ADDITION REACTIONS OF VINYL PHENYL KETONE III. MALONIC ESTER

THE ADDITION REACTIONS OF VINYL PHENYL KETONE, III. MALONIC ESTER.

A Thesis

Submitted to the Faculty of Graduate Studies and Research of McGill University in Partial Fulfilment of the Requirements for the Degree of Doctor of Philosophy

by

Homer W. J. Cressman

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TO DR. C. F. H. ALLEN

FOR THE MANY VALUABLE SUGGESTIONS,
KIND ADVICE ALWAYS CHEERFULLY GIVEN,
AND HELP, THIS THESIS IS GRATEFULLY
DEDICATED.

Homer W. J. Cressman

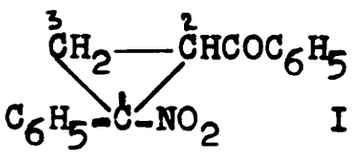
CONTENTS.

INTRODUCTION.

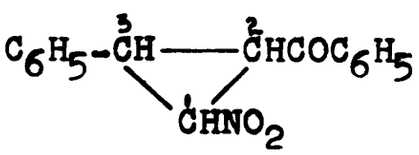
Ever since the discovery of cyclopropane by Freund (1) numerous substituted derivatives have been prepared and their stability carefully studied. It was early formulated by Perkin (2) and later by Kötz (3) that the substitutent groups have a marked influence on the stability of the cyclopropane ring. Recently Kohler and his students (4) have prepared a series of ketonic cyclopropanes in which all three carbon atoms are substituted. They have studied their reactions toward characteristic ring reagents and have obtained valuable information on the behaviour of cyclopropanes bearing substitutents on all three carbons. More recently a method (5) has been devised for the preparation of closely related ketonic cyclopropane derivatives in which only two carbons of the ring are substituted. It is, therefore, possible to compare these derivatives with the previously studied examples and so obtain additional information on the influence of substitutents on the stability and reactivity of cyclopropanes.

In the first paper of this series, Allen and Bridgess (5) compared the reactions of 1-phenyl-1-nitro-2-benzoylcyclopropane (I) with the isomeric 1-nitro-2-benzoyl-3-phenylcyclopropane (II), previously studied by Kohler and Englebrecht (4g). In a second paper, Allen and Barker

(6) have prepared 1-phenyl-1-benzoyl-2-benzoylcyclopropane (III) and compared it with the cyclopropane (IV), studied by Kohler and Jones (4f). The cyclopropanes



I



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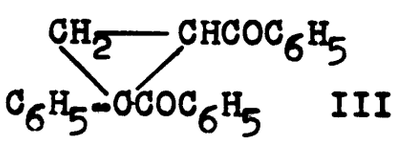
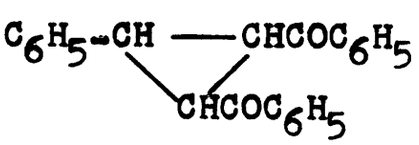


III



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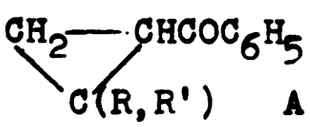
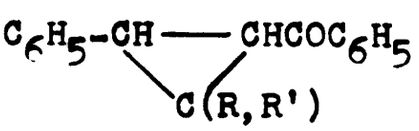


A



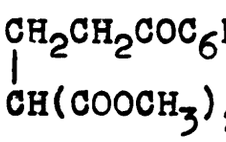
B

(I) and (III) or type (A) are much less reactive than the isomeric cyclopropanes (II) and (IV) or type (B). In the latter derivatives, the ring has been opened in all 3 positions, the same reagent frequently giving two types of products. Regardless of the nature of the reagent, the derivatives of type (A) have only been opened between the two carbon atoms bearing substitutents or the 1,2 position.

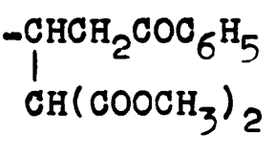
It was of interest to prepare other cyclopropane derivatives belonging to type (A) to see whether they too would react like the previously studied examples in this series.

We have added methyl malonate to vinyl phenyl ketone

$CH_2=CHCOC_6H_5$ and obtained the keto ester, methyl γ-benzoyl-ethylmalonate (V), closely related to methyl β-phenyl-γ-benzoyl-ethylmalonate (VI) studied by Kohler and Conant (4a). The latter ester has been converted into a cyclo-

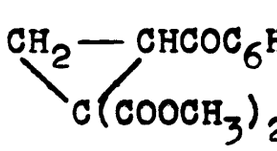


V



VI

ester (VIII) belonging to type (B). Employing similar methods, our ester was converted to the closely related ketonic cyclopropane ester (VII) belonging to type (A).



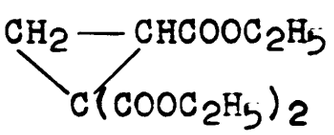
VII

VIII

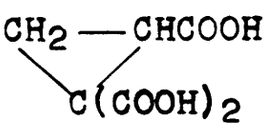
The reactions of the cyclopropane derivative (VII) have been studied and the results compared with the previously studied reactions of (VIII) and all cyclopropane derivatives bearing one or more unsaturated groups on two carbons of the ring. Before discussing these results it is necessary to find all known cyclopropanes of this type.

In 1884 Guthzeit and Conrad (7) prepared ethyl 1,1,-2-cyclopropane -tricarboxylate (IX) by condensing the sodium salt of ethyl malonate with ethyl α - β -dibromo-

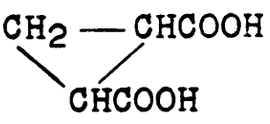
propionate. The cyclopropane ester distilled under di-



IX



X

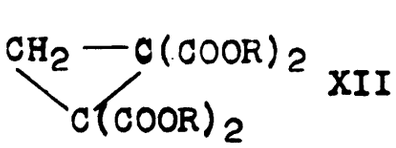


XI

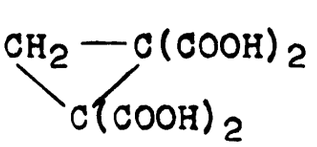
minished pressure without decomposition. At that time the main criteria of the stability of a cyclopropane was its behaviour on pyrolysis. The ester on hydrolysis with aqueous sodium hydroxide gave the corresponding cyclopropane tricarboxylic acid (X), which on heating lost carbon dioxide and gave the anhydride of the 1,2-cyclopropane-dicarboxylic acid (XI). The free acid was obtained by heating the anhydride in a sealed tube with water.

Michael (8) obtained the cyclopropane ester (IX) by condensing ethyl α-bromopropionate with ethyl-sodium-malonate.

Perkin (9) prepared the methyl 1,1,2,2-cyclopropane ester (XII) by treating the sodium salt of methyl propane-



XII



XIII

tetracarboxylate with bromine. On pyrolysis the tetra-

carboxylic acid (XIII) gave the anhydride of cis-1,2-cyclopropane-dicarboxylic acid (XI).

Guthzeit and Dressel (10) prepared both the ethyl and methyl cyclopropane esters (XII) by the same procedure. On pyrolysis of the corresponding acid, they isolated the cis acid (XI), which on distillation under reduced pressure was converted into its anhydride.

Perkin and Gregory (11) prepared the same cyclopropane ester (XII) by condensing ethyl α,α'-dibromo-propane-tetracarboxylate with the sodium salt of the same ester. The pyrolysis of the cyclopropane tetracarboxylic acid (XIII) gave the higher melting trans-1,1-cyclopropane-dicarboxylic acid (XI). This acid heated with acetic anhydride gave the anhydride of the cis-cyclopropane acid (XI).

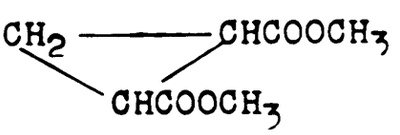
Guthzeit and Lobeck (12) using the same procedure prepared both the ethyl and methyl esters (XII). They obtained both isomeric acids (XI) on pyrolysis of the cyclopropane acid (XIII).

The ester (XII) and the acids (XIII) and (XI) were also prepared by Kötz and Stalmann (13) by digesting the sodium salt of ethyl succinate with methylene iodide. Later Kötz and Sielich (14) prepared them by eliminating

hydrogen bromide from ethyl ∝-bromopropane-tetacarboxylate with ammonia or iodine.

Perkin and Bowtell (15) and later Perkin and Tatterstall (16) obtained trans cyclopropane acid (XI) by refluxing ethyl ∝ -bromogluturate with either alcoholic potassium hydroxide or quinoline.

Buchner (17) and Buchner and Papendieck (18) prepared methyl 1,2-cyclopropane-dicarboxylate (XIV) by distilling



XIV

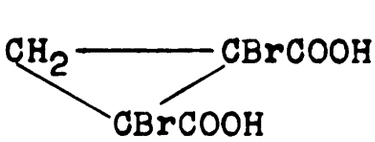
methyl 3,5-pyrazoline-dicarboxylate. Hydrolysis of this ester gave the two stereoisomeric cyclopropane acids (XI).

Pechmann (19) prepared the same ester by distilling methyl 3,4-pyrazoline-dicarboxylate. The latter was obtained by condensing methyl fumurate with diazo-methane.

All the preceding esters and acids are stable toward potassium permanganate. The two stereoisomeric 1,2-cyclopropane-dicarboxylic acids (XI) are very stable substances. Neither acid (20) when heated at 100°C. decolorized an alkaline potassium permanganate solution nor are they

reduced by a concentrated sodium amalgam solution. Both acids are stable toward heat. The trans acid distilled under reduced pressure without change. The cis acid on distillation or when digested with acetyl chloride was changed into its anhydride. The latter was also obtained by heating the neutral silver salt of the trans acid with tile clay. This conversion (11) was better effected with acetic anhydride. An 80 % yield of the trans acid (20) was obtained by heating at 240-250°C, the calcium salt of the cis acid with potassium hydroxide. A small amount of cyclopropane monocarboxylic acid was obtained as a by-product in this treatment. A small amount of trans acid was obtained by heating the cis acid at 150°C in a sealed tube with a 1:1 aqueous sulfuric acid mixture. In this treatment, a considerable amount of hydroxy acid was also formed. The cis acid (XI) did not react with concentrated hydrochloric acid (17) even when heated in a sealed tube at 180°C. for 6 hours.

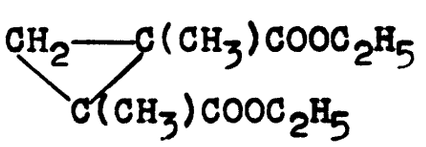
Buchner and Wedemann (21) heated the acid chloride of the cis modification (XI) with phosphorous and bromine in a sealed tube and obtained two isomeric 1,2-dibromo-1,2-cyclopropane-dicarboxylic acids (XV). The trans acid



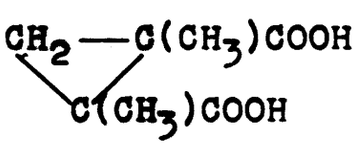
XV

gave the same two di-bromo acids (XV). These acids are stable toward potassium permanganate and boiling water. Sodium amalgam reduced both modifications to the trans-1,2-cyclopropane-dicarboxylic acid (XI).

Paolini (22) prepared ethyl 1,2-dimethyl-1,2-cyclopropane-dicarboxylate (XVI) by eliminating hydrogen chloride from ethyl trimethyl-chlorogluturate with di-



XVI

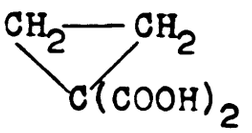


XVII

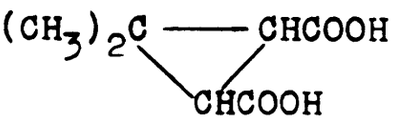
ethyl-aniline. Both the ester and the corresponding acid (XVII) are stable toward potassium permanganate. The acid was also prepared and its saturated character determined by Henstock and Woolley (23). The substituted 1,2-cyclopropane-dicarboxylic acid (XVII) exhibits the same stability (24) as shown by the preceding unsubstituted cyclopropane dicarboxylic acids (XI).

In comparison to the cyclopropane acids bearing substitutents on two carbons of the cyclopropane ring, the 1,1-cyclopropane-dicarboxylic acid (XVIII) and the 3,3-dimethyl-1,2-cyclopropane-dicarboxylic acid (XIX) are much less stable. Fission of the ring in these deriva-

tives takes place with greater ease. The cyclopropane-

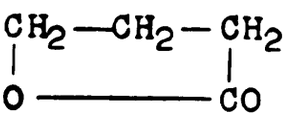


XVIII

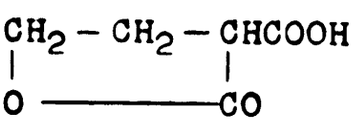


XIX

1,1-dicarboxylic acid on distillation (25), (26) formed the butyrolactone (XX). The acid (XVIII) readily reacted with hydrobromic acid at 0°C. and formed an unstable bromoacid which when boiled with water produced the carboxylactone (XXI). The latter was also obtained by refluxing

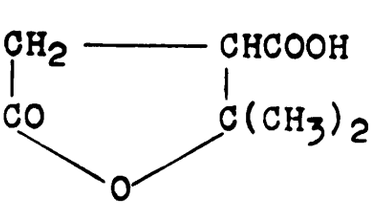


XX



XXI

the cyclopropane acid (XVIII) with a 50 % sulfuric acid solution. The carboxylactone when heated at 120°C. lost carbon dioxide and formed the saturated lactone (XX). The 3,3-dimethyl-1,2-cyclopropane-dicarboxylic acid (XIX), a derivative of type (B), on heating (27) was converted into dimethyl paraconic acid (XXII). In all these ex-



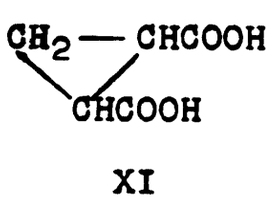
XXII

periments with the cyclopropane derivatives (XVIII) and

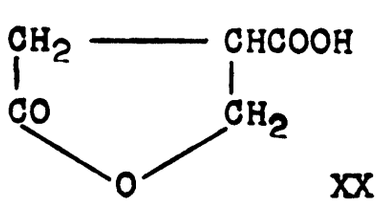
(XIX), the cyclopropane ring was cleaved.

Small amounts of the two isomeric cyclopropane acids (XI) were obtained by Farmer and Ingold (28) as reduction products from 1,2-cyclopropene-dicarboxylic acid. The latter was prepared by treating ∝-bromoglutaconic acid with a concentrated alcoholic alkali solution.

Ingold (29) also prepared the cyclopropane acids (XI) by treating ethyl ∝-bromogluturate with concentrated alcoholic potassium hydroxide solution. In addition to these acids and hydroxylation products, a small amount of paraconic acid (XXIII) was isolated. The author ac-



XI

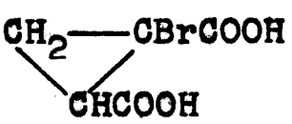


XXIII

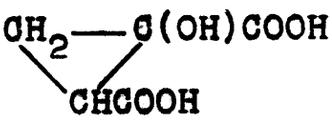
counted for its presence by assuming ring fission of the cyclopropane acids (XI). The paraconic acid could only have formed by cleavage of the ring in the 1,3 position; this is one of the few cyclopropane derivatives of type (A) in which the ring opened other than in the 1,2 position, or between the two carbon atoms bearing substitutents.

Ingold (29) prepared the bromo-1,2-cyclopropane-di-

carboxylic acid (XXIV) by hydrolyzing ethyl α,α'-dibromo-

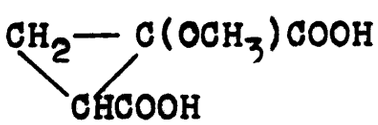


XXIV

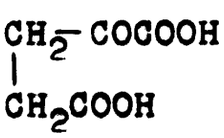


XXV

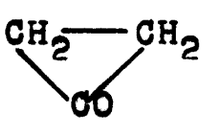
gluturate with dilute aqueous sodium carbonate solution. The acid is stable toward concentrated hydrochloric acid and potassium permanganate. It was not decomposed when heated with a dilute nitric acid solution. By digesting with a 2 N sodium carbonate solution for 500 hours, it was converted into the cyclopropanol -1,2-dicarboxylic acid (XXV). This acid is stable toward potassium permanganate, concentrated hydrochloric acid, and dilute aqueous sodium hydroxide. The bromoacid or the cyclopropanol acid when digested with concentrated alkali in methyl alcohol gave the methoxy-cyclopropane acid (XXVI) and the α-keto-glutaric acid (XXVII). The cyclopropanol acid (XXV)



XXVI



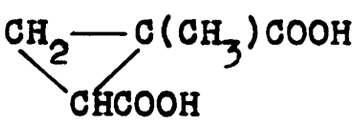
XXVII



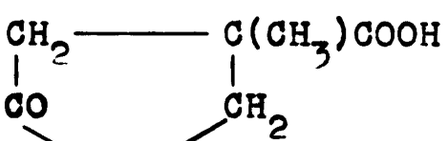
XXVIII

when refluxed with concentrated sulfuric acid gave a very small amount of cyclopropanone (XXVIII). The existence of this ketone and the probability that Ingold ever had it is questioned by Demjanow (30) and Lipp (31).

Ingold (32) prepared the two stereoisomeric methyl-1,2-cyclopropane-dicarboxylic acids (XXIX) by digesting ethyl ∝-bromo- ∝'-methyl-gluturate with concentrated alcoholic potassium hydroxide solution. A small amount



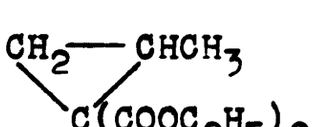
XXIX



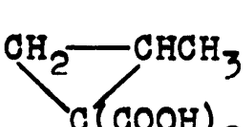
XXX

of methyl paraconic acid was also isolated. The author again assumed that it must have formed from the cyclopropane acids (XXIX). The cis acid when heated at 160° C. was converted into its anhydride. This same anhydride was obtained by heating the trans acid with acetyl chloride. The conversion of the cis acid into the trans acid was effected by heating with hydrochloric acid.

