THE ACTION OF RING OPENING REAGENTS ON CYCLOPROPANE DICARBOXYLIC ACID-1,2

A Thesis

Submitted to the Faculty of
Graduate Studies and Research
of McGill University in Partial Fulfillment of the Requirements for the Degree Master of Science.

by

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Acknowledgement

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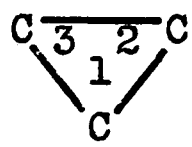
INTRODUCTION

Research on the application of Baeyer's strain theory to alicyclic rings has revealed that the stability of these cyclic structures depends not only upon the number of carbon atoms in the ring, as was originally postulated by Baeyer, but also on the kind, number, arrangement, relative to each other and to the plane of the ring, of the substituents, and on the experimental conditions such as temperature and concentration.

The ring opening reactions of cyclopropane derivatives have been especially instructive in this field, and have been widely studied. The early studies on the unsaturation of the cyclopopane ring, prompted by Baeyer's strain theory, were concerned almost exclusively with the stability of the ring, as measured by its resistance to pyrolysis. It was Kohler who first directed attention to the importance of the type of ring opening in elucidating the nature of this unsaturation. With a highly substituted cyclopropane the relative effects of various substituents may be compared, and even some generalizations developed. Thus there are two factors to be determined in such a study, the ease of opening of the ring, and type of opening.

The resemblance of the unsaturation of the cyclopropane ring to that of the ethylenic double bond is striking. In fact, for the purpose of this discussion, the ethylenic double bond may be considered a two-carbon ring. In many cases the chemistry of the two types of derivatives is completely analogous, the differences being (1) in a sufficiently substituted cyclopropane compound there are three possible modes of addition, corresponding to an opening of the ring on each of the three sides, whereas in an ethylenic compound there is only one; (2) a difference in reactivity, the ethylenic compound being in general more reactive than the cyclopropane compound.

The nomneclature used throughout this thesis makes use of the new system of numbering the carbon atoms of the cyclopropane ring:



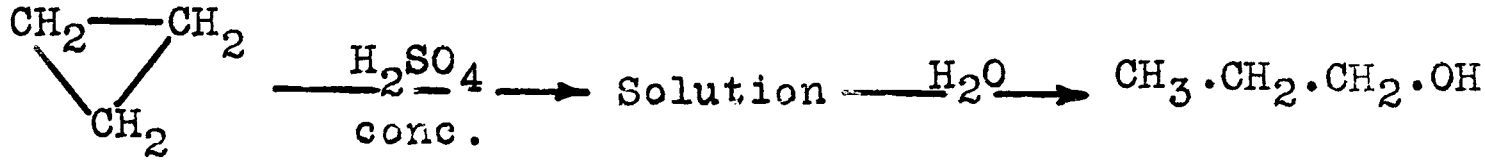
The following conventions are also observed: that carboxyl groups are placed on carbon atom number 1, acyl groups on number 2, and others on number 3.

Factors Affecting the Ring Opening of Cyclopropane Derivatives

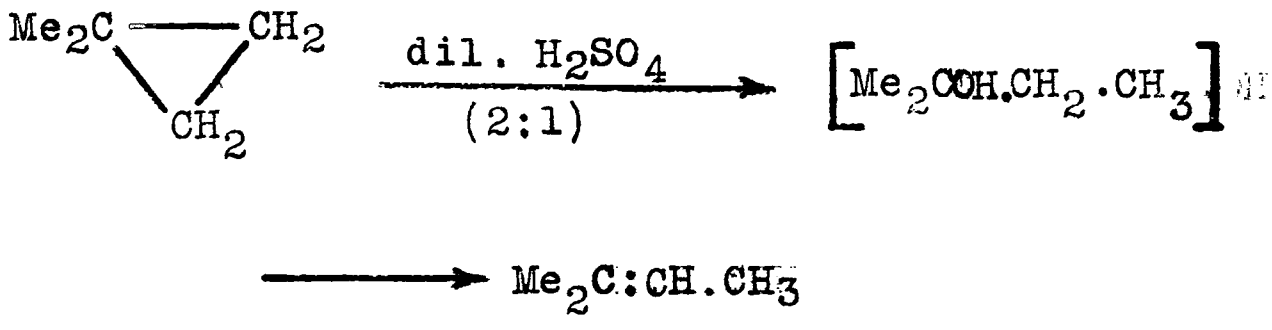
(1) Kind of Substituents

In general, negative substituents, e.g. -Ar, -X, -CO-, -CO.O.R, $-CO_2H$, -CN, and unsaturated substituents, stabilize the ring, whereas positive substituents, e.g. -R, render it more reactive.

