MECHANISMS OF EPOXIDE REACTIONS

by

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Submitted to the Department of Chemistry and the Faculty of the Graduate School of the University of Kansas in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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August, 1949

ACKNOWLEDGMENT

The author wishes to express his appreciation to Dr. C. A. VanderWerf for his directive assistance during the course of this investigation.

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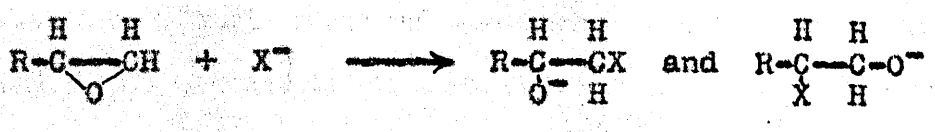
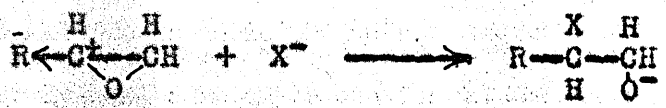
INTRODUCTION

The reactions of epoxides have been enumerated (1) as generally involving the attack of a nucleophilic group on one of the carbon atoms of the epoxide ring. Kinetic studies (2) on epoxide reactions and the occurrence of inversion then support the fact of a nucleophilic displacement on carbon (3,4,5,6). If the epoxide is perfectly symmetrical, the union of an attacking group with a carbon atom of the epoxide ring will be the same regardless of which carbon is attacked. If, on the other hand, the epoxide is unsymmetrical, there is the possibility of the formation of two isomeric products. For this reason the epoxides are particularly well adapted to studies in the mechanism of reactions, since a group substituted for hydrogen into the epoxide ring may influence reaction at one or the other carbon atom of the ring, depending upon the nature of the substituent group. Several such studies have been conducted (7-17). The implications may be pointed out graphically with the following equation in which X^- represents a nucleophilic group and R is any atom or group other than the hydrogen atom.



It is ordinarily assumed that the nucleophilic group will attack, at least predominately, the more positive carbon atom of the

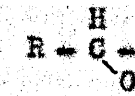
epoxide ring. A significant difference in the relative charges on the two epoxide carbon atoms will result if there is considerable difference between the electronegativities of the R group and the hydrogen atom. Thus, if the R group is rather strongly electronegative, there would be an electron withdrawal from the epoxide carbon to which the R group is attached. That carbon atom would then be the more positive of the two, since an inductive effect is diminished as it is propigated along a carbon chain (24). This effect is indicated as follows,



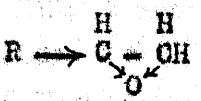
If the R group is substantially less electronegative than hydrogen, the movement of electrons would be in the opposite direction and the isomeric secondary alcohol carbanion would result.

The exclusive formation of either of these two possible isomers has been implied only in the case of an appreciable difference in the electronegativity of the R group and the hydrogen atom. If the differences are only very subtle, random addition of the nucleophilic group would undoubtedly occur and a mixture of the two isomers would be anticipated. Application of these principles then becomes a means of comparing the relative electronegativities of groups attached to the epoxide ring.

DISCUSSION OF THE PROBLEM

Most of the base catalyzed condensations with epoxides thus far reported have been with alkyl or aryl substituted ethylene oxide of the form  in which R is a hydrocarbon residue. Almost without exception* (16) the attack of a nucleophylic group in these instances has proceeded according to the mechanism which has become known as the normal displacement. This is characterized by the rupture of the terminal carbon-oxygen bond of the oxirane ring. The eventual product in this case is a secondary alcohol.

The generally accepted mechanism for the reaction involved in the formation of the normal product is one in which the R group—being less electronegative than hydrogen—releases electrons to the nonterminal oxirane carbon.



The terminal carbon thus becomes the more positive of the two oxirane carbons and the attack of the nucleophylic group is on that carbon. The resulting ion is then produced by the rupture of the terminal carbon-oxygen bond.

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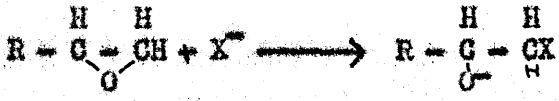
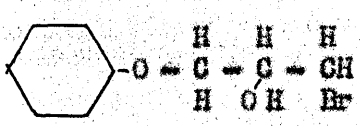
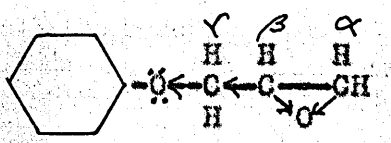
* Swern, Billen and Knight reported the isomeric "abnormal" product in base catalyzed reactions with allyl alcohol. This might easily be explained on the basis of the atypical nature of allyl alcohol, which in structure is a primary but in chemical reactions a tertiary alcohol.

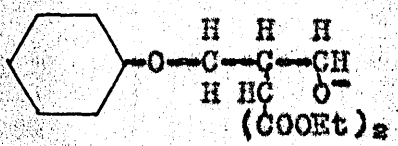


Since all the reactions, in which the addendum is unquestionably of nucleophilic character, involve hydrocarbon R groups on the epoxide it was proposed to determine, in the first part of the present investigation, whether the inclusion of more highly electronegative atoms would alter the mode of addition. With this objective in mind, three epoxides were chosen to react with the malonic ester carban-ion. The first of these was phenyl glycidether  and the second the para bromo derivative of the first. These compounds were readily obtainable through the reaction of epichlorohydrin with phenol and p-bromophenol, respectively, in a Williamson type synthesis. A reaction somewhat similar to the first has been carried out by Fischer and Krämer (25) in which they reacted the bromohydrin  with sodium malonate. It was assumed by them that the mechanism of the reaction was merely the replacement of bromine by the malonate ion. Though this is probably a justifiable assumption, there is, nevertheless, the possibility of removing the elements of H Br from the bromohydrin and forming the epoxide which then could react according to either of the two mechanisms suggested above. With the p-bromo derivative the bromine atom would be expected to increase slightly the electronegativity of the substituent group as a whole and possibly bring about abnormal addition even if it did not occur with the unsubstituted phenylglycidether.

The possible reactions with these compounds can be best illustrated by indicating the electronic interactions

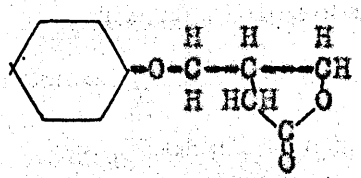


The comparatively strong electronegativity of the phenoxy and epoxy oxygens would tend to withdraw electrons from both the α- and β-carbons, but the β-carbon, being nearer the phenoxy should be the more positive of the two as the result of this effect alone. Thus if the -I effect of the phenoxy group operating through the γ-carbon insulator is stronger than the competing -I effect of the α-hydrogen, the primary alkoxide ion should form upon addition of the malonic ester carbanion.



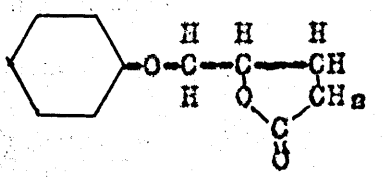
If the γ-carbon is too good an insulator, the effect may be diminished to such an extent that the normal addition would operate, forming the isomeric ion.

Alkalin hydrolysis followed by acidification of either ion would produce an acid lactone which would yield the free lactone when decarboxylated.



from abnormal addn.

or

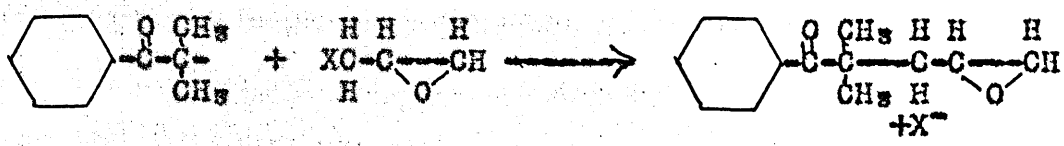


from normal addn.

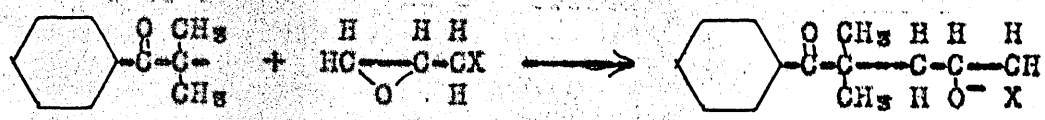
The third epoxide to be studied in its reaction with malonic ester was p-chlorostyrene oxide. The normal addition has been reported (15) with styrene oxide itself in this reaction, so here it was desired to determine whether the presence of an electronegative atom on the benzene ring would alter the point of attack of the carbanion. p-chlorostyrene oxide is not readily available so it was necessary to devise a method of synthesis. The detailed procedure will be given in the experimental section of this dissertation. In brief, the steps involved were the preparation of p-chlorophenacylbromide from p-chloroacetophenone, reduction of the bromide to the bromohydrin by the Meerwein-Ponndorf-Verley reduction, and elimination of hydrogen bromide from the bromohydrin.

The second phase of the problem dealt with the relative rectivity of bromine as compared to epoxides when the two functions are in the same molecule.

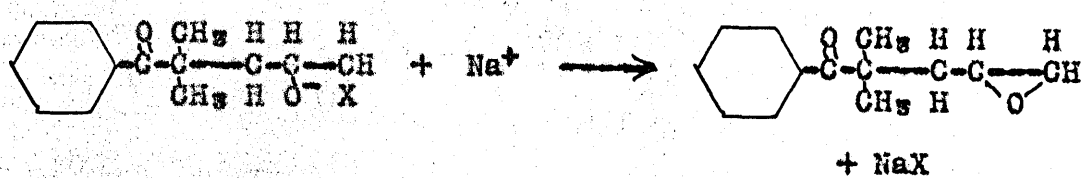
The results of such an experiment have been reported by Haller and Ramart-Lucas (26)(27). In this experiment these authors reacted the carbanion of isobutyrophenone with epichloro and epibromohydrin. They stated that it was interesting to note that the epihalohydrins reacted as alkyl halides by replacement of the halogen atom. The reaction as represented by them is as follows.