Marburg (33) prepared the methyl 1,1-cyclopropane-dicarboxylic ester (XXXI) by condensing ethyl-sodium-malonate with propylene dibromide. Hydrolysis with aqueous



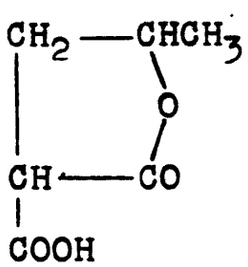
XXXI



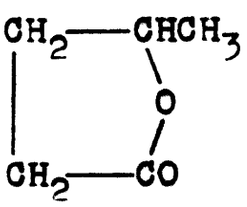
XXXII

barium hydroxide gave the corresponding cyclopropane acid (XXXII). The ester and the acid are stable toward

potassium permanganate and sodium amalgam. The ester distilled under reduced pressure without decomposition. The acid (XXXII) readily reacted with hydrobromic acid at 0°C. and formed an unstable bromide, which when boiled with water for 15 minutes was converted into the carboxylactone (XXXIII). This lactone was also obtained

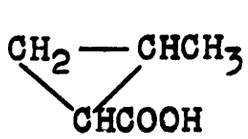


XXXIII

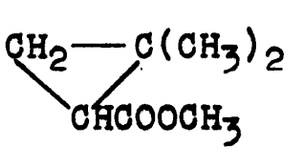


XXXIV

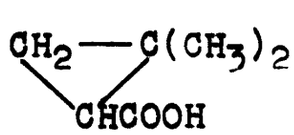
by refluxing the dibasic cyclopropane acid (XXXII) with a 50 % sulfuric acid solution. The carboxy lactone on pyrolysis (34) lost carbon dioxide and formed the saturated lactone (XXXIV). This valerolactone and a small amount of methyl-cyclopropane-carboxylic acid (XXXV) were obtained by dry distilling the methyl 1,1-cyclopropane-dicarboxylic acid (XXXII). With bromine the latter acid gave an open chain dibromoacid. In all these reactions the cyclopropane ring was opened in the 1,2 position.



XXXV



XXXVI

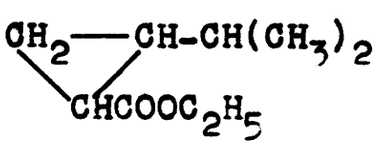


XXXVII

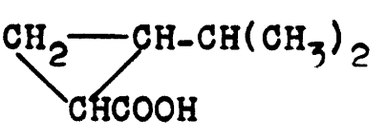
The methyl 2,2-dimethyl-cyclopropane-carboxylate (XXXVI)

was prepared by Blanc and Haller (35) from methyl 3,3-dimethyl-butyrate and methyl-sodium-malonate. The ester and the corresponding acid (XXXVII) distilled in vacuo without decomposition. Kishner (36) obtained the same acid by oxidizing 2,2-dimethyl-1-isobutenylcyclopropane with permanganate.

Blanc and Haller (35) also prepared 2-isopropyl-cyclopropane carboxylate (XXXVIII) by condensing ethyl γ-bromo-β-isopropylbutyrate with the sodium salt of ethyl malonate. The ester and the corresponding acid



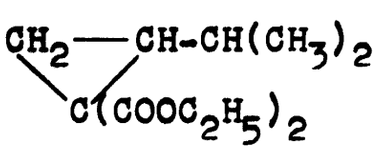
XXXVIII



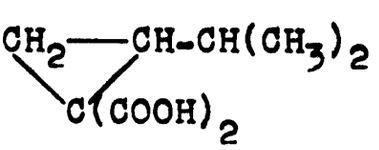
XXXIX

(XXXIX) are stable toward heat. Neither decolorized potassium permanganate.

Ipatieff (37a) prepared ethyl 2-isopropyl-1,1-cyclopropane-dicarboxylate (XL) by condensing isopropyl ethylene bromide with ethyl-sodium-malonate. The correspond-



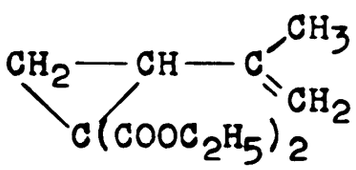
XL



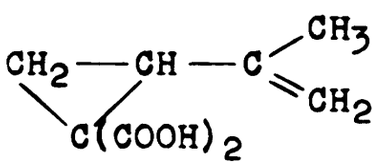
XLI

ing acid (XLI) on pyrolysis gave the 2-isopropyl-cyclopropane monocarboxylic acid (XXXIX).

The same author (37^{b}) also prepared 2-isopropylene-cyclopropane-1,1-dicarboxylic ester (XLII) by condensing 1,2-dibromo-3-methyl-butene 3 with the sodium salt of ethyl malonate. The ester on hydrolysis gave the unsaturated cyclopropane dicarboxylic acid (XLIII), called isoprenic acid by the author.

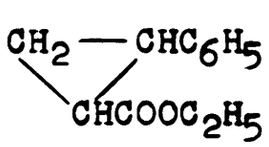


XLII

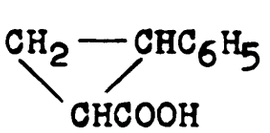


XLIII

Buchner and Geronimus (38) on distillation of ethyl Δ'-4-phenyl-pyrazoline-3-carboxylate obtained ethyl 2-phenylcyclopropane carboxylate (XLIV). The structure



XLIV

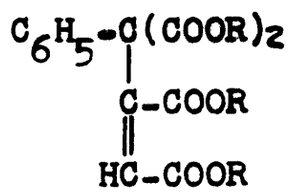


XLV

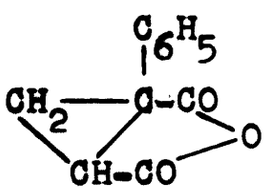
of the ester was determined by hydrolysis and oxidation of the nitrated acid to the known trans-1,2-cyclopropane-dicarboxylic acid (XI). On pyrolysis of the cyclopropane acid (XLV) two unsaturated hydrocarbons, styrene

and phenyl-1-propene, were isolated. The authors assumed that they resulted from the decomposition of the intermediate phenylcyclopropane. None of the latter could be obtained.

Ruhemann (39) by condensing ethyl phenyl malonate with ethyl chloro-fumarate in the presence of sodium ethylate obtained a 6 % yield of ethyl phenyl-carboxy-aconitate (XLVI). This ester when refluxed with an excess



XLVI

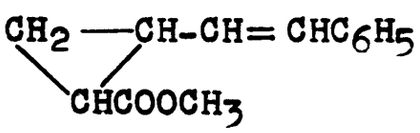


XLVII

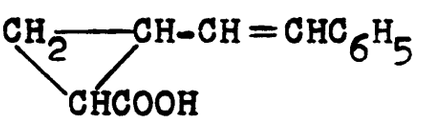
of alcoholic potassium hydroxide was converted into the anhydride (XLVII) of 2-phenyl-1,2-cyclopropane-dicarboxylic acid. The latter was obtained by boiling the anhydride with water. The tendency for anhydride formation is very marked; on cooling it is again reformed. The cyclopropane derivative (XLVII) is stable toward potassium permanganate and bromine. Sodium amalgam solution reduced it to symmetrical methyl phenyl succinic acid. The ring in the reduction was cleaved in the 2,3 position.

von der Heide condensed methyl diazo-acetate with phenyl butadiene and obtained on the distillation of the

pyrazoline derivative the methyl 2-styrylcyclopropane carboxylate (XLVIII). The ester distilled in vacuo with-

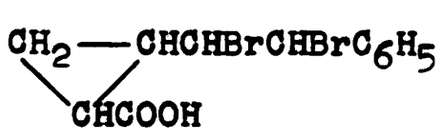


XLVIII

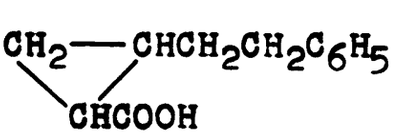


XLIX

out decomposition. The corresponding acid (XLIX) was oxidized by an alkaline potassium permanganate solution to the known trans-1,2-cyclopropane-dicarboxylic acid (XI) and benzoic acid. The unsaturated acid (40) readily reacted with bromine and formed the dibromocyclopropane acid (L). This acid is stable toward permanganate. Sodium



L

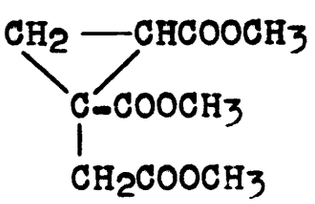


LI

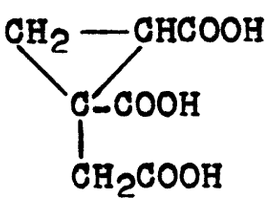
amalgam reduced it to the 2-β-phenylethylcyclopropane-1-carboxylic acid (LI). Sodium in amyl alcohol reduced the bromoacid to a saturated open chain acid, the constitution of which was not determined. The acids (XLIX) and (LI) on treatment with phosphorous pentachloride and ammonia gave the corresponding amides.

Buchner (41) on distillation of methyl 5-acetoxy-3,5-

pyrazoline-tricarboxylate obtained methyl 1-acetoxy-1,2-cyclopropane-tricarboxylate.(LII). Hydrolysis with aqueous alkali gave the corresponding tribasic acid (LIII). The



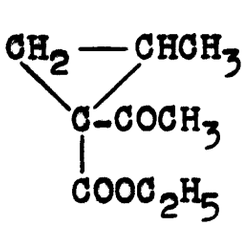
LII



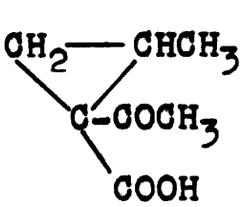
LIII

cyclopropane ester (LII) distilled under diminished pressure without decomposition. The acid was slowly decomposed by heat.

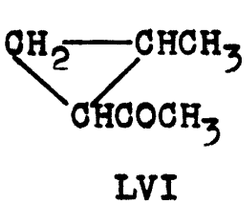
Perkin (42) condensed propylene bromide with the sodium salt of aceto-acetic ester and obtained the cyclopropane derivative ethyl 2-methyl-1-acetyl-1-cyclopropane-carboxylate (LIV). The ester on hydrolysis with alcoholic



LIV



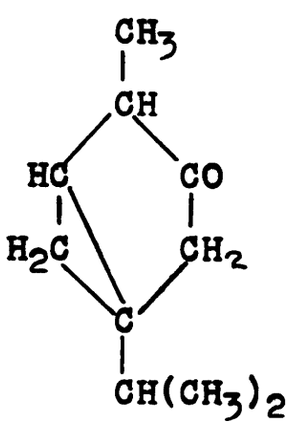
LV



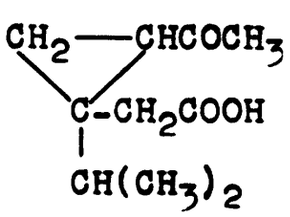
LVI

potassium hydroxide gave the corresponding acid (LV). A very small amount of 2-methyl-1-acetylcyclopropane (LVI) was obtained on pyrolysis of the cyclopropane acid (LV). The acid was not decomposed when heated with an alcoholic potassium hydroxide solution.

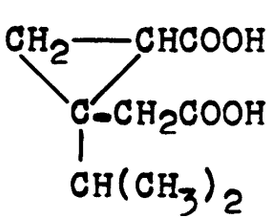
On oxidation of thujone (LVII), whose constitution was then unknown, Wallach (43) obtained two stereoisomeric acids which he named ∝ and β-thujaketonic acids. Later Semmler (44) proved that these acids were the ketonic cyclopropane acid (LVIII). This acid was further



LVII

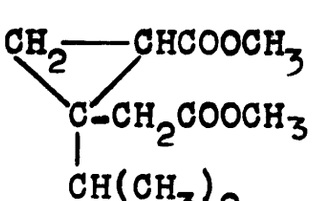


LVIII

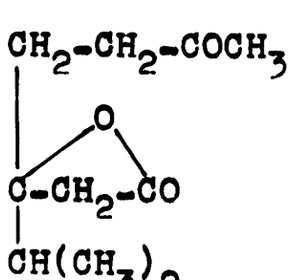


LIX

oxidized with sodium hypobromite to the stable cyclopropane dicarboxylic acid (LIX). This acid readily formed an anhydride and was stable toward dilute acids. The corresponding cyclopropane ester (LX) was obtained (45) by saturating a solution of the acid in methyl alcohol with hydrogen chloride. The ketonic cyclopropane acid



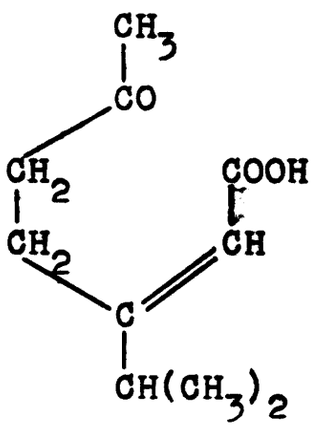
LX



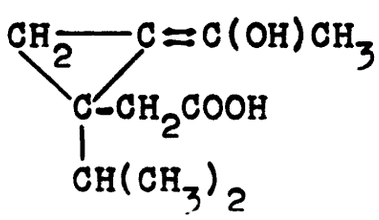
LXI

(LVIII) when treated with dilute sulfuric acid solution

was converted into the saturated lactone (LXI). The ring was cleaved in the 1,2 position. The ketonic acid (LVIII) when distilled under diminished pressure or when digested with water formed the unsaturated β-thujaketonic acid (LXII); the ring was again opened in the 1,2 position.



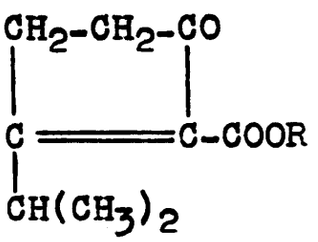
LXII



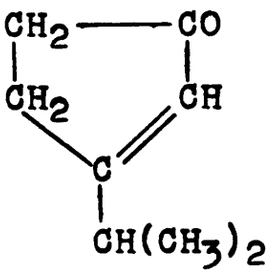
LXIII

Wallach (45) assumed that this acid resulted from the intermediate, unstable, enol form. The instability of the enol (LXIII) can be explained by the mechanism forwarded by Allen and Boyer (46). They consider a double bond attached to a cyclopropane ring equivalent to the reactive allene linkage. The saturated cyclopropane dicarboxylic acid (45) is stable because enolization is excluded. The corresponding cyclopropane ester (LX) was converted by a concentrated alcoholic sodium methylate solution to the isopropylcyclopentanone carboxylic ester (LXIV), which on distillation lost carbon dioxide and alcohol and formed tanacetophorone (LXV). Since enolization is possible in the ester, this transformation (45) was again explained through the intermediate enol

form.

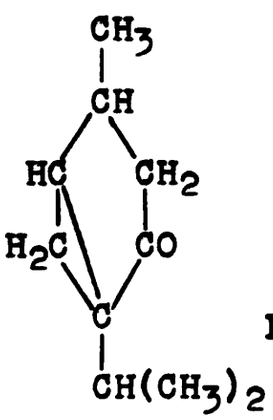


LXIV

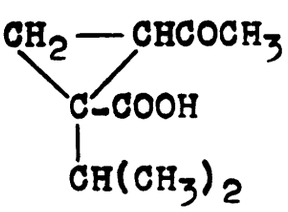


LXV

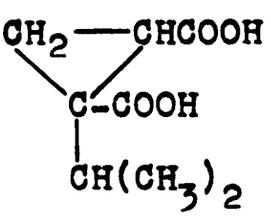
Umbellulone (LXVI), a derivative of the dicyclic terpene thujane, may also be considered as a cyclopropane derivative belonging to type (A). Tutin (47) and Lees (48)



LXVI



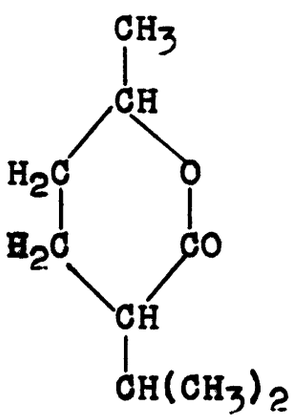
LXVII



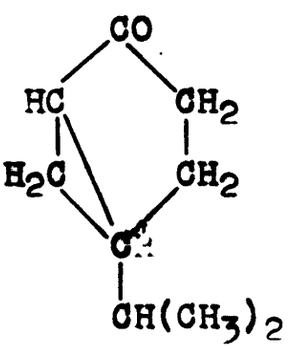
LXVIII

on the oxidation of umbellulone obtained a ketonic saturated acid which they called umbellulonic acid. Later Semmler (49) proved that this umbellulonic acid was the ketonic cyclopropane acid (LXVII). This cyclopropane acid on distillation gave an unsaturated lactone which was readily oxidized to the stable cyclopropane dicarboxylic acid (LXVIII), called umbellularic acid. This acid formed an anhydride and is stable toward concentrated hydrochloric acid . The ketonic cyclopropane acid

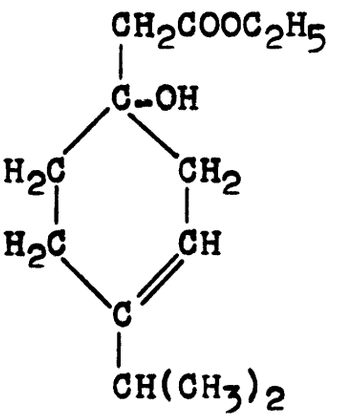
(LXII) on reduction with sodium and methyl alcohol (47) was cleaved in the 1,2 position and formed the saturated lactone (LXIX).



LXIX



LXX

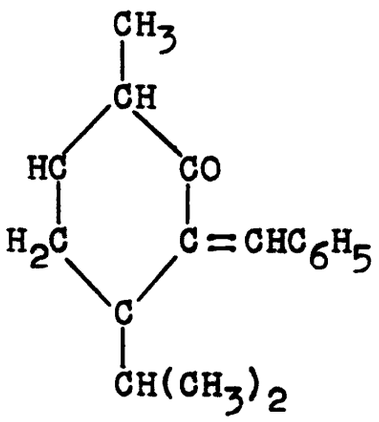


LXXI

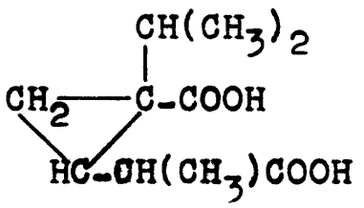
Sabina ketone (LXX) may also be considered as a cyclopropane derivative belonging to type (A). The cyclopropane ring isomerized when the ketone was condensed (50) with ethyl bromoacetate in the presence of zinc and formed the unsaturated alcohol ester (LXXI). The cyclopropane ring was opened in the 1,2 position. All the other reagents employed in determining the structure of this ketone did not attack the cyclopropane ring(51).

Semmler (52) on oxidation of benzylidene-thujone (LXXII), also called benzylidene-tanacetone, obtained the cyclopropane dicarboxylic acid (LXXIII), called homotanacetone dicarboxylic acid or homothujaketonic acid. The same acid was obtained by Wallach (53) by oxidizing

thujone in an alkaline solution with bromine. The cyclo-



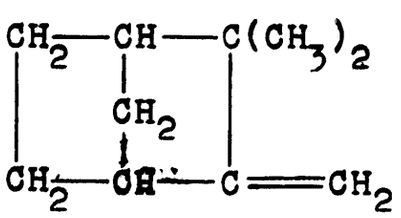
LXII



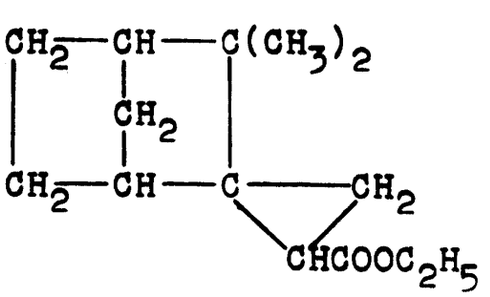
LXXIII

propane acid (LXXIII) is stable toward heat; it distilled without decomposition at 10 mm. pressure. The acid was converted into its anhydride by digesting with acetic anhydride for 15 minutes.

