# THE SYNTHESIS OF SOME

# $\alpha$-SUBSTITUTED $\gamma$- BUTYROLACTONES

by

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M. Sc. Chemistry

Karl Elmer Krushel

# THE SYNTHESIS OF SOME α-SUBSTITUTED γ-BUTYROLACTONES

## ABSTRACT

α-Benzyl- γ-butyrolactone is produced when ethylene oxide, ethyl sodiomalonate and benzyl bromide are condensed and the resulting ester hydrolyzed and decarboxylated. When this lactone is oxidized with chromium trioxide, α-benzyl-succinic acid results. When benzyl bromide is replaced by ethyl - α-bromopropionate the reaction cannot be carried to a successful completion. This ester also fails to react in the expected manner with cyclohexene oxide and ethyl sodio-malonate.

The monobenzyl derivatives of malonic ester and aceto-acetic ester have been prepared but second stage substitution with β-chloroethyl vinyl ether in the first case and ethylene chlorohydrin in the second has failed to take place.

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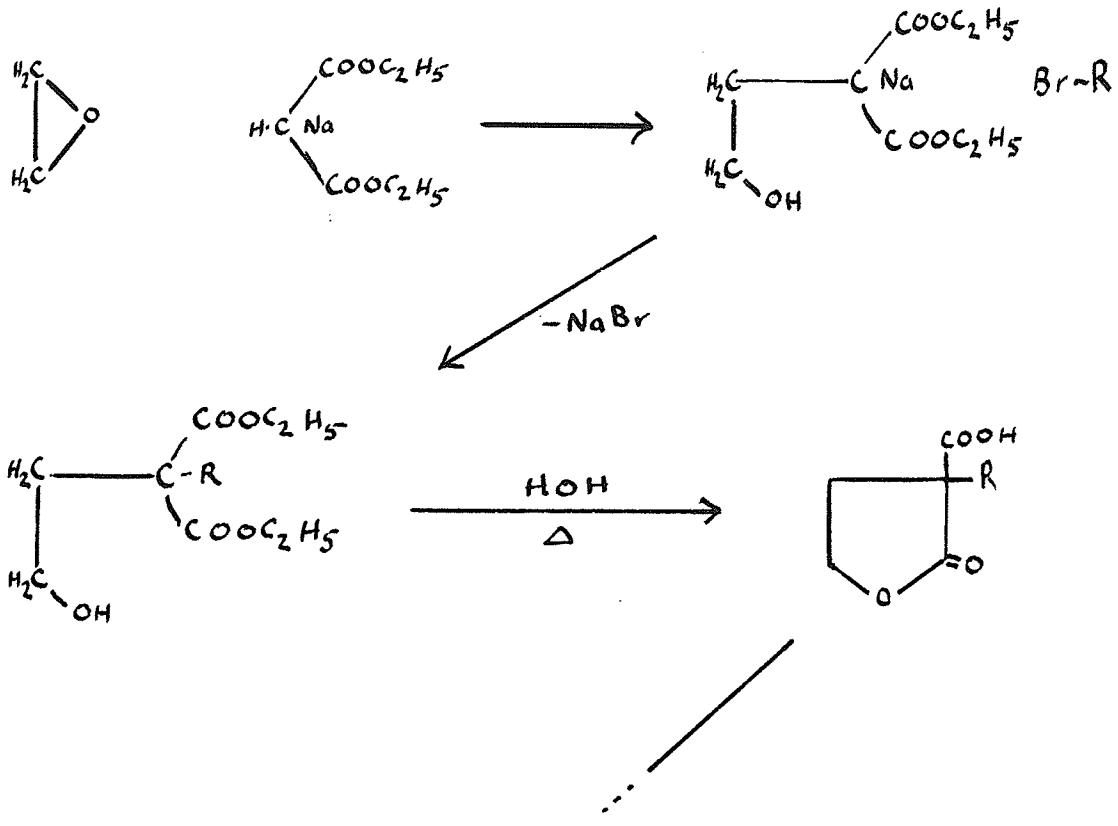
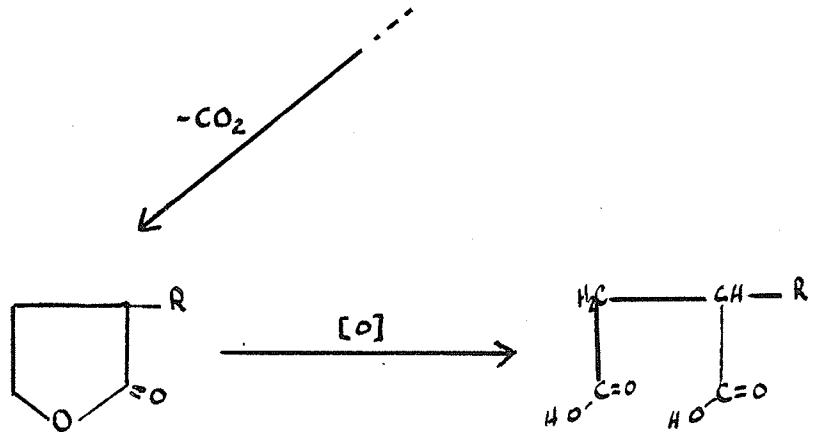
# INTRODUCTION

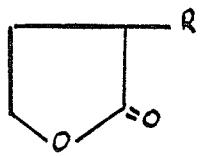
The first of a series of papers by Charlesworth, Alexander and coworkers (22) published in 1943, outlined the synthesis of a number of 2-ketocyclohexylcarboxylic acids. These acids were prepared by oxidation of the respective γ-lactones. Later this work was developed further in these laboratories by Sinder (27), Stachiw (28), and Campbell (5). On re-examining this work recently it was considered desirable to extend their work and complete certain phases. The methods used by these men are applied in the present work in an effort to synthesize three new compounds.

The general method outlined by these workers is as follows:

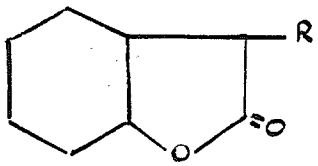





The compounds with which the present work was concerned, were of two general types:




Type I



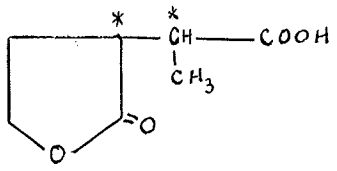

Type II

By condensing ethylene oxide with the sodio derivative of ethyl malonate in the presence of the appropriate alkyl halide RX, compounds of Type I would be obtained. The use of cyclohexene oxide in place of ethylene oxide would yield compounds of Type II.

The synthesis of two lactones of Type I was investigated. First, using Benzyl bromide, a compound was obtained where R=-$CH_2$ - $C_6H_5$. The $\gamma$-lactone was successfully synthesized and then oxidized to the corresponding succinic acid.

The second compound of Type I to be synthesized was the $\alpha$-propionic acid derivative in which R = $CH_3$ - CH-COOH.

Some difficulty was experienced in obtaining this compound, which was at first attributed to the possible existence of two racemates as suggested by the presence of two optically active carbon atoms.




As a result our attention was turned to the related lactone of Type II. Again R: $CH_3$-$\overset{|}{C}$H-COOH. The synthesis of this compound had not been attempted in earlier work, so it was decided to do so at this time.

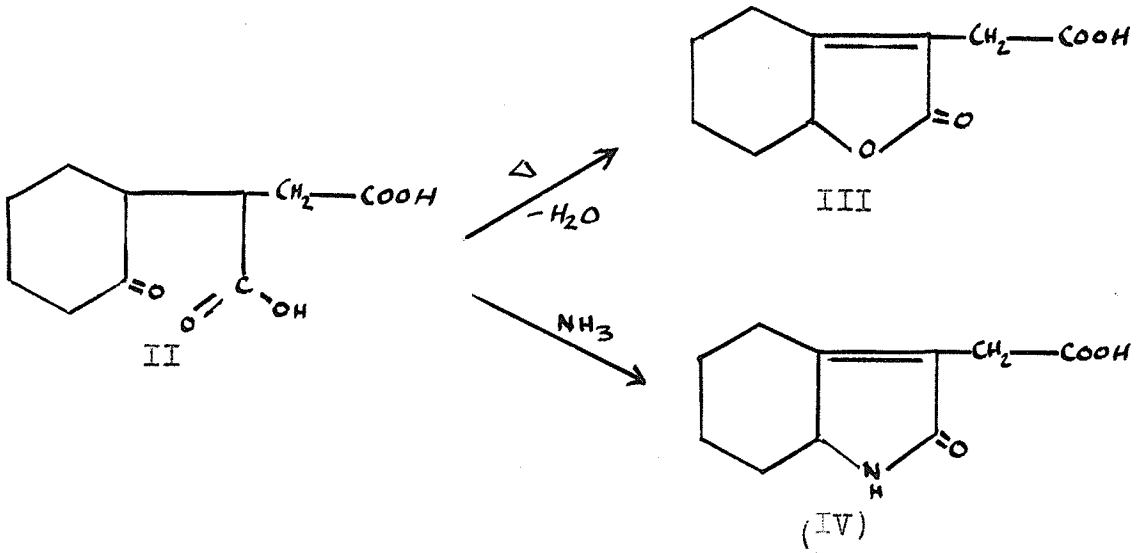
# LITERATURE SURVEY

## Cyclohexene Oxide Condensations

In 1926, Kendall, Osterberg and MacKenzie (19,20) recorded the synthesis of α- (2-ketocyclohexyl) glutaric acid (I), its anhydro derivative, and its lactam. The acid was obtained by oxidation of the corresponding lactone. The present study of certain lactones, follows a method of synthesis which stems originally from the work of these men. Their preparation is represented schematically-Diagram I.

Later, Charlesworth (7) carried out similar syntheses whereby he confirmed the preparation of 2-ketocyclohexyl-glutaric acid by Kendall, Osterberg and MacKenzie.

McRae, Charlesworth and Alexander (22) extended the method to the preparation of other ketocyclohexyl acids and their corresponding lactones. 2-ketocyclohexylsuccinic acid (II) was obtained by condensing cyclohexene oxide with the sodio derivative of malonic ester and ethyl bromoacetate, then followed by treatment as outlined above.



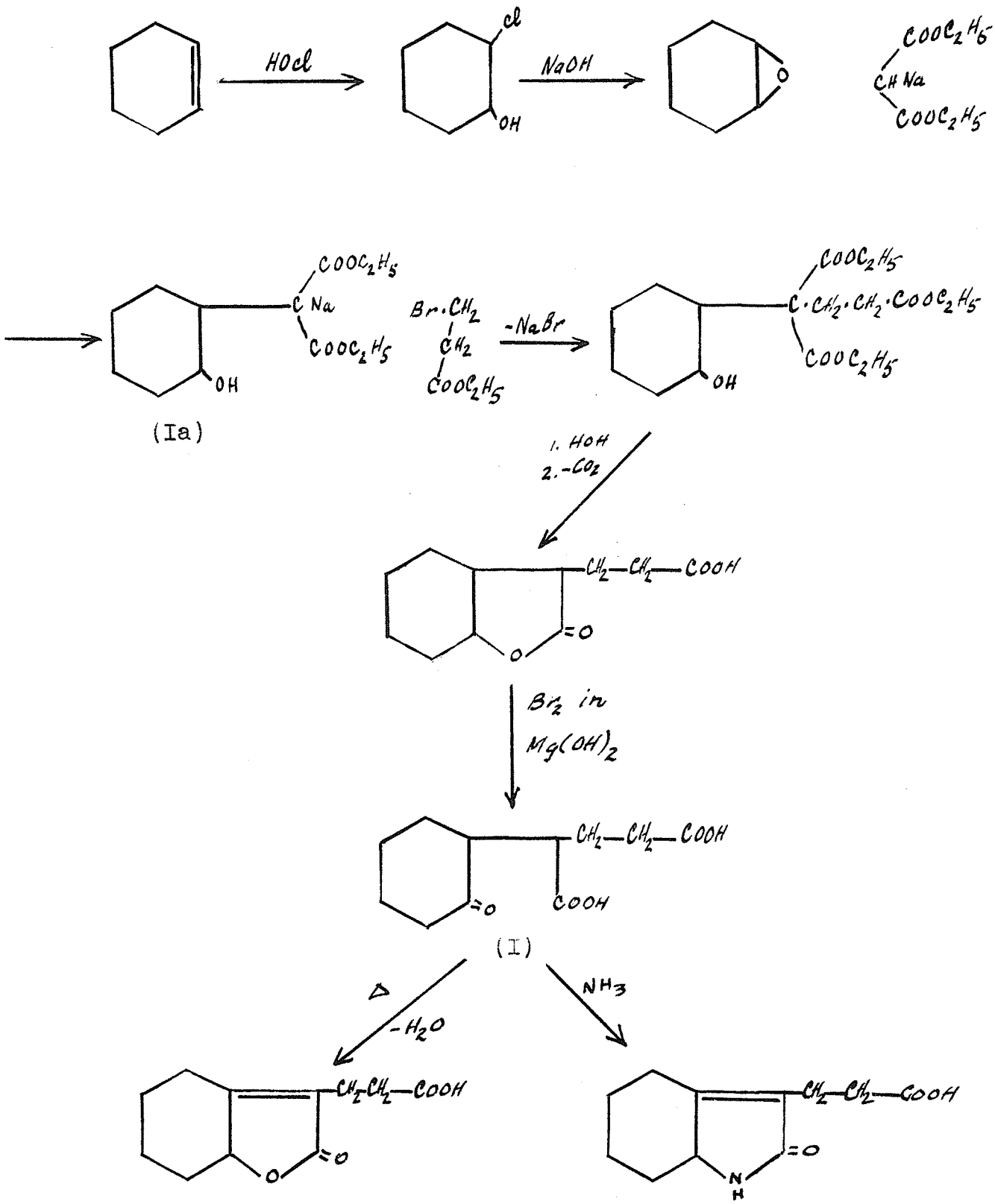



Diagram I.

