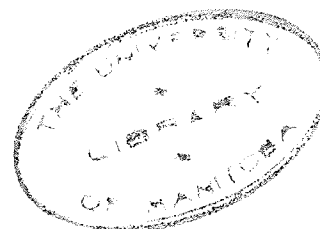SYNTHESIS OF CYCLOHEXANONE-2-α CARBOXYLIC ACIDS

BY OXIDATION OF γ -LACTONES

by

Dennis Leon Stachiw

A Thesis presented to

the Faculty of Graduate Studies and Research

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ACKNOWLEDGMENT

LIST OF TABLES

M. Sc.   Chemistry

Dennis Leon Stachiw

SYNTHESIS OF CYCLOHEXANONE-2-α-CARBOXYLIC ACIDS BY
OXIDATION OF γ-LACTONES

ABSTRACT

Reformatsky reactions were utilized to synthesize esters of
cyclohexanol-1-acetic, α-propionic, α-n-butyric, α-isobutyric,
α-n-valeric, α-isovaleric and α-benzylacetic acids. The reaction
failed with bromophenylacetic ester yielding ethyl phenylacetate in-
stead. The hydroxyesters were subsequently dehydrated and the resul-
ting β,γ-unsaturated esters lactonized by treatment with sulphuric
acid. The lactones of cyclohexanol-2-acetic, α-propionic and α-
isobutyric acids were thus obtained in a good yield, whereas those
of α-n-butyric, α-isovaleric and α-n-valeric acids were synthesized
with more difficulty and in yields decreasing in the order shown. No
lactonization occurred with ethyl cyclohexene-1-α-benzylacetate.

Oxidation of the lactones of cyclohexanol-2-acetic, α-propionic
and α-isobutyric acids produced fair yields of corresponding cyclo-
hexanone-2-α-acids. Much lower yields resulted in synthesis of
cyclohexanone-2-α-n-butyric and -isovaleric acids while cyclohexanone-
2-α-n-valeric acid could not be synthesized by this method.

A number of the new acids had been prepared in the course of
the work by saponification of corresponding esters. They include
cyclohexanol-1-α-isobutyric and isovaleric as well as cyclohexene-
1-α-valeric, isovaleric and benzylacetic acids.

Zinc was shown to react with bromobenzylacetate in toluene
yielding upon hydrolysis ethyl hydrocinnamate.
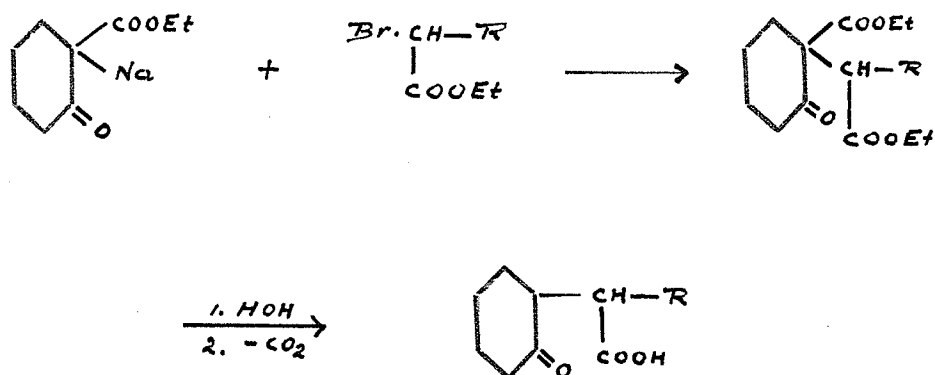
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INTRODUCTION

A synthesis of cyclohexanone-2-α-carboxylic acids
has been shown to be feasible by three methods:

1. The elimination of sodium bromide between the sodio-
derivative of ethyl cyclohexanone-2-carboxylate and bromin-
ated esters, followed by hydrolysis (9, 10, 12, 16, 23, 33).

2. Condensation of cyclohexene oxide with the sodio-derivative
of malonic ester and haloester or alkyl halide. Hydrolysis
and the decarboxylation of the condensation product yields a
lactone which can be readily oxidized to form the keto-acid
(11, 17, 18, 25).

$$\text{epoxide} + \underset{\text{COOEt}}{\overset{\text{COOEt}}{CH-Na}} + BrCH_2 \cdot COOEt \longrightarrow \underset{OH}{C}\overset{\text{COOEt}}{\underset{\text{COOEt}}{-CH_2 \cdot COOEt}}$$

$$\xrightarrow[\text{2.} -CO_2]{\text{1. HOH}} \quad \text{(lactone) } CH \cdot CH_2 \cdot COOH \xrightarrow{[O]} CH \cdot CH_2 \cdot COOH$$

$$\text{epoxide} + \underset{\text{COOEt}}{\overset{\text{COOEt}}{CH-Na}} + CH_3 I \longrightarrow \underset{OH}{C}\overset{\text{COOEt}}{\underset{\text{COOEt}}{-CH_3}}$$

$$\xrightarrow[\text{2.} -CO_2]{\text{1. HOH}} \quad \text{(lactone) } CH \cdot CH_3 \xrightarrow{[O]} \underset{O}{}CH \cdot CH_3,\ COOH$$
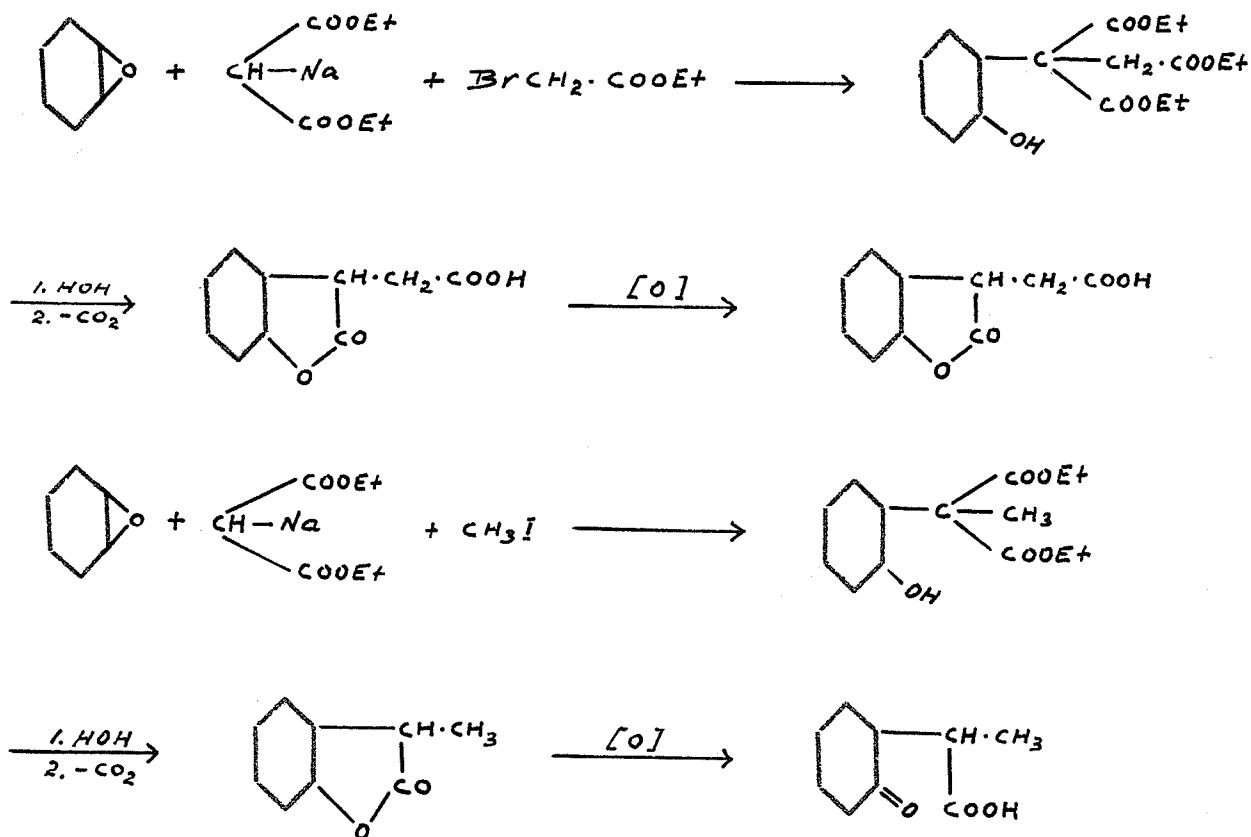
3. The oxidation of the γ-lactones of cyclohexanol carboxylic acids which are prepared by Reformatsky reactions between cyclohexanone and α-brominated esters, followed by treatment with mineral acid.

$$\text{cyclohexanone} + \underset{\text{COOEt}}{\overset{}{Br\,CH-R}} \xrightarrow[\text{1. HOH}]{Zn} \underset{\text{COOEt}}{\overset{OH}{}CH-R} \xrightarrow{H_2SO_4}$$

$$\text{(lactone) } CH-R \xrightarrow{[O]} \underset{O}{}CH-R,\ COOH$$
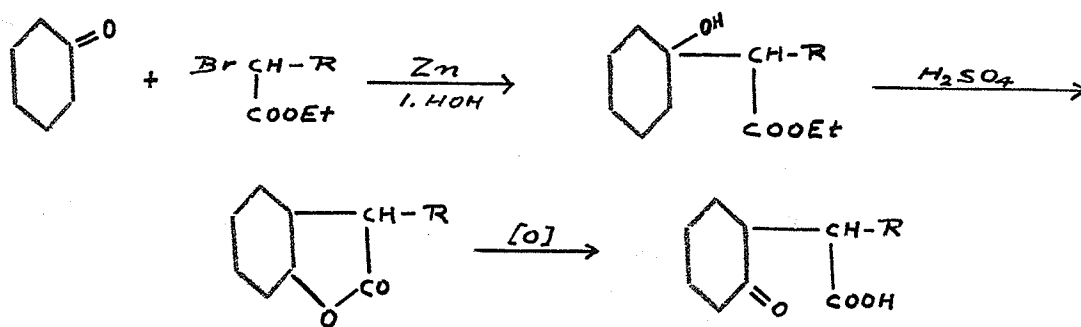
The last method has received only very little attention in the past. MacFarlane (24) started investigations in this direction and the present work represents continuation along this line and an effort to remove certain discrepancies therein. It would also permit comparison of the method with the first two previously described.

Because of the initial difficulties in direct synthesis of certain lactones from β-hydroxyesters obtained by Reformatsky reaction, an alternative method was chosen. It consisted of lactonization by the action of mineral acid of the β, γ-unsaturated esters previously produced by dehydration of the β-hydroxyesters.
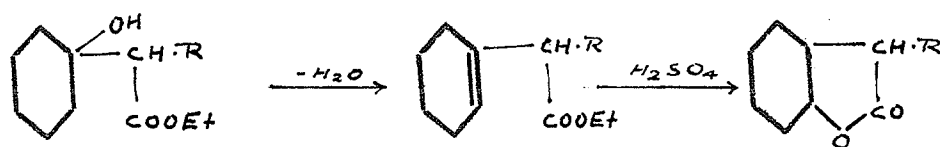
In the course of the work a considerable variation in reactivity towards lactone formation was encountered between the individual unsaturated esters. It became obvious that a more systematic study of the compounds associated with the reaction was required to gain some insight into the process of lactone formation. Accordingly, certain derivatives were made and a number of intermediate compounds isolated.

II. LITERATURE SURVEY

1. REFORMATSKY REACTION AS MEANS OF SYNTHESIS OF α-(1-CYCLO-HEXANOL) ESTERS

Reformatsky reaction offers the most convenient method of synthesis of this type of compounds. Wallach and his associates (42, 44) were the first to use it in preparation of α-(1-cyclohexanol) esters. Of the esters with which this investigation is concerned, four have been synthesized and studied in some detail by the above authors. They are esters of 1-cyclohexanol acetic, α-propionic, α-n-butyric and α-isobutyric acids. The yields, whenever stated, average 70-75 percent.

Auwers and Ellinger (2) used the Reformatsky reaction to synthesize ethyl (1-cyclohexanol) acetate and α-propionate.

In the more recent literature Boehringer (4) reports synthesis of ethyl (1-cyclohexanol) - acetate, -α-propionate and -α-n-butyrate by the Reformatsky reaction. The products are then utilized directly for the synthesis of the corresponding lactones.

Reformatsky reaction with ethyl α-bromobenzylacetate and 2-methylcyclohexanone is described by Grewe (15).

The only Reformatsky reaction involving ethyl α-bromo-

phenylacetate is that described by Blaise and Courtot (3).
It was conducted with acetone in ether solution and yielded
35 percent of dimethyltropate along with a small quantity
of ethyl diphenylsuccinate. The selection of ether as a
solvent rather than benzene was explained to be due to a
high degree of reactivity of bromine in bromophenylacetate.

No mention of Reformatsky reaction with ethyl α-
bromo-n-valerate and ethyl α-bromoisovalerate has been
found in the literature.

Newman (30) reports that yields in Reformatsky reac-
tions may be increased by the introduction of traces of
iodine. This also aids in the starting of certain diffi-
cult reactions.

Abnormal Courses of Reformatsky Reaction

a) The most common abnormality is the Wurtz-type of
reaction (34), i.e. elimination of halogen between the two
molecules of haloester leading to the formation of a diester.

b) According to Newman (30) zinc salts may cause
enolization of the ketone. The reaction will then follow
the same course as Grignard reagents with alcohols.

$$\text{(cyclohexanone)} \longrightarrow \text{(enol, OH)} \xrightarrow[\text{Br·CH·R}]{\text{Zn}} \text{(OZnBr)} + \underset{\text{COOEt}}{\overset{\text{CH}_2\cdot\text{R}}{|}}$$

with the bromoester bearing COOEt below the CH.

$$\text{(OZnBr)} \xrightarrow{\text{HOH}} \text{(=O)} + \text{Zn(OH)Br}$$
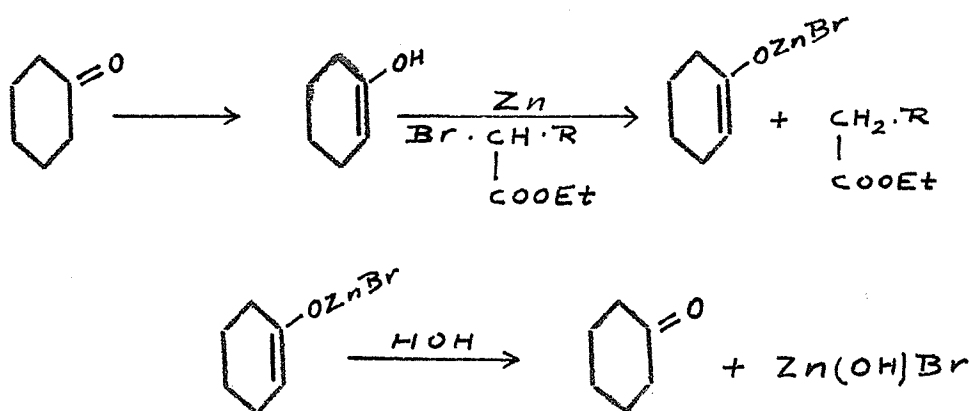
Considerable quantities of zinc may be used up while bromoester is converted to unsubstituted ester. After hydrolysis a seemingly unreacted ketone can be isolated in original quantity.

c) The temperature is one of the most important factors in Reformatsky reactions. For instance, Niewland and Daly (32) report that ethyl chlorophenylacetate in benzene solution will react with a ketone to form a normal addition product, whereas in toluene, ethyl diphenylsucci-nate is produced. Benzene is the best solvent as its boiling point temperature constitutes a medium, high enough to start most of the reactions and yet sufficiently mild not to affect materials in any undesirable way.

d) The same workers (32) point out that the length of time for the reaction has a notable effect on the yield of β-hydroxyester. If the reaction runs long enough to use the theoretical amount of zinc, a viscous residue with a high boiling point results, and the yield of β-hydroxy-

ester is low although no ketone can be recovered. High temperature and prolonged heating tend to increase the quantity of viscous material formed and for this reason runs of minimum reaction time are recommended.