It was noted that the reaction may not have been just as implied here however. Since epoxides are generally recognized as rather reactive compounds, the possibility of a less direct mechanism presented itself. This mechanism would involve the attack of the ketone carbanion at the epoxide carbon forming the intermediate ion as follows,

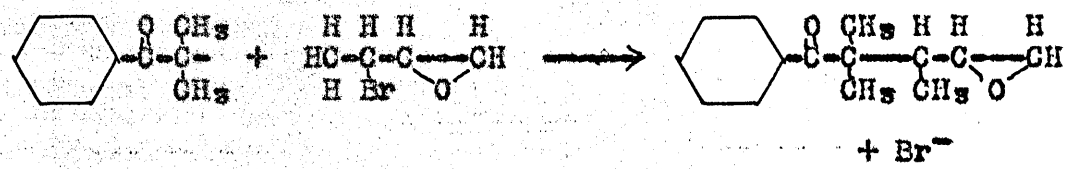


In this intermediate ion the halogen would be labilized so as to form sodium halide with the sodium ion which is also present in the solution. This would permit the formation of the neutral epoxide whose structure would be identical to the compound formed by direct replacement of the halogen.

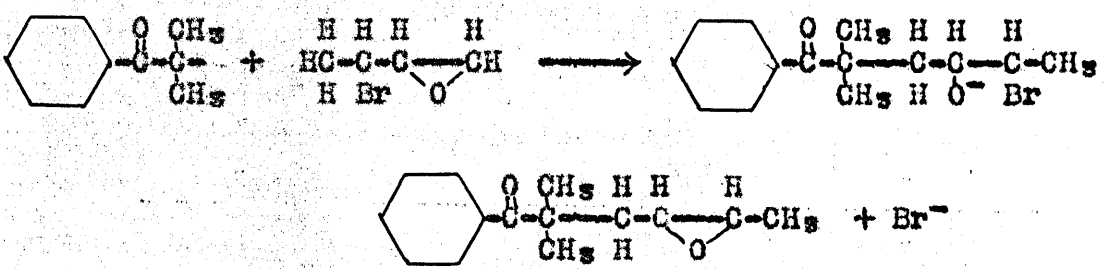


The true course of the reaction could be determined only by employing halo-epoxides capable of forming different isomers with the two possible mechanisms suggested.

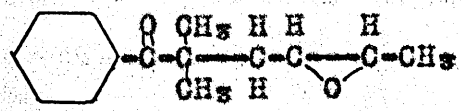
This being true the epoxides chosen were 3-bromo-1,2-epoxy butane and 1-bromo-2,3-epoxy butane. The synthesis of these two isomers has been reported (28). Equations will serve to illustrate the possible reactions. In the case of 3-bromo-1,2-epoxy butane reacting with iso-butyrophenone, a mechanism involving simple replacement of the bromine atom would give the following product



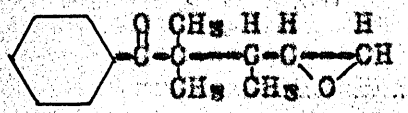
If the attack on the epoxide molecule occured on the terminal epoxide carbon on the other hand the final product would be as follows.



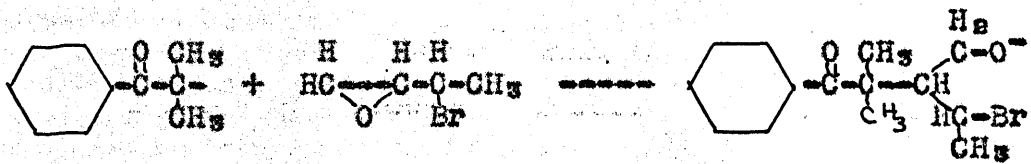
In reactions with the isomeric 1-bromo-2,3-epoxy butane and the iso-butyrophenone carbanion, the final epoxy-ketones would be just the reverse of those shown above for the two mechanisms suggested. Thus simple bromine displacement would give the following

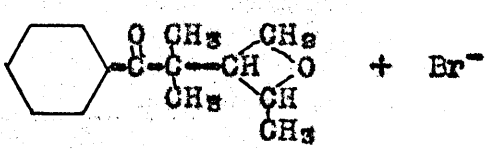


Whereas attack on the epoxide carbon farthest from the bromine would give the branched four carbon chain as follows.



In addition to the two mechanisms suggested above for reaction with the two isomeric bromo epoxides, there may be in addition a less common but nevertheless equally plausible mechanism. This third possibility involves the carbon atom of the epoxide ring nearer the bromine atom. In this case, if attack of the ketone carbanion is at the intermediate carbon, the following products may be formed.





It may be readily seen that the same final product would result in the case of either epoxide if this mechanism obtains.

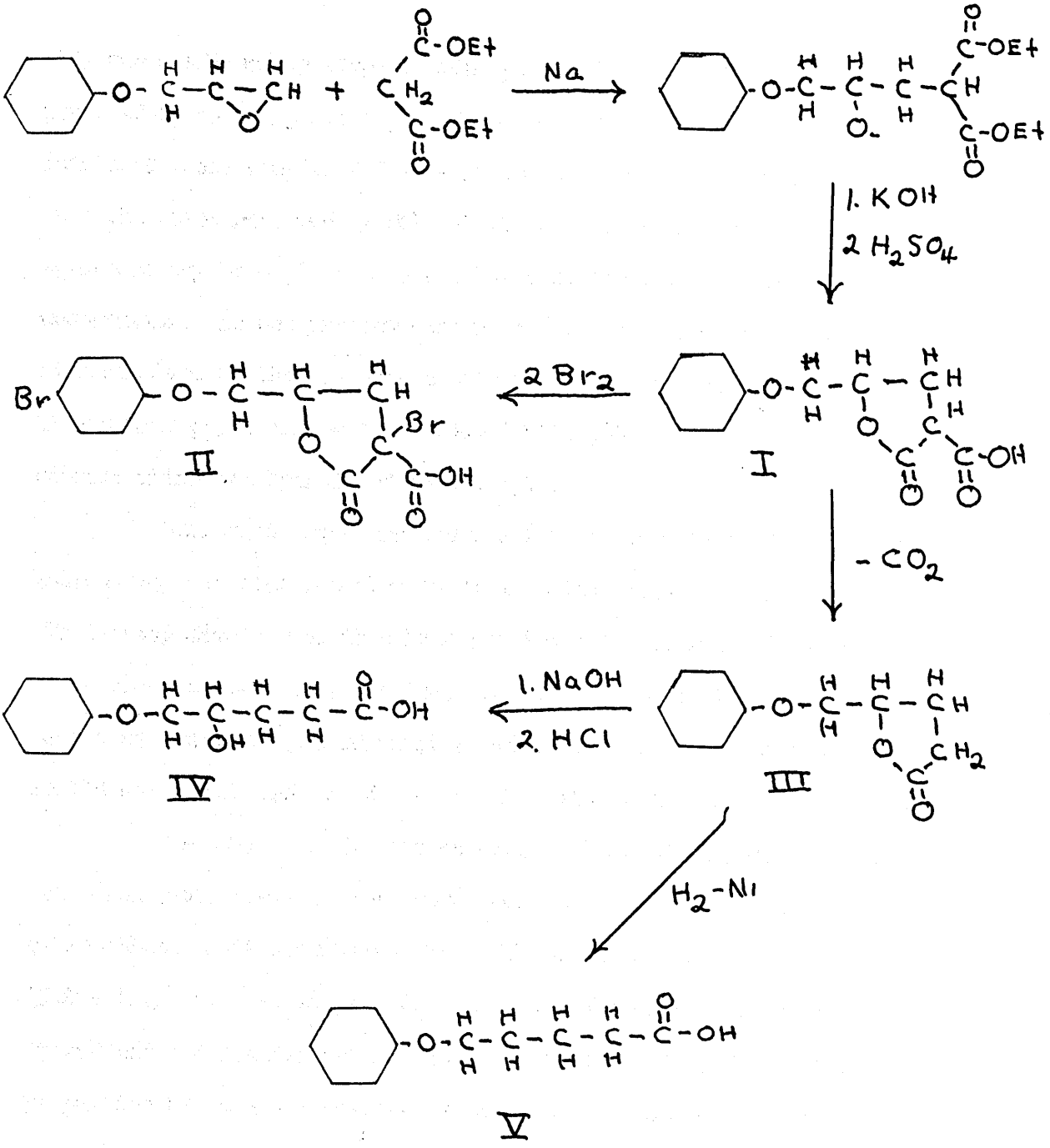
The large majority of reactions involving epoxides that have been reported in the literature have been with epoxides possessing a terminal oxirane structure. In these instances attack of a nucleophilic group in base catalyzed reactions seems to occur much more readily at the terminal carbon of the oxirane ring than at the internal or β -position. This mechanism seems to be apparent even though the β -carbon is attached to rather highly electronegative groups. These observations seem to indicate that there is some peculiar directive exhaltation which the two terminal hydrogen atoms exhibit. If this is actually the case, the reaction of the isobutyrophenone carbanion with 3-bromo-1,2-epoxy butane would not be expected to be greatly different from a great many other base catalyzed condensations with terminal epoxides. This is assuming initial reaction of the oxirane ring. However with the isomeric 1-bromo-2,3-epoxy butane, there is only one hydrogen atom on each oxirane carbon and if the observations above are a major factor in directing the attack of the carbanion, this compound should be a very useful one in pointing out any basic differences between the two types of epoxides.

DISCUSSION OF RESULTS

Phenylglycidether was treated with malonic ester enolate ion in absolute alcohol solution. Hydrolysis of the reaction product followed by acidification with mineral acid gave an organic acid lactone (I). Recrystallization of this material from benzene gave white platelets m.p. 96.5 - 97.8° C. The acid lactone reacted with bromine in chloroform solution to give a new acid lactone (II) containing two atoms of bromine per molecule of compound. This compound, recrystallized from benzene, formed white flakes m.p. 150.0 - 151.8° C.