On heating in vacuo at 200°C a molecule of water was lost and the unsaturated lactone (III) produced. When the keto acid (II) was treated with alcoholic ammonia under pressure the lactam (IV) was produced.

Coffey (11) condensed cyclohexene oxide with ethyl sodio-malonate and obtained the ester lactone (V) which on hydrolysis and decarboxylation yielded cyclohexanolacetic acid lactone (VI). By oxidation of this lactone with bromine and magnesium hydroxide, McRae, Charlesworth and Alexander (22) obtained 2-ketocyclohexylacetic acid (VIII). On dehydration, this gave the anhydro derivative which they felt had the unsaturated lactone structure (X). Treatment with alcoholic ammonia probably yielded the lactam of (VIII), but it was so unstable that it decomposed on attempts at purification. The series of reactions is represented in Diagram II.

Treatment of the hydrolyzed ester lactone (VII) with bromine and magnesium hydroxide or by alkaline permanganate yielded 2-ketocyclohexylmalonic acid (IX). This acid was rather unstable and tended to decompose with loss of carbon dioxide at the melting point.

McRae, Charlesworth and Alexander (22) obtained the lactone of cyclohexanolbenzylacetic acid (XI) by the condensation of cyclohexene oxide, the sodio derivative of malonic ester and benzyl chloride followed by hydrolysis and decarboxylation. They found that whereas condensations involving $\beta$-bromopropionic ester or bromoacetic ester occurred at room

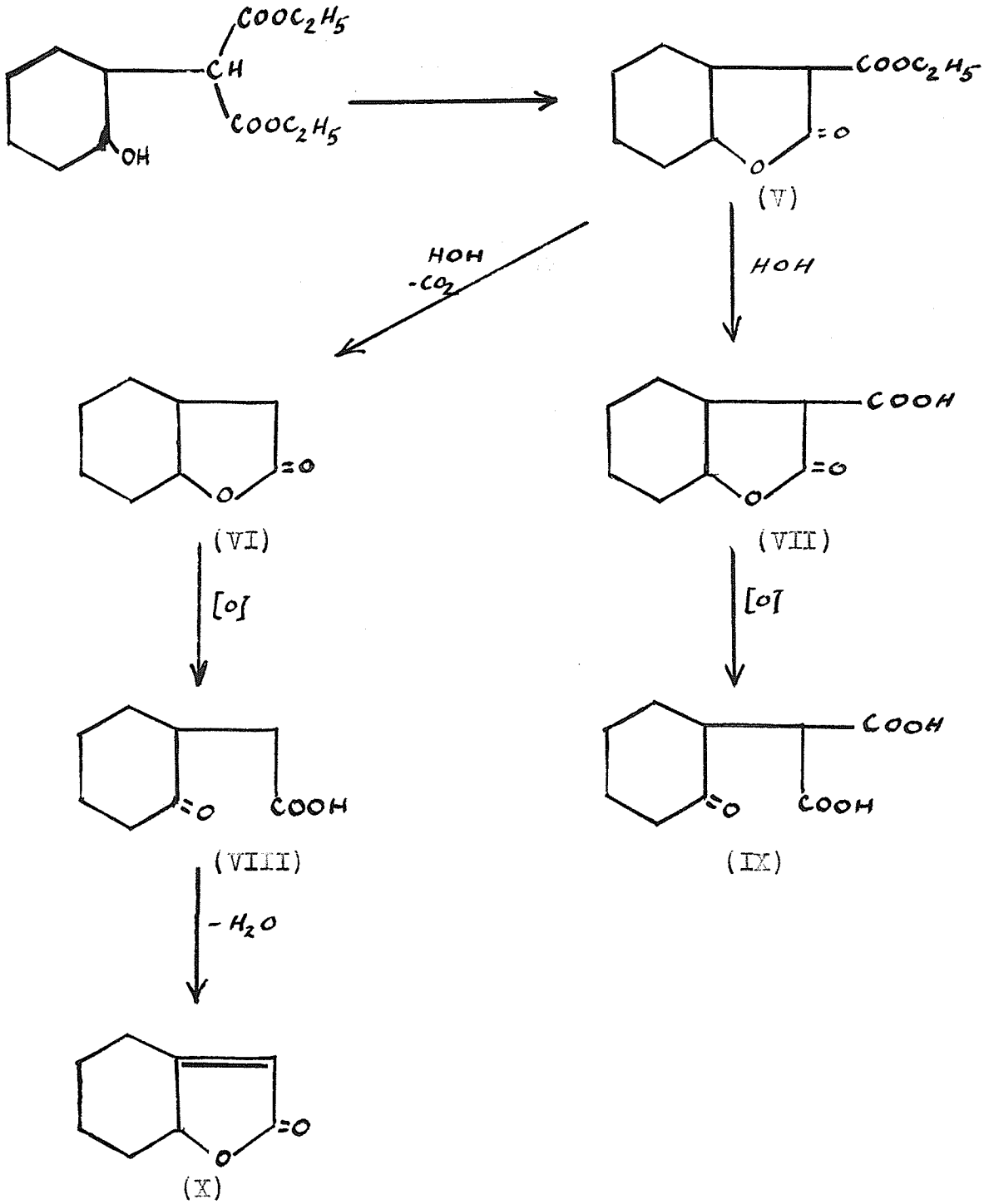
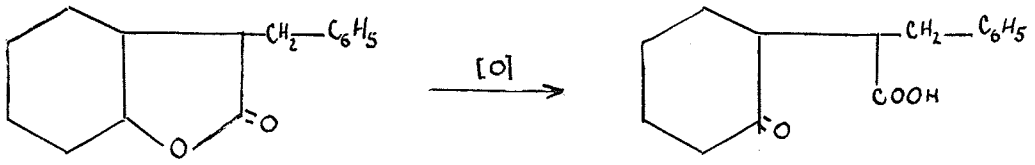

COOC2H5
CH
COOC2H5
OH
COOC2H5
=O
O
(V)
HOH
-CO2
HOH
=O
O
(VI)
COOH
=O
O
(VII)
[O]
[O]
=O
COOH
(VIII)
COOH
=O
COOH
(IX)
-H2O
=O
O
(X)

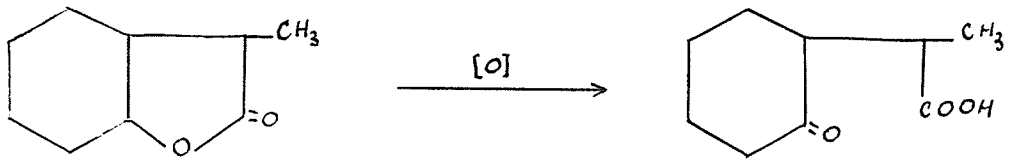
Diagram II.

temperature, those involving benzyl chloride or alkyl halides required ma ny hours of refluxing. When (XI) was oxidized in the usual way, 2-ketocyclohexylbenzyl-acetic acid (XV) was produced. On distillati on, this compound lost water and was therefore best isolated in the form of its unsaturated lactone.




(XI) (XV)

When methyl iodide replaced benzyl chloride in the above condensation, the $\gamma$-lactone of cyclohexanol -$\alpha$-propionic acid was produced (XII), which on oxidation with bromine and magnesium hydroxide produced 2-ketocyclo-hexyl-$\alpha$- propionic acid (XIII).




(XII) (XIII)

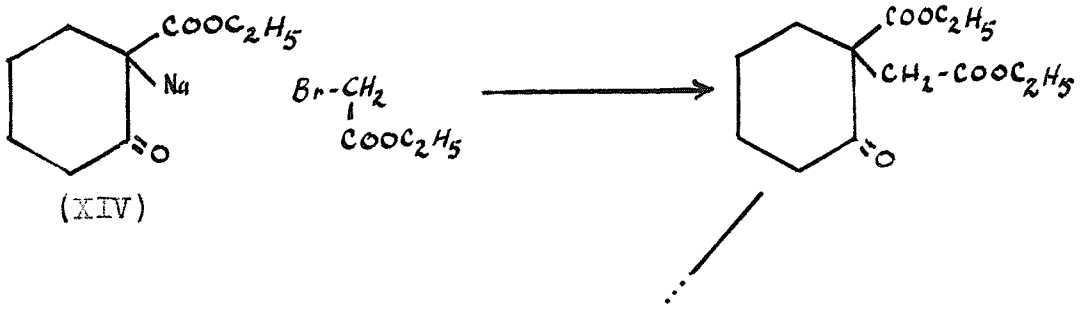
As the synthesis of 2-ketocyclohexylsuccinic acid and related substances from cyclohexene oxide are somewhat involved, Charlesworth, McRae and MacFarlane (8), in search for simpler methods, and also to confirm the structures assigned, began synthetical work using cyclohexanone as the starting material. Two methods used, were:

1) The elimination of sodium bromide between the sodio-derivative of ethyl cyclohexanone - 2-carboxylate and brominated esters, followed by hydrolysis.

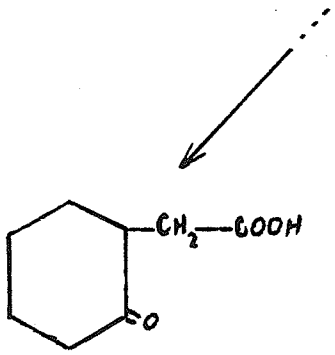
2) The oxidation of the $\gamma$-lactones of cyclohexanolcarboxylic acids which are prepared by Reformatsky reactions between cyclohexanone and $\alpha$-brominated esters, followed by treatment with mineral acid.

Method (1)

Chuang and Ma (10), Chatterjee (9), and Ghosh (18) synthesized 2-ketocyclohexylacetic acid (VIII) from the sodio derivative of ethyl cyclohexanone - 2-carboxylate (XIV) and ethyl chloroacetate. Charlesworth and coworkers (8) repeated this preparation, employing ethyl bromoacetate, and obtained a purer product than that prepared by other authors or previously by themselves.

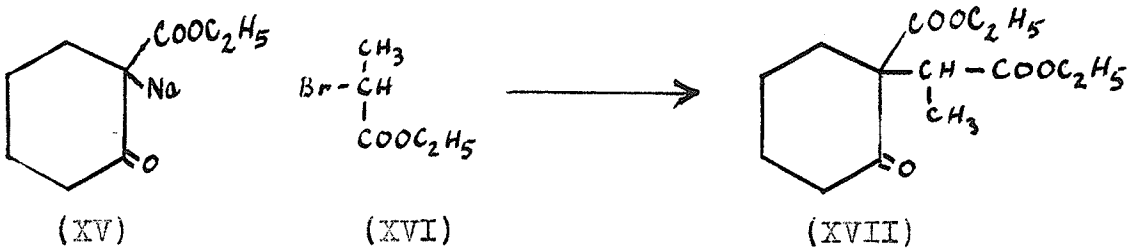



(XIV)

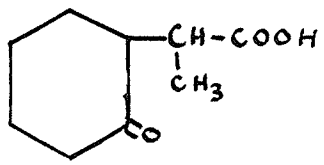


(VIII)

Using this method the corresponding 2-ketocyclohexyl -α- propionic acid (XIII) was obtained by MacFarlane (21) after experiencing considerable difficulty in purification. The sodio-derivative of ethyl cyclohexanone -2- carboxylate (XV) was condensed with ethyl α-bromopropionate (XVI) and the resulting ester (XVII) subjected to hydrolysis.