Buchner and Weigand (54) condensed camphene (LXXIV) with diazo-acetic ester and on distillation obtained the cyclopropane ester (LXXV). With sodium and alcohol, the



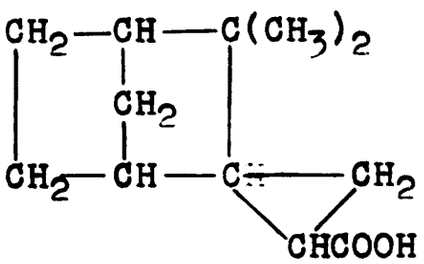
LXXIV



LXXV

ester was reduced to the cyclopropane alcohol. An alcoholic potassium hydroxide solution hydrolyzed the ester

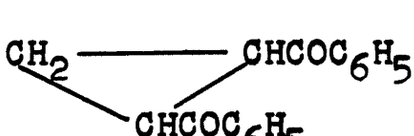
to 2,2-dimethyl norcamphene-2-spiro-cyclopropane carboxylic acid (LXXVI). The constitution of this acid was



LXXVI

determined by oxidizing with a 4 % potassium permanganate solution to the tribasic cyclopropane acid (X), which on pyrolysis gave the anhydride and some cis-1,2-cyclopropane-dicarboxylic acid (XI). This series of experiments definitely proved the position of the double bond in camphene. The cyclopropane acid (LXXVI) was reobtained by treating the corresponding amide with a 50 % sulfuric acid solution.

Conant and Lutz (55) prepared 1,2-benzoyl-cyclopropane (LXXVII) by treating the higher melting dibromo-dibenzoyl-propane isomer with zinc and sodium iodide.

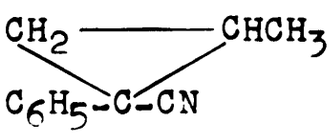


LXXVII

The lower melting isomer could not be converted into a cyclopropane derivative. The cyclopropane on reduction

with zinc and acetic acid gave the straight chain dibenzoyl-propane resulting by fission of the ring in the 1,2 position.

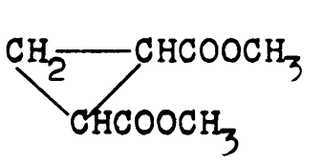
Knowles and Cloke (56) obtained the 1-phenyl-1-mitrile-2-methylcyclopropane (LXXVIII) by condensing



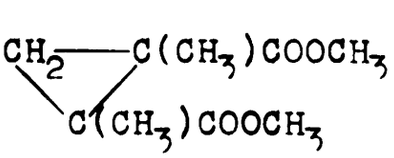
LXXVIII

propylene dibromide with benzyl cyanide in the presence of sodium amide. This cyclopropane distilled at atmospheric pressure without decomposition.

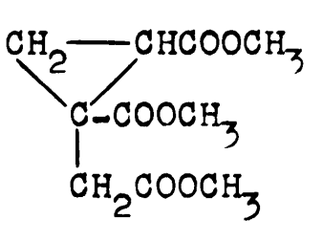
Recently Auwers and König (57) in studying the decomposition products of various pyrazoline esters isolated among other products the cyclopropane derivatives (XIV, XVII, LII, LXXIX, LXXX). The first four esters were hy-



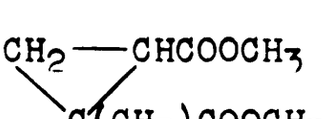
XIV



XVII



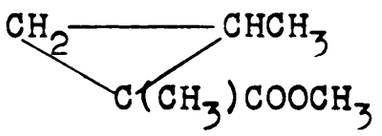
LII



LXXIX

drolyzed to the corresponding known acids. The methyl

2-methyl-1-methyl-cyclopropane-carboxylate (LXXX) was

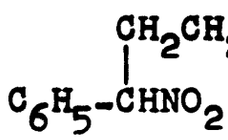


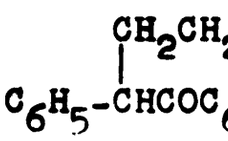
LXXX

obtained in very small quantities; its saturated character was determined spectrochemically. No other work was done with these substances.

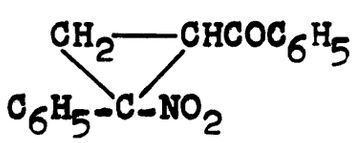
OUTLINE AND DISCUSSION OF WORK.

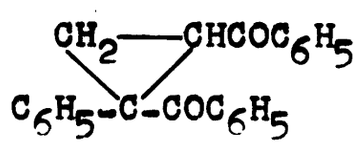
Phenyl vinyl ketone readily combines with substances having an active hydrogen atom and forms addition products that are unsubstituted in the beta position (58). It has recently been discovered (5) that the unsaturated ketone can be conveniently prepared by eliminating hydrogen chloride from the more readily available β-chloropropiophenone by the use of potassium acetate. In this way the addition products with phenylnitromethane (LXXXI) (5) and desoxybenzoin (LXXXII) (6) have been prepared and trans-


LXXXI

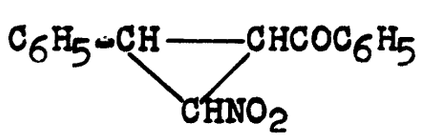

LXXXII

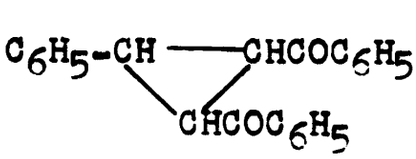
formed into the ketonic cyclopropane derivatives (I) and (III), the latter are unsubstituted in the 3 position.


I


III

Comparison with their structural isomers (II) (4g) and

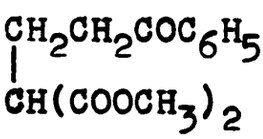

II


IV

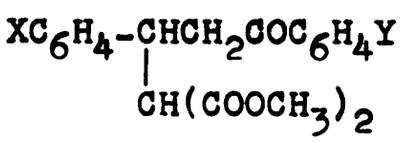
(IV) (4f)substituted in all 3 positions gave valuable

information concerning the influence of the substitutent phenyl group in the 3 position on the mode of addition of certain characteristic ring-splitting reagents.

In continuance of that work, methyl malonate has been added to vinyl phenyl ketone, resulting in the formation of the ketonic ester (V) closely related to the substituted ketonic esters (LXXXIII) (4a,b) (4c). The addition pro-

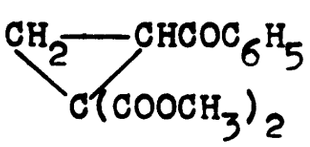


V

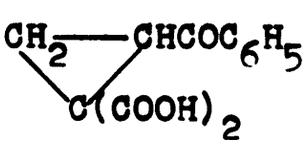


LXXXIII

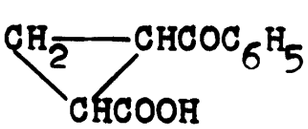
duct was converted into the cyclopropane ester and acids (VII, LXXXIV, LXXXV), derivatives of type (A), and com-



VII

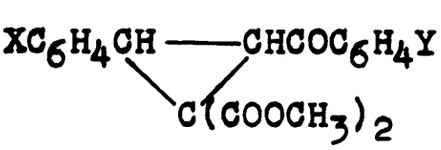


LXXXIV

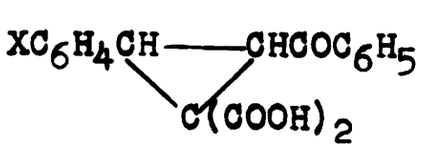


LXXXV

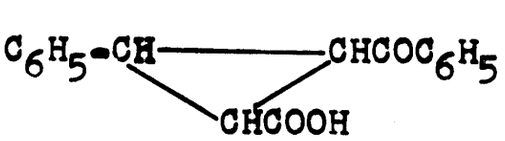
pared with the esters and acids (LXXXVI, LXXXVII, LXXXVIII), cyclopropane derivatives of type (B). The latter acid and



LXXXVI



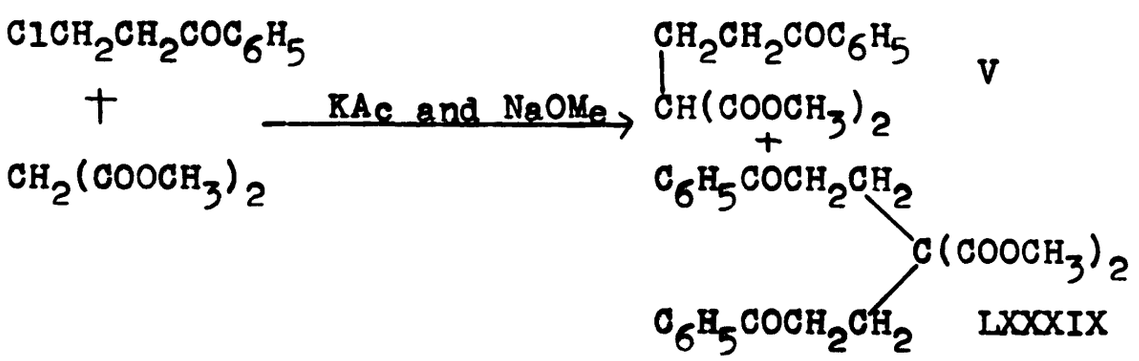
LXXXVII



LXXXVIII

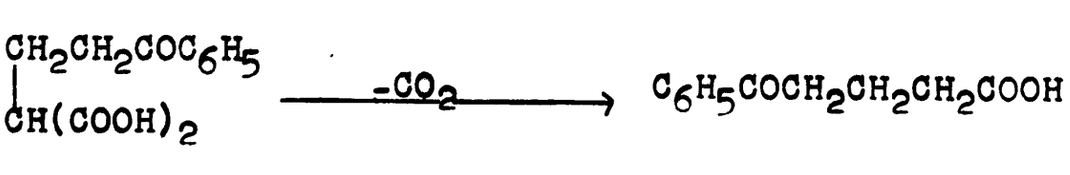
corresponding ester have been prepared and studied by Kohler and Steele (4e).

The addition of methyl malonate to vinyl phenyl ketone (simultaneously obtained by eliminating hydrogen chloride from β-chloropropiophenone with potassium acetate) took place in methyl alcohol in the presence of a small amount of sodium methylate. In addition to methyl γ-benzoyl-ethylmalonate (V), a small amount of trimolecular product (LXXXIX) was also obtained; this became



the major product if too much sodium methylate or only one equivalent of addend were used.

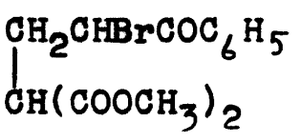
The structure of the addition product (V) was proved by hydrolysis to the corresponding dicarboxylic acid (XC), which on pyrolysis lost carbon dioxide and gave the known



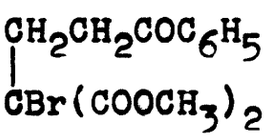
γ-benzoyl-butyric acid (XCI). The immediate formation

of a 2,4-dinitrophenylhydrazone indicated the presence of the carbonyl group.

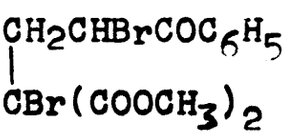
The ketonic di-ester (V), dissolved in chloroform, readily combined with one mole of bromine and gave an oily monobromoester. The constitution of this oil could not be determined but in all probability it was a mixture of the two possible monobromides (XCII) and (XCIII).



XCII



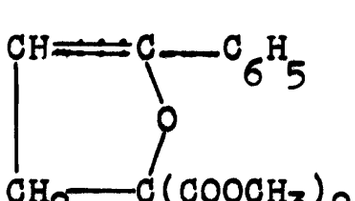
XCIII



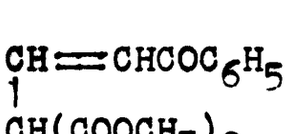
XCIV

A solution of the bromoester in methyl alcohol, standing under the ultra violet lamp, slowly reacted with another mole of bromine and yielded another oil, probably the dibromoester (XCIV). Acid hydrolysis of both esters gave only untractable tarry products.

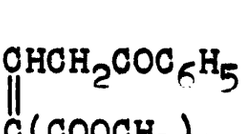
The oily monobromoester when refluxed with an alcoholic potassium acetate solution readily lost hydrogen bromide and gave the cyclic ester (VII). The other products that could have formed by loss of hydrogen bromide are represented by formulas (XCV, XCVI, XCVII).



XCV



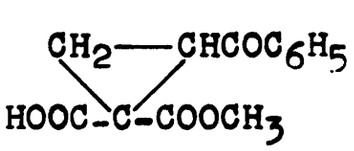
XCVI



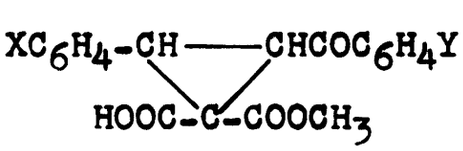
XCVII

The dihydrofurane (XCV), that might have been formed by loss of hydrogen bromide from the enolic modification of the monobromoester (XCIII) , was excluded because the product formed a 2,4-dinitrophenylhydrazone derivative. The ethylenic esters that might have resulted by loss of hydrogen bromide from two adjacent carbon atoms were also excluded because the product neither reduced potassium permanganate nor combined with bromine. The ethylenic isomers, however, may have been present in the cyclopropane residues; they rapidly decolorized permanganate.

The cyclopropane ester (VII), dissolved in moist ether, was very rapidly hydrolyzed by alcoholic sodium methylate to an oily acid that undoubtedly was the ester acid (XCVIII). The cyclopropane esters (LXXXVI) were



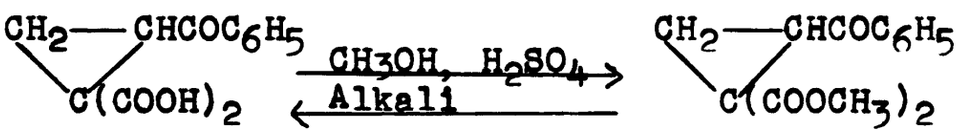
XCVIII



XCIX

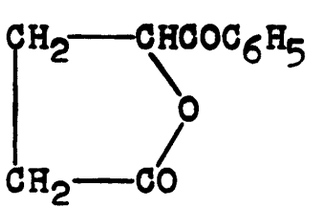
also very sensitive toward moist alkaline reagents and were hydrolyzed by sodium methylate in moist ether to the corresponding , crystalline ester acids.On further hydrolysis with aqueous alkali, the oily ester acid (XCVIII) was converted into the cyclopropane dicarboxylic acid (LXXXIV).

This cyclopropane dibasic acid on esterification with methyl alcohol and a small amount of sulfuric acid regenerated the ester (VII).



LXXXIV VII

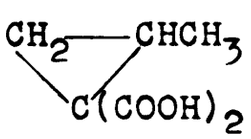
The cyclopropane dicarboxylic acid when heated above its melting point lost carbon dioxide and gave small amounts of the two possible stereoisomeric cyclopropane monocarboxylic acids (LXXXV) and the saturated lactone (C). We were unable to prove whether γ -benzoylbutyro-



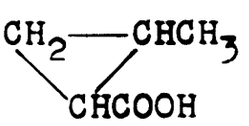
C

lactone resulted by loss of carbon dioxide first and then opening of the ring or whether the ring was first cleaved and followed by loss of carbon dioxide. Whatever the mechanism, it is clear that the cyclopropane ring was opened in the 1,2 position, or between the two carbons bearing substitutents. The structure of the lactone was established by synthesis from γ-benzoyl-butyric acid and will be described in a later section.

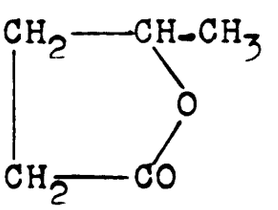
Lactone formation on heating cyclopropane dicarboxylic acids has been observed before. Marburg (33) on heating 2-methylcyclopropane-1,1-dicarboxylic acid (XXXII) obtained a small amount of monocarboxylic acid (XXXV) and



XXXII

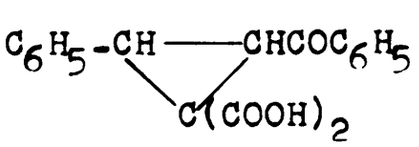


XXXV

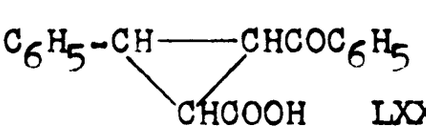


XXXIV

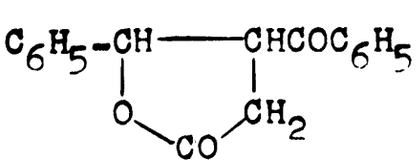
valerolactone (XXXIV); this lactone could only have formed by opening of the ring in the 1,2 position. The cyclopropane acids (LXXXVII) on pyrolysis were opened in the 1,3 and 2,3 position giving a number of varied products. For example, the cyclopropane dicarboxylic acid (CI) (4a) on heating gave a very small amount of cyclopropane monobasic acid (LXXXVIII), two unsaturated acids, the saturated lactone (CII), and two isomeric unsaturated crotolactones (CIII). These products can only be accounted for by 1,3



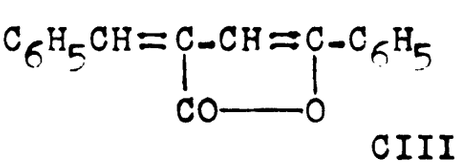
CI



LXXXVIII



CII



CIII

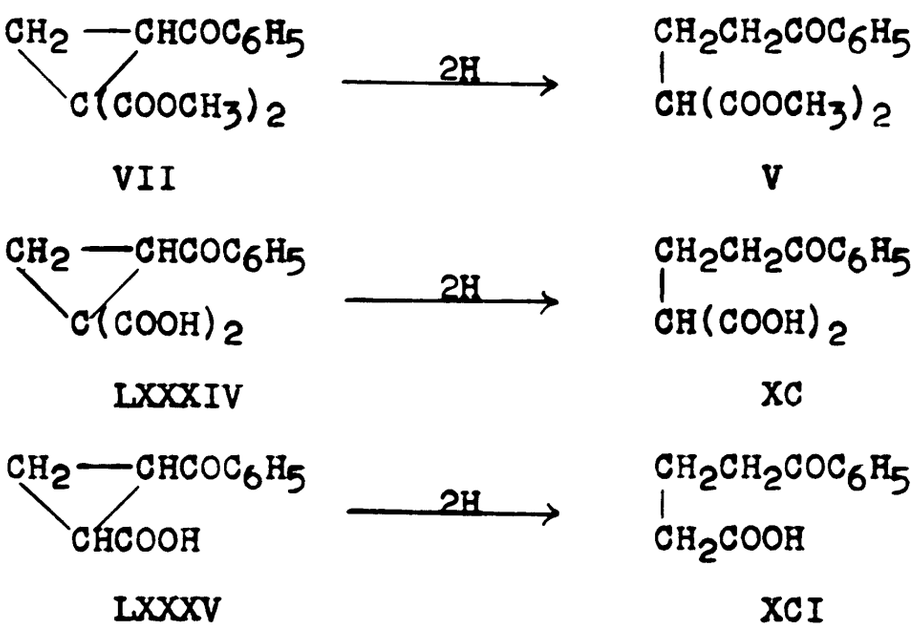
and 2,3 opening of the cyclopropane ring.