Upon heating the original product (I) to 150 - 170° carbon-dioxide was liberated yielding a neutral lactone (III). Successive treatment of the neutral product with hot sodium hydroxide solution and hydrochloric acid produced a crystallin organic acid (IV) melting at 114.2 - 114.6° C. after recrystallization from hot water.

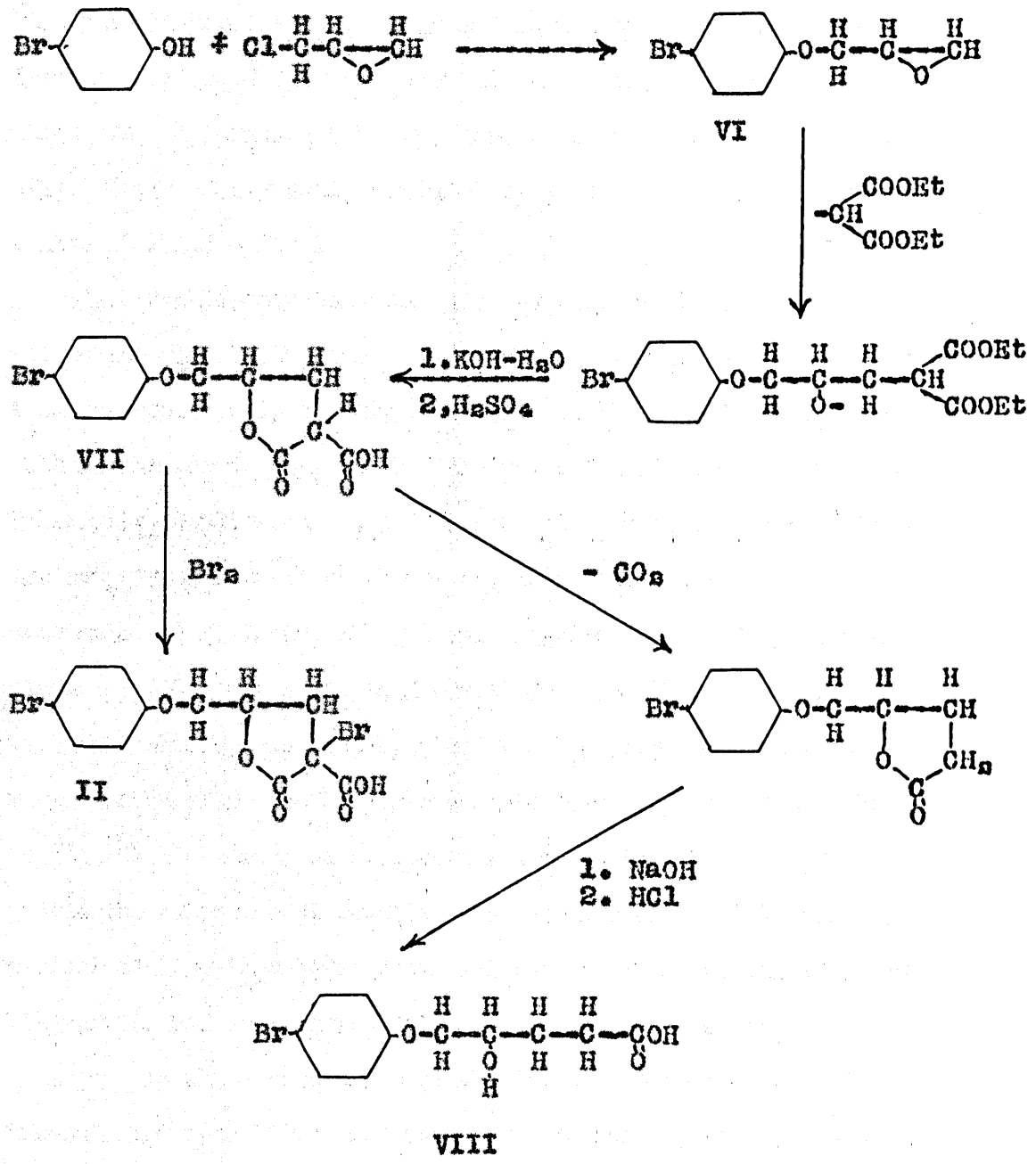
In order to establish the structure of the compounds formed and the direction of opening of the epoxide ring in the initial reaction, the neutral lactone (III) was subjected to hydrogenolysis. The reason for this step was based on the realization that δ-phenoxyvaleric acid would form upon rupture of the lactone ring if attack by the malonic ester carbanion had occured on the terminal epoxide carbon. If the attack had initially occured on the second carbon, however, the hydrogenolysis product would have been γ-phenoxyvaleric acid. Hydrogenolysis of the lactone did give δ-phenoxyvaleric acid (V);


Na
1. KOH
2 H_2SO_4
2 Br_2
I
II
$-CO_2$
1. NaOH
2. HCl
III
IV
H_2-Ni
V

this was confirmed by mixed melting point of an authentic sample prepared by an independent procedure as explained below. The melting points of these samples (101.2 - 103.0° C.) were substantially higher than the value reported by Gabriel (29). The reason for this disagreement may be explained on the basis of the two methods of preparation. In the present case phenol was combined with 1,4-dibromobutane in the presence of sodium hydroxide. The 4-phenoxy-1-bromo butane thus produced was then reacted with potassium cyanide to form the nitrile which was hydrolyzed to the acid.

Gabriel's procedure was the initial formation of 3-phenoxy-1-bromopropane which was then condensed with malonic ester. The substituted diester was then hydrolyzed and decarboxylated by heating above the melting point. In this procedure there could easily have been some undecarboxylated substituted malonic acid as a contaminant in the mono-acid that would depress the melting point.

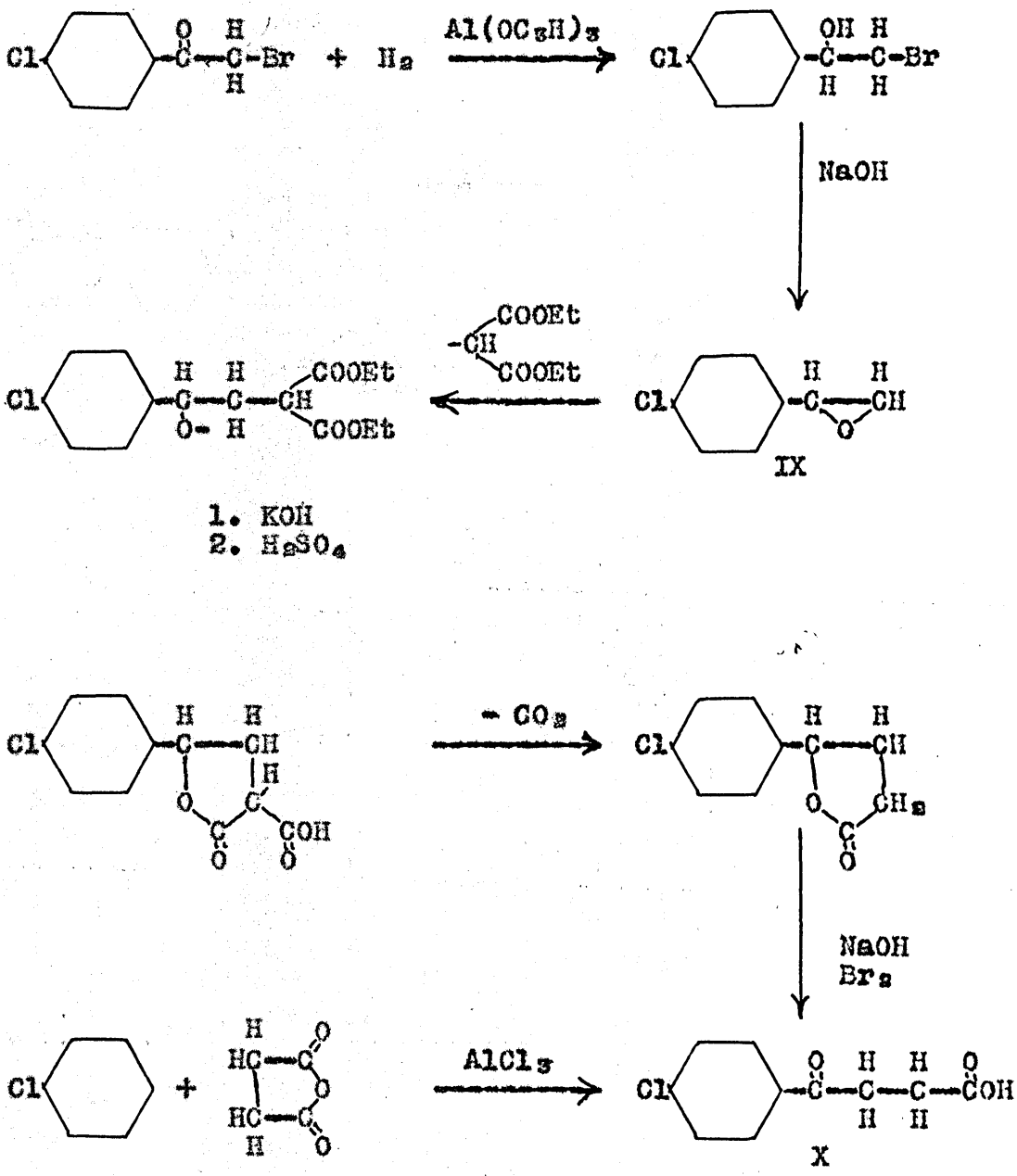
The reaction of p-bromophenylglycidether (VI) with malonic ester was investigated. The epoxyether was prepared by condensing p-bromophenol with epichlorohydrin. The ether was a solid melting at 49.0 - 49.5° C. Its condensation with malonic ester, followed by hydrolysis and acidification, gave a crude material (VII) having the properties of an acid lactone. Since this material was of poor crystalin form and resisted purification, no sample was prepared for analysis or melting point. A chloroform solution of this acid decolorized bromine in sunlight with the formation of hydrogen bromide gas and a new product. The new product proved to be identical with the

