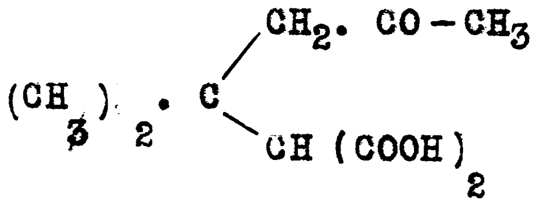
When titrated with baryta solution, this acid behaved as the monobasic compound (b); when boiled with N/10 baryta solution however, the lactone ring opened to form (a) to the extent of 95%, as indicated by titration.

On refluxing in acetic anhydride for an hour, an acetate (LXXXVIII) of (b) was formed.

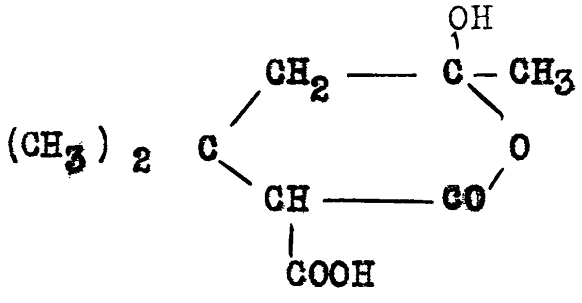


LXXXVIII.

Qudrat-i-Khuda (32a) states on rather unsatisfactory evidence, that α-carboxy-γ-acetyl-β,β-dimethyl butyric acid (LXXXIX) exists under some conditions in the hydroxy lactone form (XC)

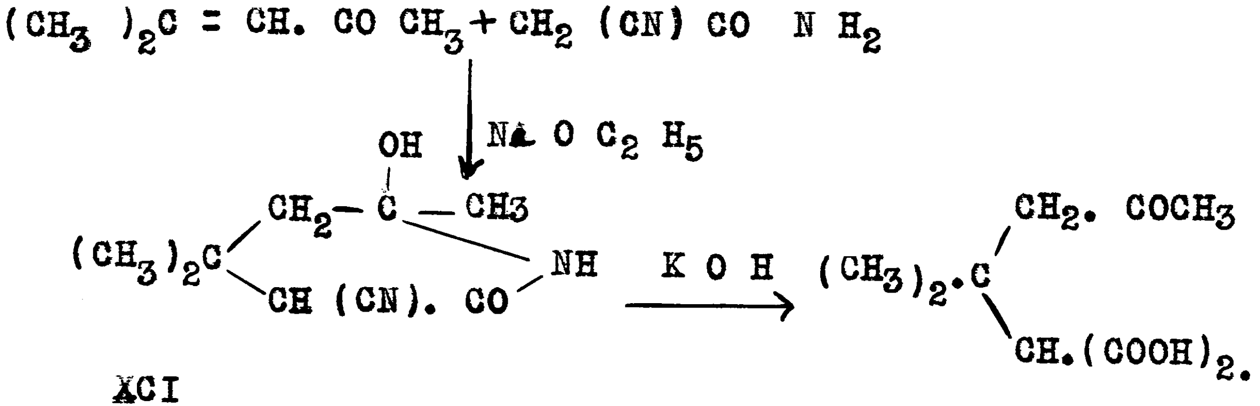


LXXXIX



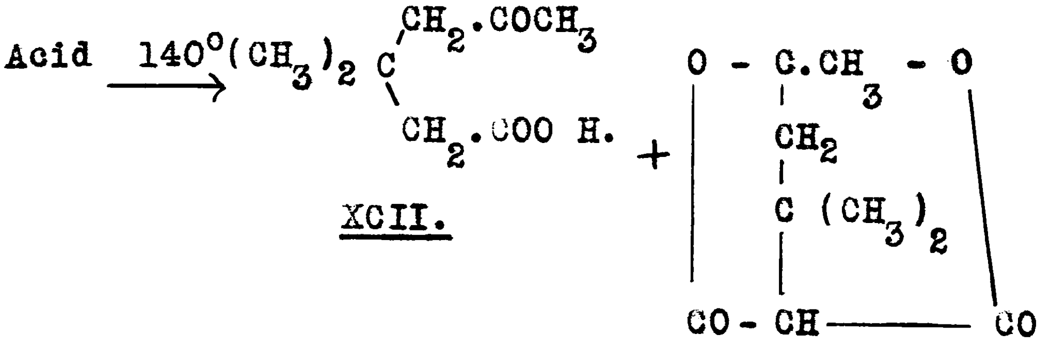
(XC)

This acid was prepared by the condensation of mesityl oxide with cyanacetamide in the presence of sodium ethylate. The resulting 6- hydroxy -2- keto -3- cyano 4,4,6, trimethyl piperidine (XCI) was hydrolysed with potassium hydroxide to the desired acid.



XCI

On heating this acid to 140°, a monobasic acid (XCII), and a neutral substance to which the dilactone structure (XCIII) was ascribed, were formed.

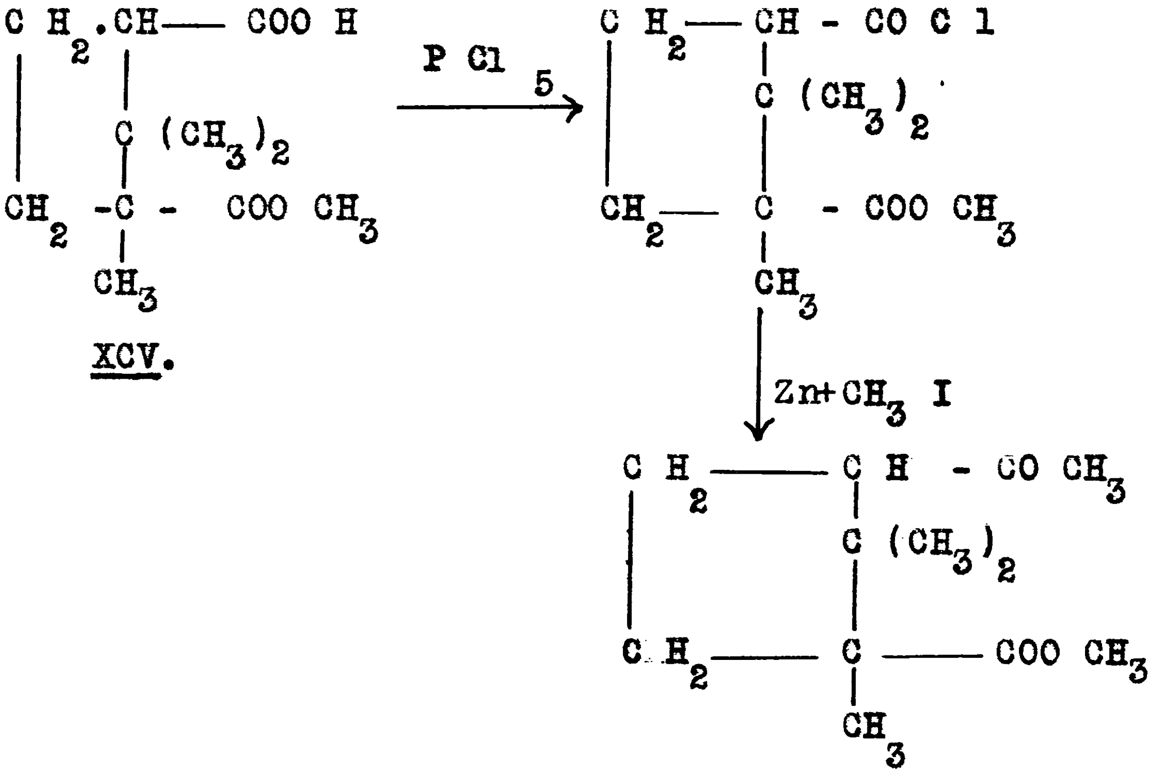


XCII.

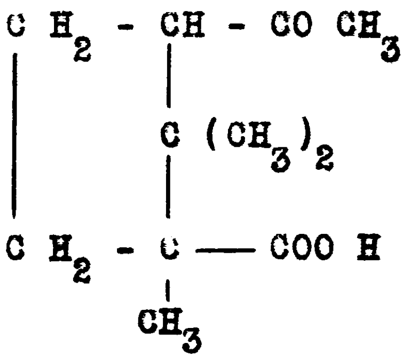
XCIII.

The monobasic acid was assumed to be derived from the open chainform, while the dilactone was a derivative from the hydroxy lactone structure.

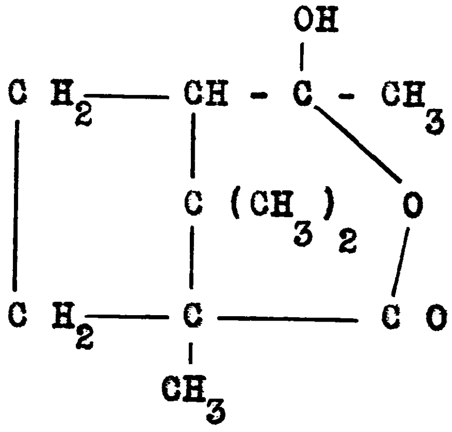
The same author, (32b) obtained both the keto and hydroxy lactone forms of 5 - acetyl - 1,1,2,- trimethyl cyclopentane 2- carboxylic acid (XCIV). This acid was prepared from allo-methyl hydrogen camphorate (XCV) as indicated below.



This ester on hydrolysis with alcoholic potassium hydroxide formed the desired acid which exists in the two forms.

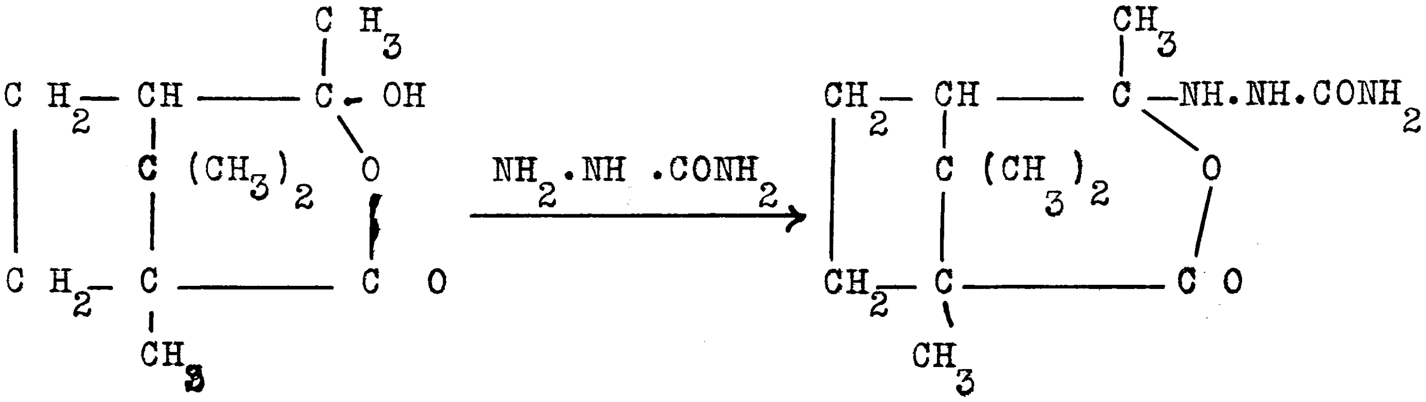


XCIV.



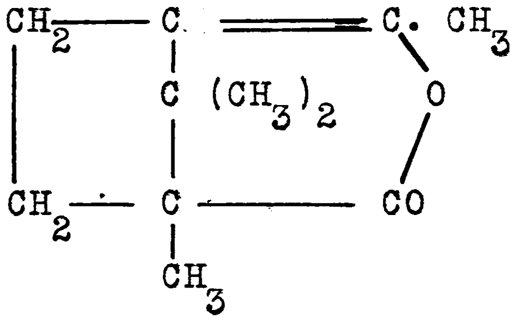
XCVI.

(XCIV) was a crystalline solid which easily formed a semi carbazone: (XCVI) was an oil which with semi carbazide formed an isomeric substance of indefinite crystalline structure, which the authors represented as (XCVII).



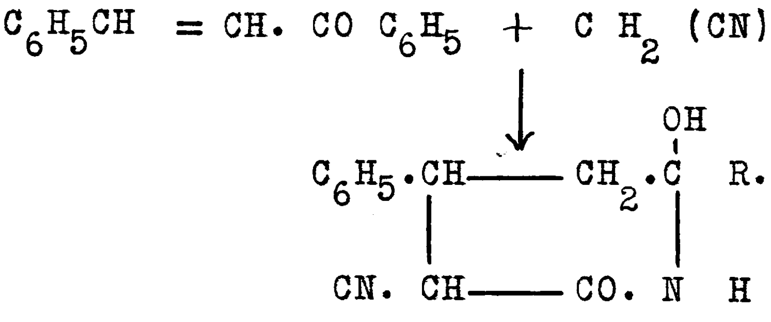
XCVII.

Both the keto and hydroxy lactone substances on treatment with acetic anhydride, formed the unsaturated lactone (XCVIII).



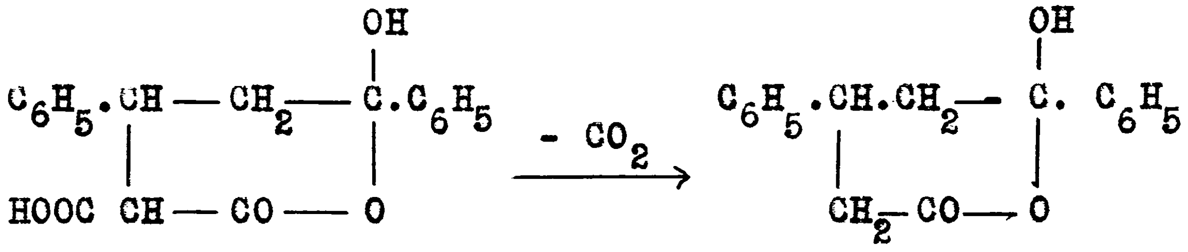
XCVIII.

Barat (33) obtained a substance (XCIX) to which he assigned a hydroxy lactone structure, by the hydrolysis of the condensation product (C) of benzal acetophenone with cyanacetamide.



C.

On hydrolysis with hydrochloric acid, the substance (XCIX) resulted.