2. DEHYDRATION OF β-HYDROXYESTERS

If the temperature of the reaction mixture is high the product from the Reformatsky reaction is occasionally the unsaturated ester. This may happen if toluene or xylene is used as a solvent (34). Schroeter (38) reports that the tendency of some of the β-hydroxyesters to lose water during distillation makes their isolation in a pure state and a good yield rather difficult, whereas dehydration of the crude reaction mixtures leads to higher yields of the unsaturated products.

Dehydration may be accomplished by heating the β-hydroxyester with acetic anhydride, fused potassium bisulphate, 85 percent formic acid, sulphuric acid of various strength, phosphorus pentoxide in benzene or thionyl chloride in pyridine (34).
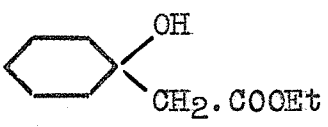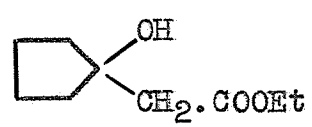
Natelson and Gottfried (29) pass dry hydrogen chloride through the β-hydroxyester at 90-100° followed by distillation. They claim nearly quantitative yields of the unsaturated ester.

For many years it had been assumed that the product of the dehydration reaction was the conjugated α,β -unsaturated ester. More systematic study established that it is subject to following empirical rules:

$$R_1 - \underset{\underset{R_2}{|}}{\overset{\overset{OH}{|}}{C}} - CH_2\text{-}COOH \longrightarrow \begin{cases} R_1 - \underset{R_2}{\overset{|}{C}} = CH.COOH \\[2em] = \underset{R_2}{\overset{|}{C}} - CH_2.COOH \end{cases}$$
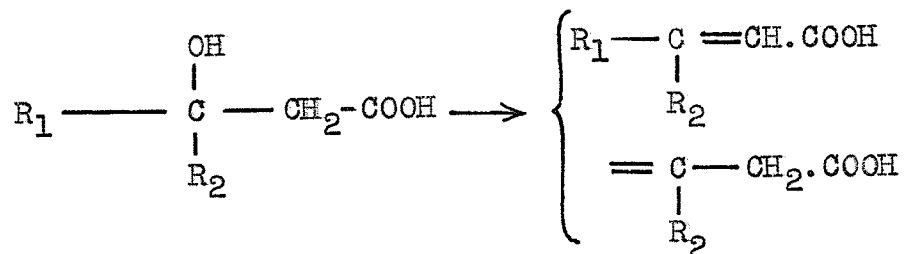
a) If R_1 = H and R_2 = Alkyl or aryl or if R_1 = CH_3 and R_2 is CH_3 or aryl the chief product is an α,β - unsaturated ester.

b) If R_1 is CH_3 and R_2 alkyl other than CH_3, both α,β - and β,γ - unsaturated esters are produced. The proportion of the two isomeric esters depends on the reagent used and on the structure of the compound. This is best illustrated in Table I, based on studies by Kon and Nargund [20]. The figures represent the percentage of the α,β - unsaturated ester present in the mixture of α,β - and β,γ -unsaturated esters.

TABLE 1

β -hydroxyester	% of unsaturated α,β -ester			
	P_2O_5	$POCl_3$	$SOCl_2$	$KHSO_4$
OH | Et-C-CH$_2$.COOEt | CH$_3$	39	62	53	57
OH | Et-C-CH$_2$.COOEt | Et	23	68	50	63
OH | C$_3$H$_7$-C-CH$_2$.COOEt | C$_3$H$_7$	24	51	31	51
OH CH$_3$ | | Et-C -CH.COOEt | Et	28	43	33	28
cyclohexane-OH / CH$_2$.COOEt	19	43	62	54
cyclopentane-OH / CH$_2$.COOEt	30	58	50	38

It is seen that phosphorous pentoxide is the best dehydrating agent for cyclohexanol-1- α·esters if a high yield of β,γ -isomeride is desired.

3. CHEMISTRY OF LACTONES

A very concise and systematic survey of the methods
of synthesis as well as general reactions of lactones has
been made by Rodd (35).

A) Synthesis of Lactones

Of the numerous methods of preparation, none is more
generally applicable than Fittig's sulphuric acid method
(14). Originally believed to be successful with β,γ -
unsaturated acids only, it yields lactones by heating these
acids to boiling with a large excess of 50 percent sulphuric
acid. The use of the method is commonly known as appli-
cation of "Fittig's Conditions". Linstead (5, 6, 22)
extended it to include several α,β -unsaturated acids
which he showed to tautomerize under Fittig's conditions
to yield β,γ -unsaturated acids.

Finally Boehringer (4) applied Fittig's conditions to
cyclohexanol-1-α-esters. The fact that these compounds
convert to lactones implies that the sulphuric acid acts
successively as a dehydrating and hydrolysing agent.

B) Mechanism of the Formation of Lactones from Unsaturated Acids

The formation of lactones from unsaturated acids is at
present regarded as an addition process in which the portions

of the carboxyl group, H and R.CO.O become attached to
the unsaturated centre. The mechanism has been postulated
by Linstead (5, 6, 22) and this section represents an
abstract of his work. The process has certain things in
common with other heterogeneous additions such as those
of hydrogen halides. The direction of addition of hydrogen
bromide to an olefinic acid largely depends on the effect
of solvents and alkyl substitution about the double bond.
In polar solvents the effect of the carbonyl group is
"neutralized" and the addition is directed entirely by the
order of substitution about the unsaturated centre. It
is this type of addition that will be discussed here,
since all the lactonizations described in this work have
been performed in polar solvents.

The formation of lactones from β,γ -unsaturated
acids in polar solvents is influenced largely by the order
of substitution about the double bond. Other factors in-
volved are stability of the lactone ring and the ease of
approach of the two active centers. A large number of
α,β - unsaturated acids can be converted to lactones
because, as was shown by Linstead, they are in the state
of tautomeric equilibrium with their β,γ - isomeride.
The relationship of these acids to lactones can be illus-
trated schematically as:

$$\alpha,\beta - \text{unsaturated acid} \underset{2}{\overset{1}{\rightleftharpoons}} \beta,\gamma-\text{unsaturated acid}$$
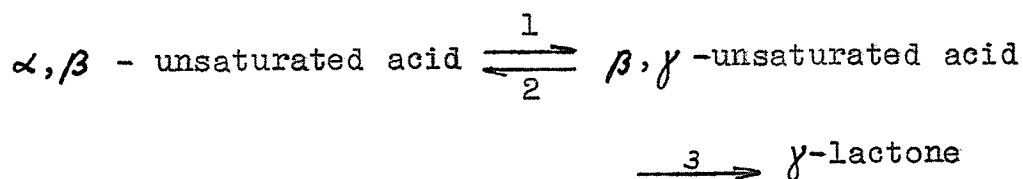
$$\xrightarrow{\quad 3 \quad} \gamma\text{-lactone}$$

the equilibrium generally shifting to the right under
Fittig's conditions. The variation between the different
acid-lactone systems can be attributed to differences in
the ratio of the velocity of the tautomeric change (1 and 2)
to that of ring closure (3). Four types of acids can be
distinguished:

a) Those in which both changes are slow but lactoni-
   zation is much faster than tautomeric change (acids
   with one γ-alkyl and no β-alkyl substituent).

b) Those in which lactonization is fast and tautomeric
   change slow (acids with two γ-alkyl substituents).

c) Those in which tautomeric change is faster than
   lactonization (acids with one γ- and one β- sub-
   stituent).

d) Those in which tautomeric change is fast and irrever-
   sible in the direction $\beta,\gamma \longrightarrow \alpha,\beta$ no lactoni-
   zation being possible (acids without γ-substituents).

<u>a</u>) The first type is exemplified by n-hexenoic acids.

$$\underset{\substack{|\\ CH_2}}{\overset{C_2H_5}{}}\cdot CH=CH\cdot COOH \xrightarrow[\underset{2}{slow}]{1} \overset{C_2H_5}{\underset{|}{}} CH=CH\cdot CH_2\cdot COOH \xrightarrow[\text{faster than 1,2}]{\text{slow but}} \overset{C_2H_5}{\underset{\substack{|\\ CH\cdot CH_2\cdot CH_2\\ |\\ O\text{------}CO}}{}}$$
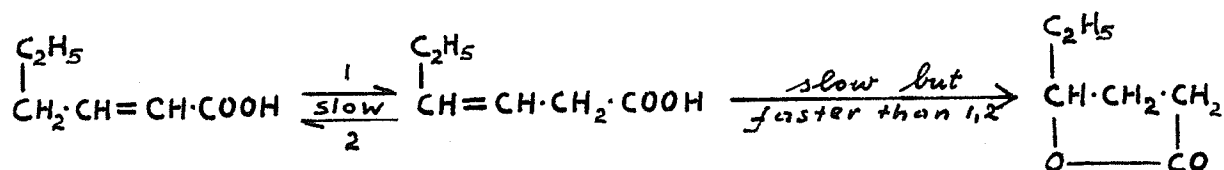
The β,γ -acid is very rapidly changed into the γ - lactone by boiling with 50 percent sulphuric acid. At room temperature, 50 percent sulphuric acid has little effect, but 60 percent acid produces a fairly rapid lactonization. The α,β -isomeride is completely unaffected by cold 60 percent acid, but boiling 50 percent acid rapidly produces the γ -lactone. No lactone forms from either of the acids on prolonged boiling in absence of sulphuric acid.

These results show that, as regards the α,β -unsaturated acid, tautomeric change into the β,γ -isomeride precedes lactonization and, as it is the slower reaction, it determines the velocity of ring formation. In the cold, no tautomerism occurs and there is no lactonization of the α,β -acid under conditions under which the β,γ -acid lactonizes.

b) The isohexenoic acids which illustrate the second type, differ from the n-acids in the extraordinary ease of lactonization of the β,γ -isomeride.

$$\begin{array}{c} CH_3 \\ \diagdown \\ CH \cdot CH = CH \cdot COOH \\ \diagup \\ CH_3 \end{array} \underset{slow}{\rightleftarrows} \begin{array}{c} CH_3 \\ \diagdown \\ C = CH \cdot CH_2 \cdot COOH \\ \diagup \\ CH_3 \end{array} \xrightarrow{fast} \begin{array}{c} CH_3 \\ \diagdown \\ C \cdot CH_2 \cdot CH_2 \\ \diagup | \quad\quad | \\ CH_3 \; O \!-\!\!-\! CO \end{array}$$
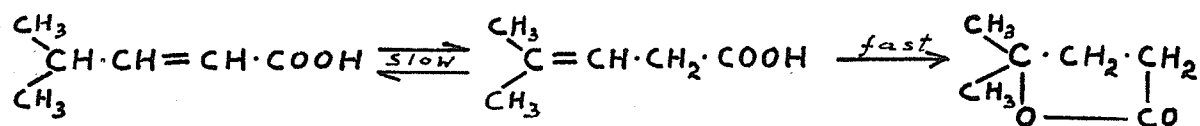
It converts completely to γ -lactone on being boiled alone for three hours. Other γ,γ -dialkyl β,γ -unsaturated acids show a similar ease of lactone formation (7) and it

is clear that this is connected with molecular substitution, but is independent of the nature of the specific process used to effect lactonization. In agreement with this, the β, γ -isohexenoic acid is lactonized completely by fifteen minutes' treatment in the cold with 50 percent sulphuric acid.

The introduction of the second γ -alkyl group thus produces a marked effect on lactonization in agreement with that required on the assumption of cationic attack in the β -position.

Unlike the β, γ -acid, α, β -isohexenoic acid is lactonized with but little more readiness than is the α, β -n-hexenoic acid. This is in agreement with the hypothesis that the tautomeric change is slower than and precedes the formation of lactone. The tautomeric mobilities of the two series would be expected to be of the same order and the greater facility for ring formation of the iso- β, γ -hexenoic acid would make no appreciable difference.

c) The trans- β -methyl- β -ethyl-acrylic acid is an example of the third type.

$$CH_3 \cdot CH_2 \cdot \underset{\underset{CH_3}{|}}{C} = CH \cdot COOH \;\underset{\longleftarrow}{\overset{fast}{\longrightarrow}}\; CH_3 \cdot CH = \underset{\underset{CH_3}{|}}{C} \cdot CH_2 \cdot COOH$$

$$slow \downarrow$$

$$CH_3 \cdot \underset{\underset{O}{|}}{CH} \cdot \underset{\underset{CH_3}{|}}{CH} \cdot \underset{\underset{CO}{|}}{CH_2}$$
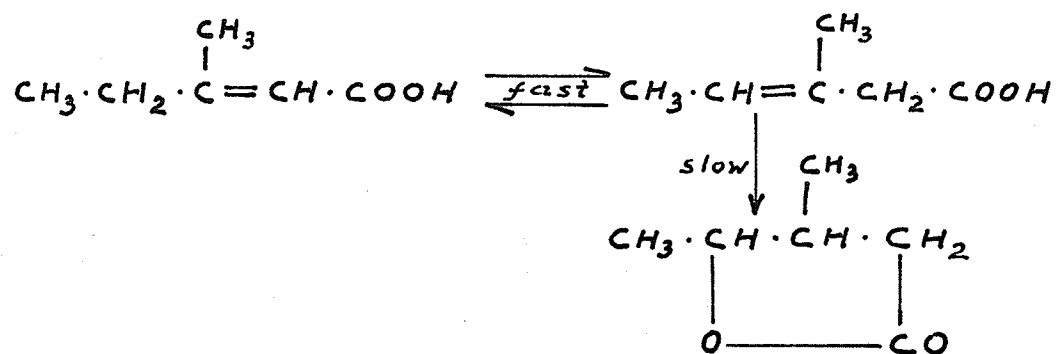
it is lactonized in the cold by 60 percent sulphuric acid
at about the same rate as is the corresponding β, γ -
unsaturated acid. It is necessary to assume here that the
tautomeric change is unusually facile.

d) The system: trans-crotonic acid (I) - vinylacetic
acid (II) - γ -butyrolactone illustrates the fourth type.
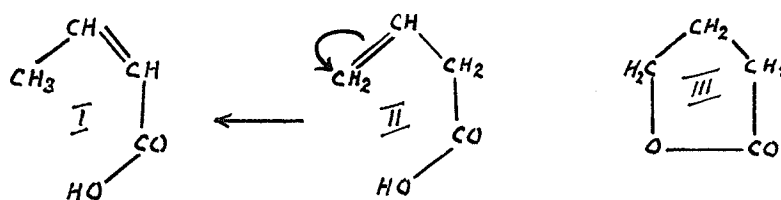
Addition of hydrogen bromide to II follows the Markovnikov's
rule indicating polarization of the double bond as shown by
the arrow. Hence the addition of the elements of the car-
boxylic group in the same compound would result in the
formation of β -butyrolactone and would oppose the forma-
tion of γ -butyrolactone (III). The formation of the
former, however, is ruled out as the coiling of the chain
with tetrahedral angles makes it impossible for the oxygen
of the carboxyl group to approach the β -carbon atom as
closely as is necessary for the formation of β -butyrolac-
tone. Moreover, no β -lactone would be stable under the
experimental conditions.

Theory thus suggests that the lactonization of viny-
lacetic acid in either sense (β or γ) will be inhibited
by constitutional factors and that the principal reaction

will be tautomeric change into the stable Δ^α form (I).
Experiments fully verify this conclusion.