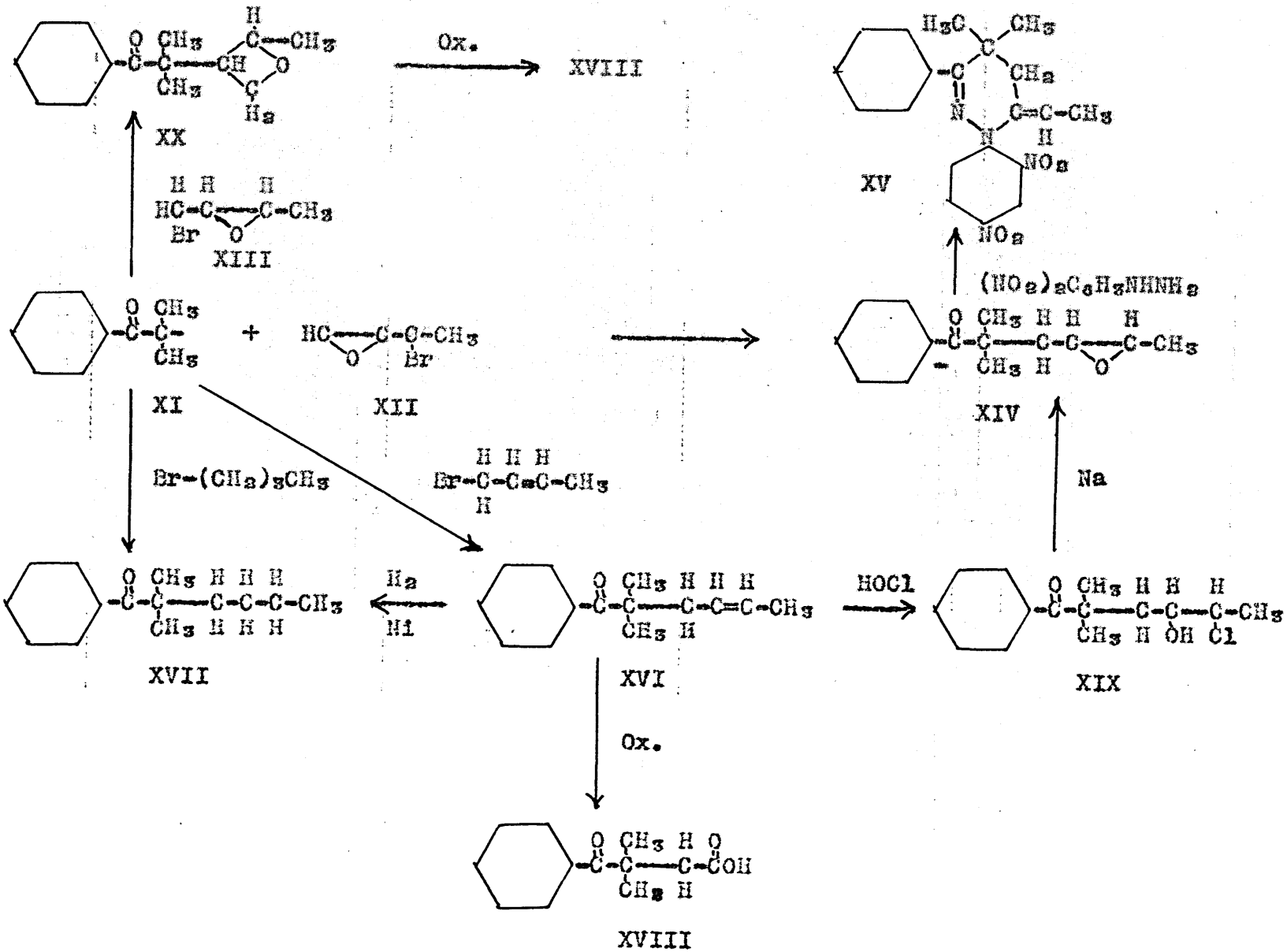

VI
VII
II
VIII
1.KOH-H2O
2.H2SO4
Br2
- CO2
1. NaOH
2. HCl

bromoacid (II) formed by similar treatment of the acid lactone (I). This established that the attack of the malonicester was on the terminal carbon of VI. Decarboxylation of VII gave a crude lactone which was not purified but used directly to form the hydroxy acid VIII. This hydroxy acid, recrystalized from hot water and toluene, melted at 111.5 - 112.2° C.

p-chlorostyreneoxide (IX) was prepared by reducing p-chlorophenacylbromide to the bromohydrin and removing the elements of HBr from the bromohydrin to form the epoxide. The malonic ester synthesis with IX was carried out in the same way as with the other epoxides. Hydrolysis, acidification, and decarboxylation of the condensation product gave a lactone which was oxidized with bromine directly to a keto acid (X) following the general method of McRae, Charlesworth and Alexander (30). The m.p. of X was 131.0 - 131.4° C. This checked with the melting point and by mixed melting point with an authentic sample of p-chloro -β- benzoylpropionic acid prepared by the Friedel Crafts reaction from chlorobenzene and succinic anhydride. This proved the existence of a continuous carbon chain in the condensation product of IX with malonic ester and thus that the normal addition to the epoxide had occured rupturing the terminal C - O bond.

In the second phase of the investigation the carbanion of iso-butyrophenone XI was condensed with 3-bromo-1,2-epoxybutane (XII) and 1-bromo-2,3-epoxybutane (XIII). The ketone carbanion was prepared by stirring iso-butyropenone with sodamide in hot dry benzene or toluene solution. The product of reaction of XI with XII was isolated by vacuum distillation. It was a liquid (XIV) with very little color


Cl
O H
C—C—Br
H
+ H2
Al(OC3H)3
OH H
C—C—Br
H H
NaOH
COOEt
CH
COOEt
H H COOEt
C—C—CH
O- H COOEt
H H
C—CH
O
IX
1. KOH
2. H2SO4
H H
C—CH
O C
H
C COH
O O
- CO2
CH2
NaOH
Br2
H
HC—C
O
HC—C
H
AlCl3
O H H O
C—C—C—COH
H H
X


Ox.
XVIII
XX
XIII
XV
XI
XII
XIV
Br-(CH2)3CH3
Na
Ha
Hl
HOCl
XVII
XVI
XIX
Ox.
XVIII

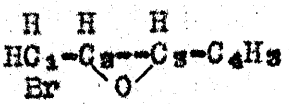
and odor that gave semitransparent reddish orange plates, with extreme facility, when treated with 2,4-dinitrophenylhydrazine. This compound (XV) melted at 233.8 - 234.5° C. and upon analysis indicated that a six membered heterocyclic ring containing two nitrogen atoms had been formed by loss of a mole of water from the dinitrophenylhydrazone. The structure of XIV was established as follows. Crotyl bromide was reacted with XI to give a liquid product (XVI). Hydrogenation of XVI gave another liquid (XVII) that was no longer unsaturated. Reaction of XI with n-butylbromide also gave XVII as demonstrated by the melting point of the semicarbazone. This proved that crotylbromide had reacted with XI by replacement of bromine and thus that the double bond was between the second and third carbon atoms from the end of the chain in compound XVI. Permanganate oxidation of XVI produced an acid (XVIII) containing twelve carbon atoms, as shown by analysis. This acid (m.p. 99.8 - 100.4° C.) was the same as the acid obtained by Haller (26) upon oxidation of the product of reaction of XI with allylbromide. This step further substantiated the structure of XVI. Hypochlorination of XVI gave a liquid XIX which lost the elements of HCl upon treatment with sodium in refluxing toluene. The compound thus produced was shown by mixed melting point of the derivative XV to be identical with XIV.

This sequence proves beyond any peradventure that the initial attack of XI on XII occured at the terminal epoxide carbon of XII and that the 1,2-epoxide was isomerized to a 2,3-epoxide by loss of bromide ion from the ion intermediate.

Similar reactions of XI with 1-bromo-2,3-epoxy butane (XIII) led to the formation of a nearly colorless, odorless liquid (XX). This compound gave no derivative when treated with 2,4-dinitrophenylhydrazine. Reaction with hydroxylamine hydrochloride in pyridine-alcohol solution, however, gave a white solid melting at 122.0 - 122.7° C. An oxime of XIV was prepared in the same way and after recrystallization from dilute methanol melted at 127.8 - 129.0° C. These two products were shown by mixed melting points to be different.

Oxidation of XX in 2% potassium permanganate occured very slowly and only after 36 hours stirring at 30° C. was the permanganate substantially reduced. Isolation of the oxidation product produced an acid which after recrystallization from methanol-water solution melted at 99.0 - 100.0° C. This acid was shown by mixed melting point to be identical with XVIII.

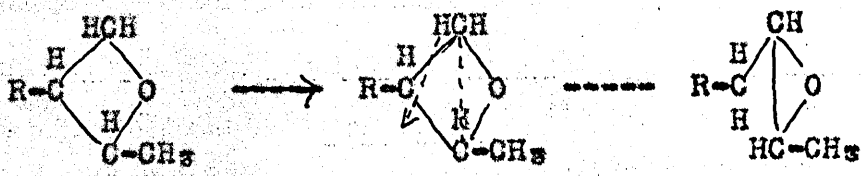
This series of reactions shows that attack of XI could have occured on XIII only on the second carbon of the chain



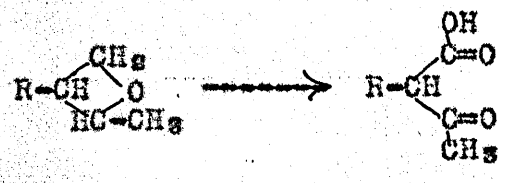
and that bromide ion was lost from the ion intermediate to give the neutral product containing a three carbon-oxygen four membered heterocycle. If attack had occured on carbon atom "1" by replacement of bromide ion the product XX would have been identical with XIV. If the attack had occured on carbon atom "3" with the oxygen swinging across to the 2-1 position by the labilization and loss of bromide ion, the resulting product would yield a thirteen carbon acid on

oxidation. The one remaining possibility is the one suggested, to wit, attack on the "2" carbon with the oxygen forming a "1-3" bridge by loss of the bromide ion.