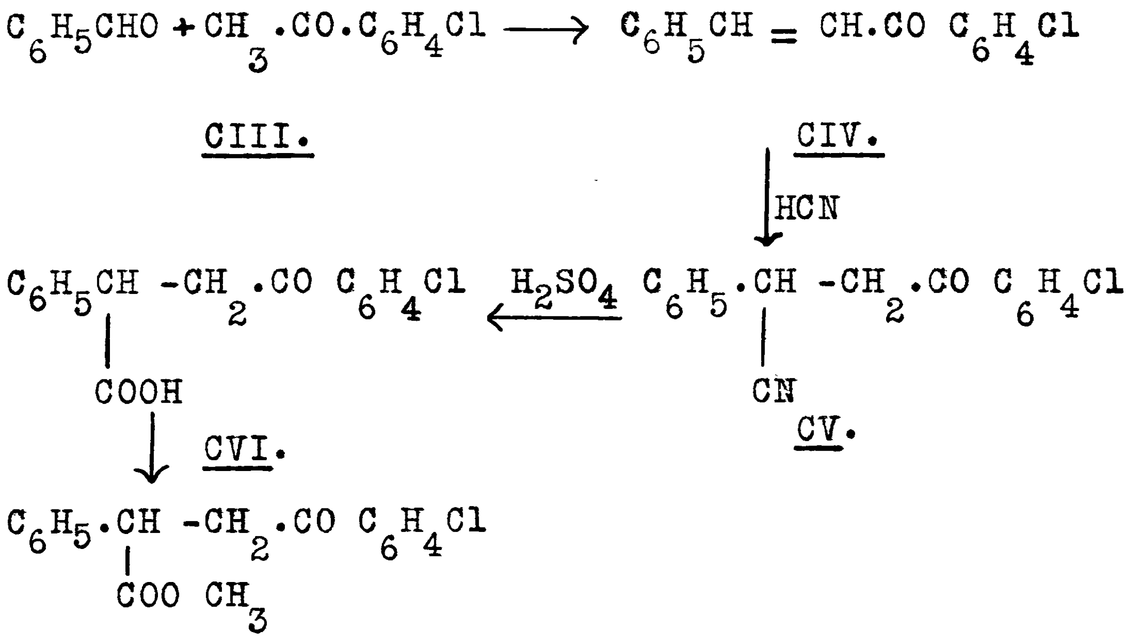
XCIX. **CI.**

This acid on heating lost carbon dioxide to form a monobasic acid to which Barat also assigned the hydroxy lactone structure (CI), because of its insolubility in sodium carbonate solution. It formed an oxime, and behaved as a monobasic acid on titration, so that the author concluded that the open chain keto form was in equilibrium with the cyclic lactol (hydroxy lactone).

AN OUTLINE OF THE WORK

Since our problem was concerned with a substance having three phenyl groups, it was felt advisable to "tag" them so that they could be followed through in degradation reactions, used to prove structure. Accordingly, the work was started with methyl α-phenyl -β- [p-chlorbenzoyl] propionate (CII) and most of the reactions were determined with substances derived from this. The aldehyde group introduced was "tagged" when necessary by a methylene dioxy group (use of piperonal). In all, six homologous lactols have been studied.

Methyl α-phenyl -β- [p- chlorbenzoyl] propionate (CII) was readily prepared by the following series of reactions. Benzaldehyde and p-chloracetophenone (CIII) were condensed in alkaline solution to form benzal p- chloracetophenone (CIV); to this hydrogen cyanide was added to form α-phenyl -β- [p- chlorbenzoyl] propionitrile (CV); on hydrolysis with sulphuric acid, α-phenyl -β-[p-chlorbenzoyl] propionic acid (CVI) resulted, which on esterification in methyl alcohol yielded the required ester.



$$C_6H_5CHO + \underset{\text{CIII.}}{CH_3.CO.C_6H_4Cl} \longrightarrow \underset{\text{CIV.}}{C_6H_5CH = CH.CO\ C_6H_4Cl}$$

$$\downarrow HCN$$

$$\underset{COOH}{C_6H_5CH} -CH_2.CO\ C_6H_4Cl \xleftarrow{H_2SO_4} C_6H_5.\underset{CN}{CH} -CH_2.CO\ C_6H_4Cl$$

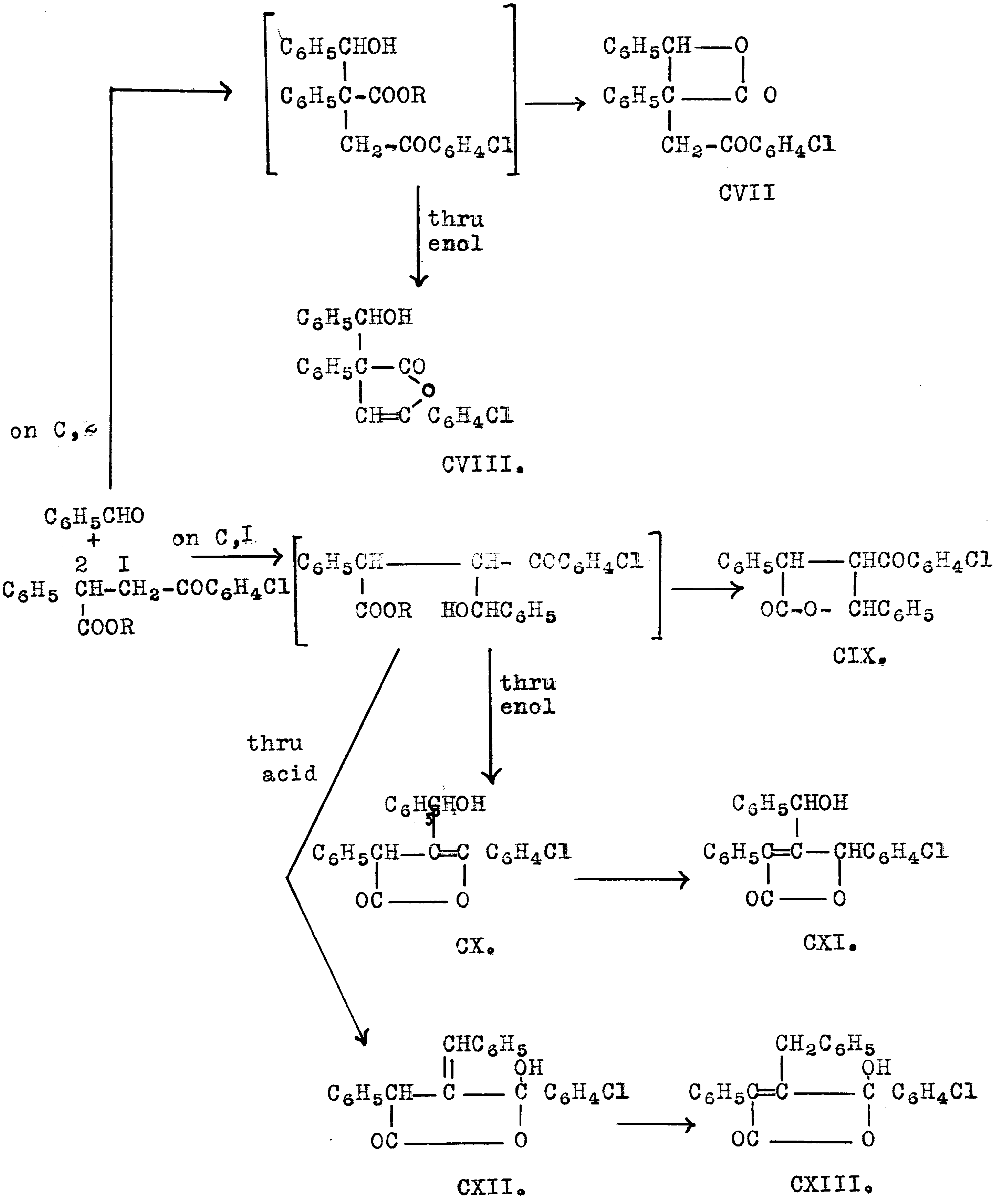
CVI. CV.

$$\downarrow$$

$$C_6H_5.\underset{COO\ CH_3}{CH} -CH_2.CO\ C_6H_4Cl$$

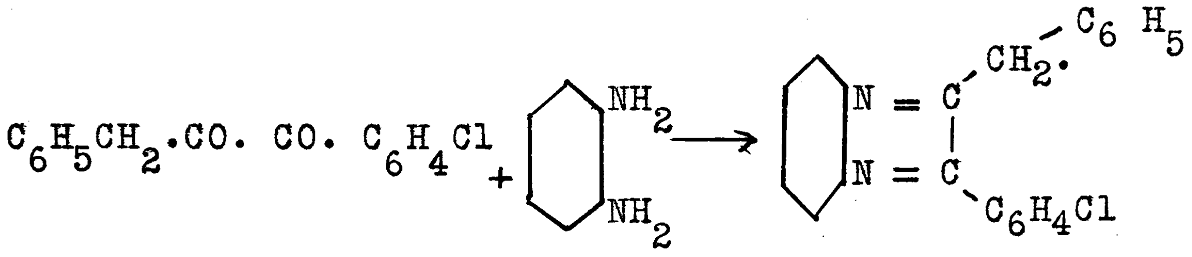
CII.

This ester readily condenses with benzaldehyde in absolute methyl alcohol in the presence of sodium methylate, to form a crystalline substance of empirical formula $C_{23}H_{17}O_3Cl$. Since it is insoluble in sodium bicarbonate solution, but dissolves readily in caustic alkali solution, a lactone structure is indicated; this is confirmed by the fact that the ester group disappears in the reaction, because the methyl and ethyl esters yield the same product. Seven possible formulas (CVII - CXIII) may then be considered.


on C,6
thru enol
on C,I
thru enol
thru acid
CVII
CVIII.
CIX.
CX.
CXI.
CXII.
CXIII.

Structure (CVII) is a β- lactone and should therefore readily lose carbon dioxide on pyrolysis. No evolution of carbon dioxide occurs on heating our substance, so that (CVII) is eliminated. The substance readily decolorizes permanganate solution in the cold, indicating unsaturation; this excludes (CIX). It is not affected by ozone, making (CXII) very improbable, since all known benzal derivatives yield benzaldehyde as one product on ozonization. In the Grignard "machine" the substance shows the presence of one active hydrogen, and adds two methyl groups. The acceptance of any one of the structures (CVIII, CX, or CXI) involves proof of the presence of a secondary hydroxyl group. But attempts to prepare derivatives with phenyl isocyanate, benzoyl chloride, p-nitrobenzoyl chloride, and 3:5 dinitrobenzoyl chloride, were all unsuccessful, and in each case the product was recovered unchanged. These structures are then improbable.

Oxidation reactions have proved the most useful in ascertaining the structure of our compound. With potassium permanganate the only products isolated were benzoic and p-chlorbenzoic acids, even on keeping the conditions as mild as possible. Chromic acid oxidation was more successful, and the principal product was found to be benzyl p- chlorphenyl diketone (CXIV), which with o- phenylene diamine forms 2-benzyl -3- p-chlorphenyl quinoxaline (CXV), and agrees in all its properties with the known compound (34)



CXIV.

CXV.

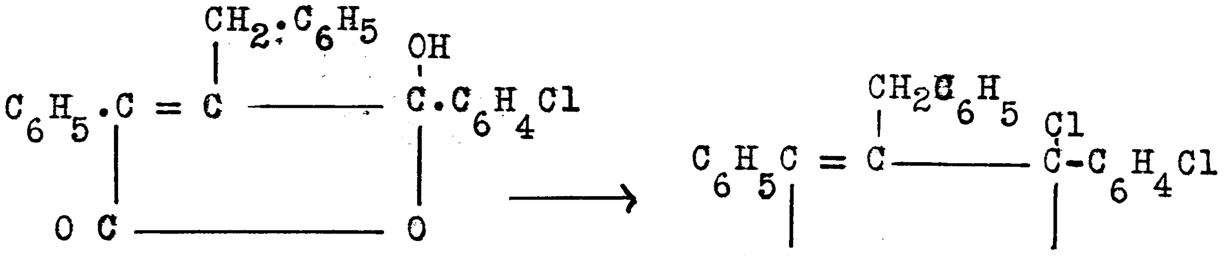
To distinguish between the two unsubstituted phenyl groups present in our substance, it was necessary to "tag" one of these; this was done by condensing the methyl ester with piperonal to obtain an analagous lactone. When oxidized with chromic acid in the same manner, piperonyl - p- chlorphenyl diketone (CXVI) was obtained.

$$C_2H_2O_2.C_6H_3.CH_2.CO.\ CO.\ C_6H_4Cl$$

CXVI.

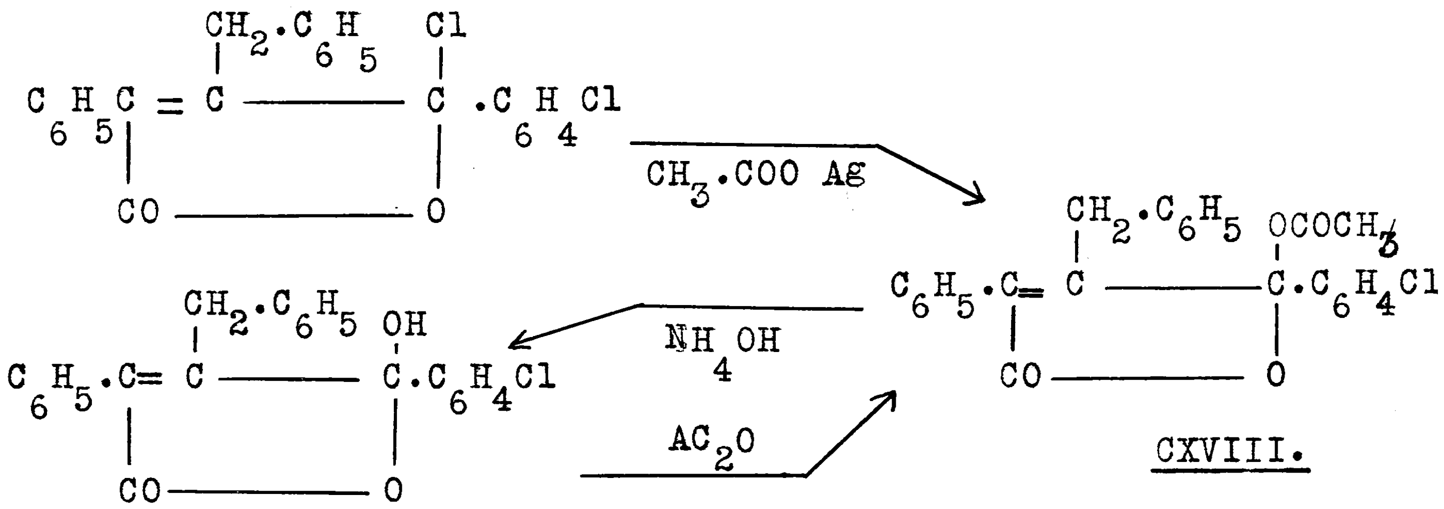
It is thus proved that the phenyl group in our substance appearing in the diketone was the one contributed by benzaldehyde.

Structure (CXIII) is the only one that agrees with these facts; therefore it is necessary to prove the presence of a tertiary hydroxyl group; this was done by reactions with acetyl and thionyl chlorides to obtain the crystalline chloride (CXVII).