With regard to tautomeric mobilities in general, it
has been observed that they decrease in higher acids,
becoming very low in higher α -alkylated homologues.
This is the type with which this project is concerned.
An assumption of practical consequence can thus be made
that the contribution of α, β -acid toward lactone for-
mation in all those compounds is negligible.

C) Oxidation of Lactones

Oxidation of lactones of cyclohexanol-2- α -carboxylic
acids alone will be discussed, as they are the only ones
with which this work has dealt.

Oxidation of lactones furnishes very important evidence
regarding the structure. The strong oxidation leads to
adipic acid which indicates the presence of cyclohexane
ring. Braun and Münch (7) report nearly quantitative yield
of adipic acid by oxidation of lactone of cyclohexanol-2-
acetic acid with nitric acid.

Controlled oxidation is much more elucidative in
establishing the structure of lactones of this type.
Kendall, Osterberg and MacKenzie (17) used bromine at
0° to oxidize γ -hydroxy-acid produced by hydrolysis of

the corresponding lactone. The conversion of the hydroxy-
to the keto-group is claimed to be 85 percent. The method
has been used by McRae, Charlesworth and Alexander (25).
They report yields up to 50 percent, the purity of keto-
acids being much superior to those obtained by alternative
methods.

The same workers (25) also use potassium permanganate
in alkaline solution at room temperature for this type of
oxidation. The yields are comparable to those obtained
by bromine oxidation.

Newman and Van der Werf (31) use CrO_3 in acetic acid
at room temperatures to oxidize free trans-cyclohexanol-2-
acetic acid to cyclohexanone-2-acetic acid identical in
physical properties with the one reported by Charlesworth,
McRae and Alexander. The yield is 62 percent.

4. THE CHEMISTRY OF THE ASSOCIATED COMPOUNDS

Cyclohexanol-1-α-Acids: Saponification of β-hydroxy-
esters, especially higher ones, is rather difficult because
of the pronounced tendency of the free acids to cleave with
the formation of ketone and corresponding fatty acid (34).
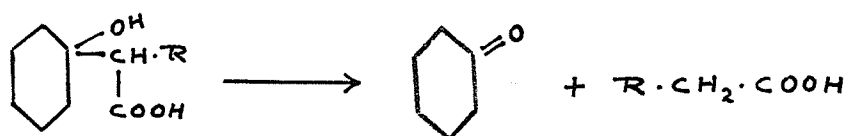
Kon and Narayanan (19) use a large excess of 50 percent potassium hydroxide to saponify ethyl α -(1-cyclohexanol)n-butyrate. The solution is heated on a water bath and some methanol added slowly. The yield is 30 percent.

Wallach (45) points out that the free acids obtained from the esters that saponify very readily, have a particularly strong tendency to decompose into the ketone and fatty acid. The same author (45) reports that a slow distillation of the acid under normal pressure produces the unsaturated hydrocarbon.
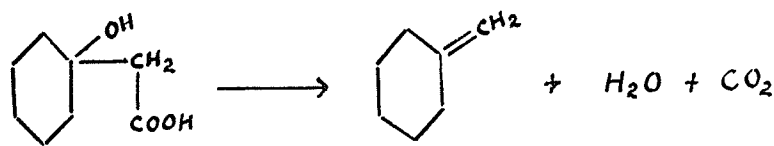
Cyclohexylidene- α -Acids: For a long time these acids were obtained by a very tedious procedure which involved dehydration of β -hydroxyester with potassium bisulphate, saponification and separation of the mixture of α , β - and β , γ -unsaturated esters by distillation with steam and fractional crystallization. Since potassium bisulphate dehydrates to yield predominantly β , γ -unsaturated acid, the quantities of α , β -isomeride thus obtained were very small and due to this fact not much was known about their properties. A typical yield reported by Wallach (43) was 2 percent. A more systematic study of

these acids followed Wallach's (45) discovery that dehydration of cyclohexanol-1-α- acids with acetic anhydride results in a good yield of α, β -isomeride.

It is interesting to note how the selection of conditions and the nature of the dehydrating agent affect the dehydration process.

main product
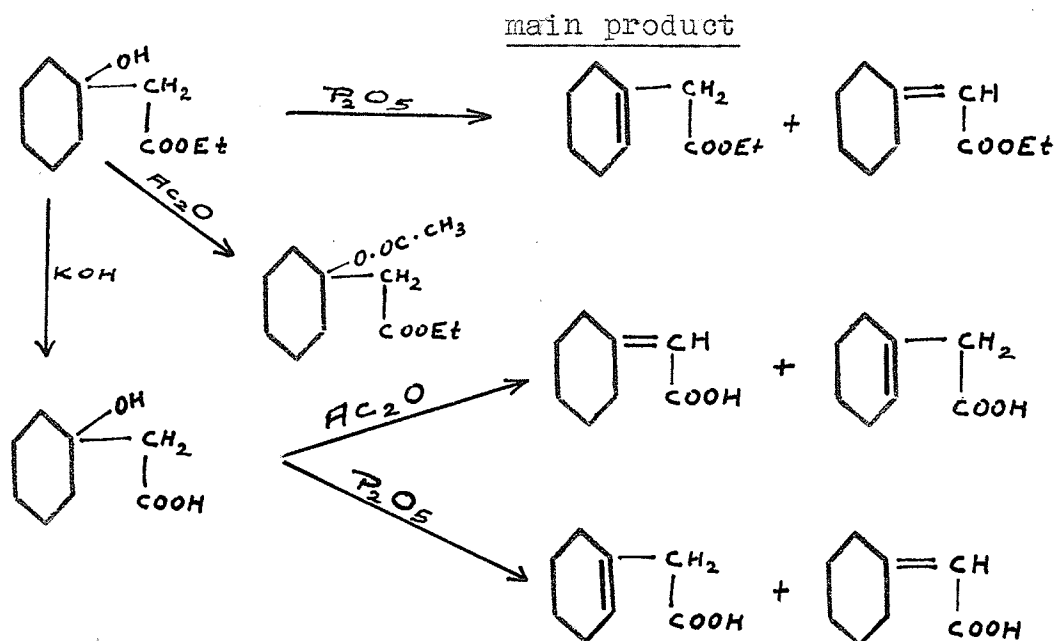
As it is seen, acetic anhydride cannot be used for dehydration of these esters because it attacks the hydroxyl group to yield acetyl derivative. This peculiar reaction has been discovered by Wallach (42, 43). According to Linstead (21) the formation of one of the isomerides in predominant quantity is due to the shift of tautomeric equilibrium between the two unsaturated acids. Strong acids generally move the equilibrium in the direction of

formation of β,γ -isomeride while strong alkali reverse the shift. The effect of strong alkali on tautomeric equilibrium between α,β - and β,γ -unsaturated acids has been first studied by Fittig (14).

A due caution has to be exercised in preparation and treatment of β -hydroxyacids to allow for instability (34). For instance heat decomposes 2-methylcyclohexanol-1- α - propionic acid.
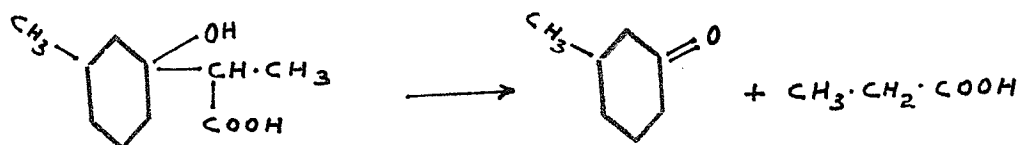
Sulphuric acid causes the cleavage of α,α -dialkyl- β - hydroxyacids.

$$CH_3-CH-\overset{\overset{\displaystyle R}{|}}{\underset{\underset{\displaystyle R}{|}}{C}}-COOH \longrightarrow CH_3CHO + R_2.CH.COOH$$
$$\overset{}{\underset{\displaystyle OH}{|}}$$
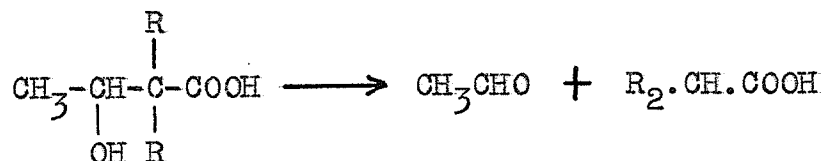
Cyclohexylidene compounds can be best distinguished from cyclohexene derivatives by oxidation. The former yield cyclohexanone while oxidation of the latter causes the cleavage of the ring.

As pointed out by Wallach (45) the melting point of semicyclic acids is always higher than that of the corresponding β,γ -unsaturated acids.

Cyclohexene-1-α-Acids: They are obtained by saponi-
fication of the corresponding β, γ -unsaturated esters.
According to Wallach (44) decarboxylation of cyclohexene-1-
α -acid leads to an unsaturated hydrocarbon in which the
double bond can be located either in the ring or in the
side chain depending on the conditions of the reaction.
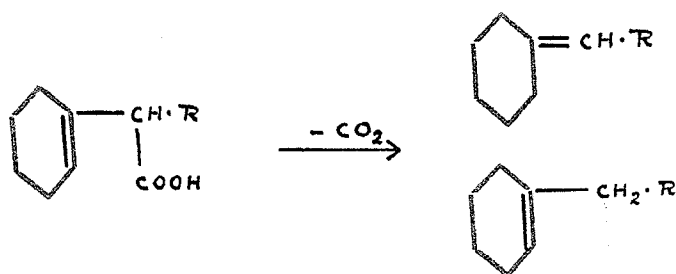
This suggests the tautomeric shift of double bond similar
to one described with α, β - and β, γ - unsaturated acids.

Addition of hydrogen bromide yields a solid product
identical with the one obtained from the corresponding cyclo-
hexylidene acid. As Wallach observed (43), action of hydrogen
bromide on cyclohexanol-1-, cyclohexylidene- and cyclohexene-
1-acetic acid results in the formation of identical product.
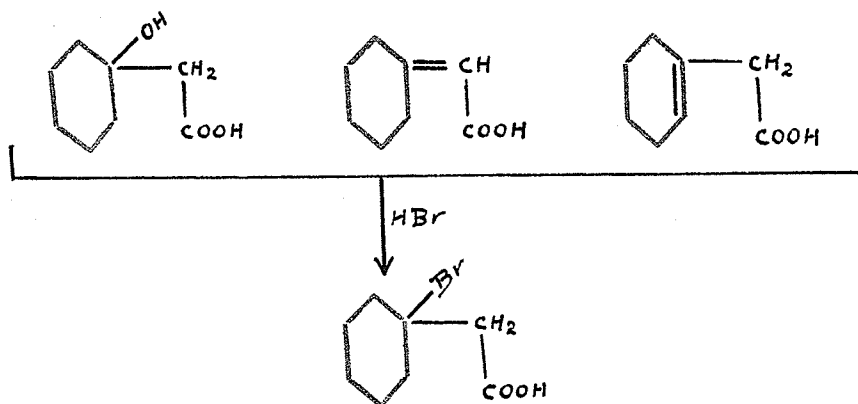
Additions are performed in polar solvents, most commonly

in acetic acid.   They follow Markovnikov's rule.

Wallach (43) reports that addition of bromine to double

bond followed by mild hydrolysis yields bromolactone.
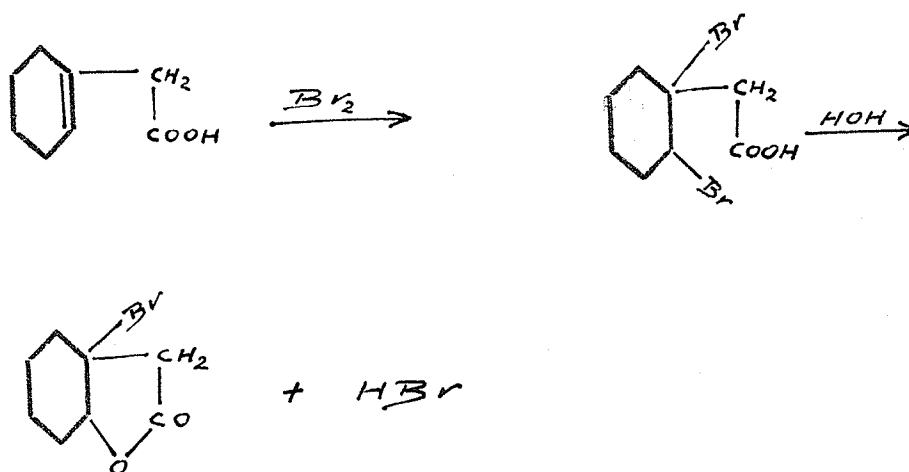
III. RESULTS AND DISCUSSION

1. SYNTHESIS OF CYCLOHEXANOL-1-α ESTERS BY REFORMATSKY REACTION

Syntheses of ethyl (1-cyclohexanol)-acetate (a), -α-propionate (b), -α-n-butyrate (c), -α-isobutyrate (d), -α-n-valerate (e) and -α-isovalerate (f) were accomplished without any difficulty. The isolated products showed generally a fair agreement with whatever data were available in the literature. The compounds and their boiling points are listed in Table II.
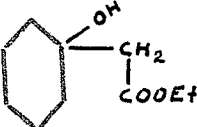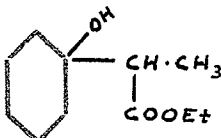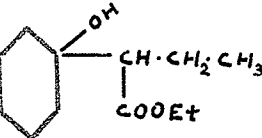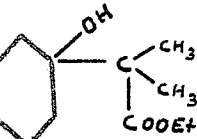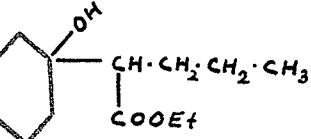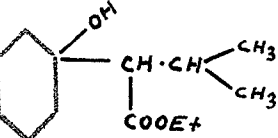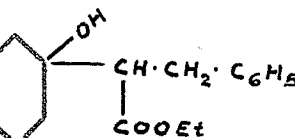
Certain irregularities occurred in Reformatsky reactions involving α-bromophenylacetate and α-bromobenzylacetate. These will be discussed in some detail partly here, and partly in the experimental section.

Attempted Synthesis of Ethyl α-(1-Cyclohexanol) Phenylacetate

No information regarding this or related compounds could be found in the literature.

The reaction proceeded very smoothly and similarly to the previous Reformatsky reactions. The fact that the main product isolated was ethyl phenylacetate suggests the possibility of enolization of cyclohexanone. The quantity of

TABLE II

Hydroxyester	Boiling Point		Yield %
	Literature	Found	
a) [structure: cyclohexane with OH, CH₂, COOEt]	141°/33 mm. 132 /19 (42)	108-118/11	72
b) [structure: cyclohexane with OH, CH·CH₃, COOEt]	125-127/12 (42)	115-119/11 85-93/1	76
c) [structure: cyclohexane with OH, CH·CH₂CH₃, COOEt]	145-150/16 (44)	124-127/10	57
d) [structure: cyclohexane with OH, C(CH₃)₂, COOEt]	125-135/14 (44)	132-138/13	70
e) [structure: cyclohexane with OH, CH·CH₂CH₂·CH₃, COOEt]		103-108/1	75
f) [structure: cyclohexane with OH, CH·CH(CH₃)₂, COOEt]		133-141/10	53
g) [structure: cyclohexane with OH, CH·CH₂·C₆H₅, COOEt]		190-205/13	38

cyclohexanone recovered does not support this, but it seems likely that considerably more may have been collected with a due caution. Alternative possibility which involves the formation of an addition product between zinc and bromo-ester has been described in the Reformatsky reaction with α -bromobenzylacetate. According to this scheme, ethyl phenylacetate should form in absence of cyclohexanone but no attempt was made to investigate this reaction. The bro-mine in bromophenylacetate has been found to be very reactive; even in ether solution the reaction was rather vigorous. High yield of phenylacetate even under very mild conditions limits considerably the possibility of synthesis of this hydroxyester by Reformatsky reaction.