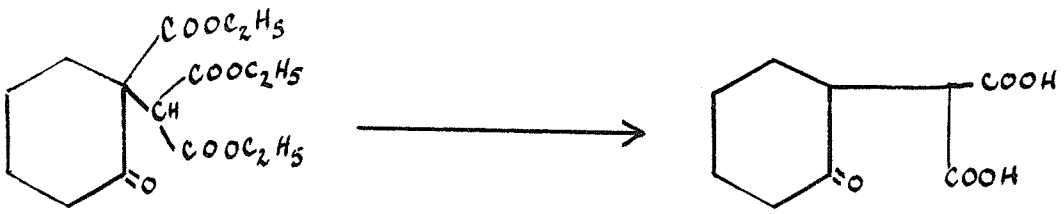


(XV) (XVI) (XVII)



(XIII)

The main interest centred in the application of this method to the attempted preparation of 2-ketocyclohexylmalonic acid (IX) and 2-ketocyclohexylsuccinic acid (II). When ethyl cyclohexanone -2- carboxylate was condensed with ethyl bromomalonate it was expected that the ester (XVIII) would result, and on hydrolysis, 2-ketocyclohexylmalonic acid (IX). However the original reactants were recovered unchanged, along with an oil, probably ethanetetracarboxylic ester.



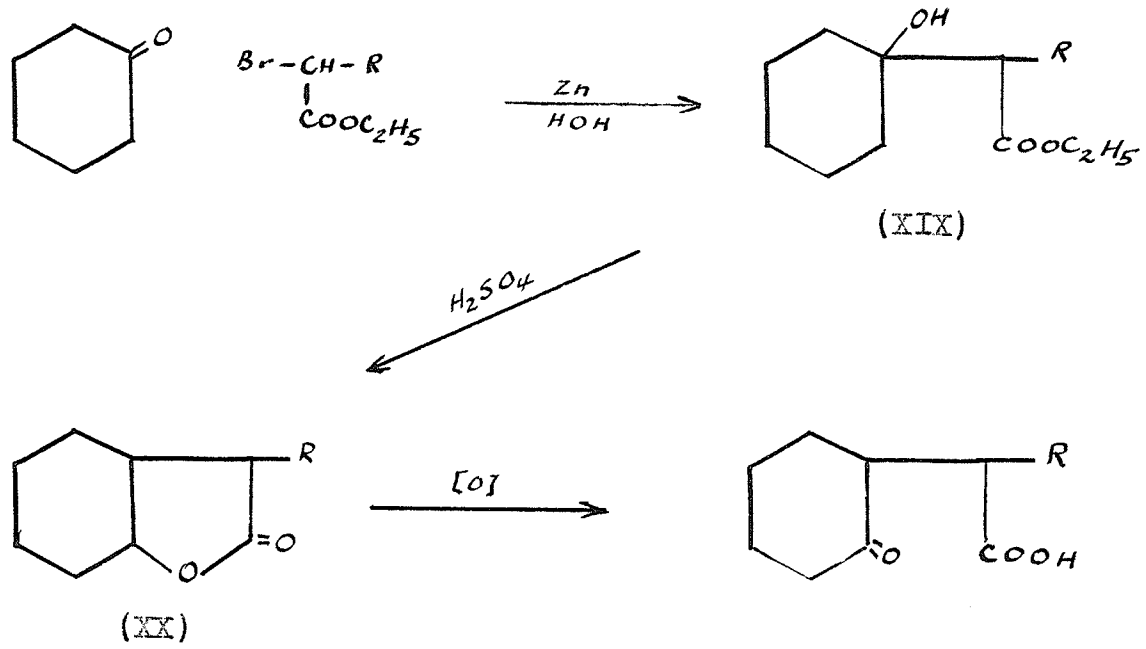

(XVIII) (IX)

The reaction failed also with ethyl cyclohexanone -2-carboxylate and monobromosuccinic ester. The products resulting were not indentified but no 2-ketocyclohexylsuccinic acid was obtained.

Method (2)

Reformatsky reactions have been utilized in the preparation of $\alpha$ -(1-cyclohexanol) fatty acid esters (XIX) by Wallach and his associates (32, 33, 34), and by Auwers and Ellinger (3). Boehringer and Sohn (4) prepared the $\delta$ -lactones of cyclohexanol fatty acids (XX) by boiling these esters with mineral acids.

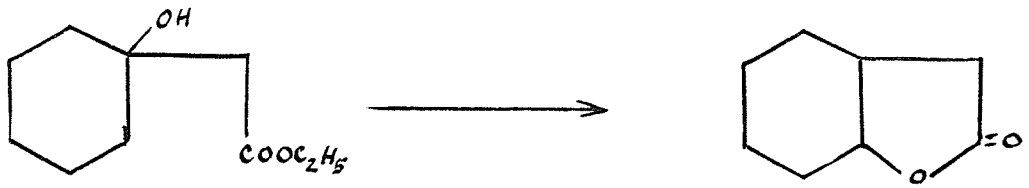
Their preparation may be represented schematically as follows:-




(XIX)

(XX)

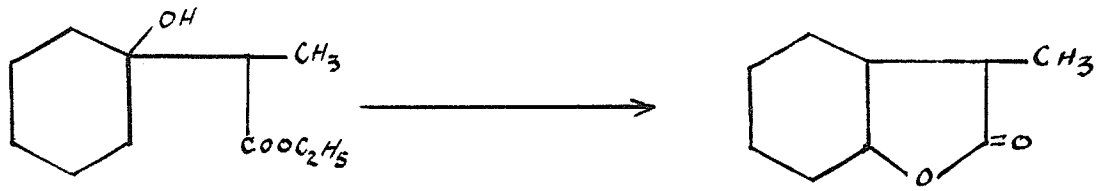
From cyclohexanone, ethyl bromoacetate and zinc, Charlesworth, McRae and MacFarlane (8) obtained the hydroxy acid (XXI) and on treatment with mineral acid the $\delta$ -lactone of cyclohexanolacetic acid (VI), identical with that prepared by Coffey (11) and by McRae and coworkers (22) from cyclohexene oxide.




(XXI)

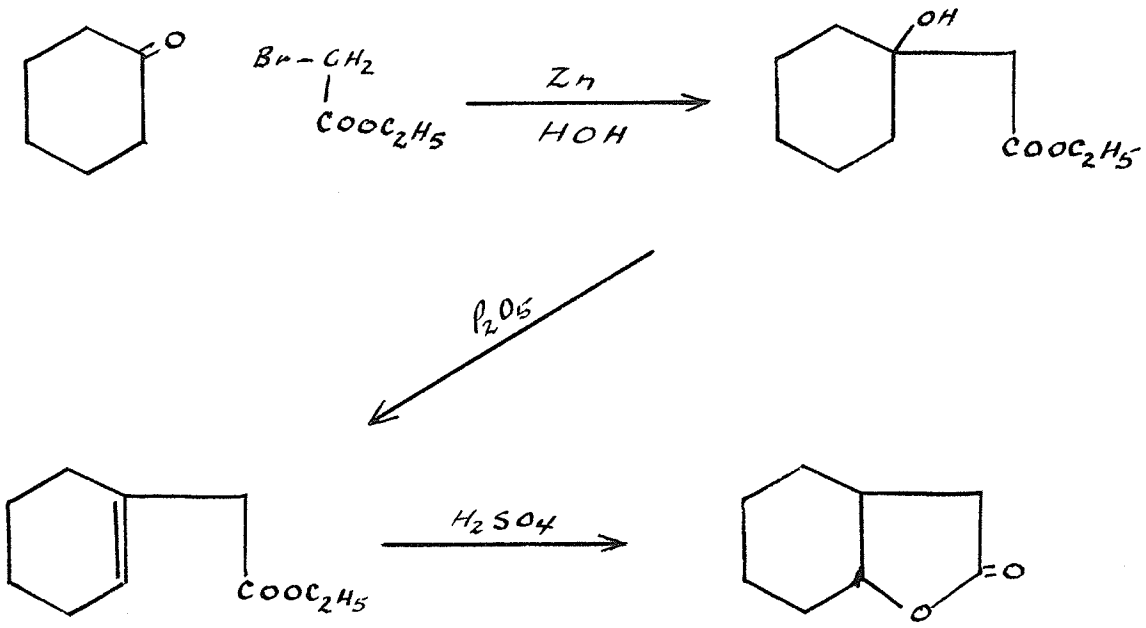
(VI)

Similarily from cyclohexanone and ethyl ∝-bromopropionate, they produced the hydroxy ester (XXII) which with mineral acid gave the ɣ-lactone of cyclohexanol - ∝-propionic acid (XII).

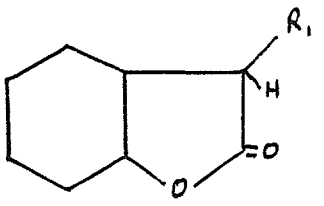



(XXII) (XII)

By a Reformatsky reaction followed by dehydration and hydrolysis, Stachiw (28) obtained a number of lactones. His work was a repetition and improvement of the method used by MacFarlane (21), and may be outlined as follows:



By condensing the appropriate $\alpha$-halo ester with cyclohexanone in the presence of zinc, he obtained the following lactones:



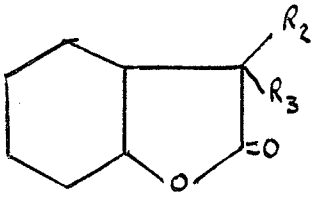
where $R_1 = H$

$= CH_3$

$= CH_2-CH_3$

$= CH_2-CH_2-CH_3$

$= CH(CH_3)_2$



where $R_2 = CH_3$

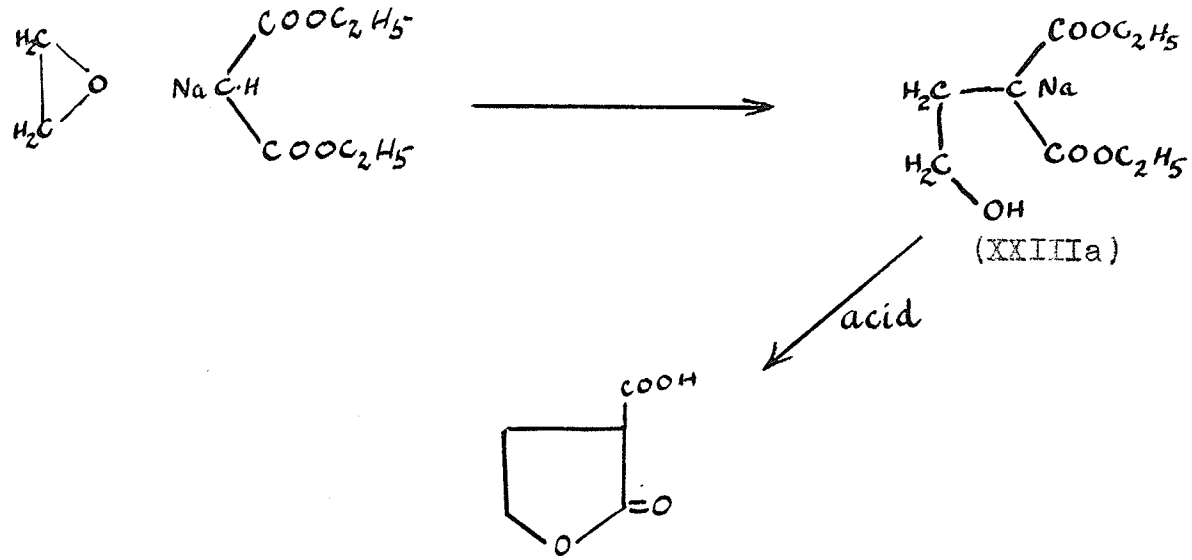
$R_3 = CH_3$

In 1957, H.J. Campbell (5) prepared the $\gamma$-lactone of cyclohexanol -2- $\alpha$-propionic acid (XII) by two different methods. He found that the two methods yielded two different geometrical isomers. Using the cyclohexene oxide method he prepared (XII) by condensing the sodio derivative of ethyl malonate with cyclohexene oxide followed by the addition of methyl iodide. He then used the Reformatsky - Fittig method condensing cyclohexanone with ethyl $\alpha$-bromopropionate as outlined by Stachiw (28). The two lactones were found to have the same elementary composition but yielded hydrazide derivatives which melted at different temperatures. By means of infra red

studies he finally established that the cyclohexene oxide method yielded the trans isomer while the Reformatsky-Fittig method, the cis isomer.