The higher melting cyclopropane acid (LXXXV) and the cyclopropane ester (VII) are stable toward heat. The ester was distilled under diminished pressure without decomposition. The acid was recovered unchanged after being heated at 185-190° for 35 minutes and from attempted decarboxylations (59, 60) to benzoylcyclopropane. The lower melting cyclopropane monocarboxylic acid and the the lactone (C) when heated at 185-190° for 35 minutes slowly decomposed and gave untractable oils; a trace of solid was isolated in one pyrolysis of the lower melting isomer that gave only a very slight depression of the melting point with γ-benzoylbutyrolactone (C). It seems very probable that the lactone was formed from the lower melting cyclopropane monobasic acid.

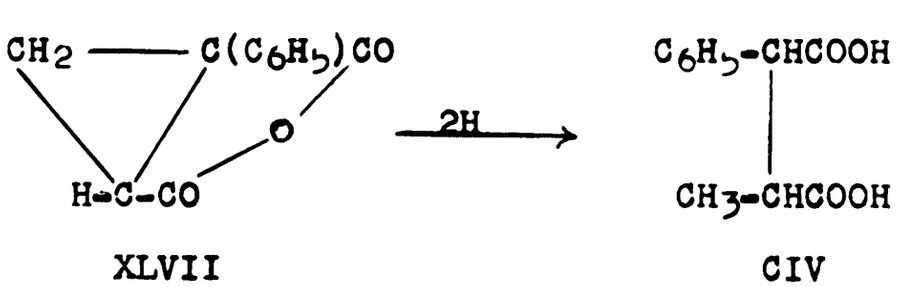
The cyclopropane derivatives are all stable toward permanganate. The cyclopropane ester (VII), the cyclopropane dibasic acid (LXXXIV), and the two cyclopropane monobasic acids (LXXXV) did not decolorize potassium permanganate in acetone solution nor did they combine with bromine in chloroform solution.

All the cyclopropane derivatives were readily reduced by zinc dust and acetic acid to the known open chain substances. The ester gave the keto-diester (V); the dibasic acid gave the corresponding open chain acid (XC); the two monocarboxylic acids gave the known γ-benzoylbutyric acid. The ring was opened by nascent hydrogen

between the two carbon atoms bearing substitutents. The cyclopropane derivatives of type (B) were also opened by reducing reagents in the 1,2 position. The cyclopropane



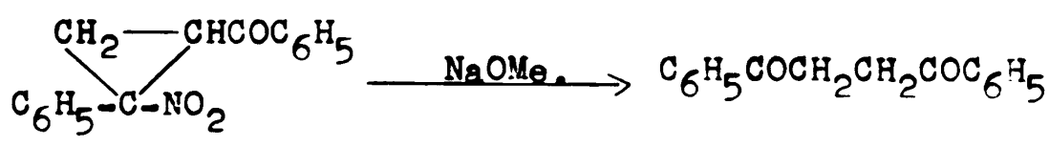
derivative (XLVII) belonging to type (A) on reduction (39) with sodium amalgam gave symmetrical methyl phenyl suc-



cinic acid (CIV). This is the only known case in which a cyclopropane ring substituted on two or three carbon atoms was cleaved in the 2,3 position by reducing agents. It is also the only known cyclopropane derivative belong-

ing to type (A) in which the ring was not opened between the two carbon atoms bearing substitutents. Since the above work was done with minute quantities, it should be re-investigated to see whether the ring really was opened in the 2,3 position .

The cyclopropane ester (V) was indifferent toward anhydrous alkaline reagents. It was not attacked by anhydrous sodium or magnesium methylate in an absolute methyl alcohol solution. These reagents rapidly transformed the cyclopropane esters belonging to type (B) (LXXXVI) to isomeric unsaturated compounds, the ring always opening between the 1 and 3 carbon atoms. Anhydrous alkaline reagents opened the ring in the cyclopropane derivative (I) (5) belonging to type (A) in the 1, 2



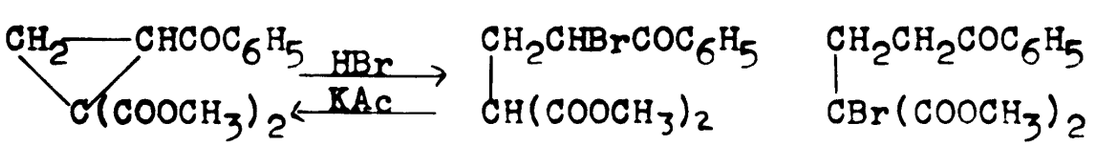
I CV

position or between the two carbon atoms bearing substitutents and formed di-benzoyl ethane (CV)

The cyclopropane ester (VII) and acids (LXXXIV) and (LXXXV) are stable toward sulfuric acid. The ester and the monobasic acids were recovered unchanged after being allowed to stand in contact with concentrated sulfuric acid for 35 minutes at room temperature. The dibasic acid when heat-

ed with concentrated sulfuric acid at 190°C. decomposed but was unaltered when refluxed with a 20 % sulfuric acid solution for one hour.

Under normal conditions hydrogen bromide in glacial acetic acid did not attack the cyclopropane ester (VII) but when heated at 100° in a sealed tube for 8 hours an oil containing bromine was obtained. It was probably a mixture of the two monobromoesters (XCII, XCIII), form-

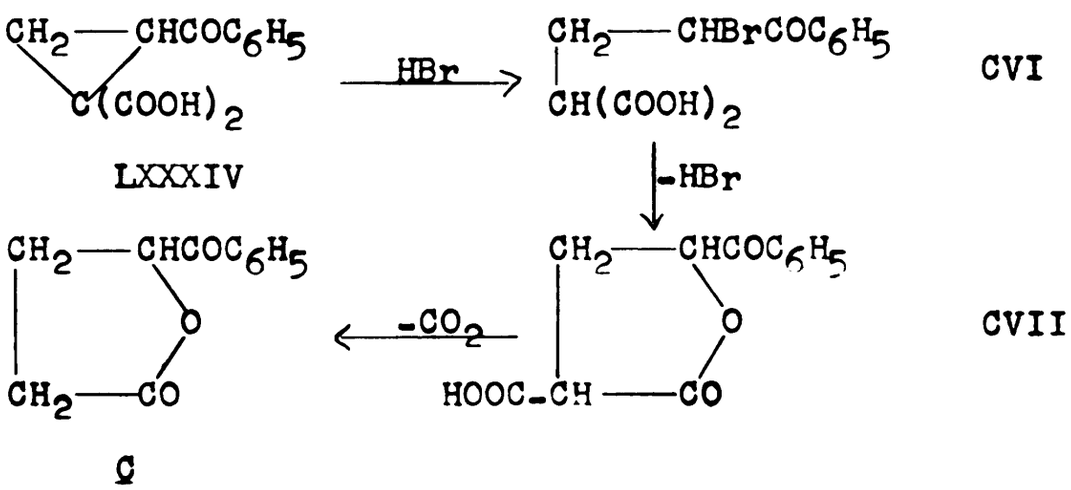


VII XCII XCIII

ed by opening of the ring in the 1,2 position, since on subsequent treatment with alcoholic potassium acetate the cyclopropane was re-formed in essentially the same yield as obtained from the oily bromoester prepared from the addition product (V). A small amount of unsaturated, oily acid was also obtained and because of this ring opening in some other way is not excluded. The cyclopropane esters (LXXXVI) reacted very slowly with hydrogen bromide in acetic acid and gave among other products lactonic esters that could only result by 1,3 opening of the ring.

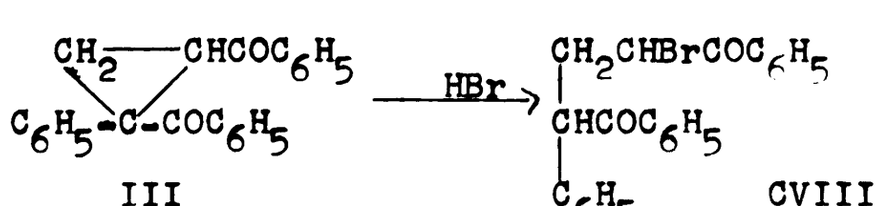
The dibasic acid (LXXXIV) readily reacted with hydrogen bromide in acetic acid at room temperature; the primary

product was an oil that on long standing in aqueous solution or when boiled with water slowly became crystalline. The solid was the carboxy lactone (CVII). It lost



carbon dioxide on gentle heating or when refluxed with alcoholic potassium acetate and formed γ-benzoylbutyrolactone (C). This lactone could only have formed from the primary bromoacid product represented by formula (CVI); again the ring was cleaved between the 1 and 2 carbon atoms.

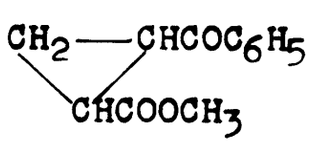
The above results with hydrogen bromide are in agreement with the results obtained in the second paper (6) of this series. The more reactive lower melting cyclopropane derivative (III) readily combined with hydrogen



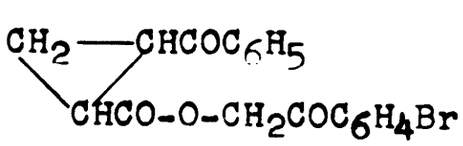
bromide in glacial acetic acid and formed one of the the known monobromides (CVIII). The ring was opened in the 1,2 position.

The cyclopropane acids (LXXXVII), derivatives of type (B), were attacked by hydrogen bromide in acetic acid and transformed into secondary bromine free products that could only have formed by an opening of the ring in the 1,3 and 2,3 position.

The small amount of the cyclopropane monocarboxylic acids (LXXXV) obtained on pyrolysis of the cyclopropane dicarboxylic acid (LXXXIV) made it impossible to study their reactions with the various ring reagents. The higher melting acid, on esterification either by way of the silver salt or by saturating a solution in methyl alcohol with hydrogen chloride, gave an oil that could not be purified. This oil was probably a mixture of the two possible stereoisomeric cyclopropane esters (CIX). The



CIX

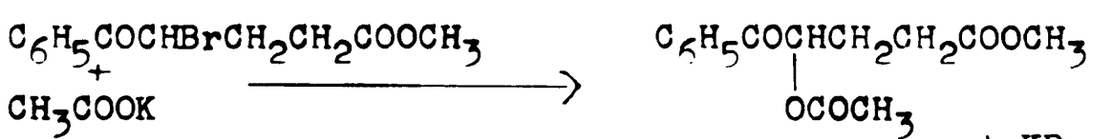


CX

sodium salt of this acid reacted with γ-bromophenyacyl bromide and gave the crystalline γ-bromophenyacyl ester (CX). The lower melting isomer was not obtained in

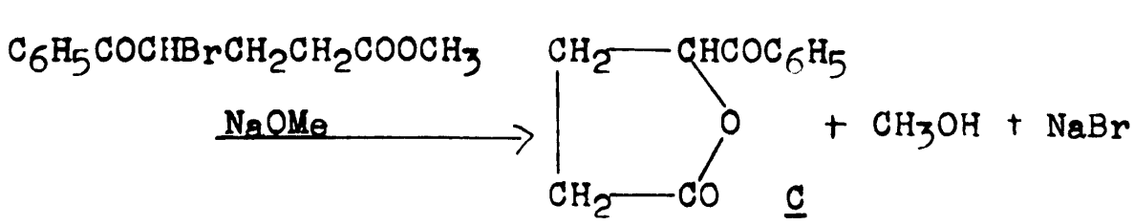
sufficient quantity to convert to the phenyacyl ester.

In an effort to obtain the cyclopropane monocarboxylic acids (LXXXV) and the corresponding esters (CIX) in quantity, we tried 1) to eliminate hydrogen bromide from α-bromo- γ -benzoylbutyric acid, 2) elimination of hydrogen bromide from methyl γ -benzoyl- γ -bromobutyrate (CXI) with alcoholic potassium acetate, 3) elimination of hydrogen bromide from the same methyl ester with alcoholic sodium methylate. All three attempts were unsuccessful. No solids could be isolated in the first procedure. Elimination of hydrogen bromide from the methyl ester (CXI) with alcoholic potassium acetate gave an acetate ester formed in accordance with the equation:



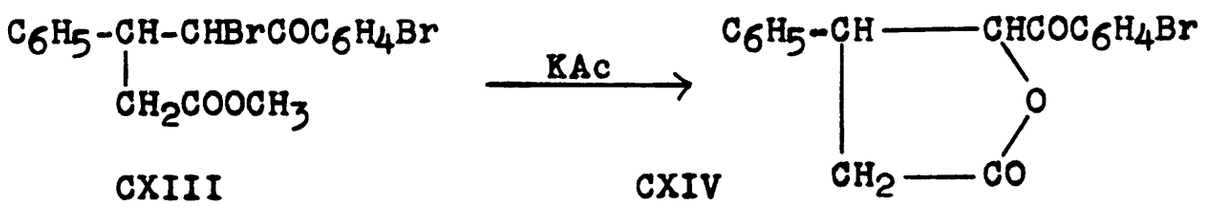
CXI CXII

The elimination of hydrogen bromide with alcoholic sodium methylate gave the lactone (C).



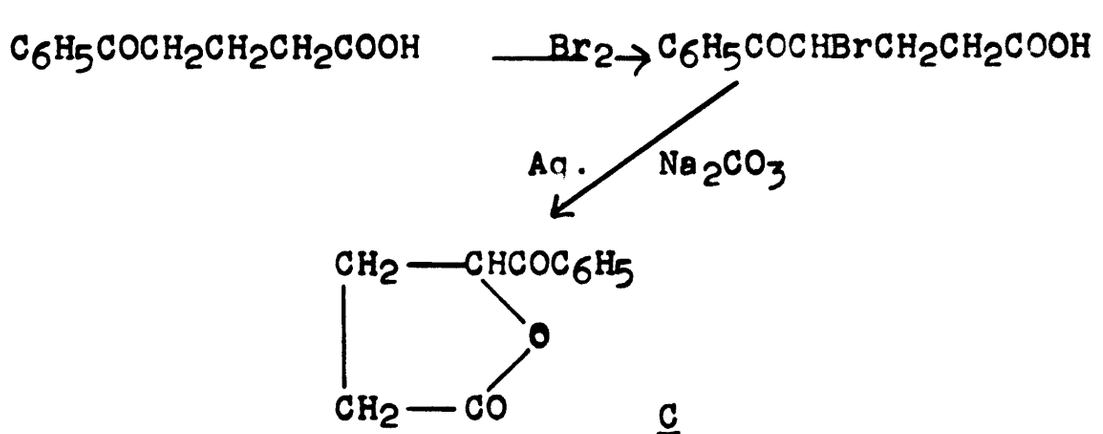
Kohler and Steele (4e) also obtained a butyrolactone

from the substututed methyl ester (CXIII) on treatment with alcoholic potassium acetate.



CXIII CXIV

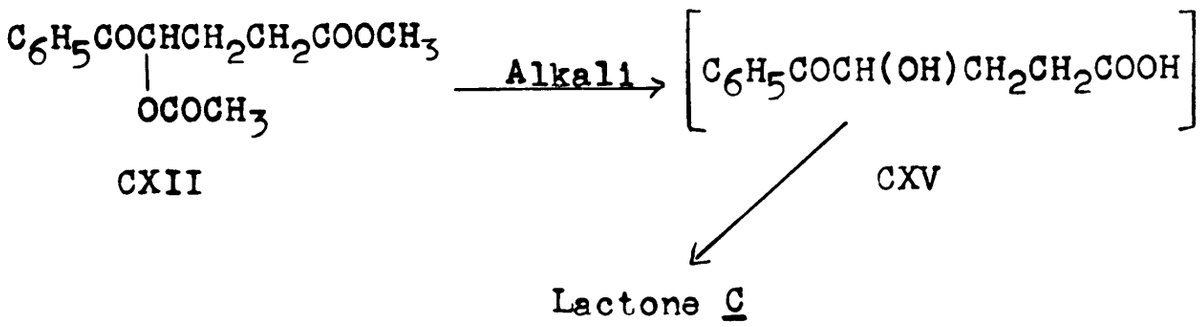
The lactone (C) was synthesized by brominating γ-benzoylbutyric acid in chloroform solution and removing hydrogen bromide from the resulting oily bromoacid with cold aqueous sodium carbonate solution, the usual procedure for preparing γ-lactones.



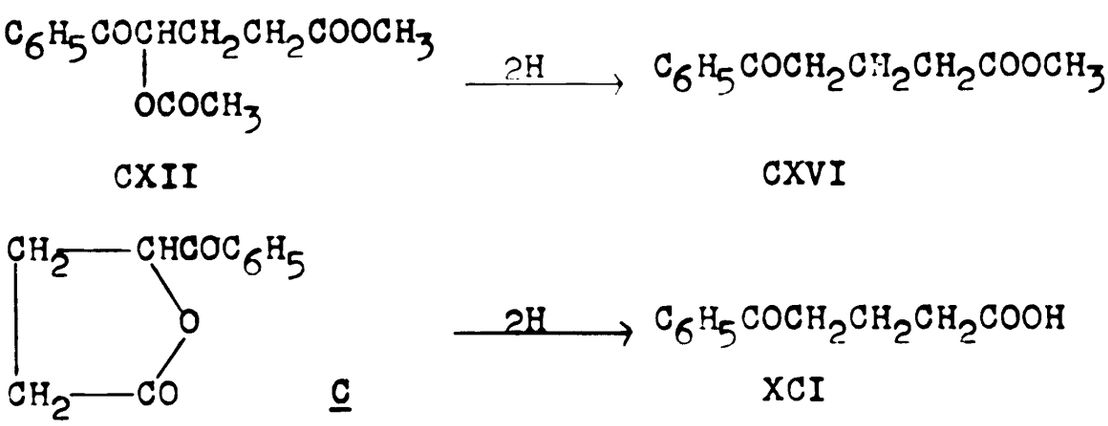
C

The acetate ester (CXII) also formed the lactone (C) when hydrolyzed with alkaline and acidic reagents; best results were obtained by the use of sulfuric acid. When alkaline reagents were used, an oily intermediate product, soluble in sodium carbonate solution, was formed. This oil probably was the hydroxy acid (CXV), since on

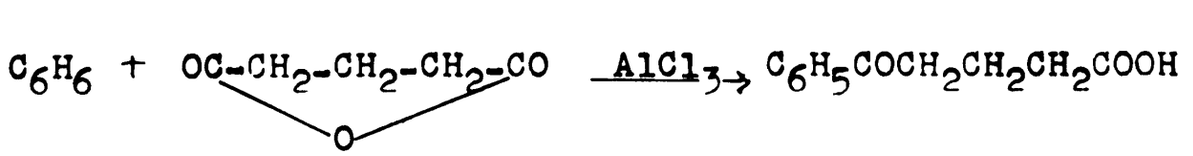
long standing, it formed the stable butyrolactone.