Ethyl α -(1-Cyclohexanol) Benzylacetate

The yield of this hydroxyester has been the lowest of all the Reformatsky reactions. The bromoester apparently enters readily some side reactions as judged by a large quantity of the by-products formed. One of these is a low boiling fraction while the other is present mainly in the distillation residue. Neither by-product has been investi-gated.

The formation of ethyl hydrocinnamate in a high yield

when toluene was used as a solvent, cannot be explained by enolization as the same compound formed when no cyclohexanone was present. It is possible that zinc reacted with the bromo-ester to form the addition product which on hydrolysis would yield ethyl hydrocinnamate.

$$C_6H_5.CH_2.CHBr.COOEt \xrightarrow{Zn} C_6H_5.CH_2.CHZnBr.COOEt$$

$$\xrightarrow{HOH} C_6H_5.CH_2.CH_2.COOEt + Zn(OH)Br$$
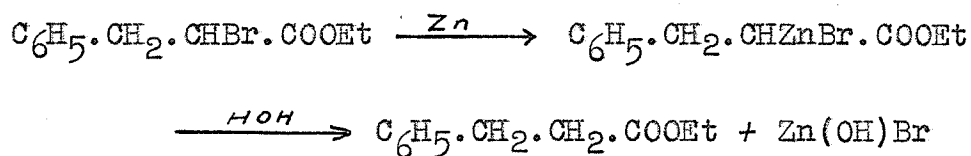
2. DEHYDRATION OF THE PRODUCTS OF REFORMATSKY REACTION

Fused potassium bisulphate was used in the early work but it was soon abandoned in favor of phosphorus pentoxide in benzene. The latter gives consistently good results, the isolation of the product being at the same time relatively simple.

It was found that prolonged heating, especially if the walls of the reaction flask are exposed to much higher temperature than that required for a mild refluxing, produces increased quantities of a dark, viscous material deposited on phosphorus pentoxide. In one experiment, it constituted 40 percent of the hydroxyester used for dehydration.

However, if moderate heating is applied, limiting the refluxing time to three hours, yields as high as 70 percent can be obtained without any difficulties. The residue is

mainly the unreacted ester. In agreement with the work of Schroeter (38), it was found that however crude the product of the Reformatsky reaction used in the dehydration, the resulting unsaturated ester was of rather satisfactory purity. It seems that phosphorus pentoxide precipitates and adsorbs most of the high boiling material which is the by-product in the Reformatsky reaction.

The unsaturated esters synthesized in this work, and their boiling points are listed in Table III.
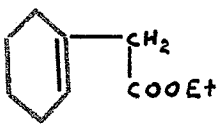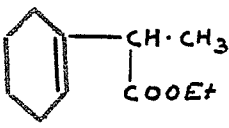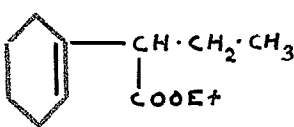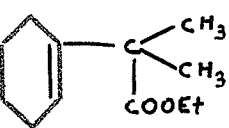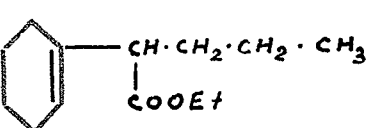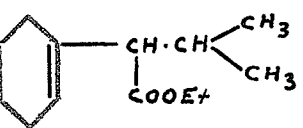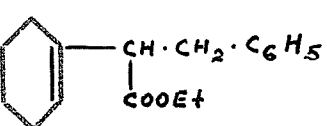
3. SYNTHESIS OF LACTONES

a) The bulk of experimental work leading to the synthesis of lactones was carried out with β, γ -unsaturated - rather than with β -hydroxyesters. The reasons have been partly mentioned in connection with synthesis of β -hydroxy- and β, γ -unsaturated esters (page 6) and they are summarized below.

(i) Good yields of fairly pure β, γ -unsaturated esters are readily obtained while isolation of pure β - hydroxyesters is more difficult. Crude products of the Reformatsky reaction could be used in dehydration to yield a constant boiling unsaturated ester in a good yield.

(ii) Some β -hydroxyesters are much less stable to Fittig's conditions than corresponding β, γ -unsaturated esters.

TABLE III

Cyclohexene-1-α-ester	Boiling Point		Yield %
	Literature	Found	
a) CH₂ COOEt	100°/12 mm. (42)	93-95°/10 mm.	68
b) CH·CH₃ COOEt	108-112°/12 mm. (42)	97-99°/11 mm. 68-70 / 1 mm.	70
c) CH·CH₂·CH₃ COOEt	122-127°/14 mm. (44)	102-105°/10 mm. 113-115 /15 mm.	60
d) C(CH₃)(CH₃) COOEt		107-113°/13 mm.	77
e) CH·CH₂·CH₂·CH₃ COOEt		82-85°/1 mm.	76
f) CH·CH(CH₃)(CH₃) COOEt		115-125°/11 mm.	65
g) CH·CH₂·C₆H₅ COOEt		140-145°/2 mm.	50

(iii) The completion of the lactonization is usually
indicated by the disappearance of the oily layer and the
formation of the homogeneous solution. This is due to the
fact that lactones, especially lower ones, are soluble in
50 percent sulphuric acid while corresponding esters and
acids are not. When β -hydroxyesters are heated with this
acid the process is always accompanied by the formation
of the considerable quantities of dark, resinous material.
It usually forms a layer or a film adhering to the top
part of the flask which prevents the visual examination of
the process. The reaction time can be more conveniently
controlled if β , γ -unsaturated esters are used because
they do not ordinarily give rise to the large scale forma-
tion of the dark, polymeric matter.

(iv) Even with very effective dehydrating agents
dehydration is incomplete. Hence, if Fittig's conditions
are applied to β -hydroxyester the reaction mixture may
likely contain two other compounds besides the product,
i.e. β -hydroxy - and β , γ -unsaturated ester. The sep-
aration of such a mixture by distillation is difficult, the
boiling points being relatively close. On the other hand,
using pure β , γ -unsaturated ester, the only possible
impurity, the unreacted ester, could be easily separated

(<u>i</u>) <u>Instability of Material</u>: The open chain unsaturated acids and corresponding lactones are stable even to a protracted boiling in 50 percent sulphuric acid (145°). Since this was the only type of compound investigated by Fittig and his school, his description of lactonization, however detailed, was found to be of little use in this project. Fittig's conditions, for instance, resulted in nearly complete destruction of material when applied to lower esters. The formation of dark, resinous material occurs as low as 80-90°. Part of it seemed to be acidic in nature, as it was soluble in sodium carbonate. The major part of the resinous material was left as a residue after distillation of the product. Its amount and viscosity were directly related to the conditions applied in lactonization. As a rule, the more drastic the conditions the larger was the quantity of residue on distillation, and the higher the degree of viscosity.

Very little can be said about the nature of this degradative process. It appears to be at least partly oxidative in nature, as it is always accompanied by a strong evolution of sulphur dioxide. In one instance the product of degradation was identified as cyclohexanone. This, as has been already mentioned (page 17) is a logical decomposition product of β-hydroxyacid.

Another product appeared to be present rather frequently in the reaction mixture. It had a very low boiling point, a pleasant smell, refractive index much lower than any of the materials involved in the reaction. It did not react with sodium metal even on warming and did not produce an oxime with hydroxylamine. These properties would most likely fit the unsaturated hydrocarbon formed by decarboxylation of the unsaturated acid.
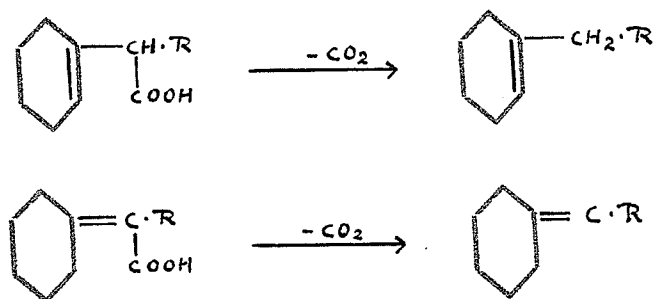
(ii) _Variation in Reactivity and Stability_: If in treatment with 50 percent sulphuric acid, a milder temperature was maintained, the unreacted ester was usually found to be present besides the desired product. In this respect, however, a considerable variation between various esters was observed.

The lactones of cyclohexanol acetic, propionic and isobutyric acids required one to two hours' heating on water bath for their formation. The distillate was pure lactone, the main loss was in the distillation residue. The amount of degradation or polymerization was small, being the lowest

with the isobutyric lactone.

Increasing difficulties were encountered in synthesis of lactones of cyclohexanol- **2**-n-butyric, isovaleric and n-valeric acids. In all these cases, the unreacted ester was recovered in considerable quantities in spite of much longer heating time compared to the first three esters. The optimum temperature and heating time for satisfactory yields could not be found. It is considered that the improvement of yields should be sought by lengthening the reaction time rather than by drastic increase of temperature.

The lactone of cyclohexanol-2-α-benzylacetic acid did not form at all under extremely drastic treatment. It appears that the compound cannot be synthesized by this method because even the free unsaturated acid did not show any tendency to lactonize under Fittig's conditions.

In general it seems that the lengthening of the chain in the α-position hinders the formation of lactones. The increased difficulties in saponification of higher unsaturated esters seem to indicate that it is probably the first step of the process, i.e. the hydrolysis of the ester which is affected. The actual lactonization of the free acid may proceed at a fairly rapid rate.

It is interesting to note that the yield of lactone of cyclohexanol-2-α-isobutyric acid is the highest in the

whole group. It is possible that because it is the only solid lactone in the series, the losses sustained in isolation are much reduced. But it seems likely that other factors may also be contributing. One of these is the presence of two methyl groups on the α-carbon atom. It was shown by Linstead (6) that α-alkylation stabilizes the lactone ring. His α-methyl γ-valerolactone was the most stable of all the lactones. The higher yield of the propionic lactone compared to the acetic may also support this opinion.
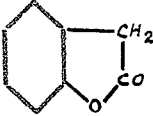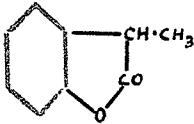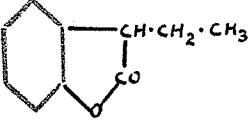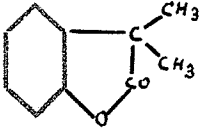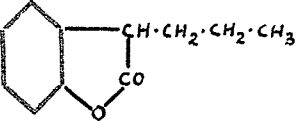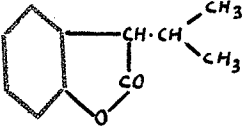
Ethyl α-(1-cyclohexanol) isobutyrate is unique in one respect. Its dehydration can lead to β, γ unsaturated ester only, the α-carbon atom being quaternary. This means that using the dehydrated product for lactonization, a yield of 100 percent is theoretically possible, whereas dehydration products of other hydroxyesters, being mixtures of α, β- and β, γ-unsaturated ester, have one component which does not contribute toward lactone formation. The tautomeric mobilities of the unsaturated acids of this type were shown by Linstead (6) to be extremely low.

The lactones synthesized in the course of this work and their boiling points are listed in Table IV.

4. OXIDATION OF LACTONES

The oxidation by bromine as described by Kendall, Osterberg and MacKenzie (17) has been used throughout this project and proved to be very reliable. The difficulties

TABLE IV

Lactone	Boiling Point		Yield %
	Literature	Found	
a)	129–130°/13 mm. (31)	131–135°/12.5 mm.	60
b)	130°/11 mm. (4)	135–138°/13.5 mm.	66
c)	141–147°/15 mm. (4)	138–144°/12 mm.	48
d)	M.P. 56° (7)	53–55° #	83
e)		155–158°/15 mm.	5
f)		140/150°/14 mm.	38

#The melting points quoted in this project have not been corrected.

centered mainly on the isolation of the product. It has
often been found that the isolated material was an oil
apparently containing too many impurities, as it would not
crystallize on long standing or cooling. In one instance
it was definitely proved that the main and practically only
impurity present was some neutral material, probably the
unreacted lactone. The separation was performed by means of
sodium carbonate and the keto-acid thus isolated proved to
be of very high purity. In all other cases ligroin was used
to eliminate the impurities. But although the pure products
are insoluble in ligroin the digestion of crude oils with
this solvent resulted in serious losses of the keto-acids.
The ligroin extracts invariably showed considerable quanti-
ties of the product. The best method appeared to be the
isolation by means of semicarbazide, but time did not permit
the studying of the conditions required for the regeneration
of the free keto-acid from the semicarbazone.

Since the presence of the unreacted lactone seemed to
be certain in most of the reactions the oxidation was carried
out over much longer periods of time than suggested in the
original method. Bromine decolorizes fairly rapidly during
the first hour slowing down considerably during the next,
but some oxidation was still taking place if the addition of
bromine was continued for a period of three to four hours.
It was found that there is little danger in carrying oxida-
tion too far, as in no case could formation of adipic acid
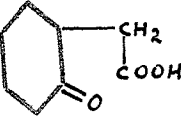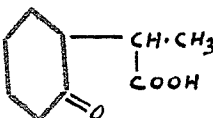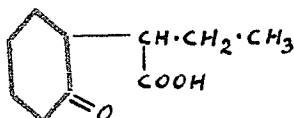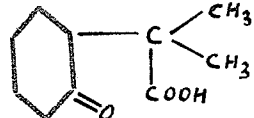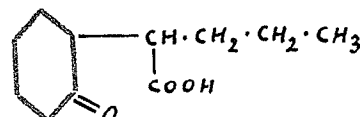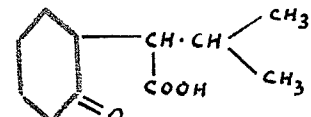
be detected. At the same time if an excess of bromine was added it did not react any further after several hours' staying at room temperature.

Cyclohexanone-2-acetic and -α-propionic acids have been synthesized in a yield comparable to that reported by McRae and Charlesworth (25). Melting points showed also a good agreement. Cyclohexanone-2-α-isobutyric acid which was obtained in the highest yield was also the keto-acid most readily processed. However, it is considered that the yield could be easily improved by more careful recrystallization. The main loss occurred in extraction, as contrary to the rest this keto-acid is only sparingly soluble in ether.

Cyclohexanone-2-α-n-valeric acid was the only one that could not be separated as such from the reaction mixture. It was eventually isolated in the form of semicarbazone.

It is interesting to note that decrease in yields and difficulties in isolation of higher keto-acids follow the same pattern as in the synthesis of corresponding lactones. However, before attempting to correlate the ease of oxidation with any constitutional effects it would be advisable to perform the oxidation with absolutely pure lactones. In the synthesis of the three keto-acids which presented the greatest difficulties the starting materials were either known to be impure or the purity was not ascertained. Thus part of the

38

TABLE V

Keto-Acid	Melting Point° Literature	Found	Yield %	Melting Point° of Semicarbazone Literature	Found
a) cyclohexanone–CH_2–COOH	74-75 (25)	73.5-74.5	43	199-200 (25)	188
b) cyclohexanone–$CH \cdot CH_3$ / COOH	133-135 (25)	132-133	30		153-154
c) cyclohexanone–$CH \cdot CH_2 \cdot CH_3$ / COOH		113-114	10		192-193
d) cyclohexanone–$C(CH_3)_2$ / COOH		150-151	58		197-198
e) cyclohexanone–$CH \cdot CH_2 \cdot CH_2 \cdot CH_3$ / COOH					195-196
f) cyclohexanone–$CH \cdot CH(CH_3)_2$ / COOH		134-135	poor		209-210

cyclohexanol-2-n-butyrolactone used in oxidation showed on
analysis some 20-30 percent of unreacted ester while the
corresponding n-valeric lactone analysed to about 40 percent
unreacted ester. The isovaleric lactone was not analysed,
but distillation of the reaction mixture yielded some 30
percent of unreacted ester and it is likely that the product
was contaminated with it to a considerable extent.
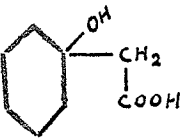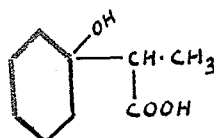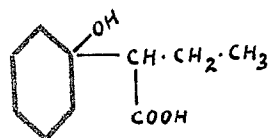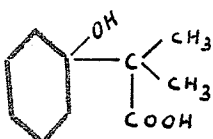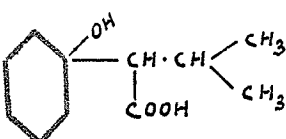
The higher degree of purity of lactones of cyclohexanol
acetic, propionic and isobutyric acids coincides with very
satisfactory yields of corresponding keto-acids. This seems
to support the opinion that the quality of the starting
material used in oxidation is essential in securing good
yields and the purity of keto-acids.