Ethylene Oxide Condensations

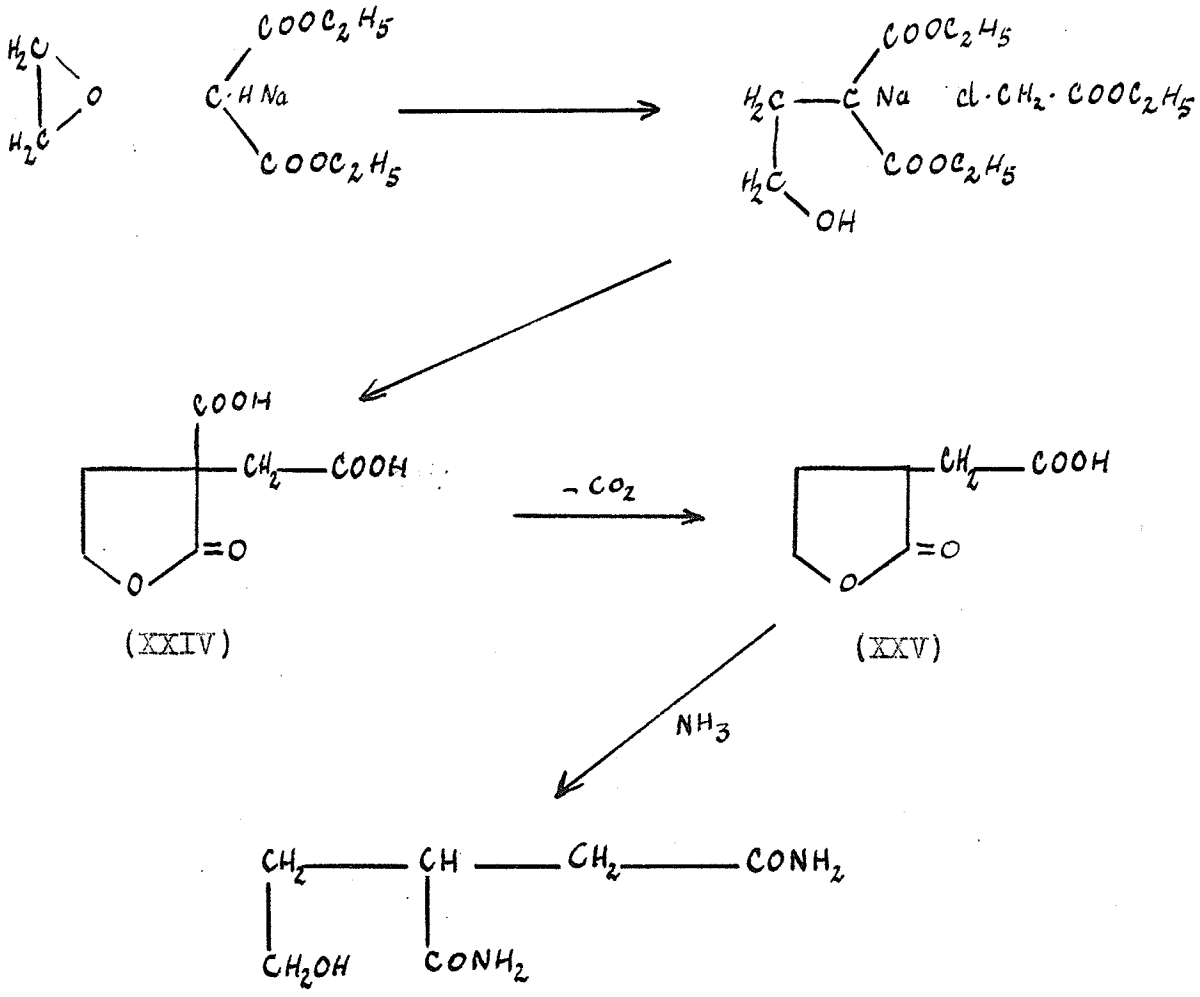
The synthesis of the γ-lactone of cyclohexanolsuccinic acid by McRae, Charlesworth and Alexander (22) from cyclohexene oxide suggested that this method might be extended to other ethylenic oxides. Prior to this, such condensations between sodio-activated methylene groups and ethylenic oxides had been rather infrequent. Traube and Lehmann (30,31) condensed ethylene oxide with ethyl sodiomalonate and on acidification obtained γ-2-carboxybutyrolactone. (XXIII).




(XXIIIa)

(XXIII)

McRae, and colleagues, (22) obtained 2-oxo-3-carboxytetrahydrofuran -3-acetic acid (XXIV) when the sodium salt resulting from the condensation of ethylene oxide and ethylsodiomalonate was treated with ethyl chloroacetate, and the product hydrolyzed. On decarboxylation this yielded 2-oxotetrahydrofuran-3-acetic acid (XXV). When (XXV) was treated with alcoholic ammonia under pressure, the lactone ring opened and the diamide (XXVI) was formed.

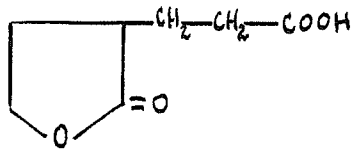


(XXIV)

(XXV)

(XXVI)

When ethyl chloroacetate was replaced by ethyl -$\beta$- bromopropionate in the above reaction, 2-oxotetrahydrofuran-3-propionic acid (XXVII) was obtained.

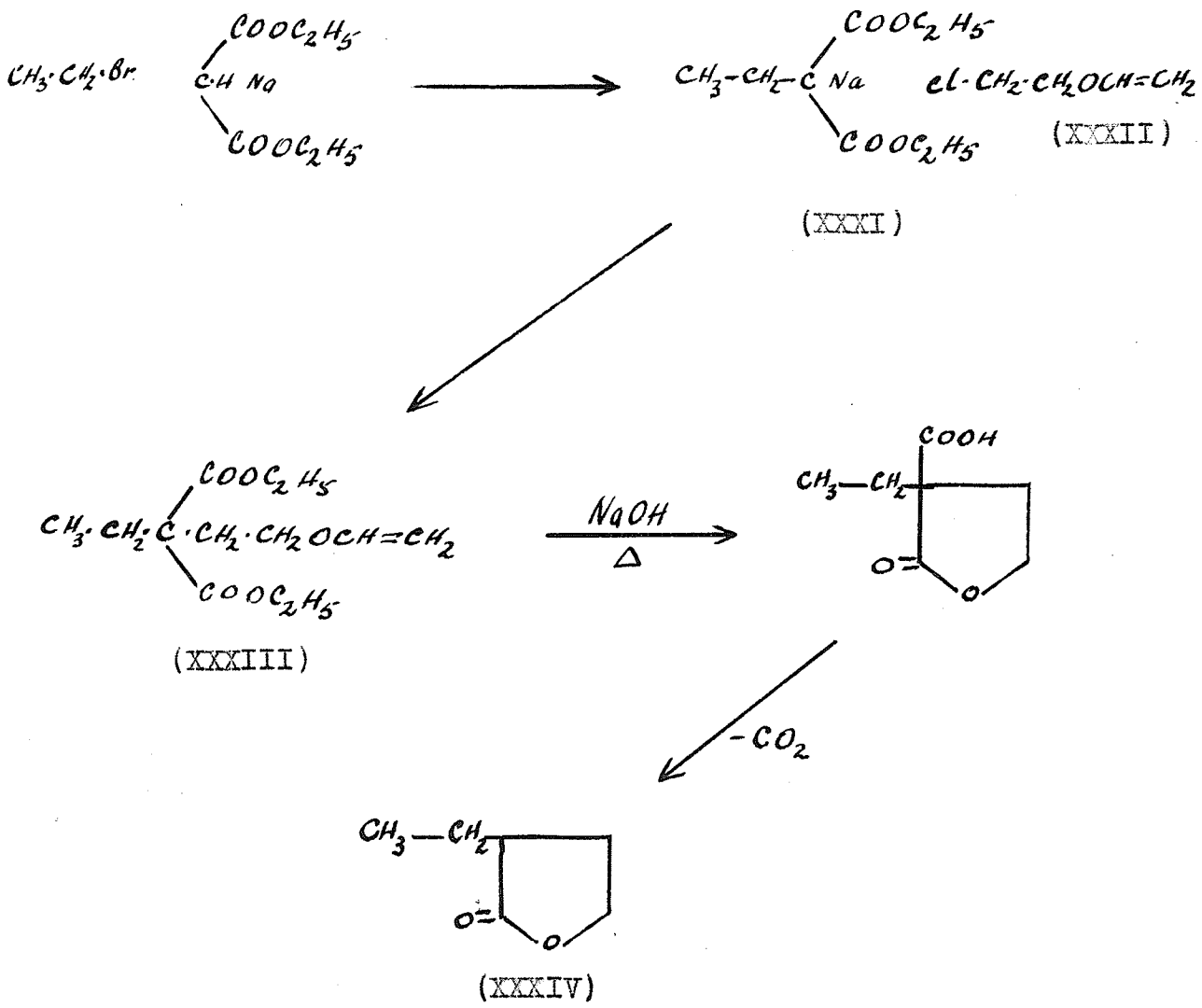



(XXVII)

In his thesis, Alexander (2) reports experiencing difficulty obtaining (XXV) and (XXVI) in crystalline form. However, he finally isolated pure (XXV), but not (XXVII). Later Sinder (27) in the same laboratories repeated Alexander's work and obtained pure crystalline 2-oxotetrahydrofuran-3-propionic acid (XXVII).

Condensation with $\beta$ -chloroethyl vinyl ether.

The preparation of certain $\gamma$-lactones by a method quite similar to that described above, was used by Nelson and Cretcher (12,24). They found that $\beta$-chloro-ethyl vinyl ether (XXXII) readily reacted with sodium diethyl malonate and mono-alkyl substituted malonic esters (XXXI) to form diethyl-vinyloxyethyl malonate and its corresponding alkyl substitution products. (XXXIII). In this way they prepared $\alpha$-ethyl - $\gamma$-butyrolactone (XXXIV). Their method may be outlined as follows:



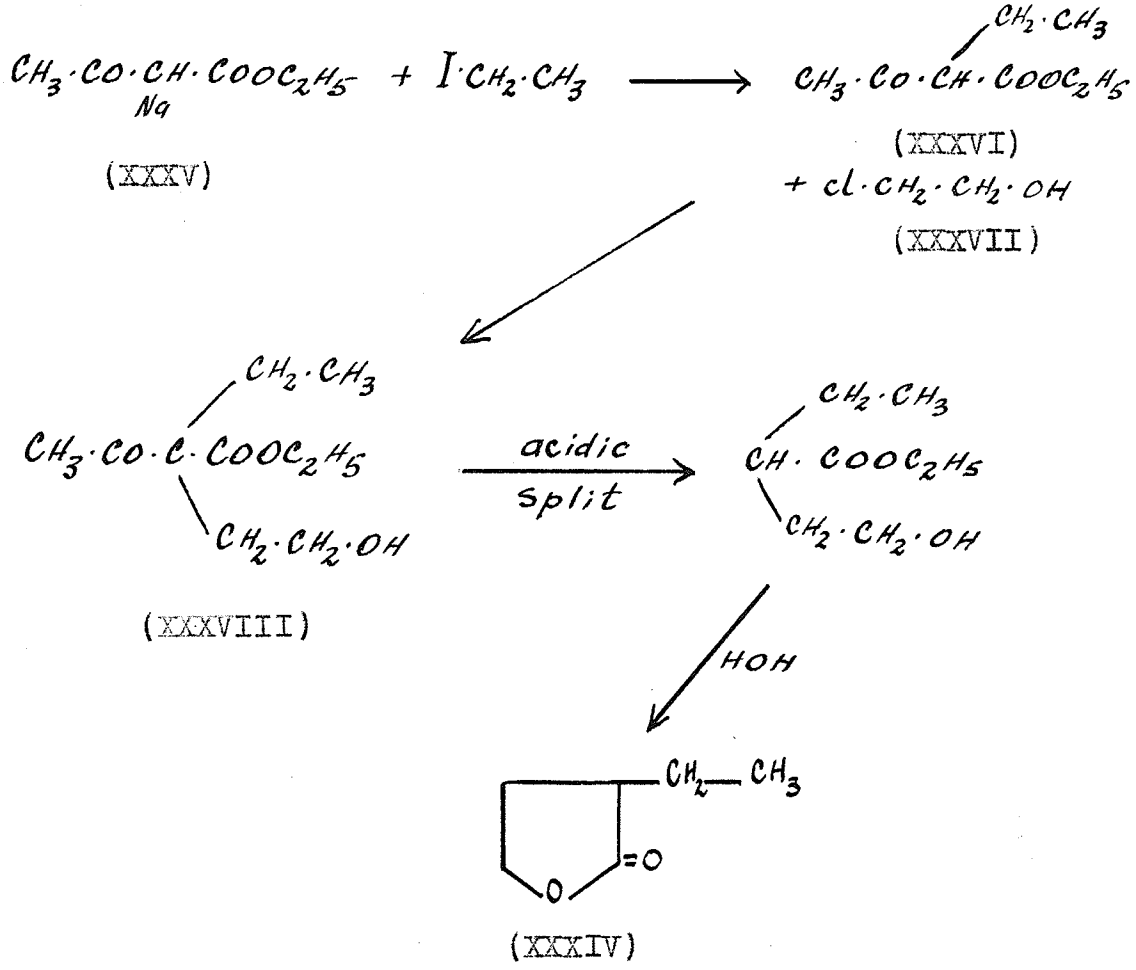

(XXXIII)

(XXXIV)

Condensations with ethyl acetoacetate

Some of the earliest work concerning γ -hydroxy acids and lactones was done by Fittig and Chanlaroff (6, 14). They prepared butyrolactone and α -ethyl butyrolactone from ethyl acetoacetate. Substituting one of the active hydrogen atoms by ethylene chlorohydrin, they obtained butyrolactone. Replacing the other active hydrogen atom by an ethyl group, they obtained α -ethylbutyrolactone.