The acetate ester (CXII) and the lactone (C) were reduced by nascent hydrogen to the known methyl γ-benzoylbutyrate (CXVI) and γ-benzoylbutyric acid (XCI).



γ-Benzoylbutyric acid, the starting material in this series of experiments, was prepared by the Friedel-Craft reaction£ from glutaric anhydride and benzene.



£ This procedure was developed by Mr. L. F. Somerville of this laboratory.

The methyl ester (CXVI) was best obtained by saturating a solution of the acid in methyl alcohol with hydrogen chloride. This ester reacted very readily with one mole of bromine and gave the oily monobromoester (CXI).

$$\underset{\text{CXVI}}{C_6H_5COCH_2CH_2CH_2COOCH_3} \xrightarrow{Br_2} \underset{\text{CXI}}{C_6H_5COCHBrCH_2CH_2COOCH_3}$$

THE PREPARATION OF β-CHLOROPROPIOPHENONE.

Collet (61) and later Boeseken (62) reported the preparation of β-chloropropiophenone by the Friedel-Crafts reaction from benzene and β-chloropropionyl chloride.

$$C_6H_6 + ClCH_2CH_2COCl \xrightarrow{AlCl_3} ClCH_2CH_2COC_6H_5$$

Hale and Britton (63) improved their procedure so that when using small quantities of reactants, yields of the order of 80-90 % were obtained. The chloroketone prepared in this way always has a low melting point and is probably contaminated with benzylacetophenone, formed in accordance with the equation:

$$C_6H_6 + ClCH_2CH_2COC_6H_5 \xrightarrow{AlCl_3} C_6H_5CH_2CH_2COC_6H_5$$

A considerable amount of the latter was obtained (6) when large quantities of reacting materials were used. It was found that the secondary reaction was favored when a small amount of the acid chloride was in contact with a relatively large amount of aluminum chloride. By using a large excess of benzene, Allen and Barker (6) were able to prepare 80-90 % yields of low melting β-chloropropiophenone starting with 50 grams of β-chloropropionic acid. However, since this method of preparation

involved a long series of reactions and required the use of rather expensive chemicals, it was thought advisable to devise a more suitable procedure.

Kohler (58) in his study of vinyl phenyl ketone, which he prepared by the elimination of bromine from α,β-dibromopropiophenone with alcoholic potassium iodide,

$$BrCH_2CHBrCOC_6H_5 \xrightarrow{KI} CH_2{=}CHCOC_6H_5$$

obtained the chloroketone by saturating a solution of the unsaturated ketone in alcohol with hydrogen chloride.

Norris and Couch (64) reported the preparation of small quantities of vinyl phenyl ketone by the Friedel-Craft reaction from benzoyl chloride and ethylene. From the earlier study of this ketone (58), it was evident that β-chloropropiophenone should be an intermediate product; this was later found to be the case(65).

The problem, therefore, resolved itself into devising a suitable apparatus for carrying out the reaction, which may be represented by the following equation:

$$CH_2{=}CH_2 + C_6H_5COCl \xrightarrow{AlCl_3} ClCH_2CH_2COC_6H_5$$

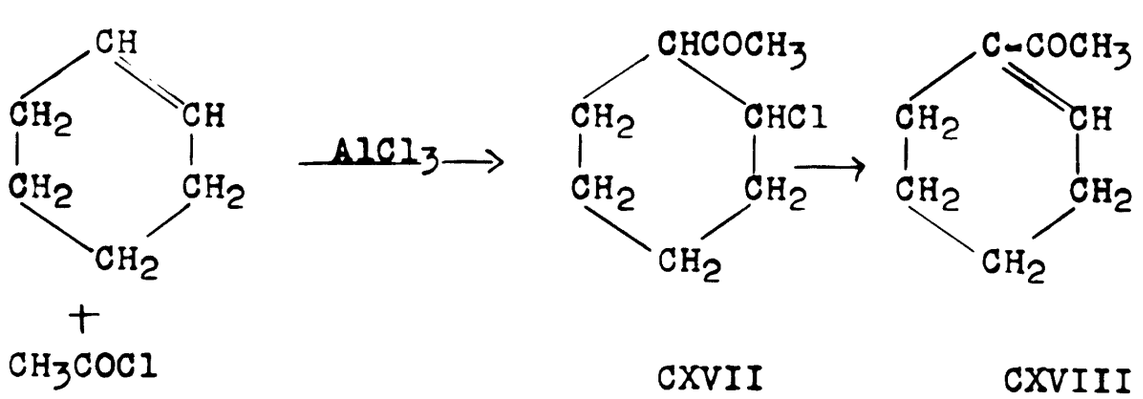
This reaction, however, is more complicated than it would appear in the preceding outline. The benzoyl chloride aluminum chloride complex is insoluble in most organic solvents except ethyl bromide (65). It is necessary to introduce the ethylene in such a way that it becomes well-mixed with the solution and not used in too great excess for economic reasons. The β-chloropropiophenone is easily decomposed by heat, so its isolation from the reaction mixture after the decomposition of the aluminum chloride complex must be carefully accomplished.

Since the absorption of ethylene proceeded very slowly, especially toward the completion of a run, it was hoped that it would be accelerated by operating under (a slight) pressure. When this was done, a large amount of oil was obtained; probably this was polymerized ethylene in view of the recent investigations (66, 67) on the preparation of synthetic lubricating oils from ethylene and aluminum chloride. The details of the construction of the apparatus that finally proved satisfactory and its operation will be described in the experimental part of this thesis. It is sufficient to say that it is now possible to prepare β-chloropropiophenone in yields of the order of 87-92 %; the limiting factor being size of apparatus used.

The Friedel-Crafts reaction has not been extensively

applied to non-benzenoid hydrocarbons. A similar condensation between unsaturated hydrocarbons and acetyl chloride or bromide has been described by Krapivin (68). He studied the reactions between acetyl bromide and propylene and cyclopropane, and between acetyl chloride and iso-butylene, cyclopropane, hexylene, heptylene, and octylene. In all these hydrocarbons, one hydrogen atom was replaced by the acyl radical. The intermediate chloroketones were not isolated.

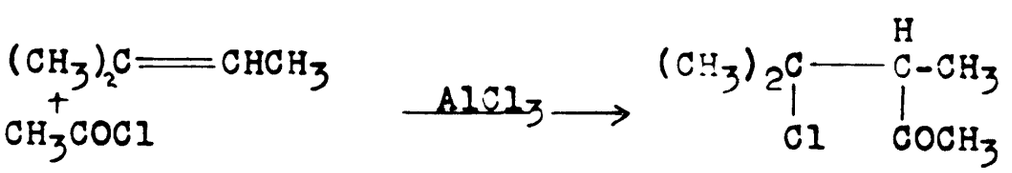
Darzens (69) reported the condensation of acetyl chloride with cyclohexene in the presence of aluminum chloride and obtained the saturated chloroketone (CXVII);



stannic chloride gave a better product. The saturated chloroketone, when treated with diethylaniline, readily lost hydrogen chloride and gave the unsaturated ketone (CXVIII).

Wieland and Bettag (70a) isolated the intermediate

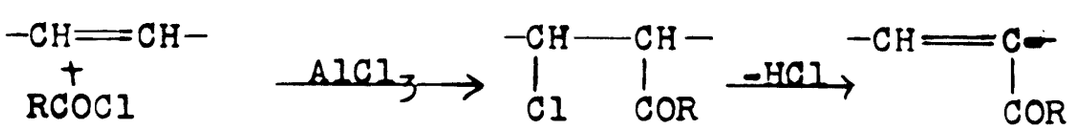
chloroaddition products in the reactions of cyclohexene with acetyl chloride and benzoyl chloride in the presence of aluminum chloride. These chloroketones were readily transformed into the corresponding unsaturated ketones by heating with aluminum chloride at slightly elevated temperatures. The addition of acetyl chloride to trimethyl ethylene took place in the presence of aluminum chloride and gave the fairly unstable β-chloroketone (CXIX). This ketone slowly lost hydrogen chloride at



CXIX

room temperature.

In a later paper continuing his study of the Friedel-Craft reactions, Wieland (70b) summarized the preceding reactions in the following general equations:

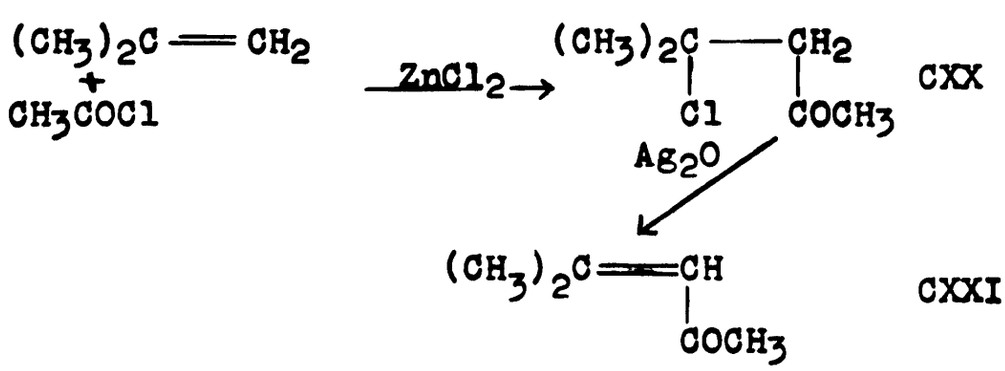


From the results obtained in the study of analogous unsaturated aliphatic and aromatic reactions, Wieland (70b, c) concluded that aromatic ketones prepared by the Friedel-Crafts reaction also resulted through the intermediate chloroaddition product.

Wieland and Hasegawa (70d) condensed cholesterine with acetyl chloride in the presence of aluminum chloride and obtained a saturated chloroester, which was transformed into a substituted chloro-cholesterol derivative by digesting with a 10 % alcoholic potassium hydroxide solution.

The reaction of Darzens (69) was made use of by Ruzicka for the preparation of certain substituted cyclic ketones, starting material for the preparation of various substituted decalins (71). In these investigations, no effort was made to isolate the intermediate chloroaddition products.

Kondakow (72) has described the preparation of β-chloroketones by condensing unsaturated aliphatic hydrocarbons with acetyl chloride in the presence of zinc chloride. From iso-butylene and acetyl chloride, he obtained the β-chloroaddition product (CXX), which was



converted into mesityl oxide (CXXI) with moist silver

oxide. The β-chloroketone prepared from trimethyl ethylene was more unstable. It lost hydrogen chloride on distillation or when boiled with water. Wieland (70a) reported that it lost hydrogen chloride at room temperature.

The condensation (73) of ethylene with acetyl chloride in the presence of aluminum chloride resulted in the formation of β-chloroethyl methyl ketone (CXXII). Ethylene

$$CH_2{=}{=}CH_2 + CH_3COCl \xrightarrow{AlCl_3} ClCH_2CH_2COCH_3$$

CXXII

has also been condensed with chloroacetyl chloride (74)

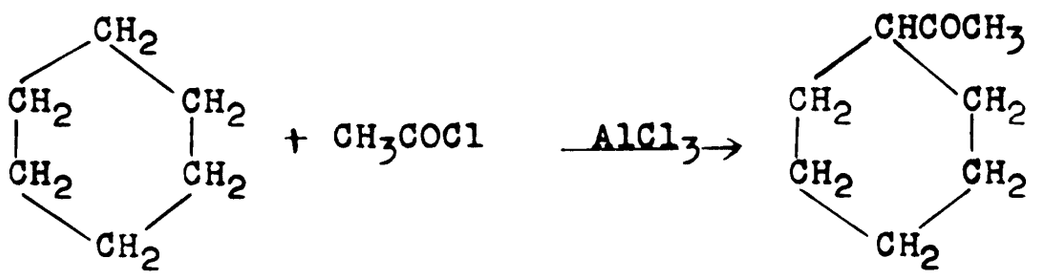
$$CH_2{=}{=}CH_2 + ClCH_2COCl \xrightarrow{AlCl_3} ClCH_2CH_2COCH_2Cl$$

CXXIII

Hopff (75) discovered that saturated hydrocarbons containing a chain of five or more carbon atoms also condensed with acid chlorides in the presence of anhydrous aluminum chloride; the yields, however, were low. Acetyl chloride reacted with normal pentane in the presence of aluminum chloride and gave iso-amyl methyl ketone (CXXIV).

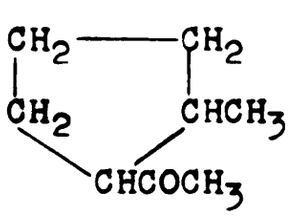
$$\begin{matrix} CH_3CH_2CH_2CH_2CH_3 \\ + \\ CH_3COCl \end{matrix} \xrightarrow{AlCl_3} CH_3CH_2CH_2\underset{\displaystyle COCH_3}{\overset{\displaystyle H}{\overset{|}{\underset{|}{C}}}}-CH_3 \qquad \text{CXXIV}$$

Hopff (75) also succeeded in condensing acetyl chloride with cyclohexane and obtained a ketone which he assumed to be methyl cyclohexyl ketone (CXXV).



CXXV

Nenitzescu (76) condensed acetyl chloride with cyclohexane in the presence of aluminum chloride and obtained among other products 1-methyl-2-acetyl-cyclopentane (CXXVI).



CXXVI

Benzoyl chloride and butyryl chloride reacted similarly.

EXPERIMENTAL.

A . PREPARATION OF β-CHLOROPROPIOPHENONE.

$$C_2H_4 + C_6H_5COCl \xrightarrow{AlCl_3} ClCH_2CH_2COC_6H_5$$

The apparatus is assembled according to Fig I, page 53. A is a 6 liter bottle set at a convenient height above E, a 6 liter flat bottomed flask containing ethylene (Note 1)£. F and G are medium sized drying towers containing anhydrous calcium chloride and small pieces of potassium hydroxide respectively. I is an Emmerling tower full of glass pearls covered with concentrated sulfuric acid. J is a small drying tower containing alternate layers of glass wool and phosphorous pentoxide. K and R are bubble counters; K contains just enough benzoyl chloride to barely seal the inlet tube, R contains water. M is a special stirrer (Note 2) Fig. II, page 54. N is a 1-liter 3-necked flask in which the reaction takes place, and is fitted with a small dropping funnel L and an exit tube connected to O, a protective calcium chloride tube, (Note 3) and P, a small drying tube filled with potassium hydroxide. Q is a trap and S a Dreehsel bottle holding a 3 centimeter layer of bromine covered with water.

In flask N is placed 60 grams (0.45 mole) of pulverized anhydrous aluminum chloride (Note 4) and 100 cc. of

£ The notes follow the description of the procedure.

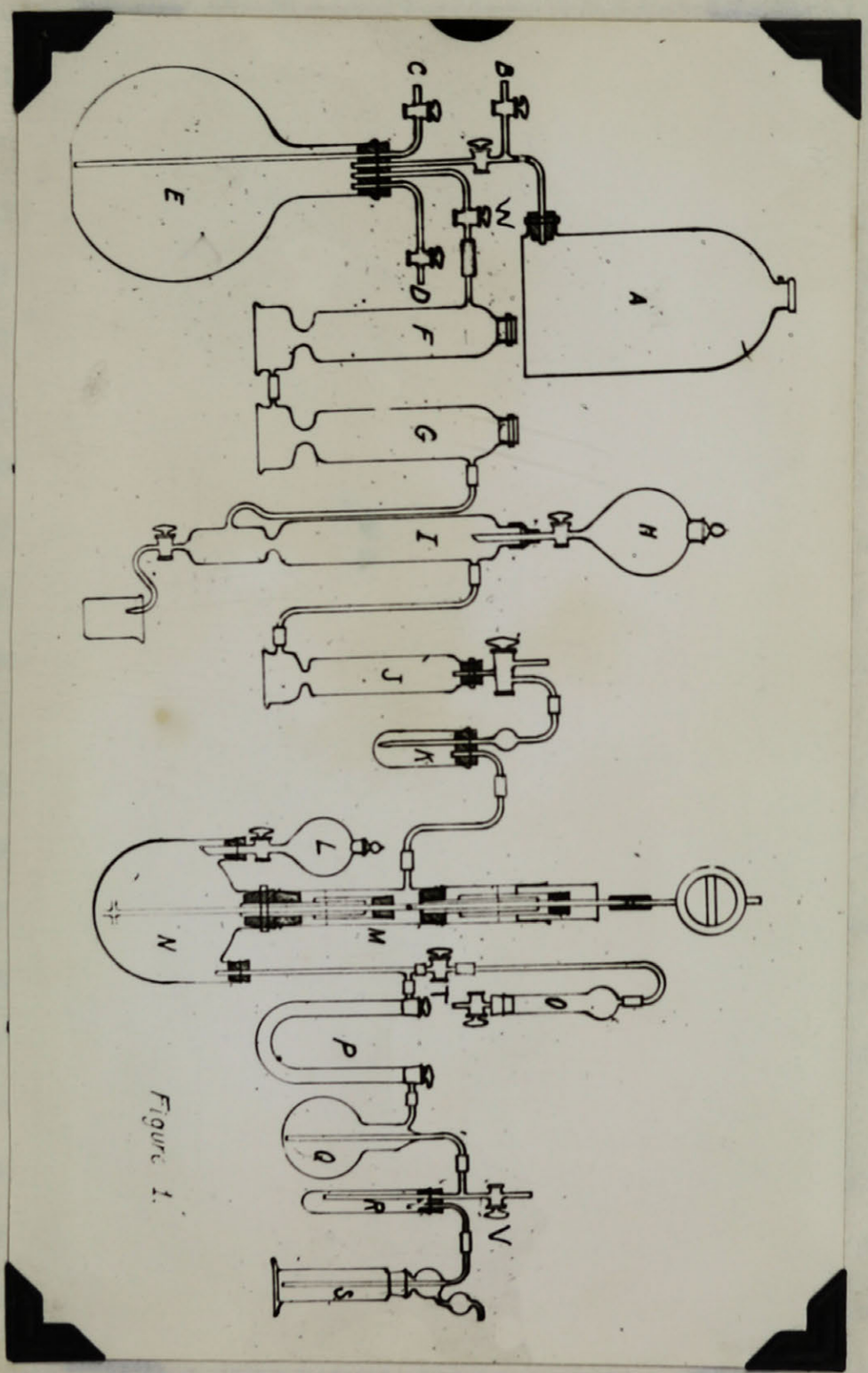
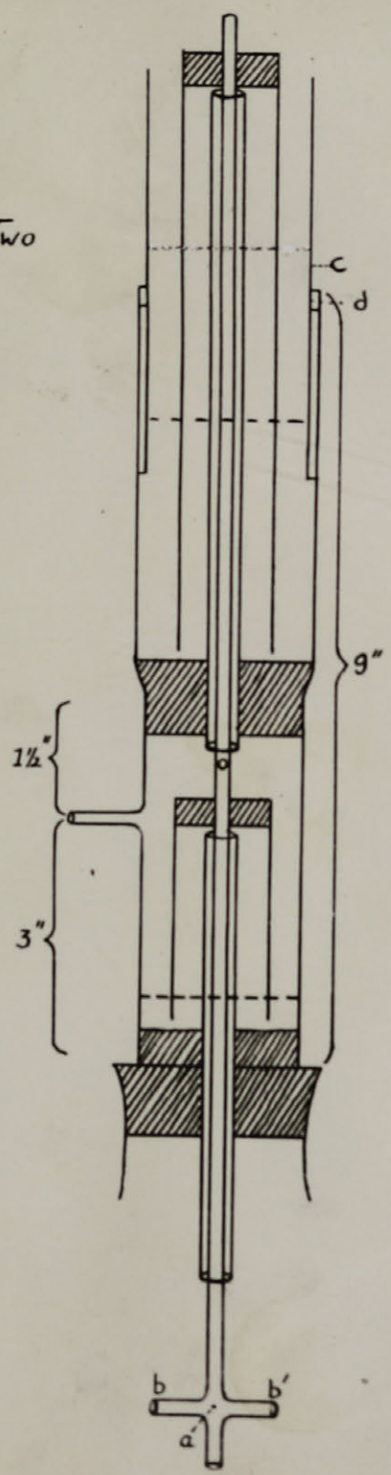


Figure 1.