Cyclohexanone-2-α-acid series is shown in Table V.

5. CHEMISTRY OF THE ASSOCIATED COMPOUNDS

Cyclohexanol-1-α-Acids: The compounds of this type
and especially higher members of the series are not readily
synthesized because of the tendency to cleave. Efforts to
isolate them were made only in cases where the products were
either known or expected to be solid. Inspection of the
series (Table VI) shows variation of physical properties
similar to the one in the series of the unsaturated acids.
The melting points are declining from acetic to n-butyric

TABLE VI

Cyclohexanol-1-α-acids

Compound	Melting Point	
	Literature	Found
i.	71-72° (45)	68°
ii.	55° not sharp (46)	54-60° (crude)
	Boil. Point 167-170°/16 mm. (19)	
iii.		84-86°
iv.		122-123°

i. (structure: cyclohexane ring with OH, $-CH_2-COOH$)

ii. (structure: cyclohexane ring with OH, $-CH \cdot CH_3$, $COOH$)

(structure: cyclohexane ring with OH, $-CH \cdot CH_2 \cdot CH_3$, $COOH$)

iii. (structure: cyclohexane ring with OH, $-C$ with CH_3, CH_3, $COOH$)

iv. (structure: cyclohexane ring with OH, $-CH \cdot CH$ with CH_3, CH_3, $COOH$)

acid, while the acids with branched sidechain are the highest
melting compounds in the series.

The greatest tendency to cleave was encountered with
cyclohexanol-isobutyric acid. This is in agreement with
what was already said (page 20) about the cleavage of α ,
α -dialkyl- β -hydroxyacids. The decomposition of cyclo-
hexanol-1-α-isobutyric acid is expected to yield cyclo-
hexanone and isobutyric acid.
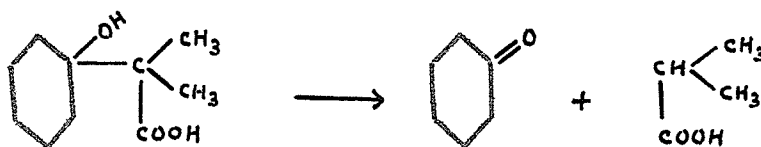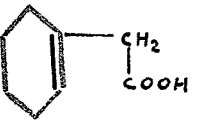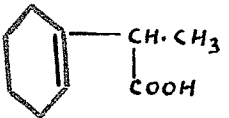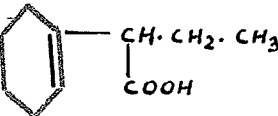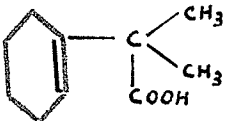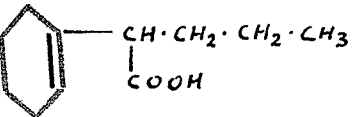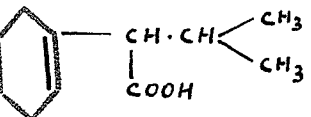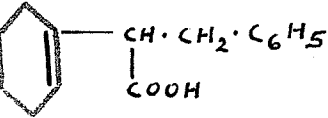
The ketone actually isolated was a high melting solid, and
it was thought that it may be a condensation product of two
molecules of cyclohexanone but elementary analysis failed
to support this.

<u>Cyclohexene-1-α-Acids</u>: The variation in melting
points (Table VII) seems to follow a pattern similar to one
observed in cyclohexanol-1-α-acid series. Lengthening of
the straight chain attached to α -carbon atom appears to
decrease the melting point, whereas branching in the same
position produces acids of higher melting point. The un-
usually high melting point of benzylacetic acid is somewhat
surprising in view of the difficulties to isolate it in a
solid form. Grewe (15) reports that he was unable to crystal-
lize his 2-methylcyclohexene-1-benzylacetic acid.

TABLE VII

Cyclohexene -1-α-acid	Boiling Point°		Melting Point°		Yield %
	Literature	Found	Literature	Found	
i. (cyclohexene)–CH$_2$–COOH	140/12 mm. (42)	135–138/13 mm.	37–38 (42)	35–36	90
ii. (cyclohexene)–CH·CH$_3$ / COOH	148–150/13 mm. (42)			32–34	
iii. (cyclohexene)–CH·CH$_2$·CH$_3$ / COOH	150/14 mm. (44)	144–145/9 mm.			75
iv. (cyclohexene)–C(CH$_3$)$_2$ / COOH	146–152/13 mm. (44)		71–72 (7)	69	70
v. (cyclohexene)–CH·CH$_2$·CH$_2$·CH$_3$ / COOH		160–164/15 mm.			58
vi. (cyclohexene)–CH·CH(CH$_3$)$_2$ / COOH				60–68	poor
vii. (cyclohexene)–CH·CH$_2$·C$_6$H$_5$ / COOH				146–148	

IV. EXPERIMENTAL

1. REFORMATSKY REACTION

a) Ethyl-(1-Cyclohexanol) Acetate

Dry, freshly distilled cyclohexanone (one mole) and purified zinc (one mole) were placed in a two-liter, three-necked flask equipped with a stirrer and a condenser. Dry, thiophene-free benzene (400 ml.) was added following which a separatory funnel containing ethyl bromoacetate (one mole) with a very small quantity of iodine dissolved, was inserted in the third neck. The solution was heated to boiling and some 20 gm. of the bromoester added. As soon as there was the first indication of reaction heating was discontinued. The reaction with larger quantities of bromoester introduced was usually quite violent and required cooling to keep it under control. When the reaction was beginning to slow down the stirring was started and the bromoester added at such a rate that a moderate refluxing was maintained. When all bromoester had been added the reaction mixture was kept at a mild refluxing for half an hour, the stirring continued, after which it was allowed to cool. No attempt should be made to dissolve the unreacted zinc by prolonged heating, as this decreases the yield and the quality of the product. A little ice was added to the cool solution, the stirring started and dilute, cold sulphuric acid (250 ml.) added slowly. The stirring was continued for some time, the

mixture transferred to a large separatory funnel and thoroughly shaken until the benzene layer appeared perfectly clear and separated sharply. The sulphuric acid layer was then removed, the benzene solution washed with water, dilute sodium carbonate and finally dried over calcium chloride. After the benzene has been removed the distillation yielded a small quantity of cyclohexanone boiling at 60-70°/11 mm. followed by the product (133 gm.) distilling at 108-118/11 mm.

b) Ethyl α -(1-Cyclohexanol) Propionate

Cyclohexanone (54 gm.) dissolved in benzene (200 ml.) was treated with zinc (36 gm.) and ethyl α -bromopropionate (100 gm.) similarly to the procedure outlined in a previous experiment.

Distillation yielded ethyl α -(1-cyclohexanol) propionate (83.5 gm.) boiling at 85-93°/1 mm.

c) Ethyl α -(1-Cyclohexanol) n-Butyrate

Cyclohexanone (51.5 gm.) dissolved in benzene (200 ml.) was allowed to react with zinc (33 gm.) and ethyl α -bromo-n-butyrate (100 gm.) under conditions employed in synthesis of ethyl (1-cyclohexanol) acetate. Distillation yielded 62 gm. of the product boiling at 124-127/10 mm.

d) Ethyl α -(1-Cyclohexanol) Isobutyrate

Ethyl α -bromoisobutyrate was obtained by drastic

bromination of isobutyric acid, followed by esterification.
The procedure employed is described by Schleier (36) for
the synthesis of ethyl α -bromoisovalerate. The compound
was obtained in 67 percent yield. It boiled at $105^{\circ}/120$ mm.
The boiling point reported by Michael (28) is $91-92^{\circ}/74$ mm.

Cyclohexanone (52 gm.) dissolved in benzene (200 ml.)
was allowed to react with zinc (34 gm.) and ethyl α -bromo-
isobutyrate (104 gm.) in a manner described for the Reformat-
sky reaction with bromoacetic ester. The product (78.7 gm.)
distilled at $132-138^{\circ}/13$ mm.

e) Ethyl α -(1-Cyclohexanol) n-Valerate

α -Bromo-n-valeric acid (100 gm.) was esterified with
three times equivalent quantity of absolute ethanol in pres-
ence of concentrated sulphuric acid (5 ml.). The mixture was
refluxed for six hours on water bath and allowed to cool.
Most of the alcohol was removed under vacuum. This resulted
in a certain loss of the ester since it is fairly volatile.
The reaction mixture was then shaken with a large volume
of water, dilute solution of sodium bicarbonate and dried
over anhydrous calcium chloride. The bromoester (85 gm.)
distilled at $81-84^{\circ}/15$ mm. The boiling point reported by
Michael (28) is $92-94^{\circ}/23$ mm.

Reformatsky reaction performed with cyclohexanone
(40 gm.), zinc (26 gm.) and ethyl α -bromovalerate (85 gm.)

yielded ethyl α -(1-cyclohexanol) n-valerate (70 gm.)
boiling at 103-108°/1mm.

f) Ethyl α -(1-Cyclohexanol) Isovalerate

Cyclohexanone (12 gm.) dissolved in benzene (50 ml.)
was treated with ethyl α -bromoisovalerate (25 gm.) in
presence of zinc (8 gm.) under conditions identical with
those described for synthesis of ethyl (1-cyclohexanol) ace-
tate. The product (15 gm.) distilled at 133-141°/ 10 mm.

g) Ethyl (1-Cyclohexanol) Benzylacetate

Ethyl α -bromobenzylacetate was prepared by the
method of Marvel (26). The acid was esterified and the
ester purified in a manner similar to that described for
esterification of α -bromo-n-valeric acid. The bromoester
boiled at 138-145/8 mm. The yield was 51 percent. The
boiling point reported by Grewe (15) is 150-152°/13 mm.

Reformatsky reaction carried out with ethyl α -bromo-
benzylacetate (30 gm.), cyclohexanone (11.5 gm.) and zinc
(8 gm.) in benzene (50 ml.) proceeded very smoothly. Dis-
tillation yielded a fraction (17 gm.) boiling at 115-190°/13
mm. followed by more constant boiling material (12 gm.) col-
lected at 190-205°/13 mm. Both were found to be bromine
free but only the second was investigated further.

Found: C = 73.4%, H = 8.98%.

Calculated for $C_{17}H_{24}O_3$: C = 73.9%, H = 8.76%.

In an attempt to improve yield toluene was used as a solvent. Cyclohexanone (36 gm.) dissolved in dry toluene (200 ml.) was allowed to react with ethyl α -bromobenzyl-acetate (100 gm.) in presence of zinc (23.5 gm.) similarly to previous Reformatsky reactions. The reaction was very vigorous and the flask had to be cooled with cold water. After the usual purification of the solution toluene was removed under reduced pressure. Distillation yielded cyclohexanone (15 gm.) collected at 57-65°/11 mm., a fraction (48 gm.) boiling at 118-125°/11 mm., n_D = 1,497, followed by a material (12 gm.) distilling at 125-160°/11 mm.

Found for 118-125°/11 mm. fraction: C = 74.4%, H = 8.20%. Calculated for ethyl hydrocinnamate, $C_{11}H_{14}O_2$: C = 74.2%, H = 7.88%. Steinkopf and Wolfram (40) report for ethyl hydrocinnamate, n_D = 1.4951 and boiling point 123°/16 mm.

Part of the fraction collected at 118-125/11 mm. (10 gm.) was saponified and the free acid distilled (boiling point 154°/11 mm.). The distillate (3 gm.) solidified at room temperature. After single crystallization from ligroin it melted at 51°. Melting point of hydrocinnamic acid reported by Weger (47) is 48.7°. Two derivatives were also prepared. The amide melting at 102° and p-bromophenacyl

ester melting at 101°. According to Taverne (41) the value of the former is 103° while the latter is reported (37) as melting at 104°.

There is no doubt that the main product of this reaction is ethyl hydrocinnamate. A likely mechanism by which it may have been formed is enolization of cyclohexanone (page 5) reported by Newman as one of the abnormalities of the Reformatsky reaction.

Another reaction was performed using toluene (10 ml.), ethyl α -bromobenzylacetate (6 gm.) and zinc (2 gm.) but no cyclohexanone. It started very readily and was fairly vigorous. The product did not have a constant boiling point probably due to a small quantity of material. Some liquid (0.5 gm.) was collected below 116°/14 mm., the rest between 116-126°/14 mm. (1 gm.) and 130-170°/14 mm. (1 gm.). The refractive index of the first two fractions was found to be 1.497. The fraction collected at 116-126°/14 mm. was saponified, the free acid extracted with ether and ether solution dried over anhydrous sodium sulphate. The oily residue left after removal of ether solidified on standing at -20°. After one crystallization from ligroin it melted at 48-49°. Mixed melting point with the hydrocinnamic acid obtained in a previous reaction showed no depression. The fraction collected at 130-170°/14 mm. had $n_D = 1.506$. It was not investigated further.

This last reaction makes it rather doubtful that the formation of ethyl hydrocinnamate in the previous synthesis was due to enolization of cyclohexanone. It seems to be more likely that hydrocinnamate formed on hydrolysis of the addition product produced in a reaction between zinc and bromoester alone.

h) Attempted Synthesis of Ethyl α -(1-Cyclohexanol) Phenylacetate

Ethyl α -bromophenylacetate was prepared by drastic bromination of phenylacetic acid followed by esterification. The procedure employed is described by Anschütz (1). The compound was obtained in 84 percent yield and boiled at 139-144/12 mm. The boiling point reported by Anschütz (1) is 150-152/13 mm.

Cyclohexanone (8 gm.) dissolved in benzene (40 ml.) was allowed to react with ethyl α -bromophenylacetate (19 gm.) in presence of zinc (12.5 gm.). The reaction proceeded very smoothly. Distillation yielded cyclohexanone (3.5 gm.), a liquid (9 gm.) boiling at 110-115/4 mm, n_D = 1.495 and a fraction (2 gm.) boiling at 120-170/4 mm. n_D = 1.502. The last fraction yielded a white solid on cooling. It melted at 139° after crystallization from ethanol. Blaise and Courtot (3) isolated a solid melting at 140° which analysed to ethyl diphenylsuccinate in a Reformatsky reaction with acetone and bromophenylacetic ester.

Found, (fraction 110-115/4 mm.): C = 73.25%, H = 8.12%, the figures being the average of three determinations. Calculated for ethyl α -(1-cyclohexanol) phenylacetate, $C_{16}H_{22}O_3$: C = 73.3%, H = 8.475%. Calculated for ethyl phenylacetate, C_5H_6O: C = 73.3%, H = 7.37%.

A small quantity of the analysed fraction was saponified. On acidification of the solution a solid compound separated. It was filtered, washed with water and crystallized from ligroin. It melted at 77° and mixed melting point with phenylacetic acid showed no depression. n_D of ethyl phenylacetate reported by Eijkman (13) is 1.48097. The distillation residue (3 gm.) showed some solid material. It was separated from the oil by digestion with ethanol. After crystallization from ethanol it was found to be identical with the solid isolated from the last fraction (ethyl diphenylsuccinate).