The formation of acid XVIII by permanganate oxidation of XX in a weakly basic solution made basic only by the potassium hydroxide formed when potassium permanganate was reduced in water solution, may be explained in either of two ways. During the course of the lengthy oxidation period the four membered heterocycle may have rearranged to the typical epoxy-structure which was then oxidized to the acid XVIII.



The second explanation may have been an initial oxidation of the four membered ring to a derivative of acetoacetic acid.



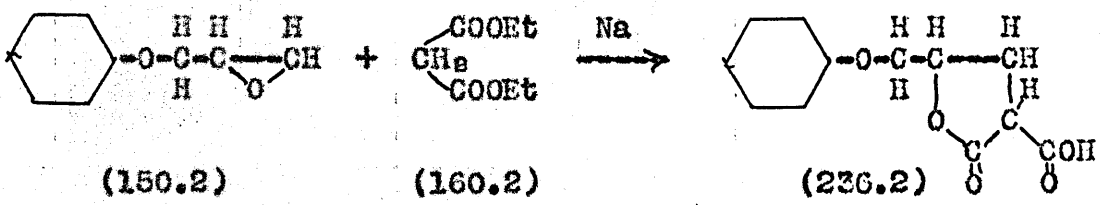
The acetoacetic acid thus formed could decarboxylate to the methyl ketone which if oxidized could produce the desired acid. Another alternative would be ketone cleavage of the substituted acetoacetic acid which would produce the acid directly. A third variation of this general approach would be oxidation of the methyl ketone before decarboxylation to a

derivative of malonic acid. The malonic acid could then easily decarboxylate during the evaporation step in the recovery of the oxidation product.

The investigation has shown that with the terminal epoxides employed "normal" addition of malonic ester has occured. Reaction of iso-butyrophenone with 3-bromo-1,2-epoxybutane also proceeded according to "normal" reaction on the terminal epoxide carbon. With 1-bromo-2,3-epoxybutane—the only internal epoxide studied—attack was on the "2" carbon, but in neither case did reaction occur by the simple replacement of bromine as stated by Haller and Ramert-Lucas (27).

EXPERIMENTAL

Reaction of 3-Phenoxy-1,2-propylene oxide with Malonic Ester



(150.2) (160.2) (236.2)

333 g. (2.22 M) 360 ml. (2.38 M) 342 g. (1.54 M)

$$\frac{342}{525} \times 100 = 65.2\%$$

A 5 liter, three neck flask, arranged in a water bath capable of maintaining constant temperature, was equipped with stirrer, condenser, and dropping funnel. The flask was charged with 1800 ml. of carefully dried ethanol in which was dissolved 56 g. (2.44 atoms) of metallic sodium. The temperature was lowered to 20° C. and 360 ml. (2.38 M) of malonic ester was added dropwise to the stirred solution. After the addition was complete (about 1½ hours), 333 g. (2.22 M) of phenylglycidether was added dropwise (2½ hours). During this period the solution became somewhat more viscous, necessitating the further addition of 500 ml. of ethanol. The temperature was then raised to 35° C., and stirring was continued over night. The ester was hydrolyzed by the addition of 200 g. of potassium hydroxide in 600 ml. of water and heating to boiling. The ethanol was distilled and the residual solution was treated with 161 ml. of concentrated sulfuric acid dissolved in 500 g. of ice. The liberated oil was extracted with three 250 ml. portions of ether and dried by filtration of the ether solution through anhydrous sodium sulphate. The ether solution

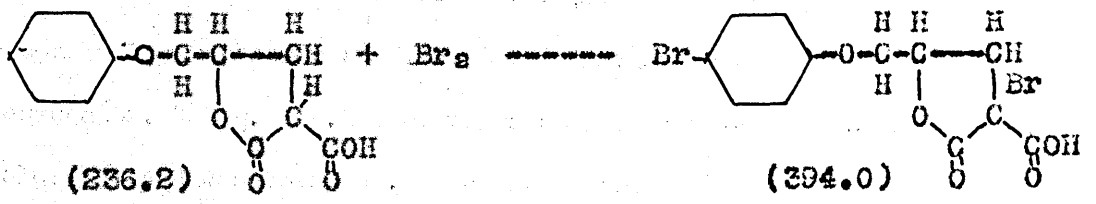
was saturated with dry ammonia to precipitate the ammonium salt from any soluble nonacidic material. The ammonium salt was then dissolved in 500 ml. of water and the free acid was liberated by adding an excess of hydrochloric acid. After filtration and drying in a vacuum desiccator, 342 g. (65.2%) of white amorphous α-carboxy-δ-phenoxy-γ-valerolactone was obtained. Recrystallization of a small portion from benzene gave white platelets, m.p. 96.5 - 97.8° C. Fischer and Kramer (25) observed sintering at 93 - 96° C.

Anal. Calculated for $C_{12}H_{12}O_5$: C, 61.01; H, 5.11. Found: C, 61.03, 61.18; H, 5.33, 5.16.

Preparation of the Ammonium Salt

A pure sample of the ammonium salt of the above acid was prepared by dissolving 2.36 g (.01 M) of the acid in acetone and bubbling in dry ammonia until precipitation was complete. The white, solid ammonium salt was filtered and dried in vacuum to produce 2.5 g. (essentially quantitative) of α-carboxy-δ-phenoxy-γ-valerolactone ammonium salt, m.p. 133.6 - 134.2° C. with effervescence at 135° C.

Preparation of δ-(p-Bromophenoxy)-α-bromo-α-carboxy-γ-valero-lactone



(236.2) (394.0)

2.36 g. (.01 M) 3.5 g. (.009 M)

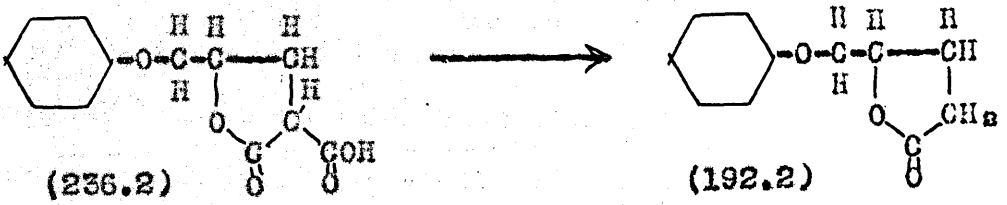
$$\frac{3.5}{3.9} \times 100 = 89\%$$

A chloroform solution of 2.36 g. (.01 M) of the free acid was treated intermittently with 3.2 g. (.02 M) of bromine. Irridation with sunlight followed each addition of bromine. The bromine color gradually disappeared and hydrogen bromide was liberated. A white solid precipitated and upon recrystallization from benzene 3.5 g. (89%) of white flaky solid δ-(p-bromophenoxy)-α-bromo-α-carboxy-γ-valero-lactone (m.p. 150.0 - 151.8° C.) was obtained.

Anal. Calculated for $C_{12}H_{10}O_5Br_2$: C, 36.58; H, 2.56; Br, 40.56.

Found: C, 36.81; H, 2.73; Br, 40.58.

Preparation of δ-Phenoxy-γ-valerolactone



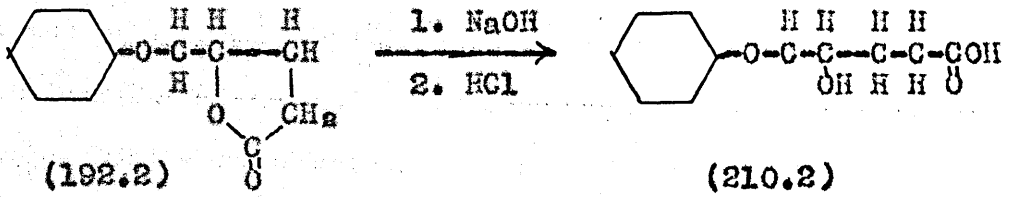
(236.2) (192.2)

23.6 g. (.1 M) 15.8 g. (.08 M)

$\frac{15.8}{19.2} \times 100 = 82\%$

Decarboxylation of the acid lactone was accomplished by heating 23.6 g. (.1 M) to 150 - 170° C. until there was no more evolution of carbon dioxide. About two-hours heating was required for this operation. The residue was then shaken thoroughly with 10% sodium bicarbonate solution to remove any unchanged acid. The lactone was then filtered, washed with several portions of cold water, and dried to give 15.8 g. (82%) of a crude white solid, δ-phenoxy-γ-valerolactone.

δ -Phenoxy- γ -hydroxyvaleric Acid



(192.2)

3.85 g. (.02 M)

(210.2)

4.1 g. (.02 M)

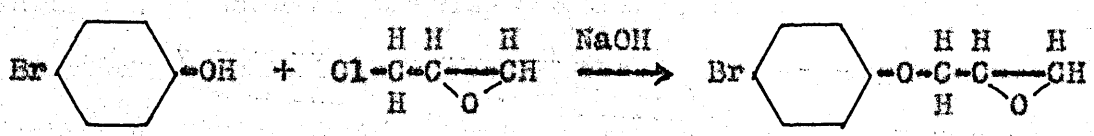
$\frac{4.1}{4.2} \times 100 = 96.5\%$

The hydroxy acid was prepared by dissolving 3.85 g. (.02 M) of the lactone in excess 20% sodium hydroxide solution by warming. After solution was complete the container was cooled to room temperature and acidified with an excess of dilute hydrochloric acid. The hydroxy acid precipitated immediately as a white granular solid weighing 4.1 g. dry (96.5%). Recrystallization of the solid first from benzene and then from hot water gave white glistening plates m.p. 113.2 - 114.6° C.