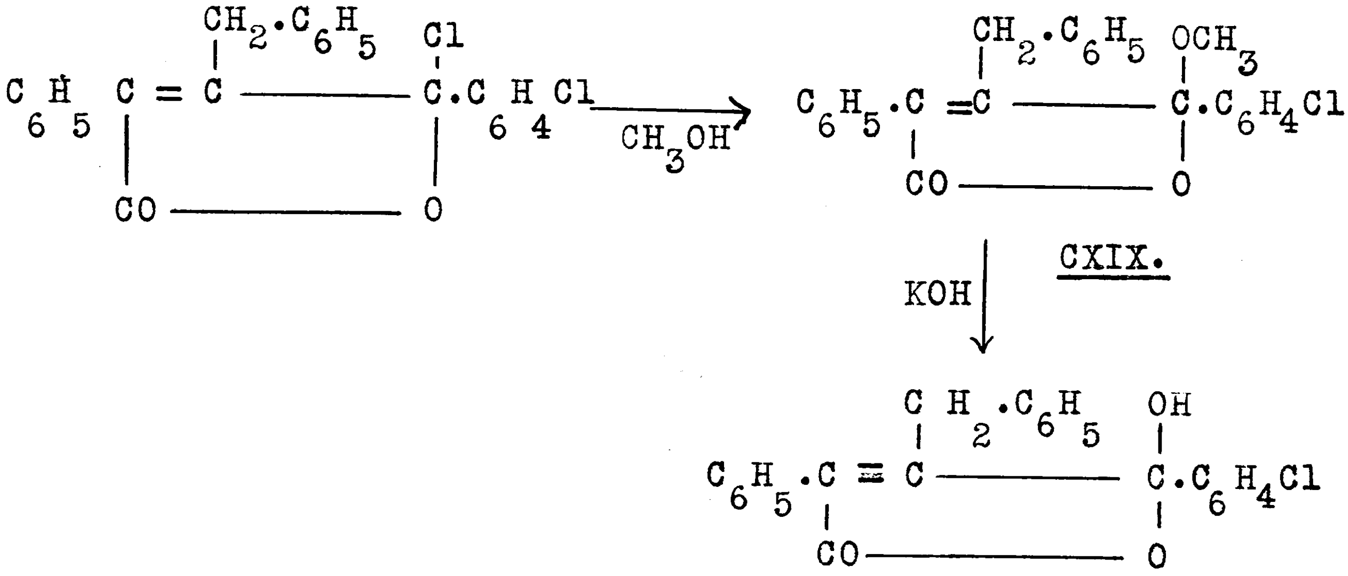
CXVII.

The chloride reacts with silver acetate in absolute ether to form an acetate (CXVIII) . With acetic anhydride in the presence of a little sulphuric acid, the lactol forms the same acetate. It is hydrolysed by alcoholic ammonia to the original lactol.



CXVIII.

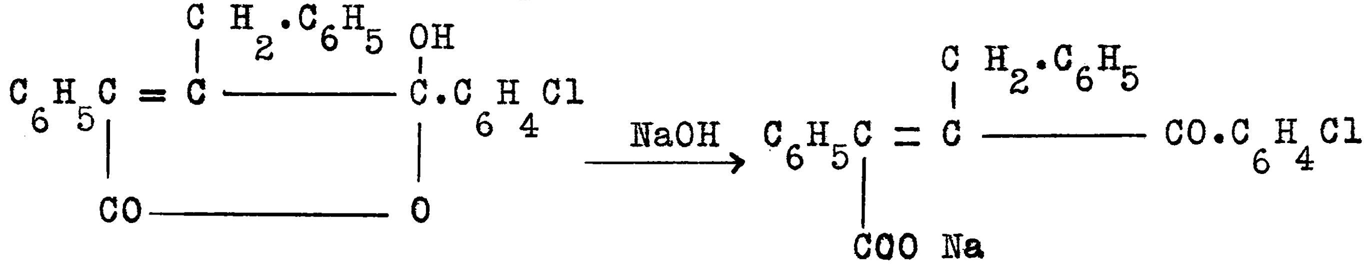
On refluxing the chloride in methyl alcohol it forms the methyl ether (CXIX); the latter is unaffected by alcoholic ammonia, but is hydrolysed by alcoholic potassium hydroxide to the lactol.



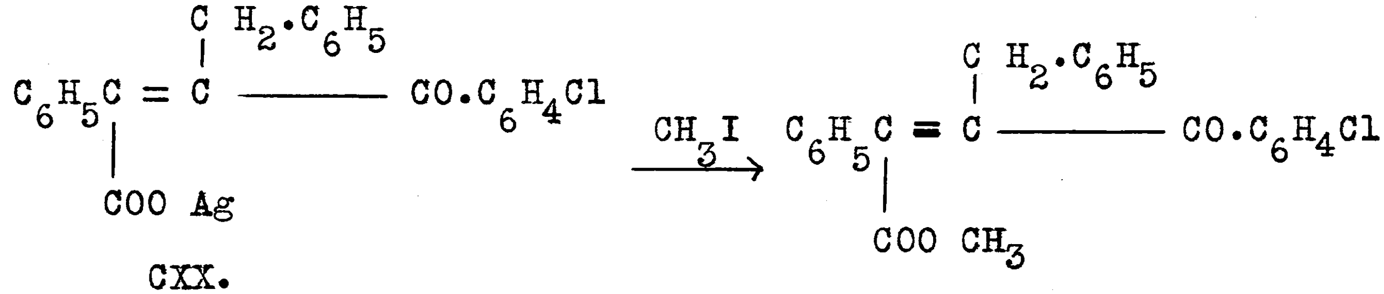
CXIX.

This behaviour is analogous to that of triphenyl chlor methane.

When lactols dissolve in alkalies, they form the sodium salts of the tautomeric open chain acid.



When silver nitrate is added to such a solution, the silver salt (CXX) precipitates. On refluxing the latter with excess methyl iodide in absolute ether, the open chain ester (CXXI) is formed.



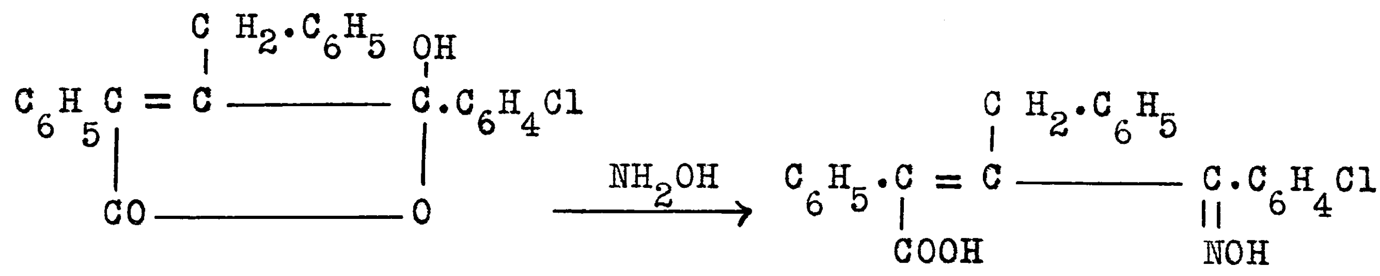
$$C_6H_5C(COO\,Ag)=C(CH_2.C_6H_5)-CO.C_6H_4Cl \xrightarrow{CH_3I} C_6H_5C(COO\,CH_3)=C(CH_2.C_6H_5)-CO.C_6H_4Cl$$

CXX.

CXXI.

This open chain ester is a perfectly stable crystalline compound. On hydrolysing with alcoholic potassium hydroxide and acidifying, the lactol is formed.

On refluxing the lactol with excess hydroxylamine in acid alcoholic solution the oxime (CXXII) results.

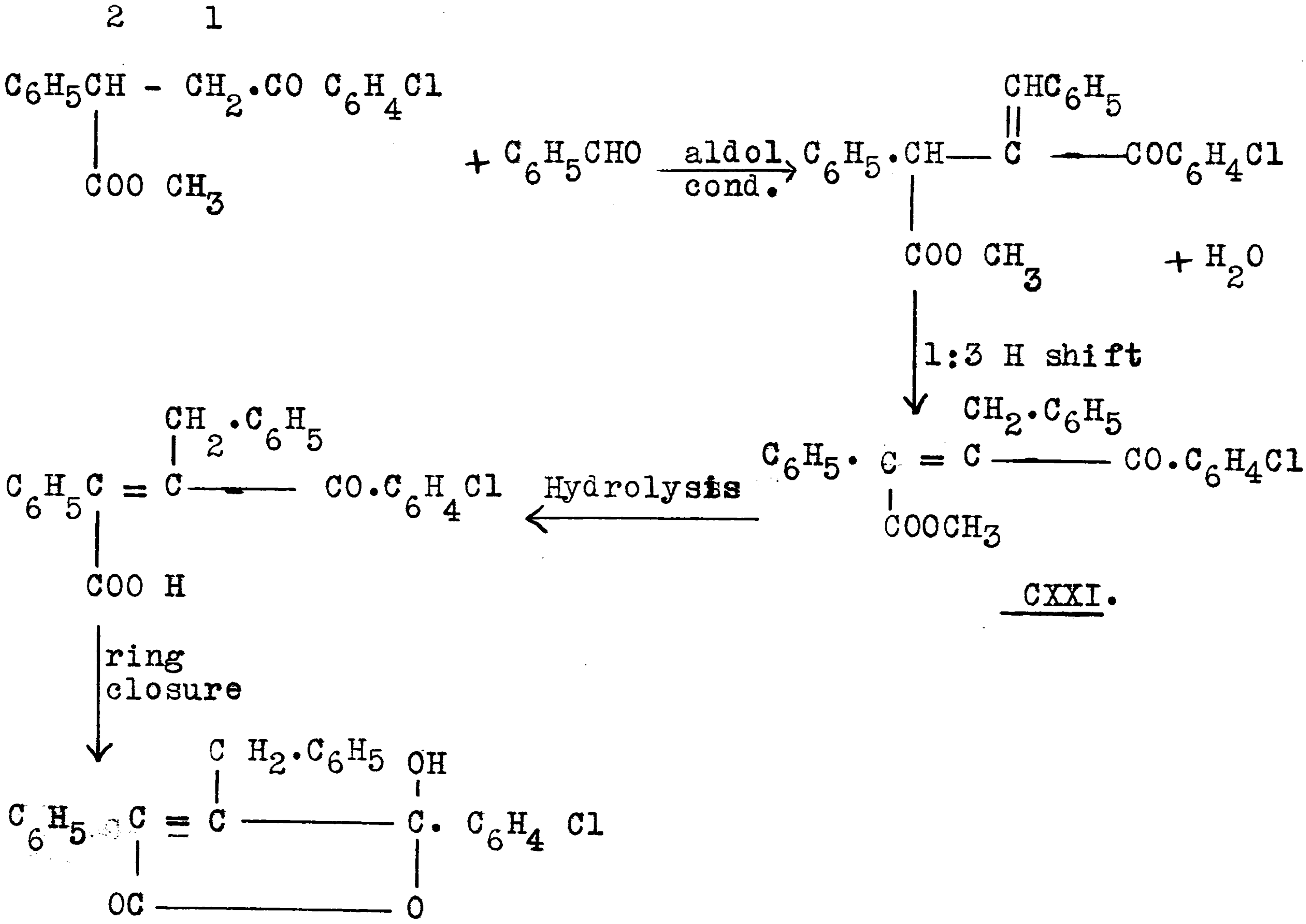


CXXII.

All this evidence, taken as a whole, excludes all structures except that of the lactol, (CXIII).

This is not an isolated example, since so far six lactols have been prepared and described in this dissertation all of which give the same types of reactions; also homologues have been made by other investigators in this laboratory.

The steps in the mechanism of this reaction are probably as follows: (a) an aldol condensation to form a benzal derivative with loss of water, combination taking place on carbon atom (1); (b) a 1:3 shift of hydrogen; (c) hydrolysis of the ester to the acid; (d) ring closure on acidification.

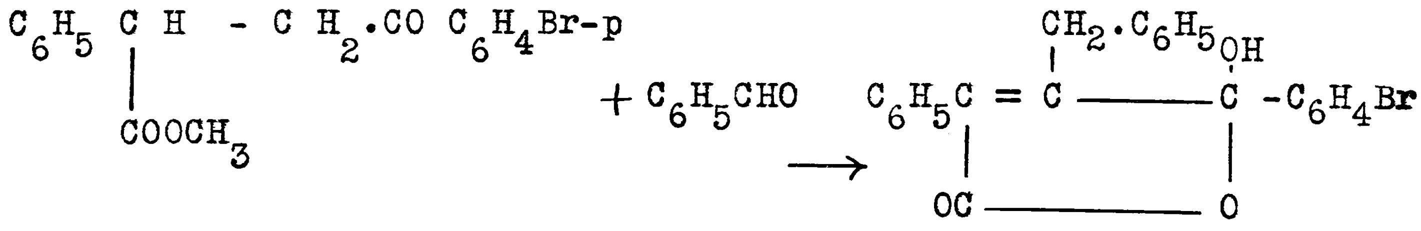


CXXI.

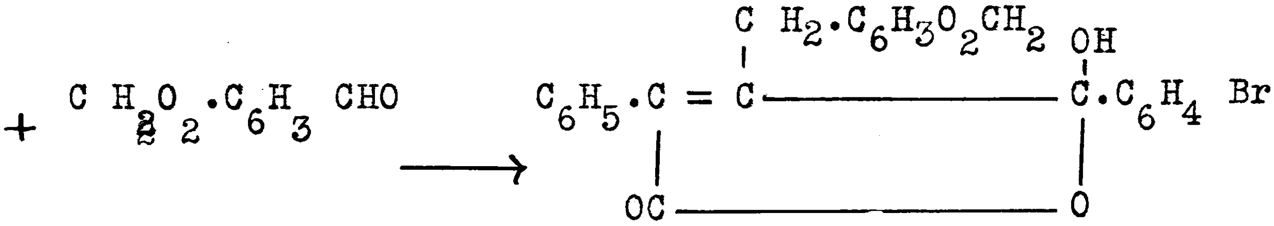
It is not possible to state whether (b) or (c) takes place first. Hoping to determine whether or not the open chain ester (CXXI) was formed as an intermediate product in the condensation, the reaction was carried out in alcohol that had been very carefully dried over magnesium methylate; the same lactol resulted. It seems extremely probable therefore, that the water liberated in reaction (a), in the strongly alkaline solution, hydrolyses the ester to the acid. The condensation could not be brought about by the use of piperidine or diethylamine.

The 1:3 shift of hydrogen (b) has been shown to take place in the rearrangements of certain β-γ to α-β unsaturated lactones under the influence of bases, as reported by Thiele and his co-workers (loc. cit.)

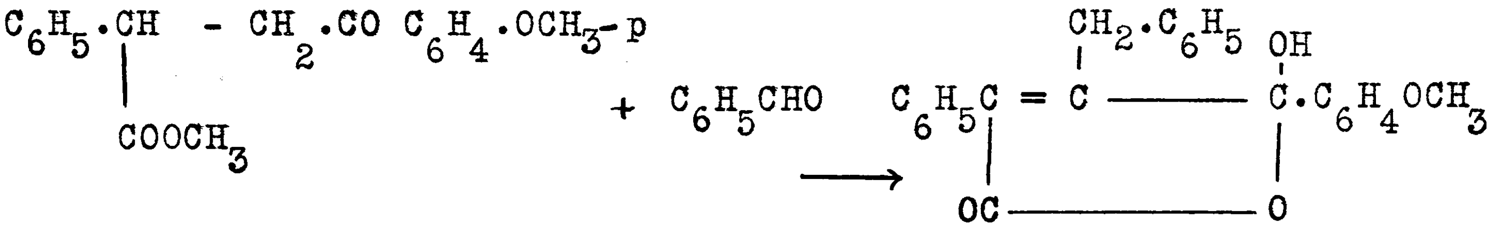
Four other homologous lactols have been prepared and studied: (CXXIII) from methyl α-phenyl - [β- p-brombenzoyl] propionate and benzaldehyde; (CXXIV) from the same ester and piperonal; (CXXV) from methyl α-phenyl - β- anisoyl propionate and benzaldehyde; (CXXVI), from this ester and piperonal.



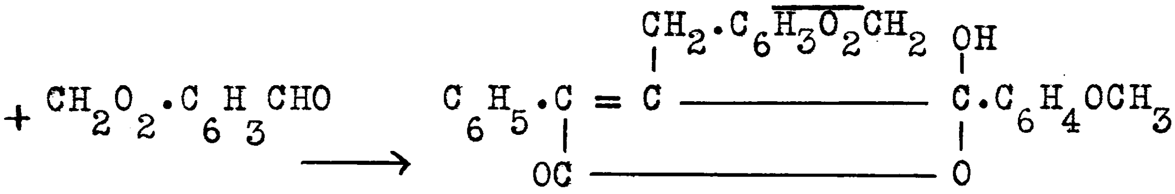
CXXIII.