The addition of ethyl iodide to the sodio derivative of acetoacetic ester (XXXV) yielded $\alpha$-ethyl acetoacetic ester (XXXVI). When the sodio derivative of (XXXVI) was refluxed with ethylene chlorohydrin (XXXVII) for 25-30 hours, $\alpha$-ethyl $\alpha$-($\beta$-oxyethyl) acetoacetic ester (XXXVIII) was formed with the precipitation of sodium chloride. The disubstituted ester (XXXVIII) on refluxing with concentrated barytawater lost acetic acid and on hydrolysis lactonized to produce $\alpha$-ethyl butyrolactone. (XXXIV).




(XXXV)

(XXXVI)

(XXXVII)

(XXXVIII)

(XXXIV)

# EXPERIMENTAL

## PREPARATION OF MONOCHLOROUREA SOLUTION

Method used: Detoeuf, A. (13)

The reaction may be represented by the following equation:

$$2\ CO(NH_2)_2 + 2\ Cl_2 + CaCO_3 \longrightarrow 2\ \begin{matrix} NHCl \\ | \\ CO \\ | \\ NH_2 \end{matrix} + CaCl_2 + CO_2 + H_2O$$

A mixture of urea (200g.), precipitated chalk (141g.) and water (150 ml.) was placed in an Erlenmeyer flask (1ℓ.) and cooled. Chlorine was passed in until the weight had increased about 105 g. (Time required: 3¼ hrs.). The mixture was then diluted to 700 ml. and the excess calcium carbonate filtered off.

Monochlorourea solution (1 ml.) was placed in a flask containing a solution of potassium iodide (10ml. 2N), enough acetic acid to make the solution acidic (10 ml.) and water (25 ml.). The strength ofthe acid was determined by titrating this solution with sodium thiosulfate (0.1N) using starch as an indicator. The monochlorourea solution (700 ml.) was found to be 9.2% in hypochlorous acid.

As the strength of the monochlorourea solution decreased on standing, it was reacted with cyclohexene without further delay.

PREPARATION OF o-CHLOROCYCLOHEXANOL

Method of Detoeuf (13) was used.

Freshly prepared monochlorourea solution (700 ml. 9.2% HOCl) was placed in a flask (2 l.) equipped with a mechanical stirrer. To this, ten percent excess of cyclohexene (111g.) was added along with, ice (150 g.), water (350 ml.) and glacial acetic acid (70 g.)

The mixture was kept below 15°C and the hypochlorous acid solution added in four equal portions over a period of 3-4 hours. Stirring was continued until the strength of the acid solution was nil by titration. Eventually a white oily layer separated on the bottom. The chlorohydrin was separated from the mixture by steam distillation. The aqueous distillate was then saturated with salt and the chlorohydrin extracted with ether. The ethereal portion was treated with Drierite, the ether removed by distillation and the residue distilled under reduced pressure.

The fraction passing over between 74-76°/ 6mm was collected.

After two runs chlorohydrin (178 g.) was obtained.

PREPARATION OF CYCLOHEXENE OXIDE

Method described in Organic Syntheses (25).

Sodium hydroxide (58 g.) was added to chlorohydrin (178 g.). The mixture was mechanically stirred for one and a half hours, and no

longer since longer stirring results in decreased yields according to Gilman(25).When stirring was stopped, an oily layer of the oxide rose to the surface. The oil was separated mechanically, treated with Drierite and fractionated with a Widmer column.

The fractions collected were:

(1) 100° - 129° This fraction contained mostly cyclohexene along with some water. The size of this fraction was so small that it was discarded. The Widmer column was removed and dried before the second fraction was collected to insure anhydrous material.

(2) 129 - 134° a very large fraction containing pure cyclohexene oxide.

(3) 134° - The residue was quite small and hence discarded.

Cyclohexene oxide (89g.) was obtained from chlorohydrin (177.5g.), giving an average yield of 68% of the theoretical.

PART I.....(Synthesis involving cyclohexene oxide)

PREPARATION OF THE LACTONE OF

α- CYCLOHEXANOL -α'- METHYLSUCCINIC ACID (XLII)

Application of Method used by: Kendall, E.C., Osterberg, A.E. and MacKenzie, B.F. (19), McRae, J.A., Charlesworth, E.H. and Alexander, O.S. (22)

Sodium (11.5 g.) was entirely dissolved in absolute ethyl alchohol (250 ml.) in a round bottomed flask (1000 ml.) equipped with a mechanical stirrer. Diethyl malonate (88 g., 10% excess) was added and the mixture allowed to stand for ten minutes with stirring. Then cyclohexene oxide (39.g.) was added

and the solution turned milky white. This was allowed to stand over the weekend at room temperature during which time it turned solid. The ethyl alcohol was then removed in a vacuum.

The solid cake was broken into small pieces and benzene (400 ml.) added. The solution was stirred mechanically until it became of thick creamy consistency. To the suspension of this sodium addition product in benzene, ethyl $\alpha$-bromopropionate was added and allowed to react at room temperature for three days. Most of the benzene was removed and after cooling the residue, water added to remove the sodium bromide formed. As a result the residue turned into a thick paste which dissolved very slowly. After letting this stand for a few hours, and then treating again with water, all the solid dissolved and the two layers were separated mechanically.

The organic layer was fractionated as follows: benzene and ethyl alcohol were removed at atmospheric pressure by raising the temperature to 90°C. The residue was then put under suction (6 mm.) and the temperature raised to 150° in order to remove any unused ethyl $\alpha$-bromopropionate (60-65°/19 mm.)malonic ester (94-96°/18 mm.) and cyclohexene oxide (100-105°/19 mm.). The residue was cooled and potassium hydroxide (170 ml. 5N.) and ethyl alcohol (100 ml.) added. The resulting solution was stirred for two hours to complete the saponification, after which time the temperature was raised to 90° and the alcohol distilled off. The potassium hydroxide

was then neutralized by bubbling hydrogen chloride gas until the solution was acid to Congo red. An oil formed at this stage which was separated mechanically, and boiled for an hour to close the lactone ring. The oil was treated with Drierite and put on an oil bath at 160° to decarboxylate. An inorganic salt which formed was removed by washing with chloroform, and then acetone. The oil was heated to 105°/ 6mm. to remove impurities. However it failed to crystallize at -20°. Purification by distillation was not attempted since the yield was quite small. It was made into a phenylhydrazine derivative as outlined in the next section.

PREPARATION OF PHENYLHYDRAZINE

DERIVATIVE OF (XLII)

Method of Stempel, G.H. and Schaffel, G.S. (29)

The oil (1 ml.) obtained in the previous reaction was refluxed with phenylhydrazine (2 ml.) in a test tube equipped with a finger condenser. The solution turned a bright red color while being refluxed for 30 minutes and on cooling solidified in orange crystals. After filtration and recrystallization from benzene, white crystals were obtained which melted at 167.7° - 169.0°C.

Analysis:

Found C: 67.25% H: 7.88% N: 11.18%

Theoretical $C_{23}H_{30}O_3N_4$ C: 67.29% H: 7.37% N: 13.65%

The analysis would indicate that the reaction did not go to completion.

PART II.....(Syntheses involving ethylene oxide.)

PREPARATION OF THE LACTONE OF

α-(β-HYDROXYETHYL) - α'- METHYLSUCCINIC ACID (XLVI)

Method of Kendall, E.C., Osterberg, A.E. and MacKenzie, B.F. (19)

Sodium (11.5 g.) was completely dissolved in absolute ethyl alcohol (250 ml.) in a round bottomed flask (1000 ml.) equipped with a mechanical stirrer. Diethyl malonate (88 g., 10% excess) was added and the mixture allowed to stand for 10 minutes while stirring. Ethylene oxide (22 g.) dissolved in twice this amount of ethyl alcohol was then added, the flask and contents, being kept below 40°. At this stage cooling was necessary since evolution of heat would cause decomposition. The reaction mixture was allowed to sit overnight to complete the reaction.

The next day ethyl alcohol (100 ml.) was added to loosen up the material, and ethyl α-bromopropionate (90.5g.) added slowly while stirring. The suspension was allowed to react for three days at room temperature. The alcohol was then removed in vacuo, and benzene (300 ml.) added to the ester. The benzene solution of the ester was washed twice with water to remove the sodium bromide, and then most of the benzene was removed, before fractionating as follows:

Benzene and ethyl alcohol were removed at atmospheric pressure by raising the temperature to 98°. The residue was then put under suction (7 mm.) and the temperature raised to 100° in order to remove any unused ethyl α-bromopropionate (60-65°/19 mm.), malonic ester (100-105°/19 mm.) and ethylene

oxide (10.7°).

The residue was cooled and then hydrolyzed with sodium hydroxide (200 ml. 5N.) The solution was stirred to complete saponification, and the alcohol then removed by raising the temperature to 98°. Neutralization of the sodium hydroxide was effected by bubbling in HCl gas until the solution was acid to Congo red. During acidification a slight effervescence was observed and considerable heat was evolved. No precipitate was observed and so the solution was boiled for an hour to close the lactone ring. After cooling at 20° below zero overnight caused no crystallization, most of the water was evaporated and the syrupy mass extracted with glacial acetic acid, (250 ml.) since it was not soluble in ether. On removing the acetic acid in vacuo, some inorganic salt was still in evidence so the whole mass was dissolved in n-propyl alcohol (200 ml.) and the sodium chloride filtered off. On evaporation of the alcohol a syrupy liquid was left which failed to crystallize at a temperature of -20°C.

Since the liquid failed to crystallize it was decided to try a fractional distillation. Considerable effervesence was noticed before the fraction distilling over at 140 - 190°/6mm was collected. The liquid seemed to decompose slightly in the side arm of the flask, (the fractionating column) since the distillate came over colored. At least half of the original solution remained in the flask as a black syrupy

residue. Refractionation yielded a distillate much clearer, but which distilled over a range of twenty five degrees, 152-177°/6mm. Cooling in an acetone-dryice bath failed to induce crystallization.

Analysis:

Found C:52.22% H: 7.05%

Theoretical, $C_7H_{10}O_4$ C: 53.16% H: 6.33%

Equivalent weight:

Found: 122

Theoretical : 158

Since the product could not be purified properly, formation of a derivative was tried.

PREPARATION OF PHENYLHYDRAZINE DERIVATIVE OF (XLVI)

Application of the method of Stempel, G.H. and Schaffel, G.S. (29)

The previously obtained liquid (1 ml.) was refluxed with phenylhydrazine (2ml.) for thirty minutes in a test tube equipped with a finger condenser. After a few minutes of refluxing the solution turned a bright red but on cooling, failed to crystallize. By diluting with benzene (approx. 5ml.) a precipitate was obtained which was filtered by suction and washed with benzene. Recrystallization attempts from benzene were not too successful so the crystals were washed a number of times with benzene until finally they melted at 155 - 160°.

Analysis:

Found: N: 13.40%

Theoretical: $C_{19}H_{24}O_3N_4$ N: 15.72%

The nitrogen value obtained is too high for a monobasic derivative yet too low for a dibasic derivative. The reaction appears to be incomplete.