Anal. Calculated for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found:

C, 62.94; H, 6.72.

p-Bromophenylglycidether



(173) (92.5) (229)

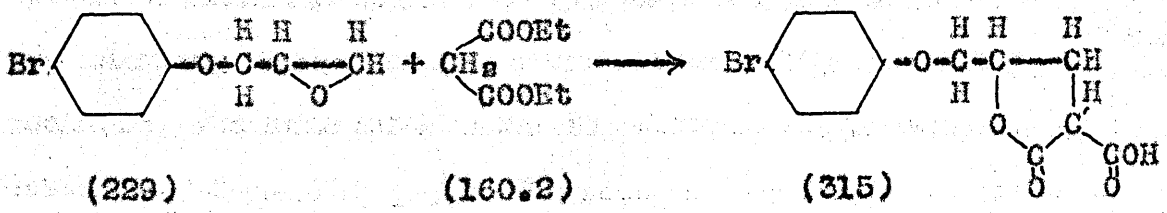
346 g. (2 M) 185 g. (2 M) 157 g. (.69 M)

$$\frac{157}{458} \times 100 = 34.3\%$$

The reaction was carried out following the general directions of Boyd and Marle (31). p-Bromophenol 346 g. (2 M) was stirred for 16 hours with 185 g. (2 M) of epichlorohydrin and 100 g. (2½ M) of sodium hydroxide in 1200 ml. of water. The temperature was that of the room. At the end of the reaction period the organic layer was separated and combined with the ether extract of the water layer which was then dried over anhydrous sodium sulphate. The solvent was removed and the residue distilled to give 157 g. (34.3%) of p-bromophenylglycidether a clear liquid b.p. 146° C. @ 5 mm. After standing for several months the liquid solidified to a white solid m.p. 49.0 - 49.5° C. after recrystallization from Skellysolve C. Anal. Calculated for $C_9H_9O_2Br$: C, 47.20; H, 3.80; Br, 34.94.

Found: C, 46.94; H, 4.10; Br, 34.73.

Condensation of Malonic Ester with p-Bromophenylglycidether



(229) (160.2) (315)

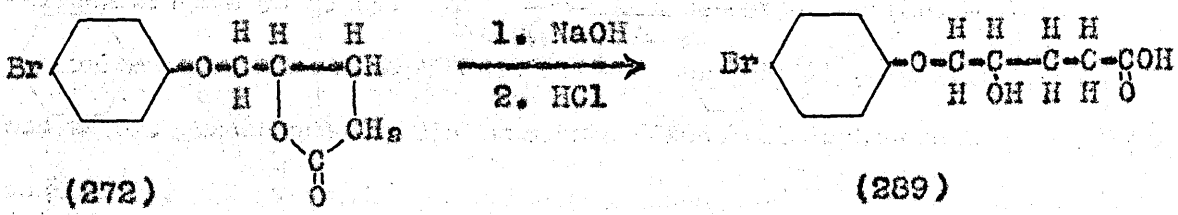
127 g. (.56 M) 90 ml. (.60 M) 90 g. (.28 M)

$$\frac{90}{179} \times 100 = 50\%$$

A 2 l. three-neck flask was equipped with a stirrer, condenser and dropping funnel and provided with a temperature control bath. The flask was charged with 600 ml. of dry ethanol in which was dissolved 14 g. (.61 M) of metallic sodium. The temperature was lowered to 20° C. and 90 ml. (.60 M) was added dropwise over the course of one hour's time. The liquid epoxide (127 g., .56 M) was then added dropwise over the course of 1½ hours with the temperature at 22° C. Stirring was continued for 24 hours. At the end of this period, 50 g. of potassium hydroxide in 200 ml. of water was added and the alcohol was removed by distillation. The residue was acidified with 41 ml. of concentrated sulfuric acid in 200 g. of ice and the oil thus produced was extracted with ether, dried over "Drierite," filtered, and saturated with dry ammonia to precipitate the acid—as the ammonium salt—from any neutral material. The ammonium salt thus obtained was washed on the filter with ether and then acetone. The salt was then dissolved in 250 ml. of water containing excess sodium hydroxide and treated with excess hydrochloric acid. The product thus formed was

gelatinous and upon continued drying on the filter and in a vacuum desiccator gave 90 g. (50%) of δ-(p-bromophenoxy)-α-carboxy-γ-valerolactone. Since the product was of poor quality no melting point was taken. The crude material was used directly in subsequent reactions.

δ-(p-Bromophenoxy)-γ-hydroxyvaleric Acid



(272)

5.4 g. (.02 M)

(289)

5.6 g. (.02 M)

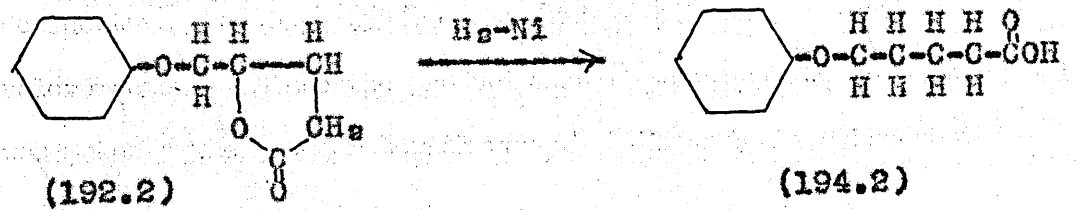
$$\frac{5.6}{5.6} \times 100 = 100\%$$

The hydroxy-acid was prepared by first decarboxylating the crude acid lactone at 150 - 170° C. The granular product, which had been freed from unchanged acid by sodium carbonate treatment, was dissolved in excess sodium hydroxide by heating. An excess of dilute hydrochloric acid was then added to the solution. Such treatment of 5.4 g. (.02 M) of the lactone gave 5.6 g (.02 M) of the white silken δ-(p-bromophenoxy)-γ-hydroxyveleric acid in essentially quantitative yield. Two recrystallizations from hot water and one from toluene gave a product melting at 111.5 - 112.2° C.

Anal. Calculated for $C_{11}H_{13}O_4Br$: C, 45.72; H, 4.53; Br, 27.63.

Found: C, 45.95; H, 4.51; Br, 27.66.

Hydrogenolysis of δ-Phenoxy-γ-valerolactone



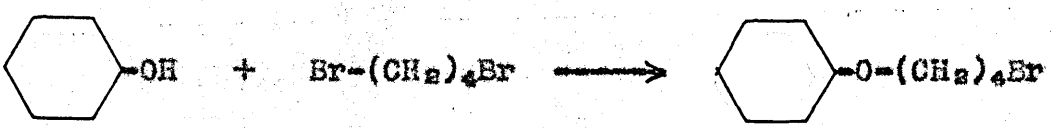
(192.2) (194.2)

24 g. (.125 M) 4 g. (.021 M)

$\frac{4}{24.3} \times 100 = 16.5\%$

A solution of 24 g. (1/8 M) of the lactone in 125 ml. of absolute ethanol was subjected to a hydrogen pressure of 3500 p.s.i. in the presence of about a gram of Raney Nickel. The temperature was gradually increased during the process and a sharp break was noted in the P-T curve at 75° C. Shaking was continued until there appeared to be no further decrease in pressure. The solution was then cooled, removed from the bomb and filtered. The ethanol was evaporated on the steam bath and the residue was triturated with an excess of 10% $NaHCO_3$ Solution. This solution was extracted with ether to remove any neutral material and then the aqueous layer was acidified with dilute hydrochloric acid. A white precipitate of δ-phenoxyvaleric acid was formed which when dried weighed 4 g. This represents about 16% conversion of the lactone to the free acid. Upon recrystallization from ethanol-water, white silken platelets, m.p. 97 - 99.5° C., were formed.

Preparation of 4-Phenoxy-1-bromobutane



(94.1) (216) (229.1)

73.5 g. (.78 M) 216 g. (1 M) 113 g. (.49 M)

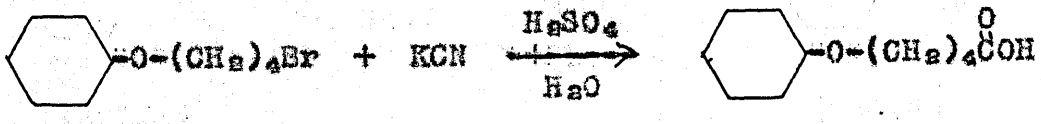
$$\frac{113}{178} \times 100 = 63\%$$

Preparation of the ether was carried out following the general procedure of Marvel and Tarenbaum (32). A three neck round bottomed 1-liter flask was provided with a stirrer, condenser, and dropping funnel. In the flask were placed 400 ml. of water, 216 g. (1 M) of tetramethylene dibromide, and 73.5 g. (.78 M) of phenol. The flask was heated to reflux temperature and 30 g. (.75 M) of sodium hydroxide in 100 ml. of water was added dropwise. The heating was continued for five hours. At the end of this time the solution was cooled, extracted with ether and dried. The residue, after solvent removal, was distilled to give 113 g. (80% based on dibromide not recovered) of clear liquid 4-phenoxy-1-bromobutane. Upon standing the liquid solidified to a white crystalline solid melting at 39.8 - 40.4° C. after recrystallization from methanol.

Anal. Calculated for $C_{10}H_{13}OBr$: C, 52.45; H, 5.72; Br, 34.88.

Found: C, 52.62; H, 6.00; Br, 34.78.