CXXIV.



CXXV.

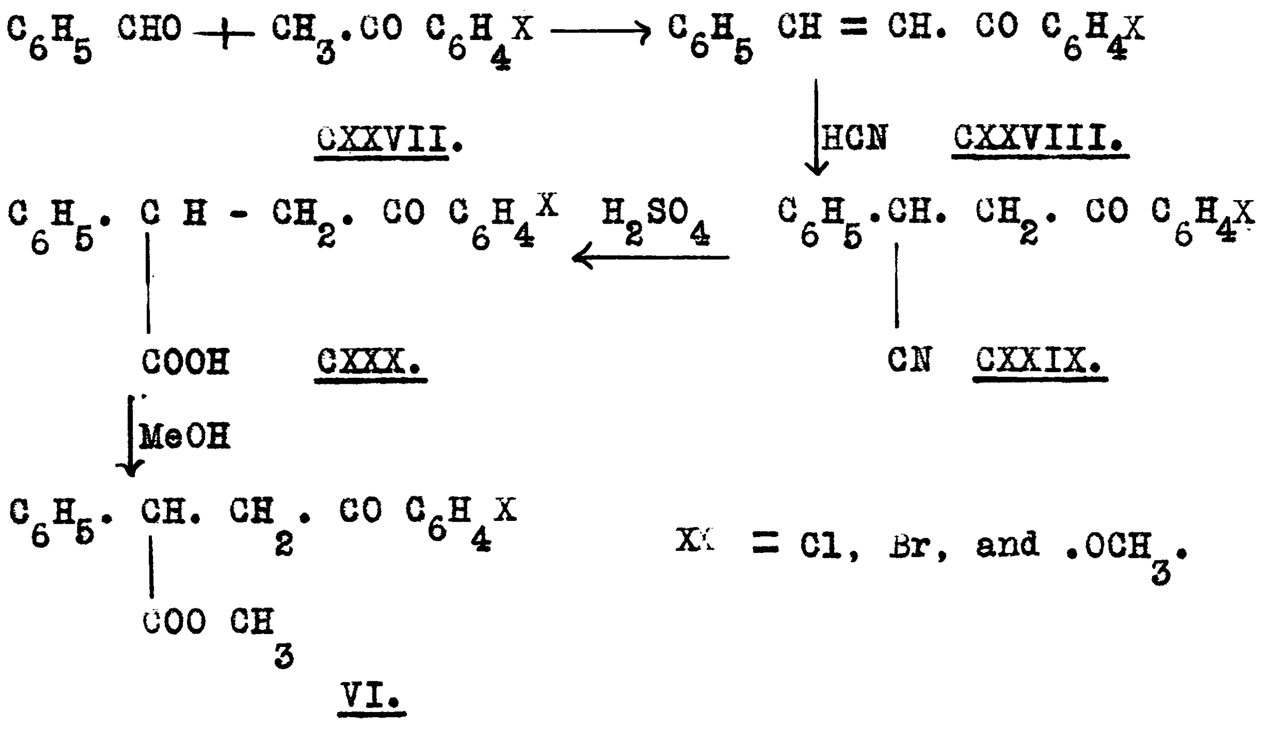


CXXVI.

EXPERIMENTAL

A. Preparation of Starting Materials

The γ- ketonic esters required for this work were prepared by the following series of reactions. A suitably substituted acetophenone (CXXVII) was condensed with benzaldehyde in alkaline solution to form a benzal acetophenone (CXXVIII); to this hydrogen cyanide was added, to form a phenyl benzoyl propionitrile (CXXIX); on hydrolysis with sulphuric acid, the corresponding phenyl benzoyl propionic acid (CXXX) resulted, which on esterification in methyl alcohol, yielded the required ester, methyl phenyl benzoyl propionate (VI).



$$C_6H_5\,CHO + CH_3.CO\,C_6H_4X \longrightarrow C_6H_5\,CH = CH.\,CO\,C_6H_4X$$

CXXVII. CXXVIII.

$$\xrightarrow{HCN} C_6H_5.\underset{\displaystyle CN}{CH}.\,CH_2.\,CO\,C_6H_4X \quad \text{CXXIX.}$$

$$\xrightarrow{H_2SO_4} C_6H_5.\underset{\displaystyle COOH}{CH}-CH_2.\,CO\,C_6H_4X \quad \text{CXXX.}$$

$$\xrightarrow{MeOH} C_6H_5.\underset{\displaystyle COO\,CH_3}{CH}.\,CH_2.\,CO\,C_6H_4X$$

VI.

$X = Cl$, Br, and $.OCH_3$.

1. Unsaturated Ketones.

(a) Benzal p. chloracetophenone. (CXXVIII, X = Cl).

To 173 g. of benzaldehyde in a 1-l. flask, was added 183 g. of p. chloracetophenone. An equal volume, 360 c.c., of ethyl alcohol (95%) was added, and then 78 c.c. of a 10% solution of sodium hydroxide. The reaction started almost immediately, and the flask was cooled under the tap. In a few minutes the contents of the flask went semi-solid, and a little more alcohol was added. Intermittent shaking was continued for one and one-half hours. The substance was filtered, washed first with dilute alcohol, and then with water until free from alkali. It melted at 96°. The yield of air dried product was 267 g., which is 93.0% of the theoretical.

Benzal p- bromacetophenone (CXXVIII, X = Br) and benzal p - methoxy acetophenone (CXXVIII, X = - OCH_3) were obtained through the courtesy of Dr. W.E. Barker.

2. Nitriles.

(a) α- Phenyl - β - [p- chlorbenzoyl] Propionitrile (CXXIX, X = Cl).

The method described below is that of Kohler and Shohan (35).

In a three neck flask provided with a stirrer, thermometer, and a dropping funnel, were placed 200 g. of benzal p - chloracetophenone and 2845 c.c. of ethyl alcohol (95%) to which 87 g. of glacial acetic acid had been added. The contents were warmed to 35° with constant stirring, and a solution of 128 g. of potassium cyanide in 354 c.c. of water was added over a period of fifteen minutes. The temperature was kept at 35° with continual stirring for eight hours.

After standing some hours in an ice-box the nitrile separated. It was filtered, washed with a small volume of 50% alcohol, and with water until free from cyanide. It melted at 121°. The yield of air-dried product was 193 g. which is 86.9% of the theoretical.

In this preparation it was found essential to have the acidity indicated. In three attempted preparations, hydrogen cyanide failed to add, because the alcohol used was that recovered from previous H C N additions and which consequently contained a considerable quantity of hydrocyanic acid.

(b) α-Phenyl -β- [p- brombenzoyl] Propionitrile (CXXIX, X = Br).

By a similar method 54 g. of this nitrile was obtained from 60 g. of benzal p-bromacetophenone, a yield of 83.8% . It was recrystallized from methyl alcohol to constant m.p. 124° in rectangular plates.

Anal. Calcd. for $C_{16}H_{12}ONBr$: Br, 25.5

Found : Br, 25.3

(c) α-Phenyl -β- anisoyl Propionitrile (CXXIX, X = OCH_3).

This preparation differed from those above in that the temperature was raised to 50° - 55°, since hydrogen cyanide did not add at a lower temperature. From 40 g. of benzal p- methoxy acetophenone, 28.5 g. of the nitrile was obtained, which is 64.6% of the theoretical yield. After repeated crystallizations from methyl alcohol it was in the form of slender white needles which melted constantly at 62°. It was very soluble in hot methyl alcohol, but only sparingly so in cold alcohol.

Anal. Calcd. for $C_{17}H_{15}O_2N$: C, 77.0; H, 5.7

Found : C, 76.8; H, 5.8

3. Esters.

(a) Methyl α-Phenyl -β- [p- chlorbenzoyl] Propionate (VI, X = Cl).

This ester was prepared in two ways.

(I). Method of Kohler and Shohan (loc. cit.)

One hundred and seventy-six grams of α-phenyl -β- p- chlorbenzoyl propionitrile was added to 433 c.c. of absolute methyl alcohol. Hydrogen chloride, dried by bubbling through sulphuric acid, was passed in until the alcohol was saturated. On standing for one week a mass of crystals separated, consisting mostly of the ester, but contaminated with a high melting nitrogen containing compound. After several crystallizations from methyl alcohol the ester was obtained pure in a yield of about 75%. It melted at 111°.

All the γ-ketonic esters prepared, showed about the same solubility in methyl alcohol; in cold alcohol they were moderately soluble, and were very soluble in hot methyl alcohol.

(II) Method of Lapworth and Wechsler (36).

The nitrile was first hydrolysed to the acid which was then esterified in methyl alcohol.

One hundred and twenty-eight grams of the nitrile was dissolved in 291 c.c. of sulphuric acid (s.g. 1.84) and 267 c.c. of water at the temperature of the water-bath. Stirring and heating at this temperature were continued for three hours. After cooking, the mixture was poured into a large volume of water and was filtered. The yield of air dried product was 150 g. For esterification, further purification was found unnecessary and the crude acid was used.

One hundred grams of the crude acid was dissolved in 1266 c.c. of methyl alcohol to which 27.2 c.c. of sulphuric acid (s.g. 1.84) had been added, and was heated on the water-bath. Refluxing was continued for three hours. On cooling, the ester separated in small plate-like crystals, and a further quantity was obtained on distilling the mother liquor to small volume. It melted at 110°, and weighed 88.0 g., which is 92.0% of the theoretical yield (on nitrile).

The ethyl ester was prepared by refluxing for four hours 10 g. of the crude acid in 100 g. of ethyl alcohol to which 5.0 g. of conc. sulphuric acid had been added. A yield of 9.2 g. of this ester was obtained, and on repeated crystallizations from methyl alcohol, it melted constantly at 63°.

Anal. Calcd. for $C_{18}H_{17}O_3Cl$: Cl, 11.2

Found : Cl, 11.5

(b) Methyl α-Phenyl -β- [p- brombenzoyl] Propionate (VI, X = Br).

Following the method of Kohler and Shohan, 30.5 g. of this ester was obtained from 51 g. of α- phenyl -β- p - brombenzoyl propionitrile, a yield of 54.1% . Evaporation of the mother liquor to small volume yielded a considerable quantity of untractable dark colored gum. The ester was recrystallized from methyl alcohol to constant m.p. 129°, and was in the form of small four sided plates.

Anal. Calcd. for $C_{17}H_{15}O_3Br$: Br, 23.0

Found : Br, 22.9

(c) Methyl α- Phenyl -β- anisoyl Propionate. (VI, X $= OCH_3$).

Following the method of Lapworth and Wechsler, 23.1 g. of α- phenyl -β- anisoyl propionic acid was obtained from 24.5 g. of the corresponding nitrile, a yield of 87.5% of the theoretical. On repeated crystallizations from methyl alcohol, it was obtained as small scales melting constantly at 150°.

Calcd. for $C_{17}H_{16}O_4$: Mol. wt., 284.

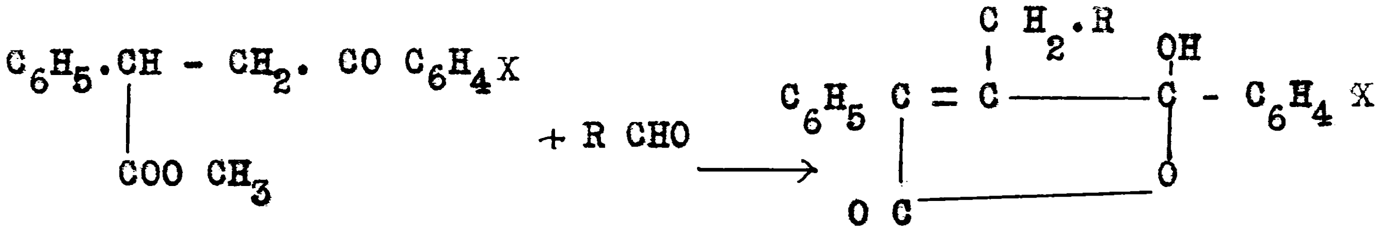
Found (by titration) : Mol. wt., 275.

From 22.0 g. of this acid 18.0 g. of the methyl ester were obtained, a yield of 77.9%. It was recrystallized from methyl alcohol to constant m.p. 97°, in well defined dense prisms.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.5 ; H, 6.0

Found : C, 72.3 ; H, 5.9

B. Condensation of the Esters with Aldehydes.



VI. CXXXI.

R = C_6H_5, and 3,4 $CH_2O_2C_6H_3$ -

X = Cl, Br, and CH_3O.

1. (VI, X = Cl) with Benzaldehyde.

To 106 c.c. of benzaldehyde (U.S.P.) dissolved in 212 c.c. of absolute methyl alcohol were added 160 g. of methyl α-phenyl - β- [p - chlorbenzoyl] propionate, and the sodium methylate from 212 c.c. of absolute methyl alcohol and 12.6 g. of sodium. The mixture was refluxed on the water-bath for two hours. After cooling, the solution was acidified with dilute acetic acid, and the alcohol and excess benzaldehyde were removed by steam distillation. An oil usually remained, although in one preparation the product was crystalline. The oil was dissolved in ether, and on spontaneous evaporation a crystalline product remained. This was dissolved in a small volume of boiling methyl alcohol, which on cooling deposited very fine crystals melting at 130°. The yield of crude product - from the ether solution - was 153 g., which was 76.9% of the theoretical. A sample of constant m.p. 132°, in small prisms, was obtained by several crystallizations from an ether petroleum ether mixture.

Anal. Calcd. for $C_{23}H_{17}O_3Cl$: C, 73.4; H, 4.5; Cl, 9.4

Found : C, 73.5; H, 4.5; Cl, 9.3

It was very soluble in ether and acetone, moderately in alcohol and benzene, and almost insoluble in petroleum ether.

In a similar manner, the ethyl ester yielded the same product in 82% yield. A mixed melting point with the product from the methyl ester was not depressed.

The lactol dissolved instantly in dilute sodium hydroxide solution, and precipitated unchanged on acidification. In cold sodium carbonate solution it dissolved slightly if finely ground; in hot carbonate solution it went into solution quite readily, and reprecipitated unchanged on acidification. It was insoluble in sodium bicarbonate solution. In concentrated sulphuric acid, it formed a deep magenta colored solution, and precipitated unchanged on dilution.

In the Grignard "machine" (37) this substance showed the presence of one active hydrogen, and the addition of two methyl groups. The active hydrogen determination was carried out by measuring the volume of methane evolved by a weighed sample of the substance in reacting with a known volume of standardized methyl magnesium iodide in amyl ether. Addition of the Grignard reagent to the substance was calculated by determining the excess of the reagent, (not reacted with the sample) by adding water. The experimental data follow.

1 c.c. of Grignard reagent = 0.0002716 moles (from previous standardization).

Weight of substance = 0.2670 g.

Temp. of Reaction Flask 23°

Bar. Pr. 761 mm.