PREPARATION OF THE PHENYLHYDRAZINE

DERIVATIVE OF BUTYROLACTONE

Application: Stempel, G.H. and Schaffel, G.S. (29)

Butyrolactone (1 ml.) was refluxed with phenylhydrazine (2 ml.) for 10 minutes in a test tube equipped with a finger condenser. After a few minutes of refluxing the solution turned a bright red, but failed to crystallize, on cooling. Benzene (3 ml.) was added and on standing overnight orange crystals formed. Recrystallization from benzene yielded white, silvery plates melting at 92-93°C. This substance does not appear to have been previously recorded in the literature.

Analysis:

Found: N; 14.59%

Theoretical: $C_{10}H_{14}O_2N_2$ N: 14.45%

PREPARATION OF α-BENZYL-γ-BUTYROLACTONE (XLVIII)

Application of original method of Traube, W. and Lehmann, E, (31)

Sodium (17 g.) was dissolved in absolute alcohol (300 ml.) in a flask ( 2 l.) equipped with stirrer. Diethyl malonate (120 g.) was added. The mixture was cooled in an ice-water bath and cold ethylene oxide (33 g.) in alcohol (80 ml.) was run in slowly. The mixture was cooled occasionally, and on prolonged stirring went into solution. It was necessary to keep the mixture well cooled at this point for a new sodio derivative (XXIIIa) separated with the evolution of a great deal of heat. If the temperature was allowed to rise above 40° or 50° considerable decomposition occurred. The condensate was allowed to sit overnight, and the next day ethyl alcohol (100 ml.) added to loosen up the solid material. Benzyl bromide (130 g.) in alcohol (100 ml.) was added and the mixture stirred. After approximately ten minutes the mixture became very warm, and more mobile as the sodium bromide separated. The mixture was allowed to react for two days at room temperature after which the ethyl alcohol was removed on a steam bath. The turbid and somewhat viscous matter remaining was treated twice with water to remove the sodium bromide. The oil which separated was drawn off and the aqueous layer heated to drive off any alcohol. This was then treated with ether to remove any more oil and the ether extract then added to the oil. After treating the oil with Drierite

it was distilled in vacuo, collecting the following fractions:

| | | | |
|---|---|---|---|
| I | - 100°/ 2mm. | ..... | 101.5 g. |
| II | 100 - 140°/ 2mm. | ..... | 20.2 g. |
| III | 144 - 146°/ 2mm. | ..... | 102.2 g. |
| IV | 148 - 153°/ 2mm. | ..... | 29.5 g. |

Fraction III solidified in the ice box overnight while Fraction IV solidified in the apparatus before distillation was finished. After filtering, the white crystals were found to melt at 45 - 50°C.

Analysis:

Found: C: 67.27% H: 6.50%

Theoretical: (for lactone XLVII) $C_{16}H_{22}O_5$

C: 67.73% H: 6.45%

The ester (10.5 g.) prepared above was dissolved in alcohol (27 ml.) and sodium hydroxide solution (20 g. in 100 ml. water) added. A clear solution resulted, which was refluxed for ten minutes to complete the reaction and the alcohol removed by distillation until the temperature had reached 100°. The alkaline solution was then neutralized by bubbling in HCl gas until acid to Congo Red paper. The oil which separated was extracted with ether and treated with Drierite. After the ether was evaporated the oil was decarboxylated in an oil bath at 160°. When the evolution of carbon dioxide ceased, the oil was distilled, since it failed to crystallize. The fraction distilling over at 202-206°C/24.4 mm. was collected and weighed (6.4 g.)

Theoretical Yield 8.4 g.

Percent yield - 76.5

Analysis:

Found: C: 74.50% H: 6.98%

Theoretical, $C_{11}H_{12}O_2$ C: 74.40% H: 6.82%

PREPARATION OF HYDRAZINE DERIVATIVE OF $\alpha$-BENZYL - $\gamma$- BUTYROLACTONE

Method as described by Shriner, Fuson and Curtin (26)

$\alpha$-Benzyl - $\gamma$-butyrolactone (3.7 g.) was added to 85% Hydrazine Hydrate (5 ml.) and the mixture refluxed for fifteen minutes. Absolute ethyl alcohol was added until a clear solution was obtained. The mixture was then heated under reflux for two hours. The alcohol was evaporated and the residue cooled in the ice box overnight. The crystals were filtered under suction and on recrystallization from water melted at 110-112°C.

Analysis:

Found: N: 13.06%

Theoretical values of $C_{11}H_{16}O_2N_2$ N: 13.46%

PREPARATION OF N-BENZYLAMINE DERIVATIVE OF $\alpha$-BENZYL - $\gamma$ - BUTYROLACTONE

Method as described by Shriner, Fuson and Curtin (26)

A mixture of $\alpha$-benzyl- $\gamma$ -butyrolactone (3.2 g.), benzylamine (11 ml.) and powdered ammonium chloride (0.3 g.)

was heated for two hours under reflux in a Pyrex test tube equipped with a finger condenser. After cooling in the ice box the reaction mixture was washed with water to remove excess benzylamine and to induce crystallization. After recrystallization from water the crystals were found to melt at 88-89°C.

Analysis:

Found: N: 5.02%

Theoretical: $C_{20}H_{21}O_2N$ N: 4.56%

PREPARATION OF α-BENZYL SUCCINIC ACID (XLIX)

α- Benzyl-γ - butyrolactone (3 g.) was added to glacial acetic acid (50 ml.) in a flask (250 ml.) equipped with a mechanical stirrer. The mixture was warmed to bring the liquids into solution and then allowed to cool to room temperature.

The oxidizing mixture was prepared by dissolving chromium trioxide (2.3 g.) in hot water (10 ml.). On cooling glacial acetic acid (25 ml.) was added.

The reaction flask and contents were then cooled in an ice-water bath to 25-30° and kept at that temperature while the addition of chromium trioxide solution took place in the course of half an hour.

After the addition, the solution was stirred for a few hours during which time it was allowed to come to room temperature and let stand for two days to complete the reaction. Isopropyl alcohol (20 ml.) was added to destroy the excess

chromium trioxide and the whole evaporated under diminished pressure to a syrupy mass. The remaining acetic acid was extracted with chloroform followed by a recrystallization from the same solvent. The chromium acetate was removed by extraction with ether, leaving white crystals on evaporation. The melting point was found to be 159-160° as compared to the value of 160 - 161° given by Fittig and Shields (16)

Analysis:

Found: C:63.36%, H: 5.77%

Theoritical, $C_{11}H_{12}O_4$ C: 63.43% H: 5.82%

PART III..... (Other methods of synthesizing $\alpha$-benzyl - $\gamma$ - butyrolactone.)

ATTEMPTED PREPARATION OF $\alpha$-BENZYL - $\gamma$ -BUTYROLACTONE (XLVIII) (Method 2)

Method of Nelson, W.L., and Cretcher, L.H., (24) Fittig, R. and Roeders, P. (15)

The addition of benzyl bromide to malonic ester was carried out by the method previously described. Sodium (23.0 g.) was dissolved in absolute ethyl alcohol (400 ml.) and ethyl malonate (160 g.) added. After standing for ten minutes, benzyl bromide (171 g.) was slowly added while continually stirring the mixture. On adding benzyl bromide no appriciable change in the white sodio derivative was observed so the mixture was refluxed for fifteen hours after which time the solution indicated a change had taken place.

The alcohol was then removed by distillation and water added to dissolve the NaBr. The oil was extracted with ether (2 x 50 mls.) and then treated with Drierite. After removal of the ether, the ester was fractionated and the following fractions collected:

Fraction I - 108°/0.5mm.

Fraction II 120 - 135°/0.5 mm. ..... 75 ml.

The sodio derivative of the ester prepared above ( 75 ml) was formed by the addition of sodium (7 g.) in absolute ethyl alcohol (150 ml.) $\beta$-chloroethyl vinyl ether (32 g.) was added and the solution refluxed for about 36 hours. After this time the product was distilled in vacuo collecting the fractions:

Fraction I 35 - 36°/o.5 mm. ..... 4 ml.

Fraction II 115 -147°/0.5 mm. ..... 44 ml.

The solution had turned a brownish color after refluxing for this time, and on fractionating remained as a dark brown residue. Fraction II was likely unchanged benzyl malonic ester and indications were that the ether had not added on.

ATTEMPTED PREPARATION OF $\alpha$ - BENZYL- $\gamma$ - BUTYROLACTONE (XLVIII)
(Method 3)

Methods of Chanlaroff, M.B. (6)

Frankland, E. and Duppa, B.F. (17)

Adams, R., and Johnson, J.R., (1)

Sodium (11.5 g.) was added to absolute ethyl alcohol (300 ml.) followed by the addition of pure ethyl acetoacetate

(65 g., B.pt. 83.0°/25.5 mm.) with stirring. Without further delay, benzyl bromide (60 g.) was slowly added. A vigorous reaction was observed so the addition had to be slowed down. The mixture was refluxed overnight and the alcohol removed the following day by taking the temperature up to 90°C. Water (200 ml.) was added in two portions to dissolve the sodium bromide. The oil was mechanically separated from the water, treated with Drierite and then distilled under diminished pressure collecting the following fractions:

Fraction I - 170°/25.0 mm. ..... 4 g.

Fraction II 170- 180°/25.0 mm. ..... 67.5 g.

α-Benzyl acetoacetic ester (67.5 g.) was obtained from ethyl acetoacetate (65.0 g.) giving a yield of 61.5% of the theoretical.

The α-benzyl acetoacetic ester of Fraction II (50 g.) was treated with sodium (5.3 g.)and absolute ethyl alcohol (90 g.) yielding a white precipitate. On adding ethylene chlorohydrin (18.3 g.) no change was observed so the mixture was refluxed for thirty hours followed by the removal of the ethyl alcohol. Water (200 ml.) was added to dissolve the sodium bromide and the oily bottom layer separated and treated with Drierite. By distillation in vacuo, the product (32.0 g.) was collected, however it came over a wide range in temperature, 145°-180°/0.5 mm.

The oil (30.0g.) prepared above was then treated with sodium hydroxide (10 g. in 50 ml. of water.). This was allowed to stand for a week with occasional stirring during which time the solution turned a dark brown.

Attempts at isolating the saponified product failed, so a second trial was begun. As before, the distillation of the condensation product of ethylene chlorohydrin and α-benzyl-acetoacetic ester resulted in the product coming over a wide range in temperature, although there seemed to be a brief halt at 165°C/0.5 mm.

Analysis:

Found: C: 69.50% H: 6.86% (LVI)

Theoretical for α-benzyl-α-[β-oxyethyl] acetoacetic ester

C: 68.20% H: 7.68%

The analysis showed the product to be mostly α-benzyl-acetoacetic ester, so work along this line was pursued no further.

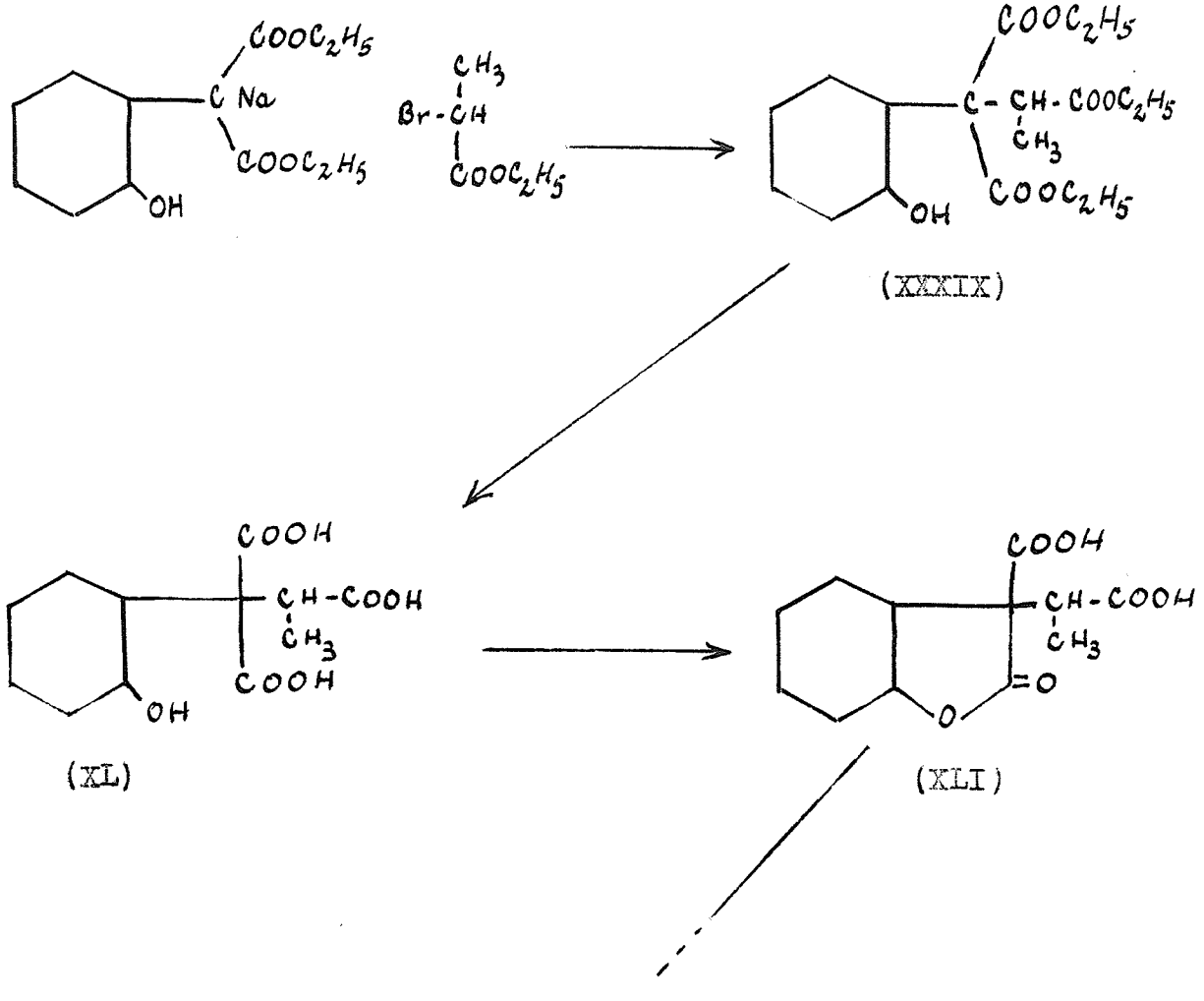
## DISCUSSION OF RESULTS.