δ -Phenoxyvaleric Acid



(229)

91.5 g. (.4 M)

(194)

44.5 g. (.23 M)

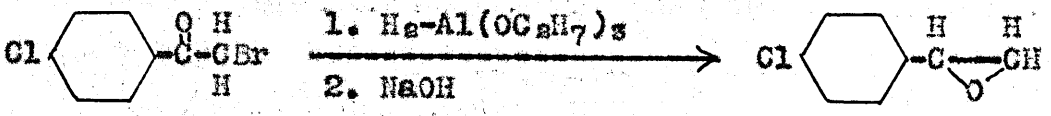
$\frac{44.5}{77.5} \times 100 = 57.5\%$

The nitrile synthesis was conducted in a 1 liter flask by the refluxing of a stirred mixture of 91.5 g. (.4 M) of the bromo-ether, 45 g. potassium cyanide, 100 ml. water, and 75 ml. ethanol for three hours. The alcohol was then removed by distillation and the crude nitrile separated and hydrolyzed without purification by heating on the steam bath and stirring with 100 ml. each of water, sulfuric acid (conc.), and glacial acetic acid. After a reaction period of 2½ hours, the solution was diluted to separate the oily layer and aqueous solution. The oil was washed by stirring in a beaker with fresh portions of water. During this time the oil solidified to a brown granular mass. Several crystallizations from alcohol water solution gave 44.5 g. (57.5%) of white amorphous δ-phenoxyvaleric acid m.p. 98 - 101° C. After three recrystallizations from Skellysolve C the m.p. was 101.2 - 103.0° C.

Anal. Calculated for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found:

C, 68.75; H, 7.51.

p-Chlorostyrene Oxide



(233.6)

234 g. (1 M)

(154.6)

68 g. (.44 M)

$\frac{68}{154.6} \times 100 = 44\%$

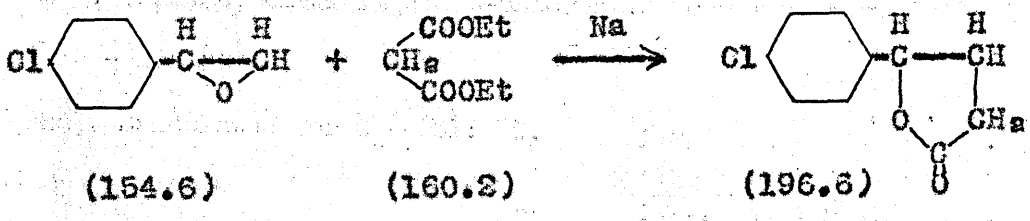
Following the general procedure of Lund (33), 234 g. (1 M) of p-chlorophenacyl bromide was dissolved in 1 liter of isopropanol (dried by distilling from calcium oxide). To the solution was added 204 g. (1 M) of aluminum isopropoxide. The mixture was stirred and refluxed for 110 hours while distillate was being removed at the rate of two to four drops per minute by means of a short vacuum-jacketed column and head. The distillate was tested periodically for acetone (33). Even after the 110 hours the test was not entirely negative. More isopropanol was added as needed to keep the volume about constant. At the end of this time the solvent was removed under vacuum. The residue was cooled and hydrolyzed with 350 ml. of concentrated hydrochloric acid in 1500 ml. of water. The oily residue was extracted with three 150 ml. portions of ether. The ether was removed without drying and the entire material was stirred with 40 g. of sodium hydroxide in 15% solution. The oil thus formed was extracted with ether, dried by filtering through anhydrous sodium sulphate, and concentrated on the steam

bath. This material was purified by vacuum distillation giving 68 g. (44%) of clear liquid p-chlorostyrene oxide, b.p. 101 - 105° C. @ 14 - 15 mm.

Anal. Calculated for C_8H_7OCl: C, ; H, ; Cl, . Found:

C, ; H, ; Cl, .

Condensation of p-Chlorostyrene Oxide with Malonic Esther



(154.6) (160.2) (196.6)

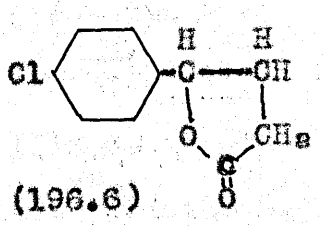
38.6 g. (.25 M) 40 ml (.26 M) 36 g. (.18 M)

$$\frac{36}{49} \times 100 = 73.4\%$$

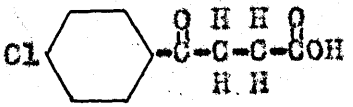
A 1 liter, three neck flask was equipped in the usual manner (p.) and charged with 250 ml. of absolute ethanol and 6.5 g. (.28 M) of sodium. After solution of the sodium was complete, the temperature was lowered to 22° C. and 40 ml. (.26 M) of malonic ester was added dropwise during the course of ½ hour. Stirring was continued for 2 hours at 22° C. and then the temperature was raised to 45 - 50° C. while stirring was being continued for an additional 6 hours. The reaction mixture was then allowed to stand over night without additional heating. The product was hydrolyzed by heating with 23 g. of potassium hydroxide in 125 ml. of water followed by removal of the ethanol by distillation. The salt of the acid was liberated by treating with 18 ml. of concentrated sulphuric acid in 150 ml. of water. The product was then extracted with ether, dried over anhydrous sodium sulphate and the ether removed by distillation. The residue was decarboxylated by heating to 130 - 150° C. until evolution of carbon dioxide had ceased. The product was distilled under vacuum to

give 36 g. (73.1%) of light, straw-colored, liquid γ-(p-chlorophenyl)-γ-butyrolactone, b.p. 124 - 127° C. @ .22 mm.

Bromine Oxidation of γ-(p-Chloropheryl)-γ-butyrolactone



Br_2, NaOH



(196.6)

5 g. (.025 M)

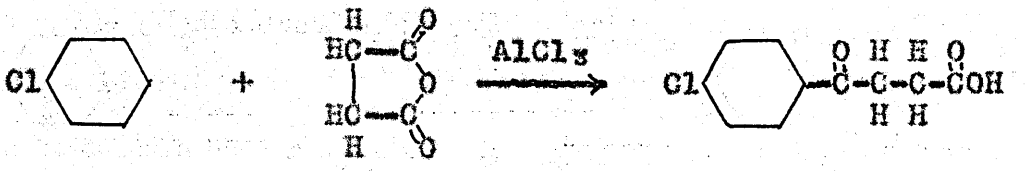
(212.6)

4 g. (.019 M)

$\frac{4}{5.3} \times 100 = 76\%$

The lactone (5 g. - .025 M) was dissolved in 19 ml. of water containing 3.75 g. of sodium hydroxide. Heating was necessary to bring the lactone into solution. To the hot solution was added a hot solution of 10.9 g. of magnesium sulphate hexahydrate in 8 ml. of water. The mixture was then cooled in ice and shaken while 1.38 ml. of bromine was added dropwise. The flask was then allowed to come to room temperature. The solution was acidified with 7.8 ml. of 6 M sulphuric acid. After acidification a solid precipitated. Upon drying the crude product weighed 4 g. (76%). Recrystallization from hot water gave white plates of p-chloro-β-benzoylpropionic acid, m.p. 131.0 - 131.4° C.

p-Chloro-β-benzoylpropionic Acid



(112.6) (100.1) (212.6)

252 g. (2.25 M) 34 g. (.34 M) 45 g. (.21 M)

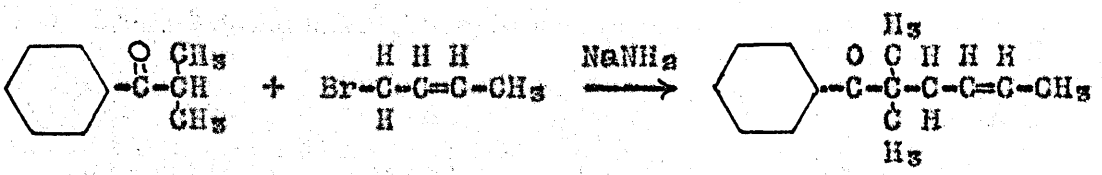
$\frac{21}{34} \times 100 = 62\%$

The preparation was carried out according to the general directions of Somerville and Allen for β-benzoylpropionic acid (34). A 1 liter three neck flask was equipped with a stirrer, and two condensers. The flask was arranged on the steam bath and charged with 34 g. (.34 M) of succinic anhydride, 252 g. (2.25 M) of chlorobenzene and 100 g. (.75 M) of anhydrous aluminum chloride. This mixture was heated to steam temperature and stirred for 1 hour. The flask was then surrounded by ice and the material hydrolyzed by dropwise addition of 150 ml. of water and then 50 ml. of concentrated hydrochloric acid. The excess chlorobenzene was removed by steam distillation. The material was then poured into a beaker where the oil soon solidified. Two recrystallizations from water, one from benzene, and one more from water gave 45 g. of p-chloro-β-benzoylpropionic acid (62%). The acid was pure white melting at 131.0 - 131.4° C.

Anal. Calculated for $C_{10}H_9O_3Cl$: C, 56.80; H, 4.26; Cl, 16.65.

Found: C, 56.68; H, 4.44; Cl, 16.34.

Condensation of iso-Butyrophenone with 1-Bromo-2-butene.



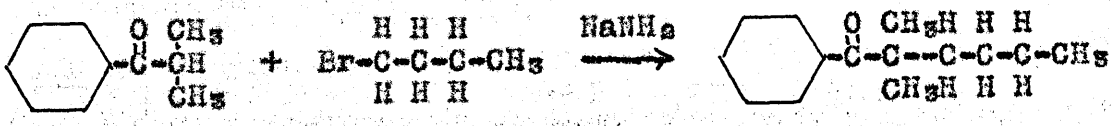
(148.2) (135) (202.3)

49 g. (.33 M) 45 g. (.33 M) 60 g. (.30 M)

$$\frac{60}{67.3} \times 100 = 89\%$$

A 1 liter three neck flask was equipped with condenser, stirrer, and dropping funnel. The flask was charged with 250 ml. of dry benzene, 13 g. (.33 M) of sodamide, and 49 g. (.33 M) of iso-butyrophenone. The mixture was heated on the steam bath and stirred until the evolution of ammonia had ceased. The solution became reddish brown in color. Stirring was continued while 45 g. (.33 M) of crotyl bromide was dropped into the refluxing solution as rapidly as the capacity of the condenser would permit. The reaction was continued for four hours during which time a greyish precipitate formed. The contents of the flask were then washed with five portions of water and the benzene solution dried by filtration through anhydrous sodium sulfate. Distillation of the residue after removal of benzene gave 60 g. (89%) of colorless liquid dimethylcrotyl acetophenone, b.p. 122.4° C. @ 5 mm., 119.7° C. @ 4 mm.