Gas Readings		Grignard Reagent (Burette Readings)	Water Added.
Sample	Water		
1.0	29.0	9.41	3.0
29.0	32.3	0.62	2.0

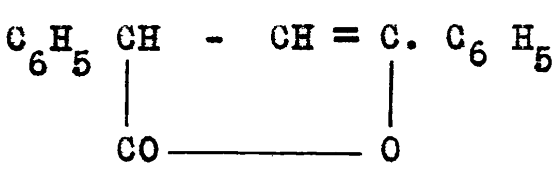
The following ratios were then calculated:

(a) $$\frac{\text{Moles of methane evolved by sample}}{\text{Moles of substance}} = 1.1$$

(b) $$\frac{\text{Moles of Grignard reacted with substance}}{\text{Moles of substance}} = 3.2$$

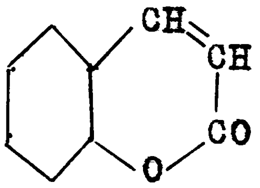
These results were interpreted to mean the presence of one active hydrogen, and the addition of two groups.

For purpose of comparison, similar determinations were made on the β-γ unsaturated diphenyl crotonlactone (CXXXII) and on coumarin (CXXXIII).



$$\begin{array}{llll} C_6H_5\,CH & - & CH = C. & C_6H_5 \\ \quad\ | & & \quad\ \ | & \\ \quad CO & \text{———} & \quad\ \ O & \end{array}$$

CXXXII.



CXXXIII.

For CXXXII, the value 0.34 was found for ratio (a); and 1.5 for ratio (b). This was taken to indicate the absence of active hydrogen, and the addition of one or two groups.

For coumarin, the value 0.23 was found for (a) and 0.78 for (b). Absence of active hydrogen and the addition of one group was thus indicated.

2. (VI, X = Cl) with Piperonal.

This condensation was carried out in a similar manner, using 37 g. of piperonal dissolved in 53 c.c. of absolute methyl alcohol, 40 g. of methyl α- phenyl -β- p-chlorbenzoyl propionate, and 3.2 g. of sodium in 53 c.c. of absolute methyl alcohol. After acidification and steam distillation, an oil remained. This was dissolved in ether and extracted with a saturated sodium bisulphite solution to remove the excess piperonal. After filtering and washing with water, the ether solution on spontaneous evaporation deposited 40.4 g. of product in very fine needles, a yield of 72.7%. On repeated crystallizations from benzene it melted constantly at 174°.

Anal. Calcd. for $C_{24}H_{17}O_5Cl$: Cl, 8.4

Found: Cl, 8.3

3. (VI, X = Br) with Benzaldehyde.

In an identical manner, 15 g. of methyl α-phenyl

-β- p- brombenzoyl propionate was condensed with 9 c.c. of benzaldehyde to form 12.4 g. of the lactol, a yield of 68.1%. It was recrystallized several times from methyl alcohol to constant m.p. 155°, in microscopic prisms.

Anal. Calcd. for $C_{23}H_{17}O_3Br$: Br, 18.9
Found : Br, 18.7

4. (VI, X = Br) with Piperonal.

Following the same procedure, 11.0 g. of this ester with 8.8 g. of piperonal gave 13.0 g. of the lactol, a yield of 88.4%. On repeated crystallizations from benzene it melted constantly at 171°, in fine needles.

Anal. Calcd. for $C_{24}H_{17}O_5Br$: Br, 17.2
Found : Br, 17.6

5. (VI, X = OCH_3) with Benzaldehyde.

Seven grams of methyl α-phenyl -β- anisoyl propionate was condensed with 4.9 c.c. of benzaldehyde to form 8.0 g. of the lactol, a yield of 91.9%. After several crystallizations from methyl alcohol, it was in the form of small dense six-sided plates, melting at 119°.

Anal. Calcd. for $C_{24}H_{20}O_4$: C, 77.4 ; H, 5.4
Found : C, 77.7 ; H, 5.4

6. (<u>VI</u>, X = OCH_3) with Piperonal.

Seven grams of the same methyl ester with 6.6 g. of piperonal, yielded 9.0 g. of the lactol, which was 91.8% of the theoretical. Recrystallized several times from methyl alcohol it was in the form of very fine needles melting at 162°.

Anal. Calcd. for $C_{25}H_{20}O_6$: C, 72.1 ; H, 4.8
Found : C, 72.2 ; H, 4.7

C. <u>Oxidation Reactions.</u>

(1). With Potassium Permanganate.

Five grams of the lactol (<u>CXXXI</u>, R = C_6H_5, X = Cl) was dissolved in 150 c.c. of acetone (distilled over permanganate and potassium hydroxide), and 8.8 g. of finely ground potassium permanganate was slowly added. Oxidation started easily and the solution became quite warm. Finally a little ethyl alcohol was added to destroy the slight excess of permanganate. The manganese dioxide was filtered, and was extracted with dilute sodium hydroxide solution. The alkaline solution was acidified with hydrochloric acid, and allowed to stand a minute or two. A precipitate weighing 2.1 g., melting at 210°, was filtered, and identified as p- chlorbenzoic acid by a mixed melting point. The acid filtrate was extracted with ether, which on spontaneous evaporation deposited 1.4 g. of white solid melting at 118°;

it was identified as benzoic acid by a mixed melting point.

The acetone solution was allowed to evaporate spontaneously. The residue was taken up in ether and shaken for ten minutes with a small volume of saturated sodium bisulphite solution; no addition product formed. The washed ether solution was extracted with dilute sodium carbonate solution, and allowed to evaporate spontaneously. The residue weighed 0.7 g., and was identified as p- chlorbenzoic acid by a mixed melting point. The total weight of benzoic and p- chlorbenzoic acids was 4.2 g.

The oxidation was repeated three times, using one-half the weight of permanganate used above, and keeping the temperature below 20°. However the only products isolated were benzoic and p- chlorbenzoic acids.

(2) With chromic Acid

(a) Lactol (<u>CXXXI</u>, $R = C_6H_5$ $X = Cl$)

Twenty grams of this lactol was dissolved in 150 c.c. of glacial acetic acid in a small three neck flask provided with a stirrer and a thermometer. Six grams of finely ground chromic acid dissolved in acetic acid was slowly added, the temperature being kept below 30°. In about one hour the color change from brown to green was complete, and the solution was poured into water. As filtration was difficult, the water solution was extracted with ether.

The ether solution was washed twice with water to remove the acetic acid, and finally was twice extracted with sodium carbonate solution. On acidification of the latter and extraction of the acid filtrate with ether, 3.0 g. of benzoic and p- chlorbenzoic acids were obtained.

The ether solution of the oxidation products deposited on spontaneous evaporation, a residue of a yellow oil weighing 10.6 g. It crystallized completely in two hours. It was quite soluble in methyl alcohol, in which it was dissolved, and after a trace of high melting substance was filtered, was recrystallized to constant m.p 103° from this solvent, and was identical with benzyl-p- chlorphenyl diketone described by Jorlander (loc. cit)

Anal. Calcd. for $C_{15}H_{11}O_2Cl$: C, 69.6 ; H, 4.2
Found : C, 69.5 ; H, 4.2

Dissolved in ethyl alcohol it gave a deep reddish violet coloration with alcoholic ferric chloride.

One-half a gram was refluxed for ten minutes in 15 c.c. of methyl alcohol with 0.5 g. of O- phenylene diamine. On pouring into water and recrystallizing from a small volume of ethyl alcohol, 2- benzyl -3- p-chlorphenyl quinoxaline, m.p. 132°, was obtained, having all the properties described by Jorlander.

Only enough of the high melting substance was obtained for one analysis; it melted at 202°, contained halogen, and on combustion gave 72.3% C and 4.2% H, corresponding to a compound of empirical formula $C_{22}H_{17}O_3Cl$.

In this oxidation it was found essential to keep the temperature below 30° ; otherwise oxidation proceeded completely to benzoic and p- chlorbenzoic acids.

(b) Lactol (CXXXI, $R = CH_2O_2C_6H_3-$, $X = Cl$).

A sample of 5.7 g. of this lactol was dissolved in 75 c.c. of glacial acetic acid, and 2.6 g. of chromic acid in a small volume of acetic acid was slowly added as before, with continual stirring and external cooling to keep the temperature below 30°. The oxidation was continued for one hour, when the solution was poured into water, and filtered after standing two hours. The filtered material was dissolved in a small volume of ether, and was extracted, as rapidly as possible, three times with dilute sodium carbonate solution. Previous to the sodium carbonate extraction the solution was dark brown in color, but became light yellow after the extraction; when the solution stood for three or four minutes in the presence of carbonate, the brown color again appeared, caused evidently by the decomposition of the diketone. After washing with water and spontaneous evaporation, the ether solution deposited 2.0 g. of piperonyl p- chlorphenyl diketone as a yellow solid; this was recrystallized to a constant though indefinite m.p. 161° - 165°, and was in the form of fine light yellow needles felted together.

Dissolved in hot ethyl alcohol it gave a deep reddish brown color with alcoholic ferric chloride, the color disappearing however in a few minutes.

Anal. Calcd. for $C_{16}H_{11}O_4Cl$: Cl, 11.7
Found : Cl, 11.6

All the substituted phenyl piperonyl diketones described in this section, were found to be very sensitive substances, being very easily decomposed in alkaline solution. The addition of a mild base, such as O- phenylene diamine, turned the solution dark brown, and in two cases no crystalline material could be isolated following this treatment,

On refluxing for twenty minutes o.8 of the yellow diketone in 15 c.c. of methyl alcohol, with 0.6 g. of o- phenylene diamine, 2- piperonyl -3- p- chlorphenyl quinoxaline, in slender white needles separated on cooling. The solution turned quite dark on the addition of the diamine, some decomposition evidently being caused by the alkaline solution. The quinoxaline was dissolved in ether, extracted twice with sodium carbonate solution, and finally crystallized from methyl alcohol to constant m.p. 161°.

Anal. Calcd. for $C_{22}H_{15}O_2N_2Cl$: Cl, 9.5
Found : Cl, 9.8

(c) Lactol (<u>CXXXI</u>), $R = C_6H_5$, $X = Br$).

In a similar manner 3.0 g. of this lactol was oxidized with 1.5 g. of chromic acid in 75 c.c. of glacial acetic acid at 25°. After pouring into water, extraction of the latter with ether, and subsequent extraction with sodium carbonate, 1.8 g. of yellow oil was obtained, which crystallized completely in one hour. On repeated crystallizations from methyl alcohol it was in the form of light yellow plates which melted constantly at 122°. With alcoholic ferric chloride, it gave a deep reddish brown color. When 1.0 g. of this diketone in 10 c.c. of methyl alcohol was refluxed with 0.5 g. of O- phenylene diamine, 2- benzyl -3- p- bromphenyl quinoxaline separated even while hot, and was filtered on cooling. After several crystallizations from methyl alcohol, it was obtained in the form of slender white needles, which melted constantly at 143°.

Anal. Calcd. for $C_{21}H_{15}N_{2}Br$: Br, 21.3
Found : Br, 21.4

(d) Lactol (<u>CXXXI</u>, $R = C_6H_3CH_2O_2$, $X = Br$).

Two and one-tenth grams of this product was similarly oxidized with 1.0 g. of chromic acid. The ether extract of the water solution was extracted three times as rapidly as possible with dilute sodium carbonate solution. On drying over anhydrous sodium sulphate, and spontaneous evaporation, 0.8 g. of yellow oil remained. It partially crystallized in some days, and melted indefinitely at 150° - 160°. Insufficient crystalline material was obtained for analysis. With alcoholic ferric chloride it gave a very deep reddish brown color. On refluxing in methyl alcohol with excess -O- phenylene diamine, the solution of the yellow oil turned very dark, and no crystalline material was isolated. The alkaline diamine evidently caused decomposition of the diketone.

(e) Lactol (<u>CXXXI</u>) $R = C_6H_5$, $X = OCH_3$).

By the same method, 1.3 g. of this lactol was oxidized with 1.0 g. of chromic acid. The ether solution deposited 0.9 g. of yellow oil, which partially crystallized in some days, and was indentical with benzyl p- methoxy-phenyl diketone described by Jorlander (loc. cit) After washing with ether, it melted at 96°. When refluxed for five minutes with 0.5 g. of O-phenylene diamine, 2 benzyl -3- p- methoxy phenyl quinoxaline precipitated in slender white needles on cooling. After three crystallizations from methyl alcohol, this substance melted at 138°, and was similar in all respects to the compound obtained by Jorlander (loc. cit.).

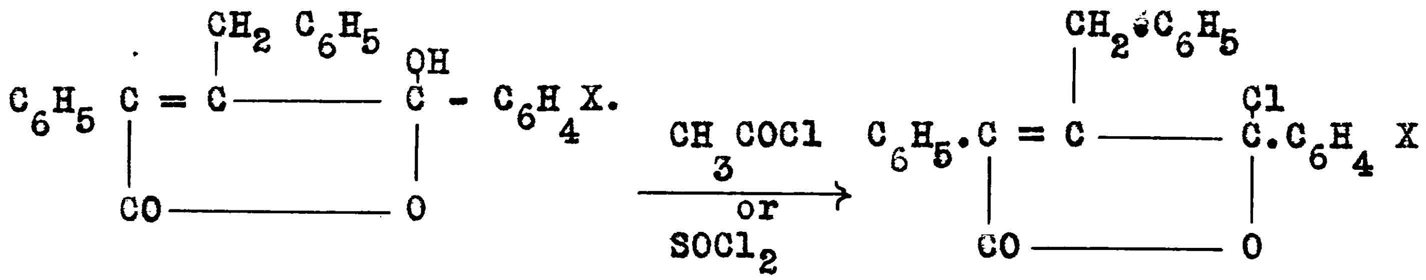
(f) Lactol (<u>CXXXI</u>), $R = C_6H_3 \cdot CH_2 \cdot O_2$, $X = OCH_3$

On oxidation of 2.1 g. of this substance with 1.5 g. of chromic acid, 0.9 g. of yellow oil was obtained. It failed to crystallize even on long standing, and when refluxed with a small quantity of O- phenylene diamine in methyl alcohol, the solution turned very dark in color, and no crystalline material could be isolated.

3. Ozonization of Lactol (CXXXI, R = C_6H_5 X = Cl)

One and two-tenths grams of the lactol was dissolved in 15 c.c. of carbon tetrachloride (dried over calcium chloride and freshly distilled). A 4% ozone mixture was bubbled through the solution for four hours. The solution turned light yellow in color; no odor of benzaldehyde was present. The solvent was allowed to evaporate spontaneously, and the residue was dissolved in ether. After extraction with sodium carbonate solution, the ether solution on spontaneous evaporation deposited the lactol in nearly quantitative yield, in unchanged form, as determined by a mixed melting point with the original material.

D. Reactions of Lactols with Thionyl and Acetyl Chlorides.



CXXXIV.

1. Lactol (CXXXI R = C_6H_5, X = Cl)

Fifteen grams of this substance was dissolved in excess thionyl chloride, and the solution was warmed gently for some minutes. On spontaneous evaporation 13.7 g.

of the solid chloride (CXXXIV, X = Cl) remained. After several crystallizations from ether, it formed glistening white needles, melting constantly at 137°. It was moderately soluble in boiling ether, sparingly so in cold ether, very soluble in benzene and acetone, and insoluble in petroleum ether.

Anal. Calcd. for $C_{23}H_{16}O_2Cl_2$: Cl, 18.0
Found : Cl, 17.8

When 2.0 g. of the same lactol was added to excess acetyl chloride with gentle boiling to dissolve the product, the same chloride resulted on spontaneous evaporation, in quantitative yield. A mixed melting point with the thionyl chloride product was not depressed.