Figure Two



ethyl bromide (Note 5). The stirrer is started, and 56.3 grams (0.4 mole) of technical benzoyl chloride is slowly dropped in from L during a half hour (Note 6); a soluble double salt results. Ethylene from E is now forced into the reaction flask N by the water pressure in A at such a rate that there is no passing of gas through R; it is absorbed very rapidly at first (5 liters in 3.5 hours). After 7-8 liters have reacted, the rate slackens (40-45 drops of water per minute from A) (Note 7). After 30-35 hours a considerable amount of solid separates and the absorption becomes exceedingly slow. When it has practically stopped (Note 8) the reaction is considered complete, although there is still some unused benzoyl chloride (Notes 9, 10).

The reaction flask is then removed and its contents poured upon a mixture of 400 grams of ice and 50 cc. concentrated hydrochloric acid (Note 11). The flocculent precipitate is filtered through glass wool. The lower layer is separated and washed twice with 100-150 cc. of water. Flask N is rinsed with 250 cc. of benzene, the latter being poured through the glass wool and then used to extract the aqueous upper layer. The combined extracts are dried a half hour with calcium chloride, filtered into a distilling flask and the solvent removed under diminished pressure (Note 12). The residual yellow-brown oil is poured out into an evaporating dish (Hood) and allowed to solidify.

The crude β-chloropropiophenone is purified by recrystallization, as follows: 250 cc. of petroleum ether (Note 13) is heated to boiling in a suitable wide mouth flask under a reflux condenser, the heat removed, and when refluxing has stopped, 25 grams of the crude product added; the solution is boiled several minutes and then filtered through a previously warmed funnel. On cooling in an ice salt mixture, yellow flaky crystals, melting point 52-53° , separate and are filtered; a second crop is secured by distilling a part of the solvent (Note 14). The combined yield is 59-62 grams, or 87-92 % of the theoretical amount. β-Chloropropiophenone thus purified will keep several months in brown glass bottles (Note 15).

NOTES.

1. The flask is calibrated in 250 cc. units in order to indicate approximately how much ethylene has been absorbed. A run requires 12-14 liters. B, C, and D are used in refilling, without disconnecting from the apparatus. The ethylene used in the preparation was obtained by slowly distilling alcohol through a heated tube containing pumice moistened with syrupy orthophosphoric acid.

2. Fig. II is a sketch of the special stirrer of Pyrex glass devised to introduce the ethylene into the solution and assure intimate mixing. A small hole is blown in the

hollow stirrer so that it comes in the open space below the upper stopper. The distance b, b' is such that it will just pass through the neck of the flask; point a is blown out slightly, any constriction is to be avoided. The tube below a is 1 centimeter long. The walls of C are best constructed of two pieces of Pyrex that fit snugly and can be fastened at d by friction tape. This arrangement allows the use of a short stirrer, since the upper portion can be raised after the motor has been attached; it prevents the throwing of mercury and facilitates dismantling. Each compartment contains mercury up to the dotted line. In operation, the arms of the stirrer are nearly immersed in the solution, and it is rotated at a moderate speed.

3. The success of the preparation depends upon absolute dryness.

4. As is usual in Friedel-Crafts reactions, the quality of aluminum chloride is very important. It is the principal source of poor results; the only sure way of determining the suitability of a given lot is to try it out on a quarter size run. Material that is satisfactory for ordinary Friedel-Crafts reactions may give only small amounts of chloroketone. The color of the recrystallized product depends on the quality of aluminum chloride used.

5. The ethyl bromide is stored over aluminum chloride for 15 minutes before use to remove any ether, alcohol, or moisture that it may contain.

6. There is a considerable evolution of halogen acid while adding the benzoyl chloride; the drying tube O is disconnected, stopcock T opened, and the gas absorbed in water. The addition of chloride evolves heat so that it must be added slowly to prevent boiling off ethyl bromide.

7. The slow absorption is somewhat accelerated by occasionally sweeping out the reaction flask. This is done by opening stopcock V for a few seconds.

8. To determine the completion of the run the flask is swept out and stopcock W closed; if there is not an appreciable rise of water in the inlet tube of R in 5 minutes, the reaction is considered complete.

9. If the operation is continued until the odor of benzoyl chloride has disappeared , the yield is considerably decreased, and much oily by-product results.

10. The operation may be interrupted at any time;it need not be continuous. When not in operation it is necessary to lift the stirrer out of the solution and open stopcocks T and V.

11. The ethyl bromide may be distilled off before decomposition and used in subsequent runs, but it is hardly worth while unless molar quantities are being used. In a molar run a 2 liter 3-necked flask is used; the oil remaining after removal of the ethyl bromide is taken up in 700 cc. of benzene and decomposed in the way described (Note 12). A molar run requires 27-30 liters of

ethylene and takes 75-80 hours. The percentage yield is practically the same.

12. It is important to heat the β-chloroketone as little as possible. The solvent is distilled in vacuo, keeping the temperature of the water bath used as a source of heat below 60°. The distillate is used to extract subsequent runs.

13. Commercial "aeroplane gas" is fractionated and the portion boiling from 65-80° taken. The 80-100° fraction may also be used provided the temperature is kept below 85° during the crystallization.

14. A second recrystallization gives an almost white product that melts at 55-56°.

15. The crude solid may be purified by vacuum distillation in 10 gram lots, if the pressure is kept below 2 mm., followed by recrystallization from petroleum ether.

In an attempt to see whether this procedure could be applied to production of the homologues of β-chloropropiophenone, we tried to condense ρ-chlorobenzoyl chloride, toluyl chloride, and anisoyl chloride with ethylene in the presence of anhydrous aluminum chloride. Although the absorption of ethylene proceeded just as rapidly with the first two chlorides as with benzoyl chloride, it was impossible to obtain any solid products from the oily reaction mixtures. The anisoyl chloride-aluminum chloride addition product was very insoluble in ethyl

bromide; the absorption of ethylene in this run was exceedingly slow.

These substituted β-chloropropiophenones have recently been prepared in this laboratory by the modification (6) of Hale and Britton's method (63). Contrary to expectation, they were all low melting and had a tendency to oil out; they required numerous recrystallizations from petroleum ether for purification. With this knowledge of their properties and with the solid obtained by this procedure for inoculation of the oils, γ-chloro and γ-methyl- β-chloropropiophenone homologues probably can be isolated from the oily, reaction mixture. The preparation of the anisoyl derivative by this procedure is doubtful.

B. THE ADDITION REACTION.

Methyl γ-Benzoylethyl Malonate (V).- To a mixture of 15 grams of β-chloropropiophenone, 12 grams of fused potassium acetate, and 75 cc. hot absolute methyl alcohol was added 12 grams of redistilled methyl malonate in 20 cc. of the same solvent and the whole made faintly alkaline to moist litmus by adding a concentrated solution of sodium methylate drop by drop. The reddish mixture was refluxed for 45 minutes. Most of the solvent was then

£ Mr. A. C. Bell has prepared a number of β-chloropropiophenone homologues.

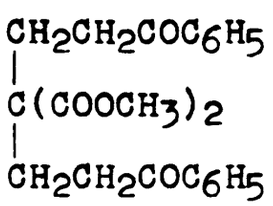
distilled, the residue acidified with acetic acid and the unused malonic ester removed by steam distillation. On inoculating with a previously prepared solid, the oil slowly crystallized. The crude solid was dissolved in the minimum amount of hot, 60 % aqueous methyl alcohol, refluxed a few minutes with animal charcoal, and filtered. On cooling in a freezing mixture, the addition product slowly crystallized. The average yield was 70 %. The condensation was also done in half mole quantities in which slightly lower yields (60 %) were obtained. By using β-chloropropiophenone that had been distilled in vacuo a better quality of ester was produced, but the loss of chloroketone during the distillation was too great to make the process economical. The ethyl ester, formed when ethyl malonate was used, was an oil.

Methyl γ-benzoylethyl malonate crystallizes from dilute methyl alcohol in needles that melt at 42°. It is very soluble in the usual organic solvents except petroleum ether. It boils with some decomposition at 165-175° at 5-6 mm.

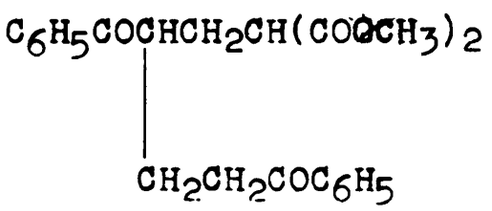
Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.6; H, 6.1. Found: C, 63.3, 63.4; H, 6.1, 6.1.

If no excess of methyl malonate was used, or if too much of sodium methylate was added, a large amount of trimolecular product resulted (LXXXIX). The 1,5 diketone

(CXXVII) that might have resulted was excluded because



LXXXIX



CXXVII

the product did not form a pyryllium salt.

The trimolecular product (LXXXIX) crystallized from methyl alcohol in hexagonal platelets, melting point 132°.

Anal. Calcd. for $C_{23}H_{22}O_6$: C, 69.4; H, 6.1; Mol.Wt., 396. Found: C, 69.5; H, 6.00; Mol.Wt., 364.

Derivatives.-(a) Semicarbazone.- One gram of semicarbozide hydrochloride and 2 grams of potassium acetate in 15 cc. methyl alcohol was refluxed on the steam bath for several minutes. The chloride was filtered off and 0.5 gram of methyl γ-benzoylethyl malonate added. The mixture was boiled for 1 hour and then water added to incipient cloudiness. On cooling, the semicarbazone separated. It crystallized from methyl alcohol in rosettes of flat needles that melted with decomposition at 138°C. The analysis for nitrogen by the Kjeldahl method gave a result that did not agree with the theoretical.

Anal. Calcd. for $C_{15}H_{19}O_5N_3$: N, 13.05. Found: N, 8.95, 8.9, 10.0.

(b) 2,4-Dinitrophenylhydrazone.- This was prepared by the general method (77). One gram of 2,4-dinitrophenylhydrazine was dissolved in 2 cc. concentrated sulfuric acid and 15 cc. methyl alcohol. To this was slowly added 1/200 mole of the ester in 15 cc. methyl alcohol. The hydrazone separated immediately. It was recrystallized from a mixture of chloroform and methyl alcohol, forming clusters of flat yellow plates, melting at 139°C.; it is moderately soluble in alcohol but very soluble in ether and chloroform.

Anal. Calcd. for $C_{20}H_{20}O_8N_4$: N, 12.6. Found: N, 12.4.

C. PROOF OF STRUCTURE.

(a) Hydrolysis to γ -Benzoylethyl Malonic Acid (XC).- Four grams of the ester were refluxed with 50 cc. of 10 % aqueous potassium hydroxide for 45 minutes. The mixture was then poured into a small amount of iced hydrochloric acid, from which 2.5 grams of dibasic acid separated; an additional 0.8 gram was obtained by extracting the water layer with ether and allowing the solvent to evaporate spontaneously. The yield was 3.3 grams or 89 %.

The acid was purified by recrystallization from an ether petroleum ether mixture, from which it separated in flaky rosettes, melting with decomposition at 168-170°C. The dibasic acid is moderately soluble in chloroform and very soluble in the other usual organic solvents ex-

cept petroleum ether.

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.0; H, 5.1. Found: C, 60.8; H, 5.2.

Esterification of the Dibasic Acid (XC).- A mixture of 1 gram of γ -benzoylethyl malonic acid, 35 cc. of absolute methyl alcohol, and 1 cc. concentrated sulfuric acid was refluxed for 3 hours and then poured into ice water. The oil that separated was extracted with ether, washed with dilute sodium carbonate solution, several times with water, and dried over anhydrous sodium sulfate. After the spontaneous evaporation of the solvent, an oil remained that partially solidified after some time. The semi-solid was purified by several recrystallizations from methyl alcohol. A melting point and mixed melting point determination indicated that the dimethyl ester (V) was regenerated . A considerable amount of oily by-product was obtained ; this was not further investigated, but it probably was methyl γ -benzoylbutyrate (CXVI).

(b) Pyrolysis.- One gram of γ-benzoylethyl malonic acid in a pyrex test tube was heated in an oil bath at 175-180° as long as carbon dioxide was evolved. The residual oil was taken up in sodium carbonate solution and the monobasic acid precipitated by addition of hydrochloric acid. It was identified as γ-benzoylbutyric acid

by a mixed melting point with an authentic sample. The keto ester, the dibasic acid, and the monobasic acid neither decolorized bromine in chloroform solution nor reduced potassium permanganate in acetone.

D. BROMINATION.

The keto ester readily reacted with bromine with evolution of hydrogen bromide. The resulting bromoesters were oils. Hydrolysis of the mono and dibromoesters in acid solution gave oily acids.

(a) Monobromination.- In a 500 cc. three-necked flask, fitted with a stirrer, reflux condenser, and dropping funnel was placed a solution of 13.2 grams of the keto ester and 20 cc. of chloroform. A slight excess over the theoretical amount of bromine in 20 cc. of chloroform was admitted, drop by drop, after the reaction had been started by heating in one spot with a small flame. Once started the reaction proceeded at room temperature with a copious evolution of hydrogen bromide. The solution was stirred 5-10 minutes after the addition of bromine had been completed, and then treated with sodium bisulfite solution to remove the excess bromine, washed with water, dried over calcium chloride, and the solvent removed in vacuo. The average weight of the crude, residual oil from a number of runs was 17 grams, or practically

quantitative yields.

(b) Dibromination.- A solution of 17 grams of oil, obtained in the preceding monobromination, 20 cc. dry chloroform, and 8 grams of bromine was allowed to stand under an ultra violet lamp for 12 hours. There was a slow evolution of hydrogen bromide. On working up as above, an oil again resulted.

(c) Acid Hydrolysis.- Hoping to obtain the corresponding bromoacids in solid form, an attempt was made to hydrolyze the oily bromoesters in acid media; the directions of Avery and Jorgensen (78) for acid hydrolysis of nitriles were slightly modified.

Three grams of the oily monobromo ester were dissolved in 30 cc. boiling acetic acid in a flask fitted with a reflux condenser. To this boiling solution was added, drop by drop, 30 cc. of a 1:1 sulfuric acid and water mixture and the whole refluxed for 2 hours. The contents of the flask were then poured into water and filtered. The semi-solid, retained by the filter, was dissolved in an ether and petroleum ether mixture, from which an oil separated. This oily acid was dissolved in dilute ammonium hydroxide solution; the excess ammonia was evaporated on the steam bath and the insoluble impurities removed by filtration. A dark, colloidal precipitate was

obtained by the addition of a slight excess of the calculated amount of silver nitrate.

The oily dibromo ester was treated similarly and again no solid products could be isolated. It was impossible to obtain any solid bromine derivatives and consequently their homogenity could not be established.

E. PREPARATION OF THE CYCLOPROPANE ESTER (VII) AND ACIDS (LXXXIV, LXXXV).

The oily bromoester readily lost hydrogen bromide in alcoholic or acetic acid solutions of potassium acetate.

Methyl 2-Benzoylcyclopropane-1,1-Dicarboxylate (VII).- A mixture of 17 grams of the oil obtained in the bromination of 13.2 grams of the open chain keto ester, 17 grams of fused potassium acetate, and 35 cc. of absolute methyl alcohol was refluxed for an hour and then poured into a large volume of water. An oil separated that very slowly crystallized; this process was greatly hastened by inoculating the oil with a little of the solid previously prepared. The crude material was dissolved in the minimum amount of methyl alcohol, refluxed a few minutes with animal charcoal, and filtered. Water was added to incipient cloudiness; on cooling in a freezing mixture

the cyclopropane slowly crystallized. The yield was 5.7 grams, which is 45 % of the theoretical calculated from the original ketoester. On vacuum distillation of the neutral fraction of 50 grams of cyclopropane residues that had accumulated from several preparations, an additional 17 grams of ester was produced, making the average total yield 78%.

Methyl 2-benzoylcyclopropane-1,1-dicarboxylate crystallizes from 80 % methyl alcohol in hexagonal plates that melt at 74°C. It separates from a 60 % acetic acid solution in needles. The cyclopropane ester is very soluble in the usual organic solvents except petroleum ether. It can be distilled under diminished pressure without decomposition, boiling at 185-190°at 4mm.

Anal. Calcd. for $C_{14}H_{14}O_5$: C, 64.1; H, 5.3. Found: C, 64.4, 64.0; H, 5.5, 5.8.

Cyclopropane Residues.- The residues that had accumulated from several preparations were dissolved in 150 cc. ether; the etheral solution was first extracted with a sodium carbonate solution and then with a potassium hydroxide solution. The neutral solution was then washed with water and dried over anhydrous sodium sulfate. The solvent was then distilled off and the neutral oil transferred to a 125 cc. Claissen flask and distilled in vacuo. The cyclopropane ester distilled at 185-190° at 4 mm.