Dimethyl-n-butyl Acetophenone



(148.2) (137) (204.3)

49 g. (.33 M) 46 g. (.33 M) 48 g. (.24 M)

$\frac{48}{68} \times 100 = 70.5\%$

The condensation was carried out in exactly the same manner as was the case with crotyl bromide. The same volume (250 ml.) of dry benzene was used as solvent and 1/3 molar quantities of all reactants were employed. After removal of the dry solvent from the product, it was distilled in vacuum to give three fractions

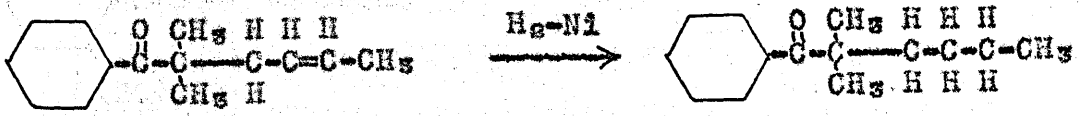
# 1	up to 102° C. @ 5 mm.	15 g.
# 2	102 - 120° C. @ 4.5 - 5 mm.	11 g.
# 3	120 - 124° C. @ 4.5 - 5 mm.	48 g.

The first fraction was solvent and a small amount of recovered isobutyrophenone; the second was a mixture of product and reagent, and the third essentially pure product. A semicarbazone of the third fraction was prepared and purified yielding white crystals, m.p. 90.0 - 90.7° C.

Anal. Calculated for $C_{15}H_{23}ON_3$: C, 68.85; H, 8.85; N, 16.08.

Found: C, ; H, ; N, .

Catalytic Reduction of Dimethylcrotylacetophenone



(202.2)

20.2 g. (.1 M)

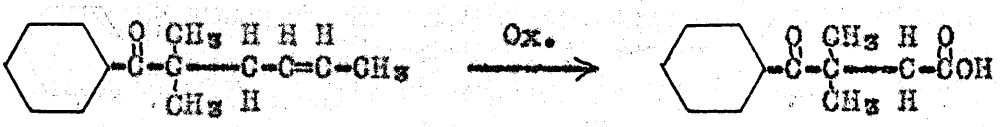
(204.3)

18 g. (.09 M)

$\frac{18}{20.4} \times 100 = 90\%$

The hydrogenation of the unsaturated ketone was carried out at room temperature and 45 p.s.i. An ethanol solution of 20.2 g. (.1 M) of the ketone was shaken for 3 hours with about 1 g. of Raney Nickel in an atmosphere of hydrogen at 45 p.s.i. pressure. When there was no more adsorption of hydrogen, after continued shaking, the pressure was released, the solution filtered from catalyst and the solvent distilled. The product was distilled at reduced pressure to yield 18 g. (90%) of colorless liquid 2-methyl-2-benzoylhexane, b.p. 108.5 - 109.2° C. @ 2 mm. The semicarbazone of this material melter sharply at 89.0 - 89.9° C.

Oxidation of Dimethylcrotylacetophenone



(202.3) (206.2)

10.1 g. (.05 M) 6.7 g. (.033 M)

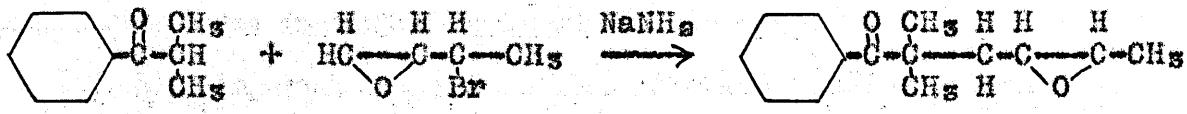
$$\frac{6.7}{10.3} \times 100 = 65\%$$

A 2% solution of potassium permanganate was prepared by dissolving 21 g. of the dry crystals in 1 liter of water. The unsaturated ketone (10.1 g. - .05 M) was stirred in this solution for 3 hours with no external heating. The temperature rose slightly due to the heat of reaction. At the end of this time the temperature was raised to 55 - 60° by heating on the steam bath and stirring was continued until the permanganate color was all discharged. Sulfur dioxide was then bubbled into the cooled solution until the suspension became clear. The oil which separated was extracted with ether, dried, and partially purified by bubbling dry ammonia gas into the ether solution. The precipitated salt was filtered off, washed with a little dry ether and then dissolved in water. Acidification of the aqueous solution with dilute hydrochloric acid caused the precipitation of white crystals. Recrystallization from dilute methanol gave 6.7 g. (65%) of snow white crystals of β-dimethyl-β-benzoylpropionic acid, m.p. 99.0 - 100° C.

Anal. Calculated for $C_{12}H_{14}O_3$: C, 69.75; H, 6.83. Found

C, 69.74; H, 6.68.

Condensation of iso-Butyrophenone with 3-Bromo-1,2-epoxy Butane



(148.2) (151) (218.3)

74 g. (.5 M) 75 g. (.5 M) 26 g. (.12 M)

$$\frac{26}{109} \times 100 = 24\%$$

As in the previous reaction with crotyl bromide, 74 g. (.5 M) of iso-butyrophenone was reacted with 20 g. (.5 M) of sodamide. After the evolution of ammonia had ceased, the flask was cooled to room temperature and 75 g. (.5 M) of 3-bromo-1,2-epoxy butane was dropped into the stirred solution during two hours time. Stirring was continued for an additional 14 hours at room temperature and then the temperature was increased to the boiling point and maintained for 45 minutes. The material was then cooled and washed with three portions of water. The benzene solution was dried by filtering through anhydrous sodium sulphate and the benzene was removed by distillation. The remaining liquid was distilled in vacuum to yield three fractions.

# 1	up to 80° C.	@ 5 mm.	48 g.
# 2	80 - 120	5 mm.	8 g.
# 3	121 - 130	5 mm.	26 g.

The first fraction was recovered iso-butyrophenone, the second was a mixture of starting material and product, and the third was essentially pure product. The third fraction was redistilled to

give a major portion boiling at 123 - 124° C. @ 5 mm. The yield of three is 68% based on starting material not recovered.

The preparation of a 2,4-dinitrophenylhydrazone of fraction three was carried out according to the directions of Shriner and Fuson (35). Upon the addition of the hydrochloric acid to the refluxing alcohol solution, solid crystals began to form almost immediately. Upon cooling of the solution, the red small flakes precipitated out in abundance. Recrystallization of the solid from hot ethanol gave a product melting at 233.8 - 234.5° C. A sample was prepared for analysis by a second recrystallization from ethanol.

Anal. Calculated for $C_{20}H_{22}O_5N_4$: C, 60.29; H, 5.57; N, 14.06.

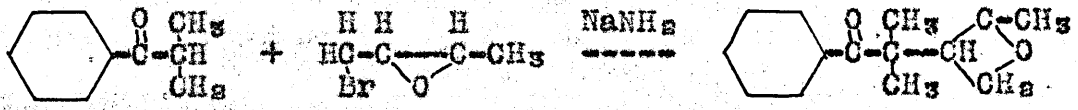
Found: C, 62.72; H, 5.24; N, 14.75.
62.82 5.20 14.76.

Calculated for $C_{20}H_{20}O_4N_4$: C, 63.20; H, 5.30; N, 14.75.

The p-nitrophenylhydrazone was prepared in the same manner. It did not form with the extreme ease of the dinitrophenylhydrazone. Upon recrystallization from ethanol it melted at 236.0 - 237.0° C.

The oxime was prepared by refluxing 1 g. of the epoxy-ketone with 1 g. of hydroxylamine hydrochloride, 5 ml. of pyridine, and 5 ml. of ethanol. Upon removal of the solvents and recrystallization from 5% ethanol, a white granular solid oxime of 5-methyl-5-benzoyl-2,3-epoxyhexane was obtained, m.p. 127.8 - 129.0° C.

Condensation of iso-Butyrophenone with 1-Bromo-2,3-epoxybutane



(148.2) (151) (218.3)

49 g. (.33 M) 50 g. (.33 M) 34 g. (.16 M)

$$\frac{34}{72.5} \times 100 = 47\%$$

The condensation was carried out in the same manner as with the previous ones. A 1 liter three neck flask was equipped with a stirrer, condenser, dropping funnel and steam bath. In the flask was placed 49 g. (.33 M) of iso-butyrophenone in 250 ml. of dry toluene and 13 g. (.33 M) of sodamide. The flask was heated until the reaction was complete as evidenced by the discontinuation of ammonia evolution. The flask was then cooled to room temperature and 50 g. (.33 M) of 1-bromo-2,3-3poxybutane was added in the course of 20 minutes time. Stirring was continued for 6 hours at room temperature and then the temperature was raised to 90 - 95° C. for another hour. The solution was then washed with three portions of water to remove any inorganic materials and the toluene solution of the organic products was dried by filtering through anhydrous sodium sulphate. The toluene was then removed by distillation and the residual product was vacuum distilled to give the following fractions:

# 1	up to 72° C.	@ .16 mm.	6 g.
# 2	72 - 74	.16 mm.	34 g.
# 3	74 - 95	.16 mm.	16 g.

Fraction #1 was principally solvent and unreacted ketone, #2 was the product sought, and #3, which came over as a very viscous oil, was probably a mixture of higher condensation products.

Attempts to prepare the 2,4-dinitrophenylhydrazone were unsuccessful. Treatment of one gram of the second fraction with one gram of hydroxylamine hydrochloride and 10 ml. of a 50% solution of ethanol and pyridine and refluxing for 2 hours on the steam bath gave a solid oxime of 2-[(1-benzoyl-1-methyl)-ethyl]-1,3-epoxybutane, m.p. 122.0 - 122.7° C. after recrystallization from 5% ethanol.

Anal. Calculated for $C_{14}H_{19}O_2N\ H_2O$: C, 66.90; H, 8.42; N, 5.57.

Found: C, 66.70; H, 8.26; N, 5.52.

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