2. Lactol (CXXXI, R = C_6H_5, X = Br)

Two grams of this substance was dissolved in excess boiling acetyl chloride. After heating for some minutes, the solution was allowed to evaporate in a hood. The crystalline chloride (CXXXI, X = Br), remained, and was recrystallized repeatedly from ether to constant m.p. 132° in rectangular prisms. It was moderately soluble in boiling ether, slightly so in cold ether, very soluble in benzene and acetone, and insoluble in petroleum ether.

Anal. Calcd. for $C_{23}H_{16}O_2ClBr$: Cl, 8.1 ; Br, 18.2
Found : Cl, 8.0 ; Br, 17.9

Br and Cl were determined by precipitating both as silver halides; the percentage of each was calculated from this weight and from the ratio of their at. wts.

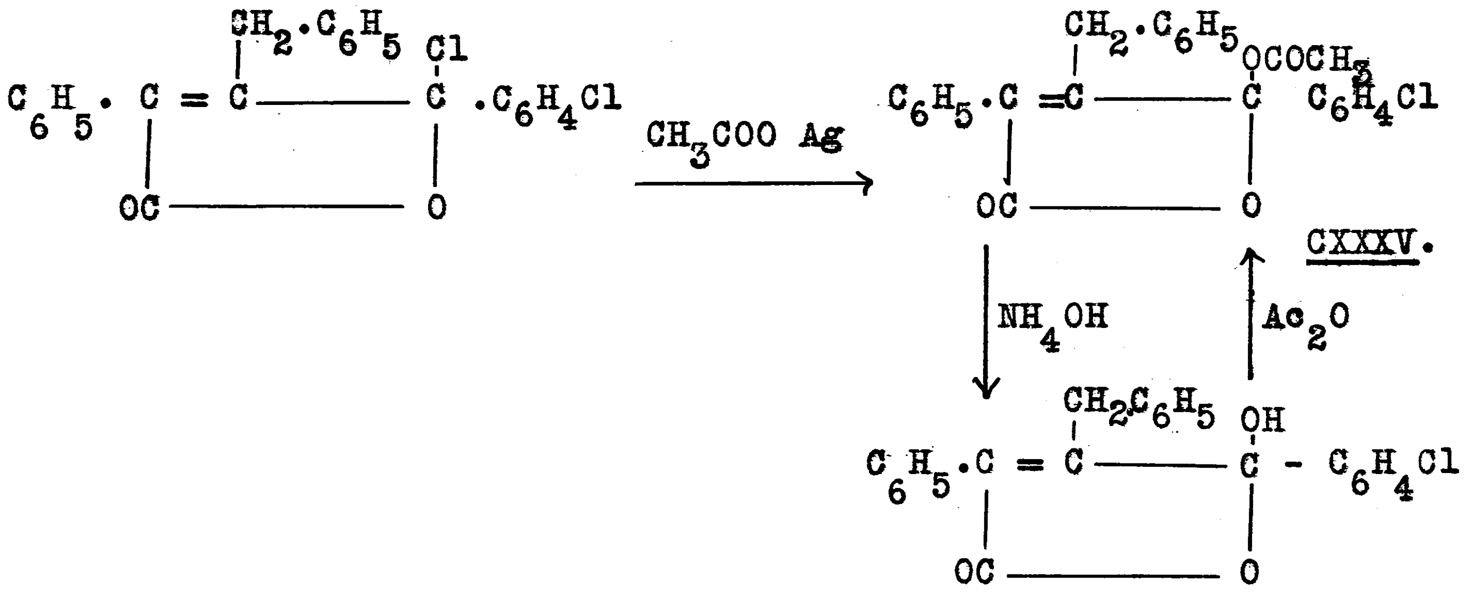
3. Lactol (<u>CXXX</u>, R = C_6H_5, X = OCH_3).

Similar treatment of this lactol with both thionyl and acetyl chlorides yielded untractable reddish oils, which failed to crystallize even on long standing. Refluxing for two hours with thionyl chloride also yielded an oil.

E. Reactions of the Chlorides.

1. Chloride (<u>CXXXIV</u>, X = Cl).

(a) With Silver Acetate.



<u>CXXXV</u>.

One and two-tenths grams of this chloride was refluxed for one hour with 1 g. of silver acetate in 15 c.c. of absolute ether. After filtering the silver chloride and excess silver acetate, the ether was evaporated in a hood.

The acetate (CXXXV) remained as a white solid, and was recrystallized from n. butyl alcohol to constant m.p. 157°. It was in the form of shining white rectangular prisms, which were difficultly soluble in boiling methyl and ethyl alcohols, and quite soluble in boiling n. butyl alcohol.

Anal. Calcd. for $C_{25}H_{19}O_4Cl$: Cl, 8.5

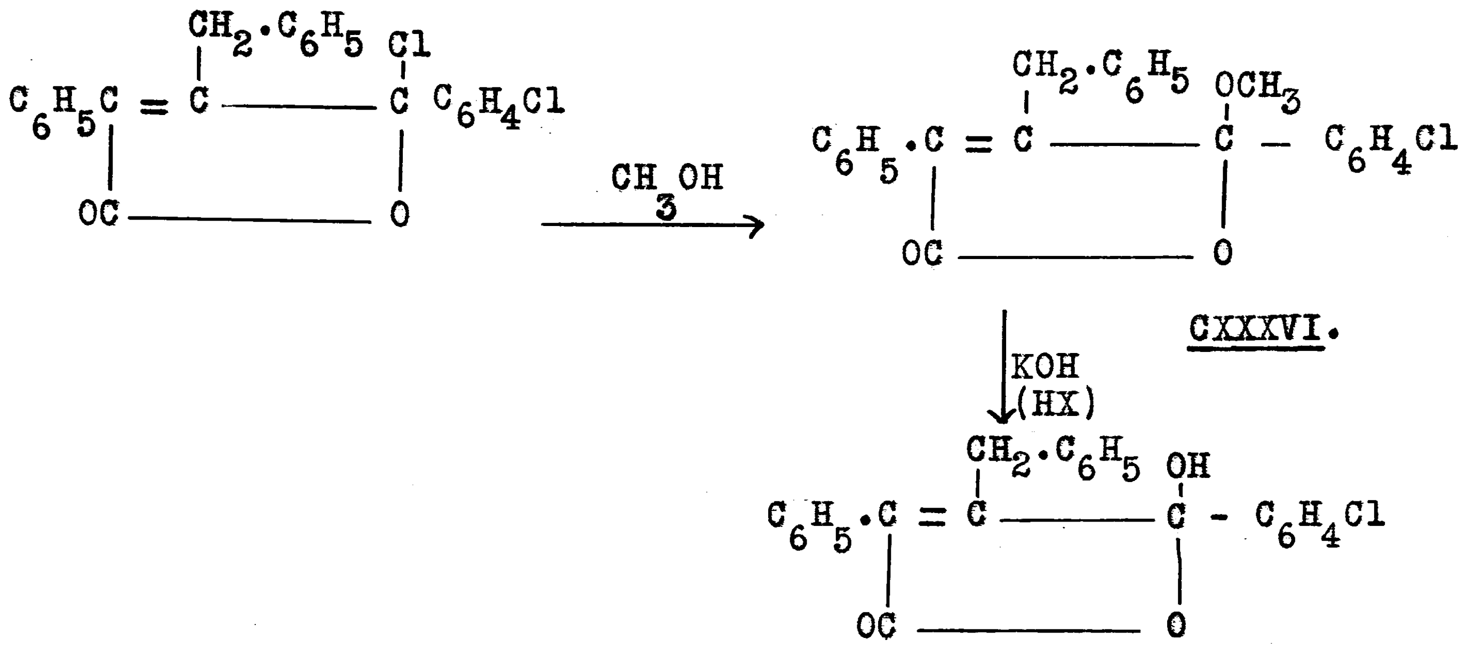
Found : Cl, 8.6

This same acetate resulted by treating the lactol with acetic anhydride in the following manner.

Three grams of the lactol were dissolved in excess boiling acetic anhydride to which one drop of conc. sulphuric acid had been added. After boiling for two or three minutes, the solution was poured into water and extracted with ether. On spontaneous evaporation of the latter, the acetate remained in quantitative yield. A mixed melting point with the acetate obtained above was not depressed.

Hydrolysis: A solution of 0.5 g. of this acetate in 50 c.c. of methyl alcohol to which 9 c.c. of conc. ammonium hydroxide had been added, was allowed to stand overnight at a temperature of 30°. After neutralizing with dilute acetic acid, crystals of the lactol separated, melting at 130°. A mixed melting point with the lactol was not depressed.

(b) With Methyl Alcohol.



CXXXVI.

Eleven grams of the chloride was reflexed in 75 c.c. of methyl alcohol for two hours. On cooling, the methyl ether (CXXXVI) separated in dense white crystals in quantitative yield, and was recrystallized from methyl alcohol to constant m.p. 79°, in rectangular prisms. It was very soluble in hot methyl alcohol, and sparingly so in cold alcohol.

Anal. Calcd. for $C_{24}H_{19}O_3Cl$: CH_3O, 7.9
Found : CH_3O, 7.6

Hydrolysis: One gram of this ether was refluxed for fifteen minutes in 10% methyl alcoholic potassium hydroxide. The potassium salt of the lactol separated, and was analysed without purification.

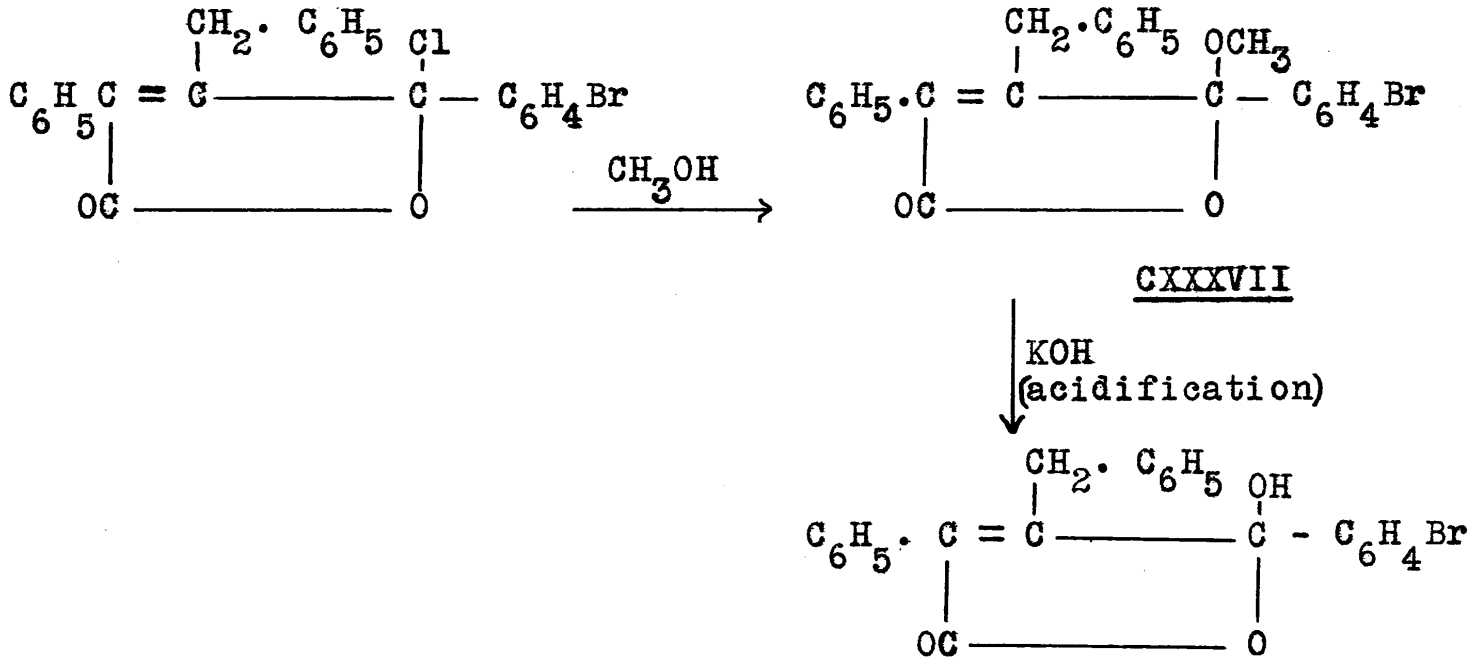
Anal. Calcd. for $C_{23}H_{16}O_3ClK$: K, 9.4
Found : K, 8.8

On acidification of a water solution of the potassium salt, the lactol, melting at 130°, precipitated. A mixed melting point with the original lactol was not depressed.

The ether was not affected by ammonium hydroxide. A solution of 1.0 g. of the ether in 50 c.c. of methyl alcohol containing 9 c.c. of conc. ammonium hydroxide, was allowed to stand overnight at 30°. On acidification with dilute acetic acid, it precipitated unchanged.

2. Chloride (<u>CXXXIV</u>, X = Br)

With Methyl Alcohol.



<u>CXXXVII</u>

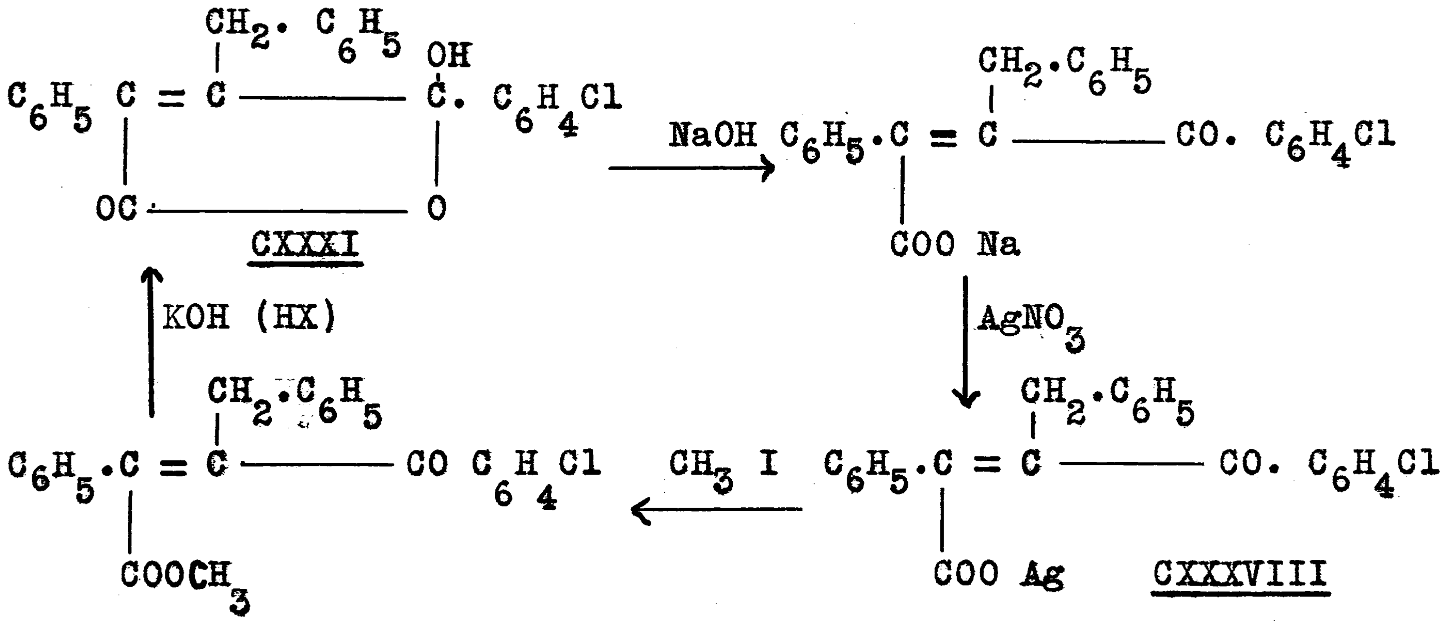
One and one-tenth grams of this chloride was refluxed in 15 c.c. of methyl alcohol for two hours. On cooling, the ether (<u>CXXXVII</u>) separated in quantitative yield, and was recrystallized from methyl alcohol to constant m.p. 75°. It was in the form of small dense rectangular plates, difficultly soluble in cold methyl alcohol and moderately so in hot alcohol.