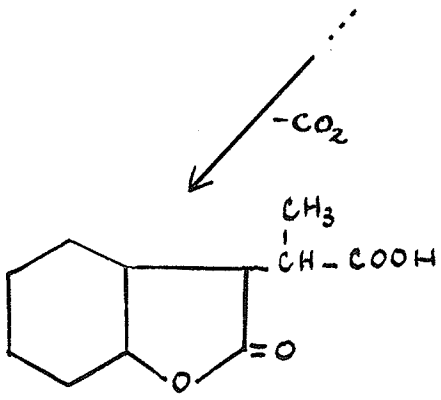
PART I..... (Synthesis using cyclohexene oxide)

SYNTHESIS OF THE LACTONE OF

α - CYCLOHEXANOL - α' - METHYLSUCCINIC ACID. (XLII)

A survey of the literature shows that quite extensive work has been carried out on compounds related to 2-keto-cyclohexylsuccinic acid ( *II* ). It was noted however, that the reaction with ethyl α - bromopropionate had never been attempted. In order to do so at this time the method of McRae, Charlesworth and Alexander (22) and Kendall, Osterberg and MacKenzie (19) was employed.



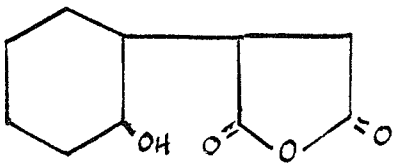



(XLII)

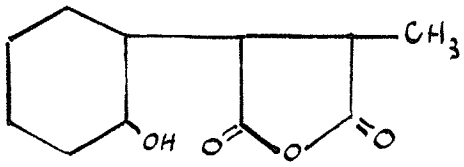
The series of reactions proceeded without any apparent difficulty at first and so no attempt was made to isolate the intermediates (XXXIX) and (XLI). However it might have been advisable to do so, since the final product was so impure it failed to crystallize. Alexander (2) mentions experiencing similar troubles when intermediates were not isolated.

It is felt however, that the main reason for obtaining impure material is not that mentioned above but rather the simultaneous formation of the anhydride (XLIV). This reasoning is based on the follwing observations:

1. Alexander (2) in preparing the lactone of cyclohexanolsuccinic acid ( II ) reports that he obtained 3-6% of the related anhydride. His compound, before lactonization was a monosubstituted succinic acid.




(XLIII)




(XLIV)

2. Succinic acid is known to form an anhydride quite readity on heating. Furthermore, it is known that the ease of anhydride formation increases with increasing substitution of succinic acid.

3. The work of Campbell (5) on lactones of the same type as (XLII) established that the method of Kendall, Osterberg and McKenzie, yields trans lactones from the corresponding acids. The trans acids, he found to be more difficult to lactonize than the isomeric cis acids.

α-Cyclohexanol-α-carboxyl-α′-methylsuccinic acid (XL) is a trisubstituted succinic acid and hence is expected to from an anhydride quite readily. On the other hand, this method of preparation should yield a lactone of the trans type. In view of the greater ease of anhydride formation as compared to the more difficult lactonization, it is felt that the ratio of anhydride (XLIV) to lactone (XLII) formation could be comparatively high.

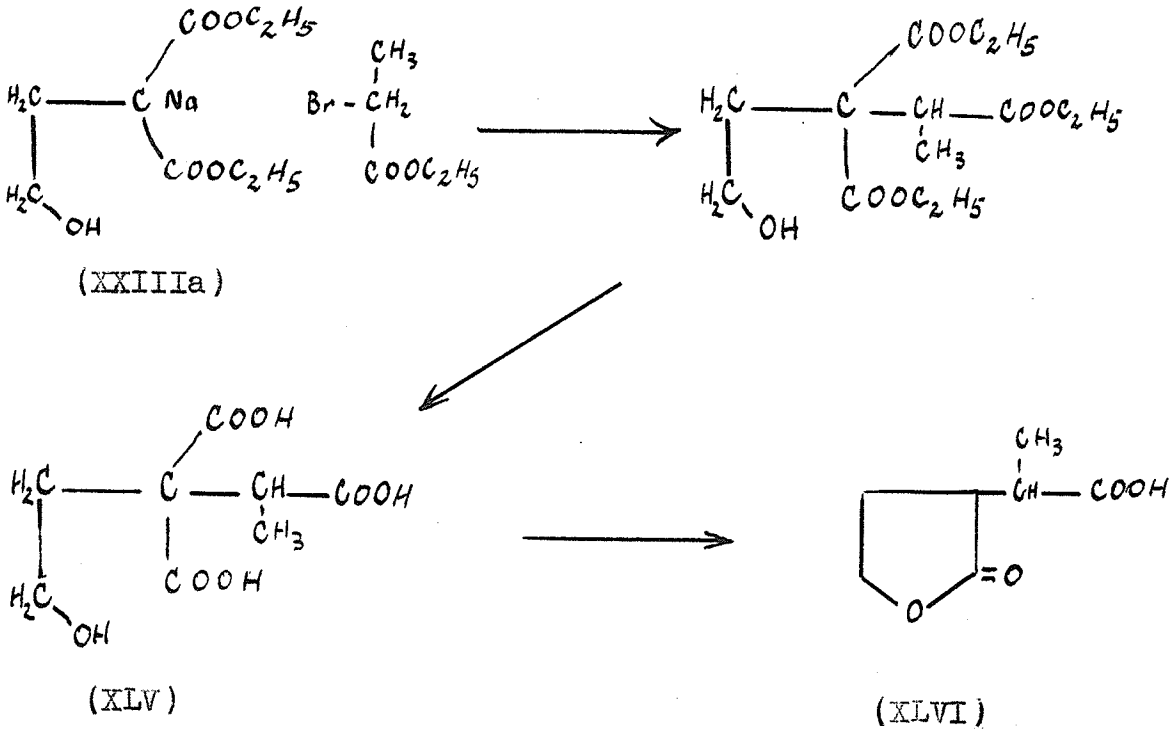
The analysis of the phenylhydrazine derivative seemed to indicate that a mixture of mono and di-phenylhydrazine derivatives had formed. Unfortunately however, the derivative does not provide any further clue as to the reaction that took place during lactonization.

PART II.....(Syntheses involving ethylene oxide)

SYNTHESIS OF THE LACTONE OF

$\alpha$-($\beta$-HYDROXYETHYL)-$\alpha'$-METHYLSUCCINIC ACID (XLVI)

The method employed closely parallels that used in the synthesis of the lactone of $\alpha$-cyclohexanol-$\alpha'$-methylsuccinic acid (XLII.) Ethyl $\alpha$-bromopropionate was condensed with the sodio derivative (XXIIIa). Previously Alexander (2) used ethyl-$\beta$-bromopropionate in a similar reaction.



(XXIIIa)

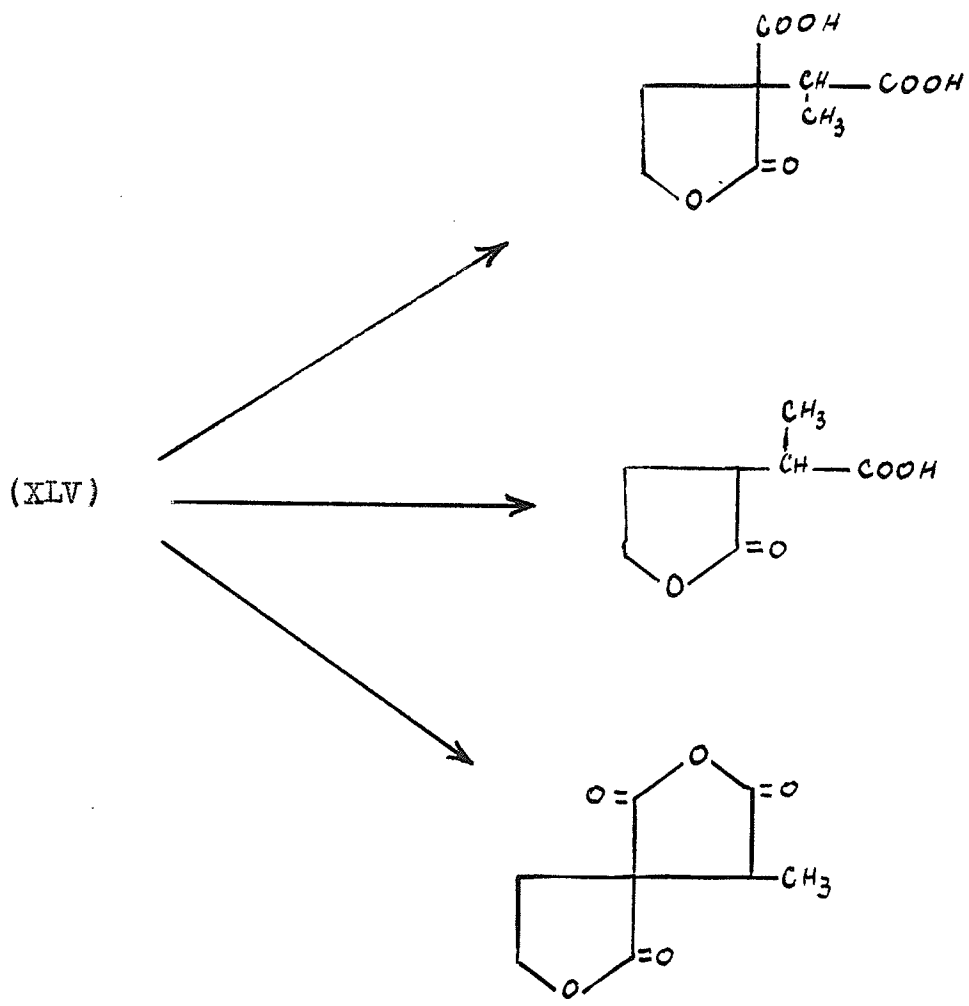
(XLV)

(XLVI)

The intermediates in this reaction were purified to some extent. However, the product still failed to crystallize after saponification and neutralization. Attempts to isolate it were hampered by the fact that, unlike similar substances previously reported, its solubility was greater in water than in ether.