A second Reformatsky reaction was performed using ether as a solvent. Cyclohexanone (17 gm.) dissolved in absolute ether (50 ml.) was treated with ethyl α -bromophenylacetate (36.5 gm.) in presence of zinc (10.5 gm.) A little iodine had to be added in order to start the reaction after which it turned out to be quite vigorous and the flask had to be cooled. The main product isolated on distillation was again recognized as ethyl phenylacetate (n_D=1.489, boiling point 121-125°/15 mm.). The quantity of ethyl diphenylsuccinate was larger than in the reaction carried out in benzene solution.

Reformatsky reaction with ethyl α -bromophenylacetate showed little tendency, if any, for the formation of normal addition product. On the other hand the reaction readily entered an abnormal course, the products suggesting two mechanisms, enolization and Wurz-type condensation (page 5). If the reaction with bromophenylacetate were shown, as is expected, to occur in absence of cyclohexanone and yield chiefly phenylacetic ester it would be very likely due to direct addition of zinc to bromoester. Ethyl phenylacetate would form on hydrolysis of the addition product.

2. DEHYDRATION OF THE PRODUCTS OF REFORMATSKY REACTION

a) Ethyl Cyclohexene-1-Acetate

Ethyl (1-cyclohexanol) acetate (50 gm.) was dissolved in dry benzene (150 ml.) and phosphorus pentoxide (40 gm.) added to the solution. It was then refluxed on water bath for three hours and allowed to cool. The benzene solution was decanted, the porous residue rinsed twice with benzene (25 ml. portions) and the washings combined with the main solution. The benzene was then removed and the unsaturated ester (30.5 gm.) distilled. It boiled at 93-95 /10 mm.

b) Ethyl Cyclohexene-1- α-Propionate

Ethyl α -(1-cyclohexanol) propionate (60 gm.) was dissolved in benzene (180 ml.) and refluxed with phosphorus

pentoxide (50 gm.) for three hours. The benzene was then removed and the product (38 gm.) distilled. It boiled at 68-72 /1 mm.

c) Ethyl Cyclohexene-1-α-n-Butyrate

Ethyl α -(1-cyclohexanol) n-butyrate (30 gm.) was dehydrated with phosphorous pentoxide (25 gm.) in benzene (100 ml.). The unsaturated ester (16.5 gm.) distilled at 103-106 /10 mm.

d) Ethyl Cyclohexene-1-α-Isobutyrate

Ethyl α -(1-cyclohexanol) isobutyrate (30.5 gm.) was dehydrated with phosphorous pentoxide (25 gm.) in benzene (100 ml.). Distillation yielded the unsaturated ester (21.5 gm.) boiling at 107-113 /13 mm.

e) Ethyl Cyclohexene-1-α-n-Valerate

Dehydration of ethyl α -(1-cyclohexanol) n-valerate (57.5 gm.) with phosphorous pentoxide (50 gm.) in benzene (150 ml.) yielded the product (40 gm.) boiling at 82-88/1mm.

f) Ethyl Cyclohexene-1-α-Isovalerate

Dehydration of ethyl α -(1-cyclohexanol) isovalerate (15 gm.) yielded the product (9 gm.) boiling at 115-125 / 11 mm.

g)   Ethyl Cyclohexene-1-α-Benzylacetate

Ethyl α -(1-cyclohexanol) benzylacetate (12 gm.)
was dehydrated with phosphorus pentoxide (6 gm.) in benzene
(40 ml.). The product (6 gm.) boiled at 140-145/2 mm.
Found: C ≟ 78.8%, H ≟ 8.73%.
Calculated for $C_{17}H_{22}O_2$: C ≟ 79.1%, H ≟ 8.59%.

3. SYNTHESIS OF LACTONES

a) Lactone of Cyclohexanol-2-Acetic Acid

(i) From Ethyl-Cyclohexene-1-Acetate: Ethyl cyclo-
hexene-1-acetate (10 gm.) was placed in a 250 ml. two-neck
flask equipped with a stirrer and a reflux condenser. Fifty
percent (by volume) sulphuric acid (60 ml.) was added and
the mixture heated on water bath for one hour with stirring.
Before the maximum temperature was reached the oily layer
disappeared, the solution assuming yellow-orange color.
Only a small quantity of dark green, polymeric material,
clinging to the walls of the flask was observed. Its
quantity, however, was steadily increasing and when the
heating was discontinued the solution was too dark to be
transparent. It was allowed to cool following which a
large quantity of water (150 ml.) was added. The solution
was heated to boiling, cooled and extracted with ether
four times (50 ml. portions). The combined ether extracts

were washed with concentrated salt and sodium carbonate
solution. The ether was removed and the residue dried
over anhydrous potassium carbonate. Distillation of the
dry material yielded a colorless liquid (5 gm.) of char-
acteristic smell, boiling at 131-135/12 mm. The refractive
index was found to be 1.481. Braun and Münch (7) report
$n_D = 1.4784$ for the lactone of cyclohexanol-2-acetic acid.
The compound was neutral to litmus. On standing at -20°
it crystallized in long, white needles which melted after
being left for a few minutes at room temperature. Cyclo-
hexene-1-acetate does not solidify at -80°.

Found: $C = 69.1\%$, $H = 8.72\%$.

Calculated for the lactone, C_4H_6O: $C = 68.6$, $H = 8.57$.

Calculated for ethyl cyclohexene-1-acetate, C_5H_8O:

$$C = 71.4\%, \quad H = 9.60\%.$$

(ii) From Cyclohexene-1-Acetic Acid: Crude cyclo-
hexene-1-acetic acid (7 gm.) was treated with 50 percent
sulphuric acid (40 ml.) following the procedure described
in the previous experiment. The acid layer disappeared
as soon as temperature of 85° was reached. The solution
was considerably darker at this stage than in the experi-
ment with the cyclohexene-1-acetate. Heating at 90°
continued for one hour after which the solution was cooled,
diluted with water and heated again to boiling. The

treatment that followed was identical with the one outlined in the previous experiment. The sodium carbonate extract showed only very little unlactonized acid present. Distillation yielded a colorless liquid (3 gm.) boiling at 130-135/12 mm., $n_D = 1.478$. It was neutral to litmus and solidified at $-20°$. Found: $C = 68.2\%$, $H = 9.00\%$. The distillation residue was very dark and viscous. The quantity (2 gm.) was larger than in previous synthesis.

(iii) <u>From ethyl Cyclohexanol-1-acetate</u>: The ester (10 gm.) and 50 percent sulphuric acid (60 ml.) were heated on water bath for one hour. The ester layer could not be detected after mixing the liquids because the solution turned very dark. It cleared a little on heating but a very close examination was required to see the layer disappear. There was a large scale formation of dark, polymeric material. The solution was processed as in the preceding experiments. Distillation yielded some very low boiling compound (0.5 gm., $30-40°/12$ mm.) of a pleasant smell. The lactone (2 gm.) followed at 128-134/12 mm. It showed the same properties as lactones from the previous syntheses. Found: $C = 68.8\%$, $H = 8.97\%$.

b) <u>Lactone of Cyclohexanol-2-α-Propionic Acid</u>

Ethyl cyclohexene-1-α-propionate (30.5 gm.) was heated on water bath with 50 percent sulphuric acid (180 ml.)

for two hours with stirring. After half an hour of heating
at 90° the ester layer disappeared, but due to the presence
of dark, viscous material this was extremely difficult to
observe. As seen through a thin layer, sulphuric acid had
a usual orange-yellow color. The solution was processed in
a normal way. Distillation yielded a liquid (17 gm.) boiling
at 135-138/13 mm. It was neutral to litmus and did not sol-
idify at -20°. Found: C = 69.5%, H = 9.24%. Required for
$C_9H_{14}O_2$: C = 70.0%, H = 9.15%. Required for ethyl cyclohexene-
1-α-propionate, $C_{11}H_{18}O_2$: C = 72.5, H = 9.96.

c) Lactone of Cyclohexanol-2-α-n-Butyric Acid

(i) From ethyl cyclohexene-1-α-n-butyrate. 1st. attempt:

Ethyl cyclohexene -1-α-n-butyrate (8 gm.) and 50 percent
sulphuric acid (50 ml.) were heated on water bath for two hours
the stirring maintained. The ester layer and sulphuric acid
were turning gradually darker until it was not possible to
make any distinction between the two. The solution was al-
lowed to cool and was then treated similarly to the preceding
experiments. Distillation yielded a liquid (2 gm.) boiling
at 105-115/13 mm. followed by a fraction (2.5 gm.) boiling
at 135-145/13 mm. A small quantity of distillate was col-
lected during a rapid climb of temperature (115-135/13 mm.).
The respective refractive indices of the three fractions were

1.467, 1.470, 1.475. n_D of pure, unsaturated ester previously determined was 1.467. Found (fraction 1): C = 73.7%, H = 10.55%. Calculated for ethyl cyclohexene-1-α-n-butyrate, $C_6H_{10}O$: C = 73.4%, H = 10.30%. Found (fraction 3): C = 72.1%, H = 9.92%. Calculated for the lactone, C_5H_8O: C = 71.4%, H = 9.57%. Elementary analysis showed that the first fraction was unreacted, starting material. The last fraction appeared to be a mixture of lactone and original material. The separation of the two was performed in the following way. The contaminated lactone (2.5 gm.) was combined with the second fraction (0.5 gm.) and dissolved in 25 percent sodium hydroxide by heating to boiling under reflux. It was necessary to add some ethanol to form a homogeneous solution. The alcohol was removed under vacuum, the solution diluted with water and extracted with ether to remove the unsaponified ester if present. The aqueous solution was cooled on ice and made strongly acidic with cold, 50 percent sulphuric acid. The solution was heated on water bath under reflux for one hour to convert all free γ -hydroxy acid to lactone, cooled and extracted with ether. The ether solution was purified by shaking with concentrated salt solution and the free acid removed by treatment with sodium carbonate solution. The ether was then removed, the residual liquid dried over anhydrous potassium carbonate and distilled. The transfer of the dry liquid was accomplished partly by decanting, partly

by extracting the residual potassium carbonate with Grignard ether and filtering the ether solution into the distilling flask. The quantity of the material was not sufficient to give a sharp boiling point. The temperature was climbing steadily during the distillation but it did stop at 140-145/13 mm. for a short time. The yield was 1.5 gm. Found: $C = 70.7\%$, $H = 9.72\%$, $n_D = 1.477$.

(ii) From ethyl cyclohexene-1-α-n-butyrate. 2nd. Attempt:

The ester (9 gm.) was heated on water bath with 50 percent sulphuric acid (50 ml.) for four hours with constant stirring. The solution turned very dark. Close examination at the end of the process could not detect the presence of oily layer. The treatment that followed was identical with those described in previous experiments. Distillation of the reaction mixture yielded the following fractions:

1. 40-50/12 mm. $n_D = 1.457$ (1 gm.)
2. 100-125/12 mm. $n_D = 1.472$ (1 gm.)
3. 138-144/12 mm. $n_D = 1.477$ (3.5 gm.)

The amount of the residual material was 1.0-1.5 gm.
Found (fraction 3): $C = 72.1\%$, $H = 9.74\%$.

(iii) From ethyl α -(1-cyclohexanol)-n-butyrate

Ester (10 gm.) was heated on water bath with 50 percent

sulphuric acid (60 ml.) for one hour after which the temperature of the solution was raised to 125° by heating with microburner. This temperature was maintained for half an hour following which the solution was allowed to cool. It turned extremely dark and the quantity of viscous, polymerous material was higher than in all previous experiments. Distillation following the usual precessing of the solution yielded a small quantity of a low boiling liquid (40-50/13 mm.) followed by a fraction (2.5 gm.) boiling at 135-145/13 mm. Found: $C = 71.9\%$, $H = 9.85\%$. The low boiling compound showed $n_D = 1.450$, did not react with sodium metal and did not produce oxime with hydroxylamine.

d) Lactone of Cyclohexanol-2-α-Isobutyric Acid

Ethyl cyclohexene-1-α-isobutyrate (10 gm.) was heated on water bath with 50 percent sulphuric acid (60 ml.) for two hours. The oily layer soon dissolved clear and the solution assumed an orange-yellow color. Only a few drops of some dark material remained on the surface of the solution. The treatment followed the same course up to the point when ether was removed. The residual oil solidified on cooling. Recrystallized from ligroin the solid (7.1 gm.) melted at 53-55°. It had a pleasant smell somewhat resembling camphor.

Found: C = 71.1%, H = 9.58%. Required for C_5H_8O: C = 71.4%, H = 9.57%.

e) Lactone of Cyclohexanol-2-α-n-Valeric Acid

(i) First attempt: Ethyl cyclohexene-1-α-n-valerate (30 gm.) was heated on water bath with 50 percent sulphuric acid (180 ml.) for six hours, the solution being continuously stirred. There was only little polymerous material formed and the solution was fairly light in color. Following the usual treatment the product was distilled yielding the liquid (24 gm.) boiling at 128-131/13 mm. There were no other fractions. The residue (2-3 gm.) was medium brown in color. The refractive index of the distillate (1.462) was identical with that of the starting material. Found: C = 73.75%, H = 10.62. Calculated for cyclohexene-1-α-n-valerate, $C_{13}H_{22}O_2$: C = 74.3%, H = 10.55%.

(ii) Second attempt: Ester (24 gm.) was heated over a micro-burner with 50 percent sulphuric acid (150 ml.) for one hour at 115-125°. The solution was stirred mechanically. The sulphuric acid turned very dark and considerable quantities of tar-like material were observed. Fractionate distillation of the material yielded:

hours the solution being stirred mechanically. At the end
of the process the solution turned very dark and the tarry,
black material formed a thick film around the upper part of
the flask rendering impossible the examination for the presence
of the unreacted material. Separation and purification of
the product were performed by the usual procedure. Following
materials were isolated by distillation:

1. 0.5 gm. boiling 35-45/15 mm.
2. 1.2 gm. " 110-140/15 mm., $n_D = 1.470$
3. 2.5 gm. " 140-150/14 mm., $n_D = 1.477$
4. 1.0 gm. of residue.

Found (fraction 3): C = 72.3%, H = 10.01%.

Calculated for the lactone, $C_{11}H_{18}O_2$: C = 72.5%, H = 9.95%.

g) Attempted Synthesis of Lactone of Cyclohexanol-2-α-Benzyl-
acetic Acid

(i) From ethyl cyclohexene-1-α-benzylacetate: Ethyl
cyclohexene-1-α-benzylacetate (2.5 gm.) was heated for four
hours at 110-120° with 50 percent sulphuric acid (15 ml.)
Following the usual treatment a small quantity of heavy,
viscous oil was distilled. Due to very small quantities of
product to be distilled no attempt was made to register the
temperature. Found: C = 79.1%, H = 8.73%. Calculated for
cyclohexene-1-α-benzylacetate, $C_{17}H_{22}O_2$: C = 79.1%, H = 8.59%.

In a second attempt the ester (2 gm.) was kept at the
boiling point of 50 percent sulphuric acid (145°) for four

hours with stirring. There was a considerable amount of decomposition and even some charred material appeared in the reaction mixture. The product was processed as usual and distilled. Found: $C = 80.4\%$, $H = 8.63\%$. Calculated for the lactone, $C_{15}H_{18}O_2$: $C = 78.2\%$, $H = 7.88\%$.