No solid products could be isolated from the sodium carbonate and potassium hydroxide extracts. From 50 grams of residues were obtained 17 grams of cyclopropane ester, 5 grams of dark oil soluble in sodium carbonate solution, 10 grams of dark, oily lactone or oil soluble in the potassium hydroxide extract, and 18 grams of neutral tarry residue. More of these oily by-products were obtained when acetic acid was the solvent in the preparation. The cyclopropane residues rapidly reduced potassium permanganate.

2,4-Dinitrophenylhydrazone of the Cyclopropane Ester.- This derivative was prepared according to the general method (77) previously described. The hydrazone crystallized from a methyl alcohol-chloroform mixture in light yellow needles that melted at 169°C.

Anal. Calcd. for $C_{20}H_{18}O_8N_4$: N, 12.7. Found: N, 12.5.

Hydrolysis to the Ester Acid.- The cyclopropane ester (VII) was very sensitive to moist sodium methylate. By the procedure of Kohler and Conant (4a), it was easily hydrolyzed to an oily acid; this oil was doubtless the ester acid.

To a solution of 5 grams of ester in 20 cc. ordinary ether was slowly added one equivalent of sodium methylate. After standing for 5-10 minutes at room temperature, the

sodium salt that immediately separated on addition of the base was extracted with water. On acidification of the aqueous extract with hydrochloric acid, an oil separated that was re-extracted with ether. The etheral solution was washed with water and dried over anhydrous sodium sulfate. On spontaneous evaporation of the solvent, an oil remained that undoubtedly was the ester acid. On further treatment with aqueous alkali it gave the dibasic acid. A small amount of the latter was also formed when an excess of sodium methylate was used.

The oily "ester acid" was very soluble in the usual organic solvents except petroleum ether, but crystallized from none.

2-Benzoylcyclopropane-1,1-dicarboxylic Acid.- This acid could be prepared by hydrolyzing the ester with an excess of alcoholic potassium hydroxide, but a better yield and purer product was obtained when the hydrolysis was carried out in 2 steps as outlined by Kohler and Conant (4a). Since the ester acid was an oil, the second step was modified as follows: the sodium salt that separated in the preparation of the ester acid was filtered and mixed with a 50 % excess of a 10 % aqueous potassium hydroxide solution and the whole allowed to stand at room temperature for a day. Upon acidification and concentration of the solvent, the acid crystallized. It was re-

crystallized from an ether and petroleum ether mixture. From 4 grams of the di-ester, 3.5 grams of acid (97 % yield) were obtained.

The dibasic acid is very soluble in ether, benzene, and alcohol: moderately in water; and sparingly in chloroform and petroleum ether. It crystallizes from an ether petroleum ether mixture in rods that melt with decomposition at 170-172°C.

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.5; H, 4.3; mol. wt., 234. Found : C, 61.3; H, 4.3; mol. wt., 246.

Esterification of the Cyclopropane Dibasic Acid.- A mixture of 1 gram of 2-benzoylcyclopropane-1,1-dicarboxylic acid, 20 cc of absolute methyl alcohol, and 0.5 cc. concentrated sulfuric acid was refluxed for 2 hours. The mixture was then poured into water and on working up as described on page 64 the cyclopropane ester was re-obtained.

Pyrolysis of the Cyclopropane Dibasic Acid.- Two grams of the dibasic acid in a 50 cc. Erlenmeyer flask were heated in an oil bath at 175-185° until there was no further evolution of carbon dioxide (15 min.). The dark melt while still hot was then poured into a large volume of ether. The acids were then extracted with sodium carbonate, boiled a few minutes with "Darco", fil-

tered, and acidified with hydrochloric acid. On cooling 0.8 gram of acid melting from 95-133°C. crystallized.

The etheral solution was extracted with potassium hydroxide solution; the extract was boiled a few minutes with "Darco", filtered, and acidified. An oil separated that did not crystallize in the course of weeks. When the water had evaporated spontaneously, the oily organic material was separated from the inorganic salt by dissolving it in dry ether. On evaporation of the solvent, 0.4 gram of crystalline product remained; it was identified by a mixed melting point determination with an authentic sample as γ-benzoylbutyrolactone (C).

The nature of the oily neutral product could not be determined.

2-Benzoylcyclopropane-1-carboxylic Acids.(LXXXV).- The acids obtained in the preceding pyrolysis were separated with some difficulty by dissolving in benzene; the higher melting form was the principal product. It was somewhat less soluble and separated first. After several crystallizations from benzene, it crystallized in rosettes of rods that melted constantly at 145°C.

The stereoisomer was very soluble in all solvents except petroleum ether. It was finally crystallized from a benzene petroleum ether mixture. It crystallized in fine rods that melted at 118-120°C. Very small

quantities of this acid were isolated.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3; mol. wt., 190. Found (145°): C, 69.4; H, 5.3; (118-120) mol. wt. by titration, 193.

p-Bromophenacyl Ester of the (145°) Acid (CX).- Three tenths gram of the cyclopropane monobasic acid was dissolved in 10 cc. water and neutralized with sodium carbonate. Just enough acid was then added to give an acid reaction to litmus. To this solution was added 0.3 gram of *p*-bromophenacyl bromide in 20 cc. methyl alcohol and the whole refluxed for an hour. On adding a few drops of water to incipient cloudiness, and allowing to cool, the ester separated. It crystallized in leaflets that melted at 122°C.

Anal. Calcd. for $C_{19}H_{14}O_4Br$: Br, 20.7. Found Br, 20.8, 20.3.

The very small amount of *p*-bromophenacyl ester obtained from 0.05 gram of the lower melting isomer could not be separated from traces of *p*-bromophenacyl bromide. The mixture melted at 90-100.

Esterification of the (145°) Acid.-A mixture of 0.5 gram of silver salt prepared in the usual manner, 25 cc. anhydrous ether, and an excess of methyl iodide was refluxed for 30 minutes and filtered. On spontaneous eva-

poration of the solvent, an oil remained that could not be crystallized from any of the usual organic solvents. Esterification in methyl alcohol with hydrogen chloride also gave an oil.

Attempted Decarboxylations to Benzoyl Cyclopropane.- Efforts to decarboxylate the cyclopropane monobasic acids by the methods of Shepard (59) (a) and Koelsch (60) (b) were unsuccessful.

(a) A mixture of 2 grams of cyclopropane dibasic acid (no attempt was made to first isolate the monobasic acids), 10 cc. of diethyl-aniline, and 0.4 gram of copper powder in a pyrex test tube was placed into a previously heated metal bath and kept at 180° until the first vigorous evolution of carbon dioxide had subsided. The temperature was then raised to 200° and kept there until there was no longer an apparent evolution of gas (1 hour). The oily, pyrolysis product was then taken up in a large volume of ether and the amine removed with concentrated hydrochloric acid. The etheral solution was extracted with sodium carbonate, washed with water, dried in the usual manner, and the solvent distilled. The oily residue was dissolved in 15 cc. methyl alcohol and treated with 2,4-dinitrophenylhydrazine according to the general method (77). Solids were isolated that melted at 115° and 132°. The 2,4-dinitrophenylhydrazone of benzoyl cy-

clopropane melts at 151° C. The oils were probably cleavage products of the lower melting cyclopropane monobasic acid. A small amount of the higher melting isomer was obtained on acidifying the sodium carbonate extract with mineral acid.

(b) A mixture of 0.25 gram of cyclopropane monobasic acid (145°) and 0.02 gram of copper carbonate in a pyrex test tube was heated in a metal bath at 230-235° until there was no further evolution of carbon dioxide (12 min.). The pyrolysis product was then dissolved in ether, filtered from the inorganic material and the etheral solution extracted with sodium carbonate. The acid was reclaimed practically quantitatively from the sodium carbonate extract.

Two tenth gram of the copper salt of this acid was heated at 230-235° until there was no further evolution of gas; again the cyclopropane monobasic acid was reobtained.

F. REACTIONS OF THE CYCLOPROPANE ESTER (VII) AND ACIDS (LXXXIV, LXXXV).

I. Effect of Heat on the Cyclopropane Derivatives.

It has already been shown in the preceding section that the cyclopropane ester and the higher melting cyclo-

propane monobasic acid are stable to very high temperatures, also that the cyclopropane dibasic acid readily loses carbon dioxide when heated above its melting point and gives two stereoisomeric cyclopropane monobasic acids and a saturated lactone. The lower melting monobasic acid and the lactone are slowly decomposed when heated at 185-195°C.

Two tenth gram of the cyclopropane monobasic acid (145°) was heated at 185-195° for 35 minutes. The dark melt was then taken up in ether and the etheral solution extracted 1) with sodium carbonate and 2) with potassium hydroxide. On acidification of the sodium carbonate extract with hydrochloric acid, the acid was reclaimed practically quantitatively.

One tenth gram of the lower melting cyclopropane monobasic acid was treated similarly. A small amount of semi-solid was obtained from the sodium carbonate extract. The potassium hydroxide extract on acidification with mineral acid deposited an oil that was extracted with ether. On evaporation of the solvent an oily residue remained. In one pyrolysis, a very small amount of solid that melted at 70° was isolated. A mixed melting point with γ-benzoylbutyrolactone, melting at 80°, gave a very slight depression.

γ-Benzoylbutyrolactone (C) under the above conditions was also decomposed and gave an untractable oil.

II. Behaviour of the Cyclopropane Derivatives with Permanganate and Bromine.

Solutions of the cyclic derivatives in acetone do not reduce potassium permanganate; their solutions in chloroform do not decolorize bromine.

III. Reduction of the Cyclopropane Derivatives.

The cyclic substances are readily reduced by zinc and acetic acid to open chain substances, the ring opening between the 1 and 2 carbon atoms. The cyclopropane ester (VII) gave the γ-ketodi-ester (V); the di-acid (LXXXIV) gave the corresponding di-acid (XC); and the two stereoisomeric monobasic acids (LXXXV) gave γ-benzoylbutyric acid. The cyclopropane ester (VII) could not be reduced with zinc dust in methyl alcohol, nor was it reduced catalytically.

The experimental details for all were practically identical; a mixture of 1 gram of the cyclic compound, an excess of zinc dust, and 20 cc. of 80 % acetic acid was refluxed for 2 hours and poured into water. The reduction product of the monobasic acids separated and was identified as γ-benzoylbutyric acid by a mixed melting point with an authentic sample. The oily reduction products of the cyclopropane ester and di-acid were extracted with benzene and recrystallized respectively

from methyl alcohol and petroleum ether. They were identified by mixed melting point determinations with the open chain substances.

IV. Action of Anhydrous Alkaline Reagents.

The cyclopropane ester (VII) was not attacked by dry alkaline reagents. It has already been noted that moist sodium methylate hydrolyzed the ester to the ester acid with unusual rapidity.

(a) Magnesium Methylate Treatment.- A solution of 1 gram of ester, 0.1 gram of magnesium turnings, a pinch of mercuric chloride and 20 cc. absolute methyl alcohol was refluxed for 2 hours. The contents of the flask were then poured into a dilute iced hydrochloric acid solution, from which 0.9 gram of starting material separated.

(b) Sodium Methylate Treatment.- A solution of 4 grams of ester, an excess of sodium methylate, and 20 cc. dry methyl alcohol was refluxed for 2 hours. The mixture assumed a light yellow color during the two hour period. It was then poured into a dilute iced hydrochloric acid solution, from which 2.8 grams or 70 % of the starting material was obtained. The aqueous solution

was concentrated and extracted with ether; the etheral solution was washed with sodium carbonate solution, several times with water, and dried in the usual manner. On spontaneous evaporation of the solvent, a small additional amount of starting material remained.

From the sodium carbonate extract was obtained 0.8 gram of oil that probably was the "ester acid". On treatment with aqueous potassium hydroxide, it gave the cyclopropane dibasic acid.

V. ACTION of Acids on the Cyclopropane Derivatives.

None of the cyclic derivatives were attacked by concentrated sulfuric acid; being quantitatively recovered unchanged when their solution was poured upon ice. Under normal conditions hydrogen bromide readily attacked the cyclopropane dibasic acid and transformed it into an isomeric lactonic acid, which when heated above its melting point lost carbon dioxide and gave γ-benzoylbutyrolactone (C). The latter could only have resulted from a primary bromine product formed by opening of the ring in the 1,2 position. The primary bromoacid was unstable and could not be isolated; it slowly lost hydrogen bromide at room temperature. The cyclopropane ester (VII) was not attacked by hydrogen bromide in acetic acid at room temperature, but when heated in a sealed tube an

oil containing bromine resulted. This oily bromine product was re-converted into the cyclopropane on treatment with alcoholic potassium acetate; thus it must be the monobromoester presumably formed by ring fission in the 1,2 position.

(a) Concentrated Sulfuric Acid Treatment.- Solutions of the ester and the two monobasic cyclopropane acids in sulfuric acid were poured upon ice after being allowed to stand at room temperature for 35 minutes. The ester separated from the aqueous solution ; the acids were obtained by extracting the aqueous layer with ether.

A solution of 1 gram of cyclopropane dibasic acid and 15 cc concentrated sulfuric acid was heated at 190° for 15 minutes and poured upon ice. No solid product could be isolated, the acid being completely decomposed.

A mixture of 2 grams of cyclopropane dibasic acid and 20 cc. of a 20 % sulfuric acid solution was refluxed for 1 hour. On cooling, the starting material separated.

(b) Hydrobromic Acid Treatment.-

α -Carboxy-γ-Benzoylbutyrolactone (CVII).- A solution of 1.5 grams of cyclopropane dibasic acid in 15 cc. glacial acetic acid was saturated with dry hydrogen bromide and allowed to stand at room temperature for 12 hours. On pouring into a small volume of water, an oil separated

that slowly crystallized in the course of weeks. When the aqueous solution was concentrated on the steam bath, the oily primary bromine containing product became solid in a few days. The yield was 60 per cent.

α-Carboxy-γ-benzoylbutyrolactone is very soluble in ether and alcohol, moderately in benzene. It crystallizes from the latter solvent in prisms that melt at 122° with evolution of gas.

Anal. Calcd. for $C_{12}H_{10}O_5$: C, 61.5; H, 4.3; mol. wt., 234. Found: C, 61.1, 61.6; H, 4.3, 4.3; mol. wt., 218.

Five tenth gram of the lactonic acid was heated at 150-155° until there was no further evolution of carbon dioxide. The pyrolysis product crystallized from ether and was identified as γ-benzoylbutyrolactone by a mixed melting point determination. The transformation was quantitative.

Two tenth gram of the carboxy lactone was refluxed for 2 hours with 15 cc. alcoholic potassium acetate solution. The solvent was then allowed to evaporate; the oily semi-solid that remained was separated from the inorganic material by dissolving it in ether. The product that crystallized on the evaporation of the solvent was identified as γ-benzoylbutyrolactone by a melting point and mixed melting point determination.

A solution of 1 gram of the cyclopropane ester (VII)

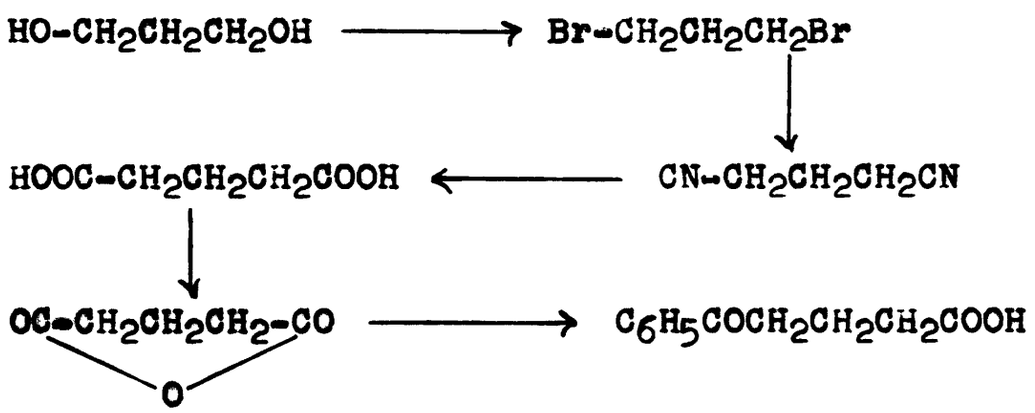
and 15 cc. glacial acetic acid was saturated with dry hydrogen bromide and allowed to stand at room temperature for 10 hours. The mixture was then slowly poured into water from which the starting material was again obtained.

A solution of 2 grams of the ester in 15 cc. glacial acetic acid saturated with hydrogen bromide was heated at 100° in a sealed tube for 8 hours. When cold the contents of the tube were poured into water and the oil that separated extracted with ether. The etheral solution was washed with sodium carbonate, several times with water, and dried in the usual manner. On spontaneous evaporation of the solvent, 1.23 grams of oil remained that was converted into 0.49 gram of cyclopropane ester by boiling with alcoholic potassium acetate. From the sodium carbonate extract was obtained 0.53 gram of oil that rapidly reduced potassium permanganate.

G. γ-BENZOYLBUTYROLACTONE.

The structure of the lactone was established by synthesis from γ-benzoylbutyric acid, which was prepared by the following series of reactions, starting from tri-

methylene glycol. Trimethylene bromide, trimethylene



cyanide, and glutaric acid were prepared by the procedures (79, 80, 81) as outlined in Organic Syntheses.

Glutaric Anhydride.- This was prepared by the method of Sircar (82). A mixture of 50 grams of glutaric acid and 100 grams of acetic anhydride was heated under reflux for 5 hours and then distilled under diminished pressure. The anhydride came over a colorless oil that soon solidified, boiling point 145-150° at 12 mm.; melting point 56-57°C. The yield was 32 grams or 78 % of the theoretical.

γ-Benzoylbutyric Acid (XCI).- In a 1-l, 3-necked flask provided with a stirrer, thermometer, and dropping funnel, and surrounded by a freezing mixture, were placed 102 grams of anhydrous aluminum chloride and 200 cc benzene, previously treated and distilled from aluminum chloride. With vigorous stirring, a solution of 32 grams

of glutaric anhydride in 150 cc. dry benzene was then slowly added (35 min.) from the funnel, keeping the temperature below 10°. Stirring was continued for 30 minutes after all the anhydride had been added. The aluminum chloride complex was then decomposed by slowly adding 150 cc. of water; the excess benzene was steam distilled. The aqueous layer when cold was decanted and the residual suspension boiled for 5 hours with 400 cc. of a 20 % sodium carbonate solution. The insoluble aluminum salt was filtered, washed with hot water, and the filtrate acidified with 200 cc. of a 1:1 hydrochloric acid and water mixture. A small amount of γ-benzoylbutyric acid was obtained from the decanted layer by addition of 20 cc. concentrated hydrochloric acid. The total yield was 70 % of the theoretical. It was not necessary to purify the acid before using in the following experiments; it melted at 125-126°C.