Anal. Calcd. for $C_{24}H_{19}O_3Br$: CH_3O, 7.1

Found: CH_3O, 7.2

On refluxing 0.4 g. of this ether in 10 c.c. of 10% methyl alcoholic potassium hydroxide for fifteen minutes, 0.3 g. of the lactol precipitated after acidification with dilute acetic acid. It melted at 152°, and a mixed melting point with the original lactol was not depressed.

F. Preparation of the Open Chain Ester of (CXXXI, R = C_6H_5, X = Cl).



CXXXIX.

To 15 g. of the lactol dissolved in sodium hydroxide solution, silver nitrate solution was added until no further precipitation occurred. The silver salt (CXXXVIII), was filtered, washed with water, alcohol, and ether, and dried in a vacuum desiccator; it weighed 20.5 g.

Anal. Calcd. for $C_{23}H_{16}O_3ClAg$: Ag, 22.3 : Cl, 7.4
Found : Ag, 22.9 : Cl, 7.5

(The residue on heating was assumed to be AgCl; Cl was calc'd from this weight)

In 75 c.c. of absolute ether, 18.2 g. of this silver salt was refluxed with 10 c.c. of methyl iodide for one-half hour. The silver iodide was filtered, and the ether solution allowed to evaporate spontaneously. The residue consisted of 7.0 g. of the white crystalline ester (CXXXIX), which after several crystallizations from methyl alcohol, melted constantly at 87°. It was a perfectly stable substance in the form of short white needles, moderately soluble in hot alcohol and slightly so in cold alcohol.

Anal. Calcd. for $C_{24}H_{19}O_3Cl$: Cl, 9.1
Found : Cl, 9.1

Hydrolysis: One-half a gram of this ester was refluxed in 10 c.c. of 10% methyl alcoholic potassium hydroxide for fifteen minutes. After neutralization with acetic acid, it was poured into water, filtered, and recrystallized from dilute methyl alcohol. It melted at 130°, and a mixed melting point with the lactol was not depressed.

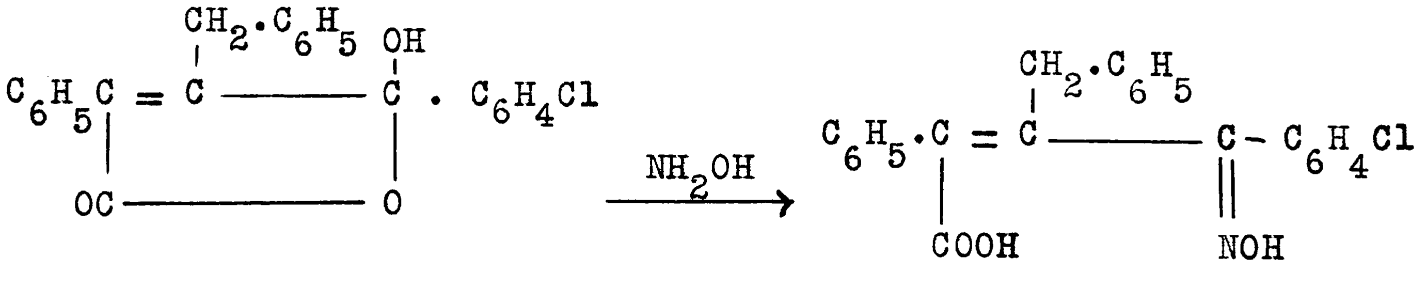
Hoping to obtain the same methyl ester, 2 g. of the lactol were refluxed for three hours in 25 c.c. of methyl alcohol containing 1.0 g. of conc. sulphuric acid. On pouring into water, and recrystallizing from methyl alcohol, the lactol was recovered unchanged, as determined by its melting point and a mixed melting point.

In a further effort to obtain the open chain methyl ester (CXXXIX), the methyl ester (VI, X = Cl) was condensed with benzaldehyde in very dry alcohol. The procedure was similar to that described elsewhere, except that the methyl alcohol used was previously very carefully dried over magnesium methylate, and the reaction flask and condenser were baked dry at a high temperature preceding the experiment. However the lactol was the only product isolated.

Using piperidine as the condensing agent, in the following manner, no reaction occurred. To 3.0 g. of the methyl ester (VI, X = Cl) and 1 c.c. of benzaldehyde in 15 c.c. of absolute methyl alcohol, 5 drops of piperidine were added, and the mixture was refluxed for six hours. On cooling, the methyl ester (VI) precipitated unchanged.

Diethyl amine was also found not to effect the condensation. To 3.0 g. of the methyl ester (VI) and 1 c.c. of benzaldehyde in 15 c.c. of absolute methyl alcohol, 5 drops of diethylamine were added, and the solution was refluxed for six hours. After cooling, the methyl ester (VI) again precipitated unchanged.

G. Reaction of Lactol (CXIII, X = Cl) with Hydroxylamine.



CXL.

Three grams (3 mol. equivs.) of hydroxylamine hydrochloride was dissolved in 30 c.c. of hot ethyl alcohol, and 7.2 g. (5 mol. equivs.) of potassium acetate were added. The precipitated potassium chloride was filtered and washed with a little alcohol. In the solution 5.5 g. (1 mol. equiv.) of the lactol was dissolved, and refluxed on the water-bath for two hours. The solution was poured into water, and the oxime (CXL) was obtained pure by crystallizing twice from dilute methyl and three times from small volumes of hot methyl alcohol. It formed short white needles, melting at 160°, moderately soluble in cold alcohol, and very soluble in hot alcohol and ether.

Anal. Calcd. for $C_{23}H_{18}O_3NCl$: N, 3.6
Found : N, 3.5

H. Treatment of the Lactol (CXXXI, R = C_6H_5 X = Cl) with Some Aromatic Acid chlorides and with Phenyl Isocyanate.

1. with 3.5 Dinitro benzoyl chloride.

To prepare this acid chloride, 0.9 g. of 3.5 dinitro benzoic acid was heated with 1.2 g. of phosphorous penta chloride for a minute or two. The phosphorous oxychloride was removed by pressing the cooled semi-solid on a porous plate, and the acid chloride was added to 2.0 g. of the lactol in a small test-tube. The tube was heated to the melting point of the mixture, and kept at this temperature for half an hour. On recrystallizing from ethyl alcohol, the lactol was recovered quantitatively unchanged.

2. With p-nitro benzoyl chloride.

Two grams of p- nitro benzoyl chloride was added to 4.0 g. of the lactol in 20 g. of pyridine. The mixture was warmed to dissolve the components, and allowed to stand over night. The solution was poured into dilute sulphuric acid, and filtered. The precipitate was dissolved in ether, and extracted with sodium carbonate. On spontaneous evaporation of the ether, the lactol was recovered quantitatively unchanged.

3. With Benzoyl chloride.

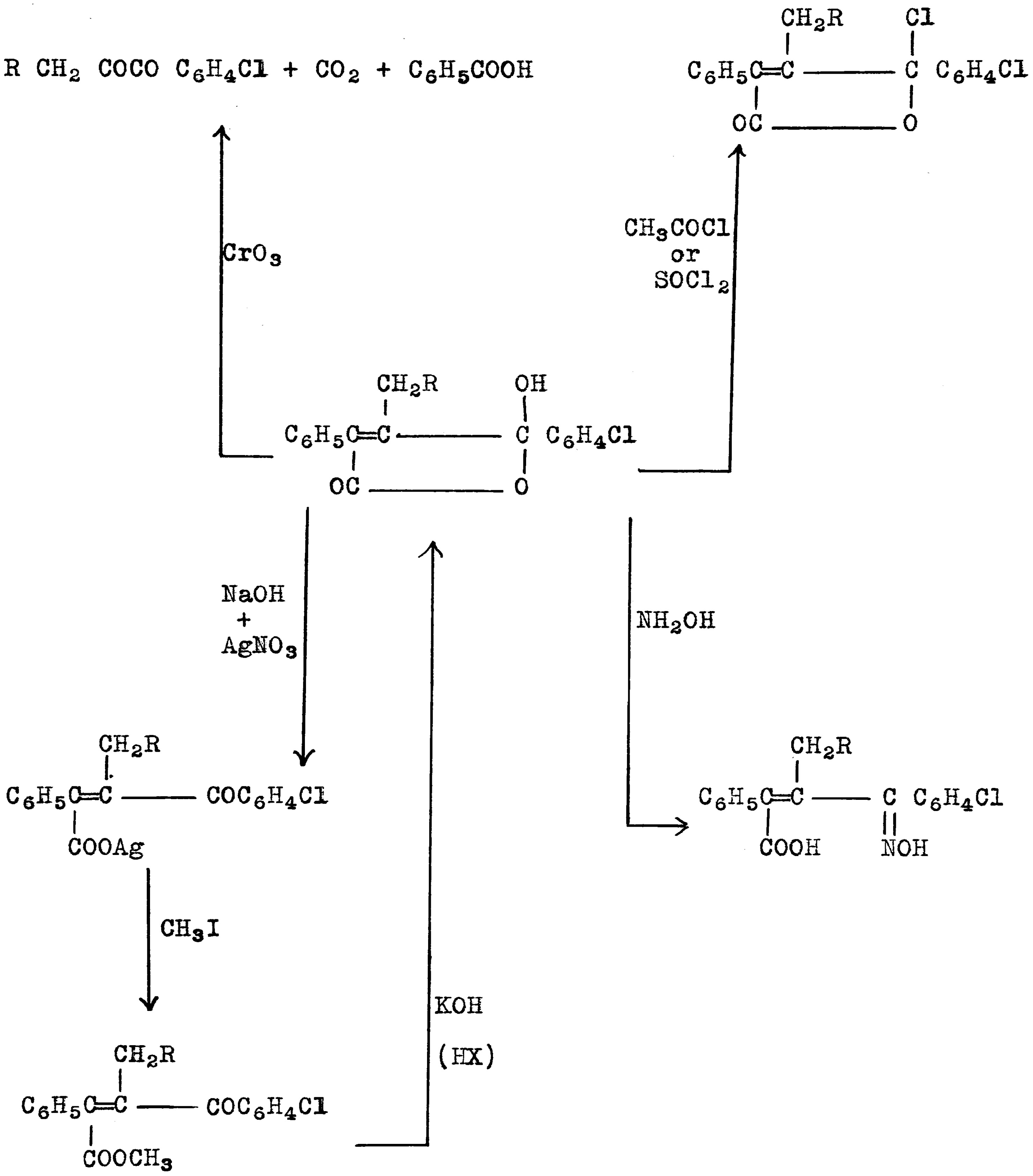
Three grams of benzoyl chloride was added to a solution of 4 g. of the lactol in 15 c.c. of ether. Thirty c.c. of 10% sodium hydroxide solution (aq.) was added, and shaking was continued for one hour. The sodium salt of the lactol separated, and was filtered. On dissolving it in water, and acidification with hydrochloric acid, the lactol precipitated unchanged.

4. With Phenyl Isocyanate.

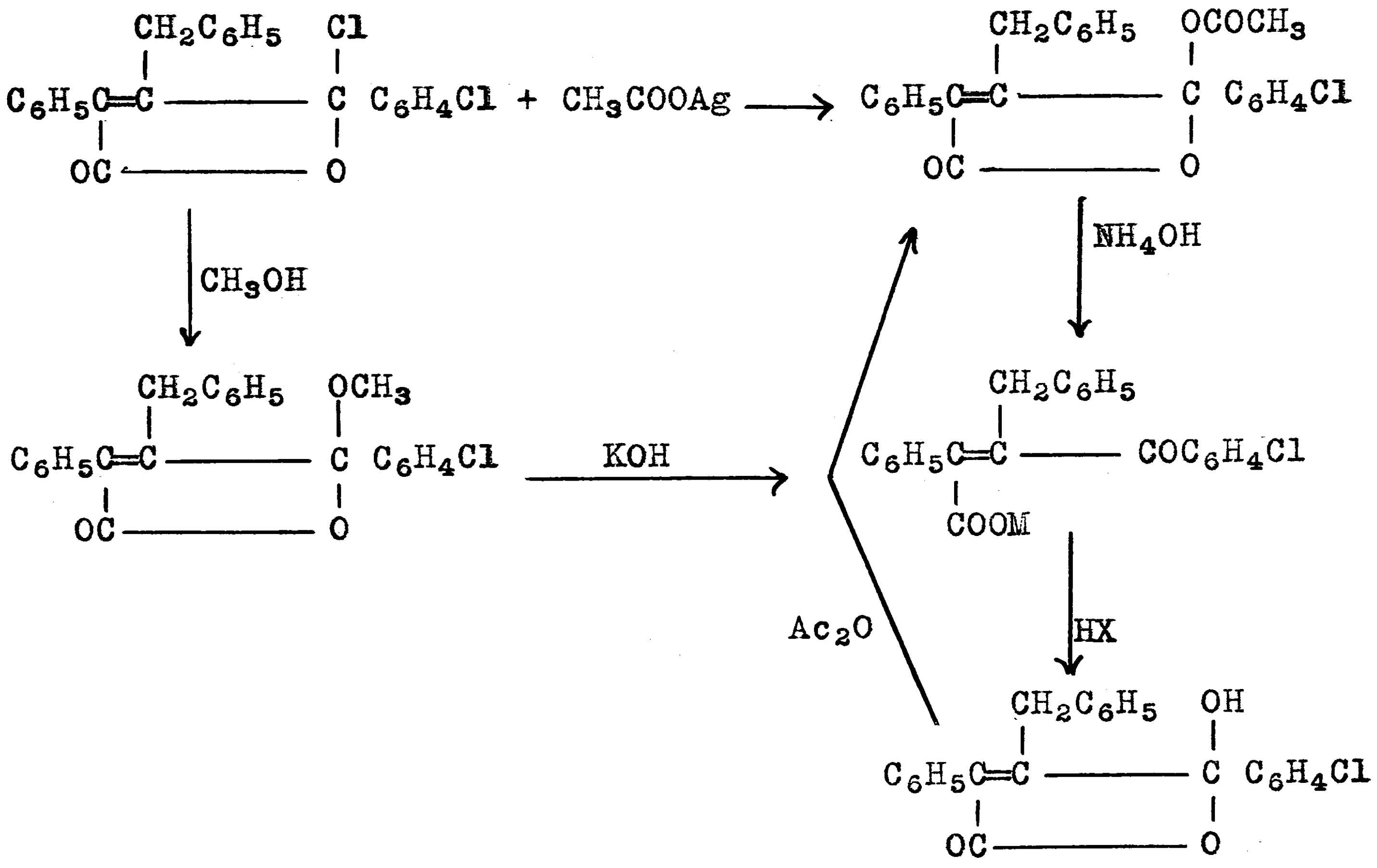
Two grams of the lactol was dissolved in 8 c.c. of dry benzene, and 1.2 c.c. of freshly prepared phenyl isocyanate was added. The solution was warmed gently, tightly stoppered, and allowed to stand for two days. The solution was allowed to evaporate in a hood, and a little water was added to the residue. After filtration, it was crystallized from dilute methyl alcohol, and so 1.9 g. of unchanged lactol was recovered. No trace of a phenyl urethane was found on the closest observation of all filtrates; the only other solid was diphenylurea.