(ii) <u>From cyclohexene-1-α-benzylacetic acid</u>: Ethyl cyclohexene-1-α-benzylacetate (4 gm.) was saponified with 50 percent alcoholic potassium hydroxide. After removal of alcohol under vacuum and addition of water a clear solution was obtained. It was cooled on ice, acidified with cold, dilute sulphuric acid, the viscous oil that separated extracted with ether and ether removed. The crude acid thus obtained was heated for two hours at 125° with stirring in presence of 50 percent sulphuric acid (25 ml.) Following the usual purification a very small quantity of extremely heavy oil was distilled. Apparently it was too viscous to be homogeneous, as two elementary analyses showed different values both being higher than the values calculated for the corresponding lactone. The sodium carbonate extract showed after acidification a considerable quantity of some oily material which solidified on standing at room temperature. After two crystallizations from ligroin the material melted at $146-148^{\circ}$. Found: $C = 78.0\%$, $H = 7.95\%$. Calculated for cyclohexene -1-α-benzylacetic acid, $C_{15}H_{18}O_2$: $C = 78.2\%$, $H = 7.88\%$. It seems that the treatment with sulphuric acid

eliminated most of the impurities present in a crude acid permitting its isolation in a solid form. Previous attempts (page 76) to isolate this acid as a solid were unsuccessful.

4. OXIDATION OF LACTONES

a) Cyclohexanone-2-Acetic Acid

The compound has been obtained using the oxidation method described by Kendall, Osterberg and MacKenzie (17).

The lactone of cyclohexanol-2-acetic acid (5 gm.) was dissolved in 5 N sodium hydroxide (25 ml.) by heating to boiling, the solution was stirred, while a hot solution of magnesium sulphate (17 gm. of the heptahydrate in 12 ml. of water) was slowly added. The flask was cooled below 10° by immersion in ice and the stirring continued while bromine (5 gm.) was dropped in slowly over a period of six hours. Fresh ice was packed around the flask and it was allowed to resume room temperature by standing overnight. Next day the solution was made strongly acidic with 10 N sulphuric acid after which it was stirred for two hours at room temperature to convert the unoxidized γ-hydroxyacid into the lactone. The oily layer was then extracted with ether, the ether removed by distillation and the residual oil shaken repeatedly with a concentrated solution of sodium carbonate. The undissolved, oily material was removed by extraction with ether. The alkaline solution was reduced to a small volume under vacuum,

acidified and the oily layer extracted with ether. The ether solution was dried over anhydrous sodium sulphate for twenty-four hours following which the ether was removed by distillation and the residual oil kept at -80° until it solidified. The solid material was pale yellow in color and apparently represented a fairly pure keto-acid, as it showed little tendency to melt. It was freed from liquid material by pressing on filter paper. After this operation it appeared as practically white powder melting at $70-72^{\circ}$. The yield was 2.4 gm. A small quantity recrystallized from n-hexane melted at $73-74^{\circ}$.

b) Cyclohexanone-2-α-Propionic Acid

The lactone of cyclohexanol-2-α-propionic acid (4.5 gm.) was dissolved in 5 N sodium hydroxide (22 ml.) by short heating under reflux. A hot solution of magnesium sulphate (15 gm. of heptahydrate salt in 11 ml. of water) was then added slowly, the lactone solution being stirred mechanically. The oxidation with bromine (5 gm.) was carried out similarly to the one in previous experiment. The separation with sodium carbonate was not attempted. The oily layer separating after acidification was extracted with ether. The residual liquid left after evaporation of ether soon solidified. It was

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purified by pressing on filter paper until most of the dark
oil had been removed. The crude keto-acid was dissolved in
hot benzene, boiled with charcoal, filtered and crystallized
by adding ligroin. Following two more crystallizations the
melting point was found to be 131.5-132.5°. The yield was
1.5 gm. Found: C = 62.7%, H = 8.35%. Calculated for
$C_9H_{14}O_3$: C = 63.5%, H = 8.23%. The semicarbazone recrystal-
lized from dilute ethanol melted at 153-154°.

c) Cyclohexanone-2-α-n-Butyric Acid

The lactone of cyclohexanol-2-α-n-butyric acid (4 gm.)
was dissolved in 5 N sodium hydroxide (20 ml.) by heating to
boiling under reflux. The addition of magnesium sulphate
solution (13 gm. of heptahydrate in 10 ml. of water) and
bromine (4 gm.) was performed in the same way as in oxidation
of lactone of cyclohexanol-2-α-propionic acid. The dark
oil that separated following acidification was extracted with
ether and the latter removed by distillation. The residual,
brown, viscous liquid did not solidify on dry ice-acetone
mixture. It was digested three times with ligroin, the sol-
vent being decanted each time. The ligroin-insoluble, semi-
solid material was pressed on filter paper to remove the
adherent oil. The crude keto-acid was then dissolved in

benzene, boiled with charcoal and filtered. Considerable difficulties were encountered in recrystallization since on adding ligroin to benzene solution the acid persisted in separating as an oil. After four crystallizations the melting point was found to be 113-114°. The yield was 0.45 gm. Found: C = 64.7%, H = 8.74%. Calculated for $C_{10}H_{16}O_3$: C = 65.2%, H = 8.75%. The semicarbazone recrystallized from dilute ethanol melted at 192-193°. The oily residue left after evaporation of solvent from the ligroin extracts showed on long standing some solid material. It was dissolved in dilute alcohol and treated with sodium acetate and semicarbazide hydrochloride. The precipitated solid (.42 gm.) was recrystallized from dilute ethanol. It melted at 190-192°.

d) Cyclohexanone-2-α-Isobutyric Acid

The lactone of cyclohexanol-2-α-isobutyric acid (3 gm.) was dissolved in 5 N sodium hydroxide (15 ml.) by heating to boiling. Hot solution of magnesium sulphate (10 gm. of heptahydrate in 7.5 ml. of water) was added slowly followed by addition of bromine (4 gm.) in a manner outlined in preceding oxidations. Some water had to be added during the addition of bromine to prevent solidification. After acidification the crude acid was extracted with ether. A white

solid forming a separate phase between the ether and aqueous

solution proved to be identical with the keto-acid later iso-

lated from the ether solution. Cyclohexanone-2-α-isobutyric

acid proved to be only sparingly soluble in ether and it

was seen to separate in a solid form after half of the solvent

had been removed. It was crystallized five times from hot

benzene by adding ligroin. After the last crystallization

the compound (1.9 gm.) melted at 150-151°. Found: C = 65.2%,

H = 8.85%. Calculated for $C_{10}H_{16}O_3$: C = 65.2%, H = 8.75%.

Semicarbazone, recrystallized once, melted at 197-198°.

e) Attempted Synthesis of Cyclohexanone-2-α-n-Valeric Acid

The lactone of cyclohexanol-2-α-n-valeric acid (3 gm.)

was dissolved in 5 N sodium hydroxide (15 ml.) and treated

with the solution of magnesium sulphate (10 gm. in 7 ml. of

water) and later with bromine (3.5 gm.) following the pro-

cedure in previous oxidations. The dark oil left after re-

moval of ether from the extract of the acidified solution

would not solidify at -80°. Digestion with ligroin likewise

failed to separate the solid material. The oil yielded a

semicarbazone derivative (0.3 gm.) melting at 195-196° indi-

cating the presence of keto-acid. An attempt to produce the

free acid by hydrolysis of semicarbazone with warm, dilute

sulphuric acid failed to isolate any solid material.

f) Cyclohexanone-2-α-Isovaleric Acid

The lactone of cyclohexanol-2-α-isovaleric acid (3.5
gm.) was dissolved in 5 N sodium hydroxide (16 ml.) and was
treated with the solution of magnesium sulphate (12 gm. in
9 ml.) and bromine (3.5 gm.). The oil left after removal of
ether did not crystallize at -80°. The digestion with ligroin
produced a small quantity of a semisolid material which after
being pressed on filter paper to remove the adherent oil
was dissolved in benzene, boiled with charcoal and filtered.
Ligroin was added to benzene solution and it was allowed to
stand. The crystals that formed were purified by two more
crystallizations. They melted at 134-135°. Found: C = 66.5%,
H = 9.13%. Calculated for $C_{11}H_{18}O_3$: C = 66.65%, H = 9.16%.
From the residual oil left after the evaporation of solvent
from ligroin extracts additional quantity of keto-acid (0.2
gm.) was isolated in a form of semicarbazone. It melted at
209-210°.

5. CHEMISTRY OF THE ASSOCIATED COMPOUNDS

a) Cyclohexanol-1-α-Acids

(i) Cyclohexanol-1-acetic acid: Ethyl (1-cyclohexanol)
acetate was saponified following directions of Auwers and
Ellinger (1). The ester (8 gm.) was refluxed for one hour
with 20 percent alcoholic sodium hydroxide (10 ml.) The

alcohol was removed under vacuum. The residue was mostly solid with some oily material. Water was added and the solid dissolved on little warming. The solution was cooled, extracted with ether, the aqueous solution placed on ice and acidified with cold, dilute sulphuric acid. The oily layer was extracted with ether and the ether solution dried over anhydrous sodium sulphate. The ether was then removed and the residue placed on ice where it soon solidified. The yield of the crude acid was 5 gm. One gram was recrystallized from benzene-ligroin mixture. The melting point was 68°.

(ii) <u>Cyclohexanol-1-α-propionic acid</u>: Ethyl α-(1-cyclohexanol) propionate (7 gm.) was treated with alcoholic sodium hydroxide similarly to ethyl (1-cyclohexanol) acetate. The dark, heavy oil left after removal of ether had to be seeded with cyclohexanol-1-acetic acid and allowed to stay for several days at -20° to induce crystallization. The crystals were freed from oil by pressing on filter paper. Attempts to crystallize it from benzene-ligroin failed, the compound persisting in separating as an oil. It had to be seeded again and allowed to stand at -20°. The crude acid (3 gm.) melted at $54-60^\circ$.

(iii) <u>Attempted saponification of ethyl α-(1-cyclohexanol) isobutyrate</u>: Ethyl α-(1-cyclohexanol) isobutyrate

(5 gm.) was refluxed for two hours with 20 percent alcoholic sodium hydroxide (7 ml.). After removal of alcohol and dilution with water the solution was extracted with ether. The ether was distilled off to leave an oily residue which showed a crop of crystals on long standing. They were isolated by digestion with ligroin which dissolved the oil leaving behind the solid. After two crystallizations from benzene-ligroin the compound melted at 143-148°. Found: C = 75.5%, H = 10.15%. Calculated for cyclohexanone, $C_6H_{10}O$: C = 73.4%, H = 10.28%. The semicarbazone derivative melted at 169-172° with decomposition.

The aqueous solution was acidified, the solution extracted with ether and the ether extract dried over anhydrous sodium sulphate. The ether was removed and the liquid residue kept at -20° for 48 hours but no crystallization took place. The oil had a strong smell of butyric acid. The refractive index was found to be 1.400. The value for isobutyric acid, reported by Brühl (8) is 1.39300. Amide derivative melted at 123-124°. The melting point reported by Meldrum and Turner (27) is 127.5°.

In a second saponification attempt procedure of Kon and Narayanan (19) was employed. Hot solution of potassium hydroxide (3 gm. in 3 ml. of water) was added to ethyl α -(1-cyclohexanol) isobutyrate (3 gm.) The flask was heated under

reflux on water bath and methanol (5 ml.) was added slowly to
the reaction mixture. The solution was refluxed for two hours.
The treatment that followed was identical to the one previously
described. The residual oil obtained after removal of ether
had a strong smell of butyric acid and similarly to one ob-
tained in the first saponification it did not crystallize on
prolonged standing at -20°. However, after a period of several
weeks some crystalline material appeared. It was separated
from the liquid material by pressing on filter paper. It
was then digested with ligroin which dissolved most of the
material leaving behind a dark, amorphous solid. After
evaporation of ligroin a white crystalline solid melting at
84-86° was left. This is considered to be cyclohexanol-1-
α-isobutyric acid but time did not permit its further inves-
tigation.

((iv) <u>Cyclohexanol-1-α-isovaleric acid</u>: Ethyl α -(1-
cyclohexanol) isovalerate (5 gm.) was treated with the solution
of potassium hydroxide and methanol as described by Kon and
Narayanan. The residual oil from the ether solution crystal-
lized on long standing. After recrystallization from methanol
the solid melted at 122-123°. Found: C = 65.7%, H = 9.98%.
Calculated for $C_{11}H_{20}O_3$: C = 66.0%, H = 10.06%. The ether
extract of the alkaline solution showed considerable quantity

of some oily liquid which appeared to be unsaponified ester but was not investigated further.

b) Cyclohexylidene- α -Acids

Cyclohexylidene acetic acid: The compound was synthesized by the method of Wallach (45). Crude cyclohexanol-1-acetic acid (4 gm.) was refluxed for three hours with acetic anhydride (6 gm.). The reaction mixture was cooled, poured on water and steam distilled. A large quantity of the distillate solidified in the condenser. The aqueous solution collected was extracted with ether, the latter removed and the residue steam distilled again. The solid trapped in the condenser was removed and recrystallized from ligroin. It melted at 91°. Wallach (45) reports 91-92°. The yield was 1.5 gm.

c) Cyclohexene-1- α -Acids

(i) Cyclohexene-1-acetic acid: Ethyl cyclohexene-1-acetate (38.5 gm.) was heated for one hour on water bath with 25 percent aqueous solution of potassium hydroxide (75 ml.). The solution was stirred mechanically. Following the acidification the crude acid was extracted with ether, ether solution dried over anhydrous sodium sulphate and ether removed. The yield of the crude acid was 29 gm. It distilled at 135-138/13 mm.

and solidified after being kept at -20° for a short time.
A small quantity of the solid was taken on filter paper and
pressed until it became completely dry. It melted at 34-36°
and attempts to increase the melting point by recrystallization
from dilute methanol failed, the compound separating repeat-
edly in the liquid form. Amide derivative melted at 151°.
Wallach (42) reports 152-153°.

Cyclohexene-1-acetic acid was found to add up hydrogen
bromide very readily when treated with fuming hydrobromic
acid at 0°. The whole reaction mixture solidified and the
process was accompanied by evolution of heat. The solid was
washed on filter with water until the filtrate was neutral
to litmus and recrystallized from methanol. It melted at
80°. After several weeks of standing in desiccator over
potassium hydroxide the melting point increased to 89-90°,
the value reported by Wallach (42). The compound is not
stable to warm water. It loses hydrogen bromide reforming
cyclohexene-1-acetic acid.

(ii) Cyclohexene-1-α-propionic acid: The saponifi-
cation was performed in a similar way to the one with ethyl
cyclohexene-1-acetate. The acid was distilled and a small
quantity (1.5 gm.) was collected at 140/11 mm. It solidified
on standing at -20°. The solid which partly melted at room
temperature was freed from liquid acid by pressing on filter
paper. It melted at 32-34°.

(iii) <u>Cyclohexene-1-α-n-butyric acid</u>: Ethyl cyclohexene-1-α-n-butyrate (13.7 gm.) was saponified with 50 percent alcoholic potassium hydroxide (15 ml.). The crude acid (9 gm.) distilled at 144-145/9 mm. It did not solidify even on dry ice-acetone mixture.

(iv) <u>Cyclohexene-1-α-isobutyric acid</u>: Ethyl cyclohexene-1-α-isobutyrate (5 gm.) was saponified using large excess of 50 percent alcoholic potassium hydroxide. The liquid that remained after removal of ether following the extraction of the acidified solution solidified without cooling. It was recrystallized from ligroin. The crystals (3 gm.) melted at 69°.

(v) <u>Cyclohexene-1-α-n-valeric acid</u>: Ethyl cyclohexene-1-α-n-valerate (5 gm.) was saponified by the procedure of Kon and Narayanan. The distillate (2.5 gm.) was a very heavy, viscous oil boiling at 160-164/15 mm. The compound did not solidify at -80°.