γ-Benzoylbutyrolactone (C$.- A solution of 5 grams of γ-benzoylbutyric acid in 30 cc. chloroform was brominated in the usual manner; the experimental details were identical with the procedure previously described on page 65. The resulting oily bromoacid was dissolved in 50 cc. cold aqueous sodium carbonate solution. In a few minutes an oil separated that slowly crystallized in the course of an hour. The solid was recrystallized

from ether and a mixed melting point showed that it was identical with the products obtained in the pyrolyses of the cyclopropane dibasic acid (LXXXIV) and carboxylactone (CVII).

γ -Benzoylbutyrolactone is very soluble in chloroform and benzene, moderately in methanol and ether. It crystallizes from ether in plates and from water in long prisms, melting point 78°C.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.5; H, 5.3. Found: C, 69.1, 69.4; H, 5.6, 5.5.

2,4-Dinitrophenylhydrazone.- This derivative was prepared by the general procedure (77). It separated from methyl alcohol in light yellow rosettes that melted when pure at 174°C.

Anal. Calcd. for $C_{17}H_{14}O_6N_4$: N, 15.1. Found: N, 14.7.

Reduction.- A solution of 1 gram of γ -benzoylbutyrolactone in 20 cc. 80 % acetic acid was boiled with an excess of zinc dust for 1 hour. On pouring into water, a crystalline substance separated that was identified as γ -benzoylbutyric acid by a melting point and mixed melting point determination. The yield was 90 %.

H. ATTEMPTED SYNTHESES OF THE CYCLOPROPANE ACIDS (LXXXV) AND ESTERS (CIX).

I. Attempted Preparation of ∝-Bromo-γ-benzoylbutyric Acid and Elimination of Hydrogen Bromide.

(a) Bromination.- Two grams of γ-benzoylbutyric acid were dissolved in 10 cc. phosphorous tribromide in a 250 cc. flask fitted through a ground glass joint to a return flow condenser. To this mixture was added, drop by drop, one equivalent (2.8 grams) of dry bromine from a dropping funnel inserted in the top of the condenser and the whole gently warmed on the steam bath for an hour. After cooling, the contents of the flask were decomposed on ice. The oil that separated was taken up in ether; the etheral solution was washed with water and dried in the usual way. On evaporation of the solvent, an oil remained that did not crystallize from any of the usual organic solvents.

(b) The oil obtained in the preceding experiment was dissolved in 35 cc. methyl alcohol and refluxed with 6 grams of potassium acetate for 2 hours. The mixture was then poured into water and the oil that separated was dissolved in ether; the etheral solution was extracted 1) with sodium carbonate, 2) with potassium hydroxide, washed with water, and dried in the usual way. Oily products were obtained from all three portions.

II. Elimination of Hydrogen Bromide from the Methyl Ester.

Methyl γ -Benzoylbutyrate (CXVI).- The methyl ester was obtained in 80 % yield by saturating a solution of 10 grams of γ -benzoylbutyric acid in 100 cc. absolute methyl alcohol with dry hydrogen chloride; the solution was allowed to stand at room temperature for 12 hours. Most of the alcohol was then distilled, the residue poured into iced water, and the ester immediately extracted with 150 cc. ether. The etheral solution was washed with sodium cabonate, several times with water to remove the base, and dried over anhydrous sodium sulfate. The solvent was then distilled and the residue transferred to a Claissen flask and distilled in vacuo. The ester boils at 147-148° at 8 mm; freezing point -2°C.

Anal. Calcd for $C_{12}H_{14}O_3$: C, 70.0; H, 6.8. Found; C, 69.7; H, 6.8.

The 2,4-dinitrophenylhydrazone, prepared in the usual manner (77), crystallized from a 1:1 chloroform methyl alcohol mixture in red leaflets that melted at 149° C.

Anal. Calcd. for $C_{18}H_{18}O_6N_4$: N, 14.5. Found: N, 14.9.

Bromination of the Methyl Ester.- The ester was brominated in carbon tetrachloride by the usual procedure. It was not necessary to start the reaction with heat; the bromination started and proceeded smoothly at room temperature. The bromoester was an oil.

Methyl γ-Acetoxy- γ-Benzoylbutyrate (CXII).- A mixture of 14 grams of the oily bromoester, an equivalent equal weight of fused potassium acetate and 35 cc. of absolute methyl alcohol was refluxed for 15 minutes, during which time a considerable amount of potassium bromide separated. The whole was poured into water; the precipitated oil slowly solidified in the course of 1 to 2 hours. The solid was recrystallized from methyl alcohol. The yield was 8 grams or 70 % of the theoretical.

Methyl γ-acetoxy- γ-benzoylbutyrate is very soluble in benzene, chloroform, and ether; moderately in carbon tetrachloride and methyl alcohol. It crystallizes from the latter solvent in long silky needles that melt at 60°C.

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.6; H, 6.1; CH_3COO, 22.4. Found: C, 63.1, 63.4; H, 5.5, 5.9; CH_3COO, 23.3.

2,4-Dinitrophenylhydrazone.- The hydrazone of the acetate ester was prepared by the method of Allen (83). A mixture of 1 gram of 2,4-dinitrophenylhydrazine, 1 gram of the ester, and 50 cc of methyl alcohol was acidified with 2 to 3 drops of concentrated hydrochloric acid and the whole refluxed for an hour. The unused hydrazine was filtered off and the solution allowed to cool. The hydrazone separated and was recrystallized

from methyl alcohol; it formed pale yellow needles that melted at 158°C.

Anal. Calcd. for $C_{20}H_{20}O_8N_4$: N, 12.6. Found: N, 11.8.

Elimination of HBr with Sodium Methylate.- A solution of 1 gram of oily γ -bromoester, a slight excess of sodium methylate, and 15 cc. of absolute methyl alcohol was refluxed for 1 hour and poured into water. The precipitated oil was immediately extracted with ether; the etheral solution was washed and dried in the usual way. The oil that remained on evaporation of the solvent was dissolved in methyl alcohol from which it again separated as an oil. It slowly solidified in the course of 4 to 5 weeks and was identified by a melting point and mixed melting point determination as γ -benzoylbutyrolactone. These results showed that it was hopeless to attempt to get the cyclopropane esters (CIX) and acids (LXXXV) from methyl γ-benzoyl- γ -bromobutyrate.

III. Reactions of the Acetate Ester (CXII).

Reduction.- A solution of 0.5 gram of methyl γ -acetoxy- γ -benzoylbutyrate in 15 cc. 80 % acetic acid was boiled with an excess of zinc dust for 30 minutes. The solution was then cooled and extracted with ether. The oil

that remained on the evaporation of the solvent was refluxed with 50 cc. of 10 % aqueous potassium hydroxide solution until all had dissolved (1 hour). On pouring into iced hydrochloric acid, a crystalline product separated that was identified by a mixed melting point determination as γ-benzoylbutyric acid. The oily reduction product was methyl γ-benzoylbutyrate.

Hydrolysis with Moist Alkaline Reagents.

(a).- A solution of 5 grams of methyl γ-acetoxy-γ-benzoylbutyrate in 30 cc. methyl alcohol was refluxed for 30 min. with a slight excess of 2:3 aqueous potassium hydroxide. The curdy precipitate that separated on acidification of the mixture with mineral acid was filtered and dissolved in ether. The etheral solution was extracted with sodium carbonate, washed with water, and dried in the usual way. On evaporation of the solvent, a small amount of solid remained that was identified by a mixed melting point determination as γ-benzoylbutyrolactone (C). The sodium carbonate extract was boiled a few minutes with animal charcoal, filtered, and acidified with hydrochloric acid. The precipitated oil was taken up in ether; the etheral solution on evaporation left an oil that did not crystallize from any of the usual solvents. The oil slowly became crystalline in the course of 4 to 5 weeks and it was identified as the saturated lactone (C)

by a mixed melting point determination.

(b).- A solution of 2 grams of the acetate ester, 0.8 gram of aqueous 2:3 potassium hydroxide, and 15 cc. methyl alcohol was allowed to stand at room temperature for 1 and 1/4 hours. On working up as above, a small amount of solid butyrolactone and oil was obtained. The oil slowly changed over into the crystalline γ-benzoylbutyrolactone. The same results were obtained when the solution was allowed to stand at room temperature for 24 hours.

(c).- A solution of 0.5 gram of acetate ester, 15 cc. of methyl alcohol, and an excess of dilute ammonium hydroxide was allowed to stand at room temperature for 5 hours. The ester was recovered unchanged.

(d).- A solution of the acetate ester in alcohol with an excess of dilute ammonium hydroxide was allowed to stand at ordinary temperature for 28 hours. On working up as above, an oil was obtained that eventually solidified. The solid was identified as γ-benzoylbutyrolactone by a mixed melting point determination.

(e).-To a solution of 2 grams of acetate ester in 25 cc. ordinary ether was slowly added a slight excess of sodium methylate and the whole thoroughly shaken (occasionally over a period of 20 minutes). The oily, yellow precipitate was extracted with water and the aqueous solution boiled a few minutes with animal charcoal, filtered, and acidified with hydrochloric acid. On working up

as above, an oil was obtained that slowly solidified ; it was identified as γ-benzoylbutyrolactone by a melting point and mixed melting point determination. A small amount of ester was reclaimed unchanged from the etheral solution.

Hydrolysis with Sulfuric Acid.- (a) A solution of 1 gram of acetate ester in 10 cc. concentrated sulfuric acid was allowed to stand at ordinary temperature for 35 minutes and then poured into iced water . The crystalline product that immediately separated was identified by a mixed melting point determination as the saturated lactone (C).

(b),- Five grams of the acetate ester were refluxed with 50 cc. of a 5 % sulfuric acid solution for 3 hours. On cooling, γ-benzoylbutyrolactone separated quantitatively.

Reaction with Halogen Acid.- A solution of 1 gram of acetate ester in 15 cc. glacial acetic acid was saturated with dry hydrogen bromide and allowed to stand at room temperature for 10 hours. On pouring into water, the ester was recovered unchanged.

Treatment with Anhydrous Sodium Methylate.- To a solution of 2 grams of acetate ester in 30 cc. absolute

methyl alcohol was added a slight excess of sodium methylate and the whole allowed to stand at ordinary temperature for 5 hours. The red, wine-colored mixture, that immediately resulted on addition of the dry base, was then acidified with dry hydrogen chloride. The oily residue that remained on evaporation of the alcohol was separated from the inorganic material by dissolving it in ether. The product separated as an oil from all the usual organic solvents.

SUMMARY.

1. A new apparatus has been devised and a procedure developed for the preparation of β-chloropropiophenone by the Friedel-Crafts reaction from benzoyl chloride and ethylene.

2. Methyl malonate has been added to vinyl phenyl ketone to form a γ-ketonic ester. The structure of the latter was determined by hydrolysis and decarboxylation to the known γ-benzoylbutyric acid.

3. This ester has been converted into several cyclopropane derivatives and their properties compared with certain closely related homologues.

4. In all reactions involving a splitting of the ring, it has been opened only between the 1 and 2 ring carbon atoms. This is in agreement with the previous ketonic cyclopropanes of this type, but different from those having a phenyl group in the 3 position.

5. The structure of γ-benzoylbutyrolactone, obtained in the pyrolysis and hydrogen bromide treatment of 2-benzoylcyclopropane-1,1-dicarboxylic acid, has been established by synthesis.

6. Methyl γ-acetoxy-γ-benzoylbutyrate was obtained in the attempted synthesis of methyl 2-benzoylcyclopropane-1-carboxylate by treating methyl γ-bromo-γ-benzoylbutyrate with alcoholic potassium acetate. Sodium methylate converted the γ-bromoester into γ-benzoylbutyrolactone.

REFERENCES.

1. Freund, J. pr. Chem. (2) 26: 367. 1882.
Monats Hefte 3: 625. 1882.

2. Perkin, J.C.S. 59: 862. 1891.

3. Kötz, J. pr. Chem. (2) 68: 174. 1903.

4 (a). Kohler and Conant, J.A.C.S. 39: 1404. 1917.

(b). Kohler and Conant, J.A.C.S. 39: 1699. 1917.

(c). Kohler, Hill, and Bigelow, J.A.C.S. 39: 2405. 1917.

(d). Kohler and Davis, J.A.C.S. 41: 992. 1919.

(e). Kohler and Steele, J.A.C.S. 41: 1093. 1919.

(f). Kohler and Jones, J.A.C.S. 41: 1249. 1919.

(g). Kohler and Englebrecht, J.A.C.S. 41: 1379. 1919.

(h). Kohler and Williams, J.A.C.S. 41: 1644. 1919.

(i). Kohler and Rao, J.A.C.S. 41: 1679. 1919.

(j). Kohler and Smith, J.A.C.S. 44: 624. 1922.

(k). Kohler and Paul Allen, J.A.C.S. 50: 884. 1928.

5. Allen and Bridgess, J.A.C.S. 51: 2151. 1929.

6. Allen and Barker, J.A.C.S. 54: 736. 1932.

7. Guthzeit and Conrad, Ber. 17: 1186. 1884.

8. Michael, A.C.S. IX: 120. 1887.

9. Perkin, Jr., Ber. 19: 1056. 1886.

10. Guthzeit and Dressel, ANn. 256: 197. 1889.

11. Perkin, Jr. and Gregory, J.C.S. 87: 358. 1905.

12. Guthzeit and Lobeck, J. pr. Chem. (2) 77: 51. 1908.

13. Kötz and Stalmann, J. pr. Chem. (2) 68: 156. 1903.

14. Kötz and Sielisch, J. pr. Chem. (2) 75: 476. 1907.

15. Perkin, Jr. and Bowtell, Proc. J.C.S. 15: 241. 1899.

16. Perkin, Jr. and Tatterstall, J.C.S. 87: 362. 1905.

17. Buchner, Ber. 23: 701. 1890.

18. Buchner and Papendieck, Ann. 273: 234. 1893.

19. Pechmann, Ber. 27: 1891. 1894.

20. Buchner, Ann. 284: 197. 1895.

21. Buchner and Wedemann, Ber. 38: 1599. 1905.

22. Paolini, G (30) II: 501. 1900.

23. Henstock and Woolley, J.C.S. 91: 1955. 1907.

24. Kötz, J. pr. Chem. (2) 75: 439. 1907.

25. Fittig and Roeder, Ann. 227: 13. 1885.

26. Perkin, J.C.S. 47: 801. 1885.

27. von Baeyer, Ber. 29: 2797. 1896.

28. Farmer and Ingold, J.C.S. 119: 2001. 1921.

29. Ingold, J.C.S. 119: 305. 1921.

30. Demjanow and Dojarenko, Bull.Acad.Sciences U.R.S.L. 7: 653. 1929; thru C. I: 930. 1931.

31. Lipp, Ann. 499: 4. 1932.

32. Ingold, J.C.S. 127: 387. 1925.

33. Marburg, Ann. 294: 112. 1897.

34. Fittig and Hjelt, Ann. 216: 56. 1882.

35. Blanc and Haller, Compt. rend. 145: 78. 1907.

36. Kishner, J. Russ. Phys.-Chem. Soc. 45; 957. 1913; through Brooks, "The Chemistry of Non-benzenoid Hydrocarbons". 1922 edition, page 250.

37.(a). Ipatieff, J. Russ. Phys.-Chem. Soc. 34: 351. 1902; (through C.II: 106. 1902.

37 (b). Ipatieff, J. Russ. Phys.-Chem. Soc. 33: 540. 1901. (through C. I: 42. 1902.

38. Buchner and Geronimus, Ber. 36: 3782. 1903.

39. Ruhemann, J.C.S. 81: 1215. 1902.

40. Carl von der Heide, Ber. 37: 2101. 1904.

41. Buchner, Ber. 27: 878. 1894.

42. Perkin, Jr., J.C.S. 47: 850. 1885.

43. Wallach, Ann. 272: 99. 1892.

44. Semmler, Ber. 33: 273. 1900.

45. Wallach, Ann. 388: 50. 1912.

46. Allen and Boyer, Ph. D. Thesis; McGill University. 1933.

47. Tutin, J.C.S. 89: 1104. 1906.

48. Lees, J.C.S. 85: 645. 1904.

49. Semmler, Ber. 40: 5022. 1907.

50. Wallach, Ann. 362: 288. 1908.

51. Simonsen, The Terpenes Vol. I.

52. Semmler, Ber. 36: 4368. 1903.

53. Wallach, Ann. 275: 180. 1893.

54. Buchner and Weigand, Ber. 46: 763. 1913.

55. Conant and Lutz, J.A.C.S. 49: 1090. 1927.

56. Knowles and Cloke, J.A.C.S. 54: 2035. 1932.

57. Auwers and König, Ann. 496: 252. 1932.

58. Kohler, A.C.S. 42: 375. 1909.

59. Shepard, Winslow, and Johnson. J.A.C.S. 52: 2087. 1930.

60. Koelsch, J.A.C.S. 54: 4748. 1932.

61. Collet, Bull. soc. chim. 17: 66. 1897.

62. Boeseken, Bull. soc. chim. 19: 349. 1898.

63. Hale and Britton, J.A.C.S. 41: 841. 1919.

64. Norris and Couch, J.A.C.S. 42: 2329. 1920.

65. Norris, Private Communication.

66. Nash, Stanley, and Bowen, Inst. Petroleum Techn. 16: 830. 1930; through Chem. Abs. 25: 1664. 1931.

67. Sullivan, Jr., Voorhees, Neeley, and Shankland, Ind. Eng. Chem. 23: 604. 1931.

68. Krapivin, S. Bull. soc. imp. nat. Moscow 1-176. 1908; through Chem. Abs. 5: 1281. 1911.

69. Darzens, Compt. rend. 150: 707. 1910.

70 (a). Wieland and Bettag, Ber. 55: 2246. 1922.

(b). Wieland and Dorrer, Ber. 58: 818. 1925.

(c). Wieland and Dorrer, Ber. 63; 404. 1930.

(d). Wieland and Hasegawa, Ber. 64: 2516. 1931.

71. Ruzicka, Koolhass, and Wind, Helv. chim. acta. 14: 1151. 1931.

72. Kondakow, J. Russ. Phys.-Chem. Soc. 26: 12. 1894; through Brooks, "The Chemistry of the Non-benzenoid Hydrocarbons". 1922 edition, p. 172.

73. Schoeller and Zöllner, USP 1,737,203. Chem. Abs. 24: 626. 1930. Swiss patent 132,024 1931.

74. Carroll and Smith, J.A.C.S. 55: 370. 1933.

75. Hopff, Ber. 64: 2739: 1931.

76. Nenitzescu, and Icnescu, Ann. 491: 189. 1931.

77. Brady, J.C.S. 756: 1931.

78. Avery and Jorgensen, J.A.C.S. 52: 3628. 1930.

79. Organic Syntheses, Collective Volume I., p. 28.

80. Organic Syntheses, Collective Volume I., p. 521.

81. Organic Syntheses. Collective Volume I., p. 283. A.

82. Sircar, J.C.S. 902: 1928.

83. Allen, J.A.C.S. 52: 2955. 1930.