I. Flow Sheets.

1. Reactions of Lactol (CXXXI, R= C_6H_5, X= Cl).



2. Reactions of the Chloride(CXXXIV).



Conclusion

1. The methyl and ethyl esters of α- phenyl β-p-chlorbenzoyl propionic acid condense with benzaldehyde in the presence of sodium methylate to form the same unsaturated lactone. This condensation is not brought about by piperidine or diethylamine. The methyl ester has also been condensed with piperonal to form an analogous product.

2. Methyl α-phenyl-β- p-brombenzoyl propionate and methyl α-phenyl-β-anisoyl propionate, when condensed with benzaldehyde and piperonal in a similar manner, form unsaturated lactones of the same type.

3. These unsaturated lactones have a tertiary hydroxyl group, and are therefore "lactols". This hydroxyl group is comparable to that of triphenyl carbinol in most respects.

4. The spontaneous closing of the ring on acidification is undoubtedly due to the increased branching of the chain, since the previous condensation products of this type that have been studied differ only in having one less phenyl group.

The Product from the Condensation of Methyl α- phenyl-β-benzoyl Propionate and Benzaldehyde.

When the unsubstituted γ-ketonic ester, methyl α-phenyl-β-benzoyl propionate, was condensed with benzaldehyde, a product was obtained only remotely resembling in its chemical properties, the lactols described in the previous section. Its structure has not yet been determined, since oxidation reactions used for this purpose, yielded only benzoic acid, and so far, no other type of reactions has given useful results. The properties of this substance are described below.

1. The empirical formula, $C_{23}H_{18}O_3$, was determined by analysis.

2. The product dissolves readily in caustic alkali solution, and precipitates unchanged on acidification. It is insoluble in sodium bicarbonate solution. A lactone structure is thus indicated. This is confirmed by the fact that the ester group disappears in the reaction, since the methyl and ethyl esters yield the same product.

3. In the Grignard "machine" it indicated the presence of two active hydrogens, and the addition of one group.

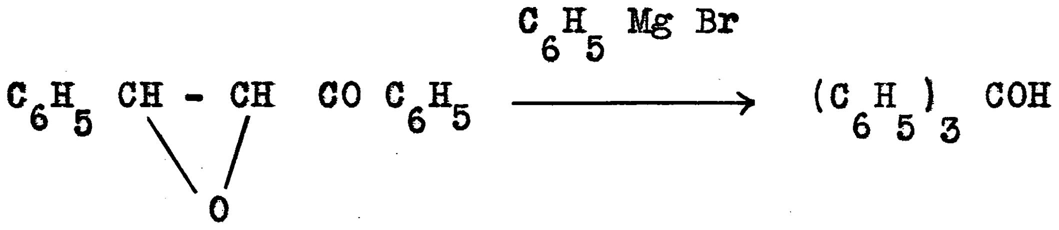
4. On pyrolysis, it readily loses carbon dioxide to form a product of empirical formula, $C_{22}H_{18}O$. This pyrolysis product is unsaturated, and is oxidized by potassium permanganate to benzoic acid. In the Grignard "machine" this substance shows the presence of one active hydrogen, and the addition of one group. It does not form an oxime or a phenyl hydrazone.

Since the original product loses carbon dioxide so readily, a β-lactone structure is indicated. Evidence against this structure is the fact that it precipitates unchanged from its solution in caustic alkali on acidification; no β-lactones yet known, exhibit this latter behaviour.

5. It is oxidized to benzoic acid on treatment with potassium permanganate in acetone solution, but does not decolorize bromine.

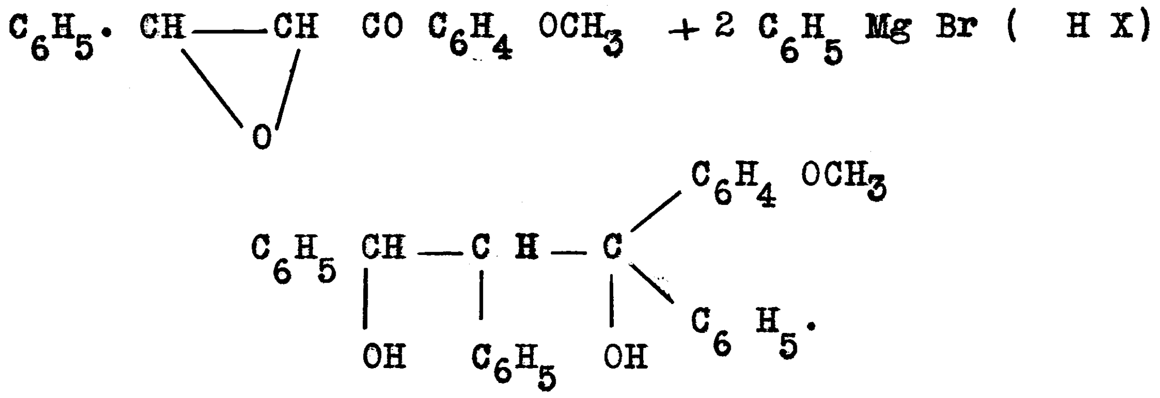
6. It forms an oxime.

The properties of this lactone are thus quite different from those of the lactols described in the first section of this thesis. In a recent communication, Bergmann and Wolff (40) have shown that the introduction of a methoxyl group in the para position of the benzoyl group of benzal acetophenone oxide, completely alters its reaction with phenyl magnesium bromide. It has been shown (41) that benzal acetophenone oxide reacts with phenyl magnesium bromide to form triphenyl carbinol.



Cleavage of the molecule occurs with the formation of benzophenone, which then reacts with the Grignard reagent to form triphenyl carbinol.

In the reaction between benzal p- methoxy acetophenone oxide and phenyl magnesium bromide, no cleavage occurs, and two moles of the latter add in the following manner:



With benzal p- phenyl acetophenone oxide, there are indications that both types of reaction occur.

The introduction of groups in the p- position of the benzoyl phenyl group in our lactols, may thus account for the difference in properties between the unsubstituted lactone just discussed, and the lactols described in the first part of this thesis.

A. Experimental

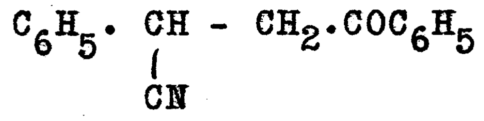
Methyl α- phenyl -β- benzoyl propionate was prepared in a manner similar to that of the other ketonic esters previously described.

1. Benzal acetophenone. $C_6H_5\ CH = CH\ CO\ C_6H_5$.

This compound was prepared according to the directions in "Organic Syntheses" (38).

From 104 g. of acetophenone and 92 g. of benzaldehyde, 165 g. (92% of yield) of benzal acetophenone m.p. 52°, was obtained.

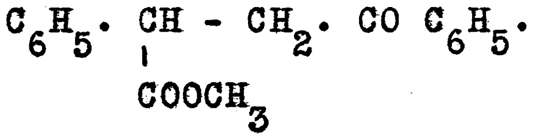
2. α- Phenyl β-benzoyl Propionitrile.



$C_6H_5 . \underset{\displaystyle CN}{CH} - CH_2 . COC_6H_5$

Following the method in "Organic Syntheses" (39) for the preparation of this compound, 198 g. of this nitrile m.p. 126°, was obtained from 208 g. of benzal acetophenone, a yield of 84.3%.

3. Methyl α- phenyl -β- benzoyl Propionate.



$C_6H_5 . \underset{\displaystyle COOCH_3}{CH} - CH_2 . CO\ C_6H_5 .$

The above nitrile was first hydrolysed to the corresponding acid which was then esterified in the usual manner. The method described below is that of Lapworth and Wechsler (loc. cit).

One hundred and two grams of α- phenyl -β- benzoyl propionitrile was dissolved in 510 g. of sulphuric acid (s. g. 1.84) and 255 c.c. of water, at the temperature of the water-bath, and kept at this temperature for three hours with mechanical stirring. The resultant pasty mass was poured into a large volume of water and filtered. The crude acid so obtained was purified by dissolving in excess hot dilute sodium hydroxide solution and filtering; the acid was reprecipitated in pulverulent form by the careful addition of dilute acetic and hydrochloric acids. After one crystallization from an ether-petroleum ether mixture, the acid melted at 153°, and weighed 97.0 g., a yield of 88.0%.

The methyl ester was prepared by refluxing for three hours 91.8 g. of this acid with 918 g. of methyl alcohol containing 45.9 g. of conc. sulphuric acid. After cooling, the contents were poured into a large bulk of water, and filtered. After one crystallization from methyl alcohol, the product melted at 103°, and weighed 93.0 g., a yield of 96.0%.

The ethyl ester was prepared in a similar manner by refluxing the acid in ethyl alcohol for four hours. From 9.2 g. of the acid, 7.2 g. of this ester, m.p. 41°, was obtained, a yield of 71% of the theoretical.

B. Condensation With Benzaldehyde.

To 25 c.c. of benzaldehyde (U . S. P.) dissolved in

50 c.c. of absolute methyl alcohol, were added 33.5 g. of methyl α- phenyl - β- benzoyl propionate, and 3.0 g. of sodium in 50 c.c. of absolute methyl alcohol. The mixture was refluxed on the water-bath for two hours. The solution was acidified with acetic acid, and the alcohol and excess benzaldehyde were removed by steam distillation. The water was decanted from the impure crystals remaining, and these were well washed with water. After one crystallization from a small volume of methyl alcohol, the product melted at 142°, and weighed 36.5 g., a yield of 84.8% (calculated as a lactone, with loss of the ester group). It was recrystallized from an ether-petroleum ether mixture to constant m.p. 145°, in microscopic plates. It was very soluble in most of the organic solvents such as alcohol, ether and acetone, moderately so in benzene, and insoluble in petroleum ether.

Anal. Calcd. for $C_{23}H_{18}O_3$: C, 80.7 ; H, 5.2
Found : C, 80.1 ; H, 5.2

The same product was obtained in 87.3% yield by condensing the ethyl ester with benzaldehyde in a similar manner, with the use of ethyl alcohol as the solvent. A mixed melting point with the product from the methyl ester condensation was not depressed. It readily dissolved in dilute sodium hydroxide solution, and reprecipitated unchanged on acidification. It was insoluble in sodium bicarbonate solution.

In the Grignard "machine" the product showed the presence of two active hydrogens, and the addition of one group. The experimental details are omitted here, since the method is described elsewhere in this dissertation.

A sample evolved two moles of methane with the Grignard reagent and reacted with three moles of the latter.

Condensations of the methyl ester with anisaldehyde, and p- chlorbenzaldehyde in a similar manner, yielded untractable oils.

C. <u>Pyrolysis of the Product</u>

$$C_{23}\,H_{18}\,O_3 \xrightarrow[-CO_2]{230^{\circ}} C_{22}\,H_{18}\,O. \xrightarrow{KMn\,O_4} 3\,C_6H_5\,COOH$$

On heating the product 80° above its melting point, it lost carbon dioxide to form a compound of empirical formula, $C_{22}\,H_{18}\,O$. The pyrolysis product was oxidized by potassium permanganate to benzoic acid, three equivalents of the latter being formed.

(a) Pyrolysis.

Twenty grams of the condensation product were placed in a 100 c.c. Claisen flask, the delivery-tube of which was connected with a glass tube leading into barium hydroxide solution. The flask was heated gradually to 230° in a metal bath, at which temperature carbon dioxide was rapidly evolved, causing a heavy precipitation of barium carbonate. The flask was kept at this temperature for 2¼ hours, when the evolution ceased. The resulting oil was distilled under a pressure of 18 mm. into three different containers, approximately one-third being collected in each. The temperature remained constant at 270° (± 2°) during the distillation, except toward the end when decomposition set in. The first portion of distillate was clear yellow, the second slightly darker, while the third was dark brown due to composition. The total yield was 16.0 g. or 92% of the theoretical.

Anal. Calcd. for $C_{22}H_{18}O$: C, 88.6 ; H, 6.0
Found : C, 88.2 ; H, 6.0 (1st portion)
C, 88.2 ; H, 5.9 (2nd portion)

A little of the oil was dissolved in hot ethyl alcohol and allowed to stand open for several days. A few crystals formed which were used to inoculate a sample of the oil, complete crystallization resulting in two weeks. A portion was recrystallized from warm methyl alcohol to constant m.p. 48°.

In the Grignard "machine" this product showed the presence of one active hydrogen, and the addition of one group. With the Grignard reagent it evolved one mole of methane, and reacted with two moles of the reagent.

Attempts to form an oxime and a phenyl hydrazone in the ususl manner were unsuccessful; no crystalline material was isolated in either case.

(b) Oxidation of the Pyrolysis Product.

Five and eight-tenths grams of the pyrolysis product (m.p. 47°) was dissolved in 100 c.c. of acetone(distilled over KOH and $KMnO_4$), and 14.5 g. of finely ground potassium permanganate was slowly added. Oxidation started easily and the solution became quite warm. A little ethyl alcohol was added to remove the slight excess of permanganate. On extraction of the precipitated manganese dioxide with sodium hydroxide solution, and subsequent acidification, 4.5 g. of benzoic acid were obtained, identified by a mixed melting point. On spontaneous evaporation, the acetone solution deposited a further quantity of 1.5 g. of benzoic acid. The total weight of benzoic acid obtained was 6.0 g., whereas the theoretical weight is 7.1 g.

D. Oxidation of the Condensation Product.

1. With Potassium Permanganate.

In a manner identical with that described elsewhere, 2.0 g. of the original lactone was oxidized with 2.6 g. of potassium permanganate. The only product isolated was benzoic acid, of which 1.6 g. was obtained.

2. With Chromic Acid.

Following the method described previously, 6.0 g.

of the condensation product in glacial acetic acid was treated with 5.0 g. of chromic acid, for one hour at 25° - 30° with continual stirring. No oxidation product was isolated, and 4.6 g. of the product was recovered unchanged. This behaviour is in marked contrast to that of the other lactones, described in the first part of this thesis.

E. Reaction with Hydroxylamine.

An oxime of the product was readily prepared in the following manner.

Three grams of hydroxylamine hydrochloride was dissolved in 30 c.c. of hot ethyl alcohol, and 4.6 g. of potassium acetate was added. After filtering the potassium chloride, 5.0 g. of the condensation product was added to the solution, and the mixture was refluxed for two hours. After cooling, the solution was poured into water, and the oxime was recrystallized repeatedly from n. butyl alcohol to constant m.p. 181°. It was obtained as small plates, sparingly soluble in hot methyl and ethyl alcohols, quite soluble in ether.

Anal. Calcd. for $C_{23}H_{19}O_3N$: N, 3.9.
Found : N, 3.7.

Conclusion.

Methyl α- phenyl -β- benzoyl propionate condenses with benzaldehyde in the presence of sodium methylate to form a lactone of unknown structure. On heating, this lactone loses carbon dioxide, and forms an unsaturated substance which on oxidation gives benzoic acid.

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