(vi) <u>Cyclohexene-1-α-isovaleric acid</u>: Ethyl cyclohexene-1-α-isovalerate (2 gm.) was saponified with an excess of 50 percent alcoholic potassium hydroxide. Ether extraction from the alkaline solution showed a large quantity of

unsaponified ester. The oil obtained after removal of ether following the extraction of the acidified solution solidified at -20°. The adhering oil was removed by adsorption on filter paper. The solid (0.4 gm.) was readily soluble in methanol, ligroin, benzene and carbon tetrachloride. Attempts to crystallize it from dilute methanol failed, as the compound separated repeatedly as a liquid. The crude product melted at 60-68°. Found: C = 72.2%, H = 10.00%. Calculated for $C_{11}H_{18}O_2$: C = 72.5%, H = 9.95%.

(vii) Cyclohexene-1-α-benzylacetic acid: Ethyl cyclohexene-1-α-benzylacetate saponified readily to yield extremely viscous, heavy oil which showed a crop of small crystals on standing at -20°. However, they melted immediately after being exposed to room temperature. It was surprising to find that what appeared to be the same compound was isolated as a high melting solid when crude cyclohexene-1-α-benzylacetic acid was subjected to Fittig's conditions (page 64).

V. SUMMARY

1. This investigation showed that oxidation of γ-lactones is a convenient and reliable method of synthesis of the lower members of cyclohexanone-2-α-acid series. The Reformatsky reaction proved to be extremely useful in securing good yields of cyclohexanol-1-α-esters. The latter were found to be readily convertible into the corresponding unsaturated esters. The treatment with mineral acid of these esters produced lactones but satisfactory yields again were obtained with lower homologues only.

2. Decreased yields of higher lactones and keto-acids are considered to be due to inadequate experimental technique rather than shortcomings inherent in the method itself.

3. The method was found inapplicable for the synthesis of the lactone of cyclohexanol-2-α-benzylacetic acid from the corresponding unsaturated ester.

4. A synthesis of three new cyclohexene-1-α-esters (Table III) and acids (Table VII) has been accomplished by the dehydration method.

5. Synthesis of two new lactones of cyclohexanol-2-α-acids (Table IV) has been performed. The lactone of isobutyric acid previously known has now been synthesized by the sulphuric acid method.

6.   Three new cyclohexanone-2-α-acids (Table V) have been prepared by oxidation of the γ-lactones.

7.   Cyclohexanol-1-α-isobutyric and -isovaleric acids have been obtained (Table VI) by hydrolysis of the corresponding esters.

8.   The reaction between zinc and α-bromobenzylacetic ester was found to take place very readily in toluene, yielding after hydrolysis hydrocinnamic ester. The same type of reaction is likely to account for the formation of ethyl phenylacetate in the Reformatsky reaction with ethyl α-bromophenylacetate.

VI. RECOMMENDATIONS FOR FUTURE WORK

1.   An attempt should be made to improve yields in the
synthesis of the lactone of cyclohexanol-2-α-n-butyric,
isovaleric and n-valeric acids from the corresponding
unsaturated esters. The optimum conditions for lactoni-
zation would appear to be two hours' heating at 110-120°
for n-butyric, three to four hours for isovaleric, and
three to five hours at 120-125° for n-valeric lactone.

2.   If yields in lactonization of cyclohexene-1-α-n-
valerate fail to improve by the application of more
drastic conditions, the corresponding free acid should
be tried instead. The free acid should also be used
in synthesis of the lactone of cyclohexanol-2-α-benzyl-
acetic acid. Lactonization of the latter would likely
require rather severe treatment, such as three to four
hours' boiling with 50 percent, possibly 60 percent
sulphuric acid.

3.   A synthesis of lactones from cyclohexanol-1-α-esters
as outlined by Braun and Münch (7) should be investigated
and extended to higher homologues.

4.   Methods of isolation of keto-acids from crude reaction
mixtures should be improved or modified. Separation of
the acid from unreacted material by sodium carbonate
may prove to be of value. Isolation of the acids in
the form of semicarbazones or addition compounds with

sodium bisulphite followed by decomposition with regeneration of the keto-acid is also likely to increase the yield of purified material.

5.   The reaction between α-bromophenylacetic ester and zinc in dry benzene and ether should be tried. If both are found to take place, yielding mainly phenylacetate, this will definitely eliminate the Reformatsky reaction as means of synthesis of cyclohexanol-1-α-phenylacetate.

6.   In the reaction between ethyl α-bromobenzylacetate and zinc in toluene, there is another compound formed having considerably higher boiling point than hydrocinnamic ester. It is expected that the product is dibenzylsuccinic ester. An attempt should be made to isolate and characterize it.

7.   The by-products of the Reformatsky reaction with cyclohexanone and α-bromobenzylacetate in benzene should be investigated. The low boiling fraction may likely prove to be hydrocinnamic ester, while the residue is expected to contain some dibenzylsuccinic ester.

8.   The alkali insoluble solid formed in an attempted saponification of cyclohexanol-1-α-isobutyric ester should be investigated further. Since it may likely be a product of alkaline condensation of cyclohexanone, treatment with mineral acid may reverse the reaction,

causing the cleavage of the molecule. Determination of the molecular weight and spectral analysis may also yield important clues regarding the structure.

9.   Another attempt of synthesis of cyclohexanol-1-α-isobutyric acid should be carried out, using the method of Kon and Narayanan. The dry, crude acid, free from the unsaponified ester or any non-acidic degradation products should be seeded and allowed to stay over a period of several days. If no crystallization occurred, vacuum distillation may be applied to free the product from isobutyric acid, which is considered to be the chief impurity.

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CERTAIN REACTIONS OF ACENAPHTHENONE

TABLE OF CONTENTS

I. INTRODUCTION

This work was intended to be a continuation of the investigations carried out by Elston (2). He has attempted a series of condensation reactions with acenaphthenone some of which did not lead to the expected product. He also pointed to certain ambiguities in the literature connected with acenaphthenone derivatives of this type. The present investigation was mainly concerned with the clarification of these two problems.

A very extensive literature survey is found in Elston's M. Sc. thesis, hence it is not included in this work.

II. DISCUSSION OF RESULTS

Reactions between acenaphthenone and aromatic aldehydes belong to the Claisen-Schmidt type of condensation.
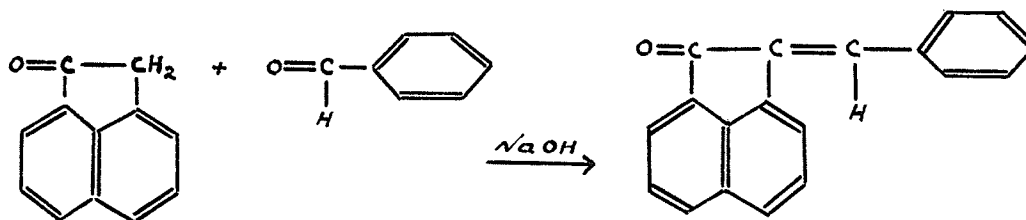
Elston (2) observed that with certain aromatic aldehydes abnormal products result. For instance, in the reaction with m-methoxy-benzaldehyde the product was identified as naphthalic acid while a similar reaction with m-tolualdehyde led to an unknown solid. It has been established in this work that the solid was naphthalic anhydride and that the same compound was also formed in a condensation with p-tolualdehyde.

From an examination of a spatial model of the acenaphthenone molecule it is apparent that the five-member ring is in a state of strain. It seems likely that if the constitution of an aromatic aldehyde does not favor the condensation reaction the attack on the five-member ring of the acenaphthenone *by the base* may take place. This is in agreement with

the work of Graebe (6) who reports the formation of naphthalic acid from acenaphthenone on boiling with sodium hydroxide.

The melting points of a number of condensation products (Table I) show two values as reported in the literature by two independent workers. This is a curious thing because the methods of synthesis employed by the two authors are only slightly different. The only explanation seems to be the isomerism, i.e. a different orientation of groups in respect to the plane of double bond. But with one exception it was found impossible to synthesize two different condensation products from the same starting materials though the conditions of the reaction were subject to drastic variation and different condensing agents were used.

The condensation with o-nitrobenzaldehyde was the only one to yield two different products. If, as was expected, the two were stereo-isomers the lower melting compound (cis) should be readily convertible into the higher melting, more stable isomer (trans) by application of standard conversion methods. However, the experimental work failed to substantiate this opinion.

TABLE I

Aldehyde	Melting Point[#] of the Condensation Product	
	Literature	Found
p-Nitrobenzaldehyde	202-203° (1) 239-240° (3)	241°
o-Nitrobenzaldehyde	241-243° dec. (1) 157° (4)	237-238 160°
p-Methoxybenzaldehyde	95-98° (1) 126-127° (3)	95°
o-Hydroxybenzaldehyde	168° (1) 186-187° (5)	184°
p-Hydroxybenzaldehyde		215-216
Cinnamal	214-215° (1) 167-168° (3)	161°

[#]All melting points quoted in this investigation have been corrected.

III. EXPERIMENTAL

a) Attempted Condensation of Acenaphthenone with m-Tolualdehyde

Acenaphthenone (2 gm.) and m-tolualdehyde (1.43 gm.) were dissolved in alcohol (50 ml.) and to the solution sodium hydroxide (10 gm. in 10 ml. of water) was added slowly over a period of three hours. The solution was allowed to stay for a period of several days after which the solid material that formed was filtered off and washed with alcohol. Following boiling with charcoal in acetic acid and filtering, the solid crystallized in white needles (0.5 gm.) melting at 273°. Found: C $=$ 71.95%, H $=$ 3.10%, in agreement with Elston's analysis. Calculated for naphthalic anhydride, C_4H_2O: C $=$ 72.75%, H $=$ 3.05%. Molecular weight determined by Rast's method (the average of three determinations) was found to be 228. Calculated for naphthalic anhydride, $(C_4H_2O)_3$: Mw $=$ 198.

The condensation was also attempted with sodium methylate as a condensing agent. Acenaphthenone (1 gm.) and m-tolualdehyde (0.7 gm.) were dissolved in absolute methanol (25 ml.) and the solution of sodium methylate in absolute methanol (3 gm. in 10 ml.) added slowly over a period of two hours. The solution was allowed to stay overnight. Next day the precipitated yellow solid was filtered off,

washed with dilute ethanol and recrystallized from chloroform.
It melted at 258° and showed no depression of melting point
with biacenone prepared by Elston.

b) Attempted Condensation of Acenaphthenone with p-Tolualdehyde

Acenaphthenone (2 gm.) and p-tolualdehyde were treated
in identical manner as in the experiment with m-tolualdehyde.
The solid isolated was recrystallized twice from glacial
acetic acid. It formed beautiful, bright, yellow needles
melting at 271°. Found: C = 72.22%, H = 3.18. Mixed melt-
ing point with the product of the previous condensation
showed no depression.

The condensation with sodium methylate as a condensing
agent yielded biacenone similarly to the previous reaction.

c) Condensation of Acenaphthenone with p-Nitrobenzaldehyde

Acenaphthenone (2 gm.) and p-nitrobenzaldehyde (1.9 gm.)
were dissolved in alcohol (50 ml.) and a solution of sodium
hydroxide (10 gm. in 10 ml. of water) was added slowly over
a period of two hours. The solution was allowed to stay for
24 hours after which a yellow precipitate was filtered off
and washed with alcohol. After two recrystallizations from
glacial acetic acid the melting point was found to be 241°.
This is the melting point reported by Sircar and Gopalan (3)

though the procedure followed is that described by de Fazi (1). The latter reported the melting point 202-203°.

Another condensation was carried out using 10 percent alcoholic potassium hydroxide which is the procedure used by Indian workers. The subsequent treatment was similar to that of de Fazi. The isolated compound had melting point identical with the one from the first reaction.

A number of condensations was carried out using either of the condensing materials at temperatures ranging from -20°C. to + 80°C. p-Nitrobenzaldehyde proved to be very suitable for these experiments because of its remarkable ease of condensation. The formation of product proceeded at a fair rate at -20°C. However, in this as well as in other experiments the product of melting point 241° was always obtained.

In the last attempt gaseous hydrogen chloride was used as a condensing agent. Acenaphthenone and an equivalent quantity of p-nitrobenzaldehyde were dissolved in glacial acetic acid and dry hydrogen chloride was passed through the solution over a period of one hour. The product started to precipitate almost immediately with the evolution of heat. At the end of the reaction it was filtered off, washed with dilute acetic acid and recrystallized from glacial acetic acid. The melting point was again found to be the same as

in previous condensations.

d) Condensation of Acenaphthenone with O-nitrobenzaldehyde

Using either 50 percent aqueous sodium hydroxide or
10 percent alcoholic potassium hydroxide a product melting
at 237-238° was isolated. With hydrogen chloride as a
condensing agent a good yield of a compound melting at
160° was produced. Both compounds were yellow in color.
The first was isolated as a powder, the second in the form
of fine needles.

e) Condensation of Acenaphthenone with p-Methoxybenzaldehyde

Condensations by all three methods, i.e. 10 percent
alcoholic potassium hydroxide, 50 percent aqueous sodium
hydroxide and dry hydrogen chloride were attempted. The
product isolated by the first two methods melted at 95°.
In a condensation with hydrogen chloride there was no separa-
tion of a solid material. Attempts to isolate any product
from the solution failed.

f) Condensation of Acenaphthenone with O-Hydroxybenzaldehyde

The alkaline condensation yielded a solid melting at
184°. No condensation with hydrogen chloride was attempted.

g) Condensation of Acenaphthenone with p-Hydroxybenzaldehyde

No condensation with this particular aldehyde has been found to be reported in the literature. The product melting at 215-216° was obtained by both alkaline and hydrogen chloride condensations.

h) Condensation of Acenaphthenone with Cinnamic Aldehyde

Only the alkaline condensation was performed. The product after two crystallizations had a very low melting point. Four more recrystallizations from dilute ethanol yielded a yellow powder melting at 161°.

j) Attempted Conversion of the Condensation Product of Acenaphthenone with O-Nitrobenzaldehyde

Assuming the lower melting product of this condensation to be a cis isomer a number of standard methods was applied to convert it into the higher melting form.

(i) Irradiation with ultraviolet light: The compound was exposed to ultraviolet light over a period of several days. The melting point of the material thus treated was found to be identical with the original substance. In a

next attempt an alcoholic solution of the compound was treated in a similar way. The melting point was found again to be the same.

(ii) <u>Using iodine as a catalyst</u>: The compound was dissolved in ethanol, a small quantity of iodine added and the solution refluxed for 4 hours. Some of the alcohol was then removed under reduced pressure and water added until the solution was beginning to turn milky. The crystals that separated on standing melted at 160°.

(iii) <u>Using palladium on charcoal</u>: The compound was dissolved in acetic acid and boiled with palladium on charcoal for two hours under reflux. The solution was then filtered, reduced to a smaller volume, diluted with water and allowed to stand. Since it did not show any tendency to crystallize the solvent was removed under vacuum. A dark, oily material was left which did not crystallize after being kept at -20° for several days. Attempts to induce crystallization by dissolving in alcohol and diluting with water also failed.

(iv) <u>Heating above the melting point</u>: A small test tube containing the compound was kept on oil bath for several hours. The temperature of 165° was maintained. The liquid

material appeared as a very dark oil. It did not crystal-
lize on cooling nor could it be crystallized from ethanol.
It appeared as though it were decomposed by this temperature.
A smell of nitrogen oxides was observed during the heating.

(v) Treatment with alcoholic potassium hydroxide:
The compound was dissolved in 10 percent alcoholic potassium
hydroxide and allowed to stay for 48 hours at room tempera-
ture. No solid separated when a small sample of the solution
was diluted with water. The alcohol was then removed under
vacuum and some water added. A clear solution of yellow color
was obtained from which no material could be extracted with
ether. It was acidified with dilute hydrochloric acid,
allowed to stay and a brown amorphous solid that separated
filtered off. The compound was washed on filter with water
and dried. It melted at 267° with decomposition and showed
a depression of 2° when mixed with naphthalic anhydride.
It is believed that the compound was impure naphthalic anhy-
dride.

IV. BIBLIOGRAPHY

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