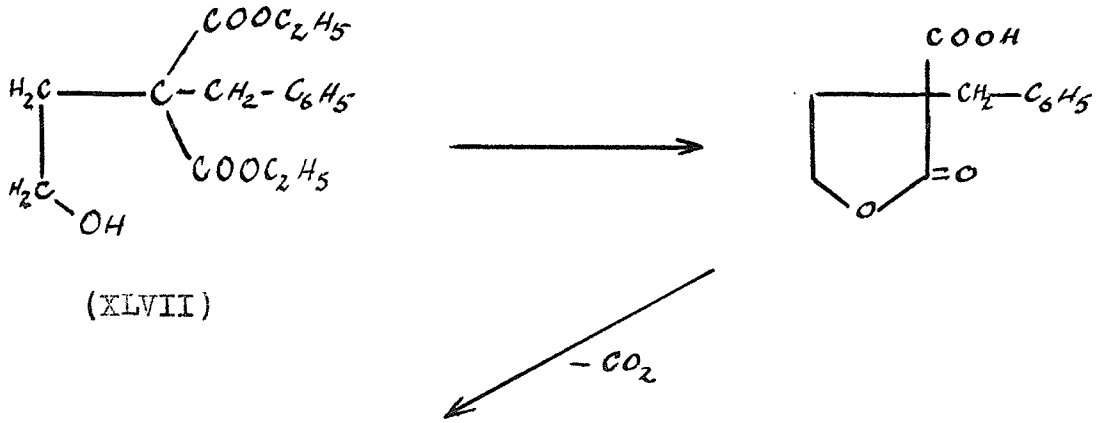
Separation from the inorganic salt was finally effected by extraction with $n$-propyl alcohol but when attempting to purify the extract by distillation the product decomposed very rapidly.

On checking through the literature, it seems that similar compounds with acid side chains were always accompanied by difficult crystallizations. However, it is felt that in this case the product may have been too impure to crystallize due to the possible simultaneous formation of a number of compounds such as the following:



SYNTHESIS OF $\alpha$-BENZYLSUCCINIC ACID AND ITS DERIVATIVES

In a similar manner to that used by McRae, Charlesworth and Alexander (22), and originally Traube and Lehmann (30,31), sodium bromide was removed from the sodio derivative (XXIIIa) and benzyl bromide to yield the addition compound (XLVII). After hydrolysis and decarboxylation, $\alpha$-benzyl-$\gamma$-butyrolactone (XLVIII) was obtained, and on chromic oxide oxidation, $\alpha$-benzyl succinic acid (XLIX)

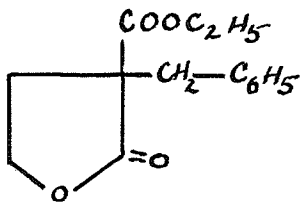



(XLVII)

(XLVIII)

(XLIX)

The condensation product of the sodio derivative (XXIIIa) and benzyl bromide, crystallized on fractional distillation. This was rather unexpected since none of the earlier substances of this type were reported crystalline. Analysis showed that this product was not (XLVII) but rather the lactone ester (L).

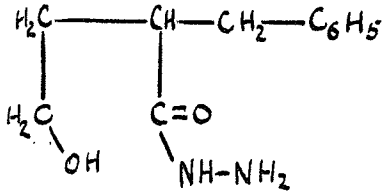


(L)

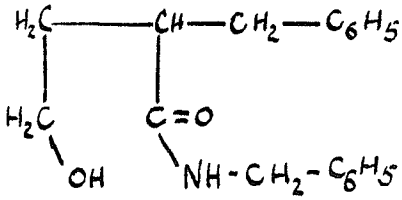
On hydrolysis and decarboxylation of this ester (L) $\alpha$-benzyl-$\gamma$-butyrolactone (XLVIII) was obtained. The corresponding succinic acid (XL) was found to melt at 159-160° as compared to the value given by Fittig and Shields (16) as 160-161°

Isolation of the succinic acid (XLIX) by oxidation of the lactone (XLVIII) revealed that chromium trioxide is too powerful an oxidizing agent to leave an alcohol or aldehyde group as an intermediate. It is felt that by using a milder oxidizing agent it should be possible to open the lactone ring and oxidize the alcohol end, stopping at the aldehyde stage.

The $\alpha$-benzyl-$\gamma$-butyrolactone (XLVIII) was characterized by forming the corresponding hydrazine (LI) and benzylamine (LII ) derivatives.



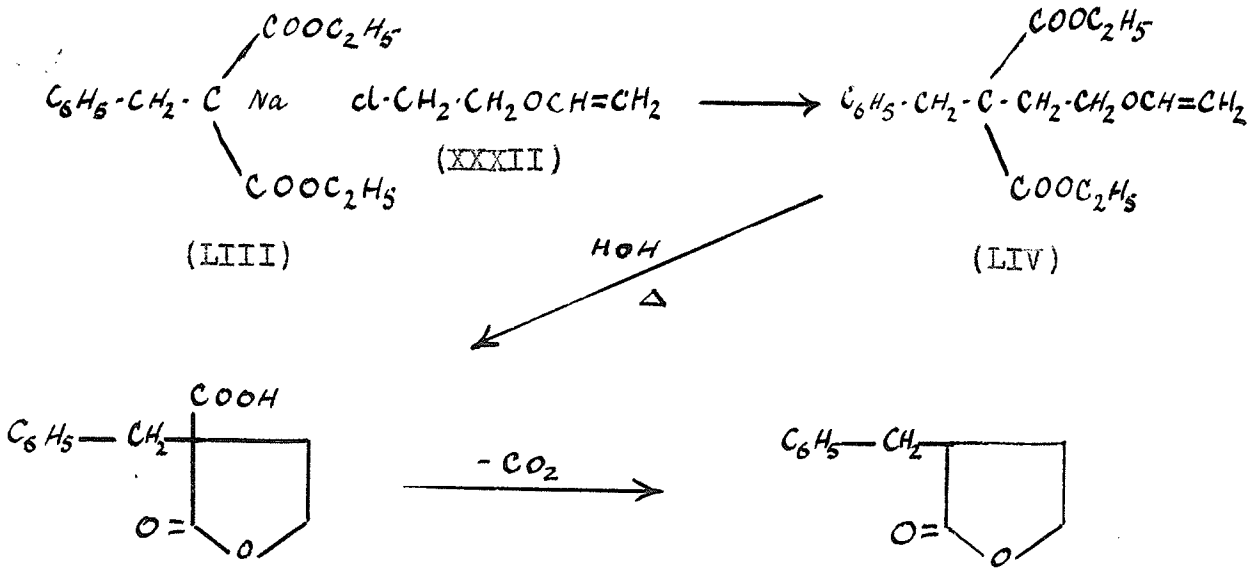
(LI)



(LII)

ATTEMPTED SYNTHESIS OF $\alpha$-BENZYL-$\gamma$-BUTYROLACTONE (Method 2).

Nelson and Cretcher (24) prepared a number of $\alpha$-alkyl-$\gamma$-butyrolactones by reacting alkyl malonic esters with $\beta$-chloroethylvinyl ether and subsequent hydrolysis. Both ether and ester are attacked in the hydrolysis and a lactone results. This method was used in an attempt to prepare $\alpha$-benzyl-$\gamma$-butyrolactone (XLVIII)

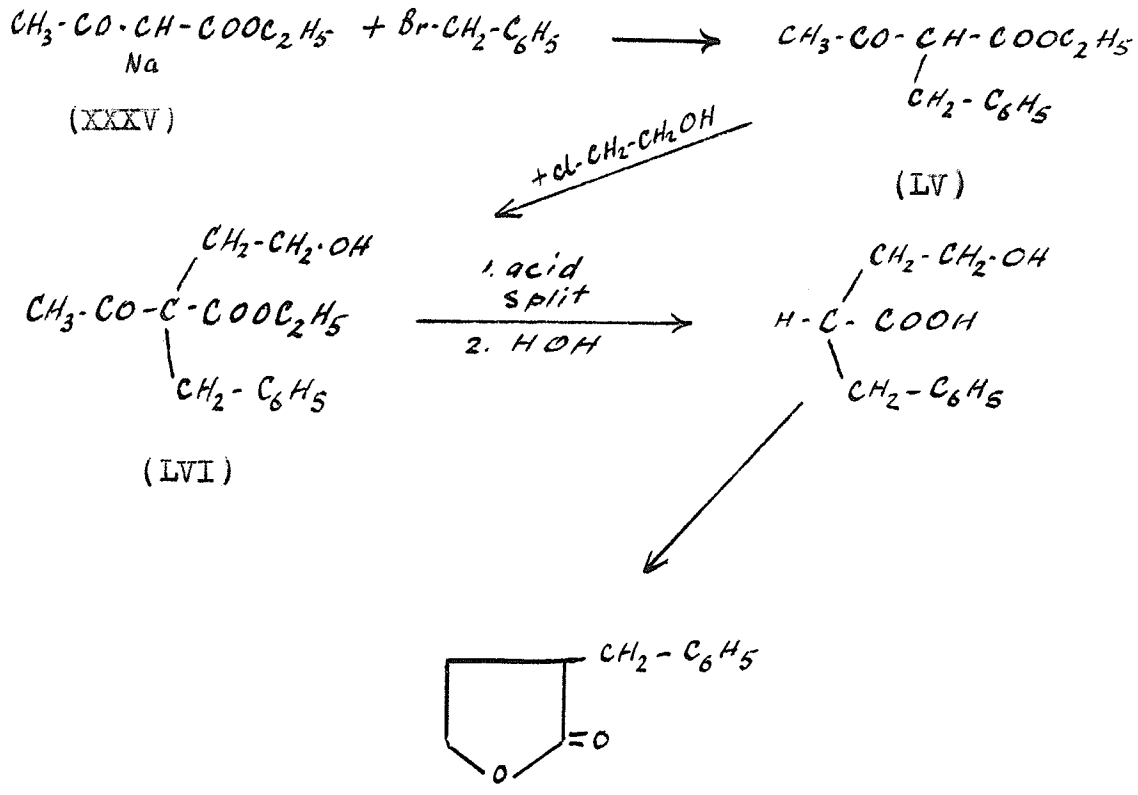



Benzylmalonic ester as prepared by the method of Fittig and Roeders (15) was condensed with $\beta$-chloroethylvinyl ether (XXXII) for thirty-six hours, after which the unchanged benzylmalonic ester was recovered. A large residue remained indicating that considerable decomposition had taken place.

It seems that the presence of the benzyl group stabilized the remaining active hydrogen atoms of the malonic ester, to such an extent that reaction with $\beta$-chloroethyl vinyl ether did not take place. As a result the addition product (LIV) was never obtained.

ATTEMPTED SYNTHESIS OF $\alpha$-BENZYL-$\gamma$-BUTYROLACTONE (Method 3.)

The Fittig and Chanlaroff (6,14) method of preparing lactones, was used in another attempt to prepare $\alpha$-benzyl $\gamma$-butyrolactone (XLVIII) The method as applied to this work is outlined as follows:



α-Benzylacetoacetic ester (LV) was obtained in the usual manner in good yields and without any trouble. However, difficulty was encountered in attempting to substitute the second active hydrogen atom of acetoacetic ester.

After refluxing the sodio derivative of (LV) with ethylene chlorohydrin for thirty hours, analysis showed that the product obtained was mostly unchanged α-benzylacetoacetic ester. (LV)

As is the case with malonic esters, disubstituted acetoacetic esters are much more difficult to form than monosubstituted acetoacetic esters. Fittig and Chanlaroff (14) found that α-ethylacetoacetic ester had to be refluxed with ethylene chlorohydrin for 25-30 hours before reaction took place. In the present work, the benzyl group seems to have stabilized the remaining active hydrogen site so that the second substitution did not take place.

## SUMMARY

1. $\alpha$-Benzyl-$\gamma$-butyrolactone has been prepared and isolated. This substance has been characterized by formation of hydrazine and benzylamine derivatives as well as oxidation to $\alpha$-benzylsuccinic acid.

2. Two other methods of preparing $\alpha$-benzyl-$\gamma$-butyrolactone were investigated, but were unsuccessful due to failure of the second stage substitution of the active methylene compounds employed.

3. The phenylhydrazine derivative of butyrolactone has been been made, which was not previously reported in the literature.

4. The lactone of $\alpha$-cyclohexanol-$\alpha'$-methylsuccinic acid has been prepared but the product was too impure to crystallize.

5. The lactone of $\alpha$-($\beta$-hydroxyethyl)-$\alpha'$-methylsuccinic acid has been prepared but again impurities prevented it from crystallizing.

## RECOMMENDATIONS FOR FUTURE WORK

1. The oxidation of α-benzyl-γ-butyrolactone with a weaker oxidizing agent such as hydrogen peroxide (30%) or alkaline permanganate would be interesting. It should be possible to open the lactone ring and oxidize the alcohol end, stopping at the aldehyde stage.

2. To further characterize the above lactone, it might be valuable to run some infra red spectra of the compound.

3. The stability of the lactone ring could be investigated by determining the rate of hydrolysis.

4. The syntheses involving ethyl -α-bromopropionate should be further investigated in an attempt to prepare the compounds in a purer form. It might prove helpful for a re-investigator to first prepare similar compounds using ethyl -β-bromopropionate, in order to gain some experience and technique with this type of synthesis.

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