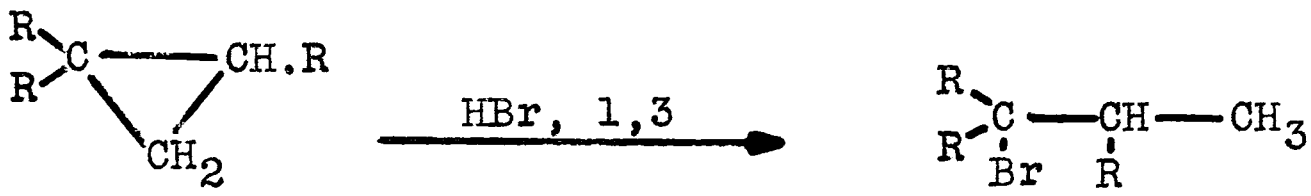
Alkyl substituted cyclopropanes usually undergo ring opening more readily than cyclopropane itself. An example is the reaction with sulfuric acid. Cyclopropane dissolves in concentrated sulfuric acid (1), and the solution on dilution contains propyl alcohol:



Whereas 3,3-dimethyl cyclopropane will react with dilute (2 volumes acid to 1 volume water) sulfuric acid at 0° C; (2) the final product is an olefin:

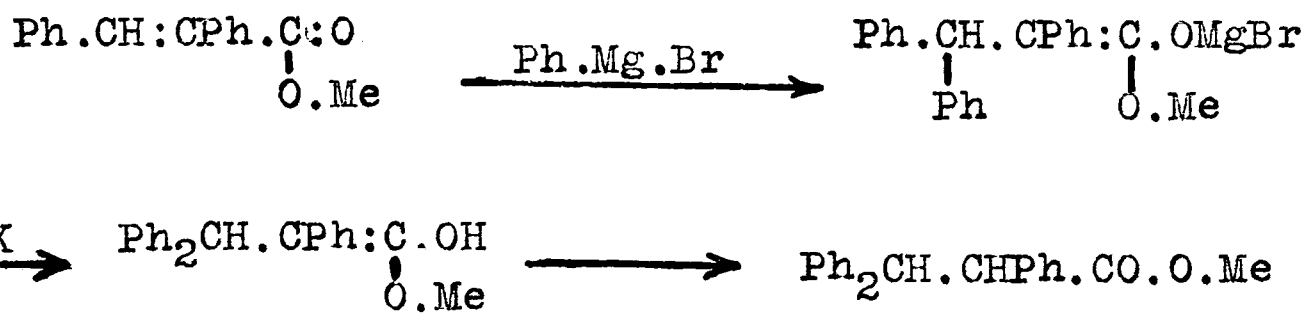


Unsymetrical addends add according to Markownikoff's rule: the negative fragment goes to the carbon atom carrying the largest number of alkyl groups or the smallest number of hydrogen atoms.

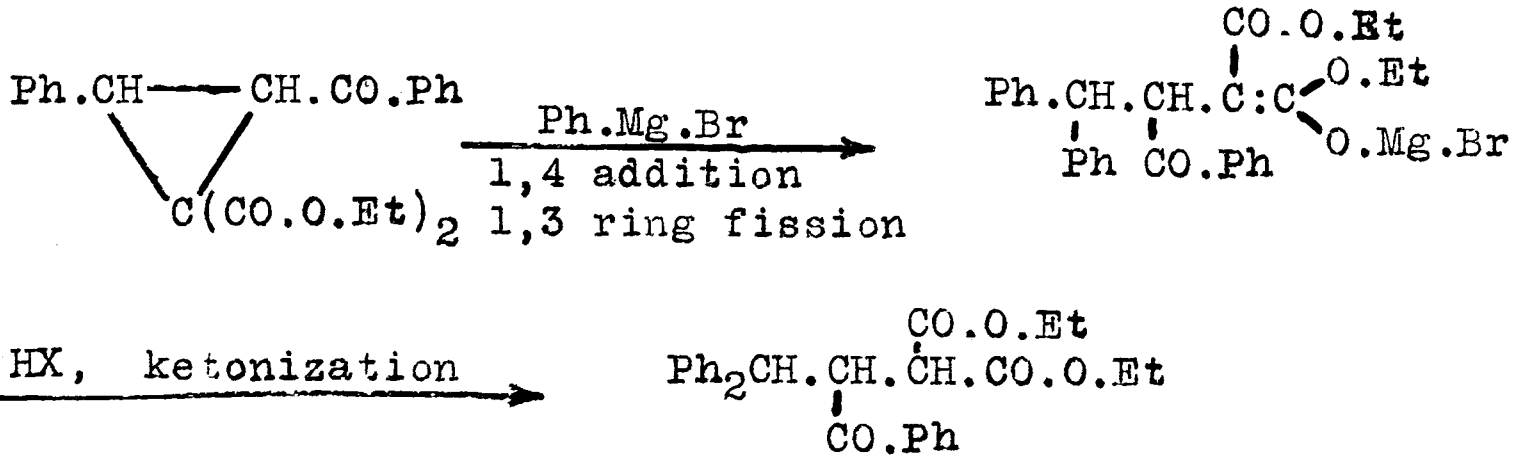


Unsaturated substituents tend to conjugate with the unsaturation of the cyclopropane ring, in a manner completely analogous to the conjugation of the alpha-beta unsaturated carbonyl compounds. Following are a few "hand-picked" examples illustrating some reactions of alpha-beta unsaturated carbonyl compounds and the analogous reactions of the corresponding cyclopropane compounds:

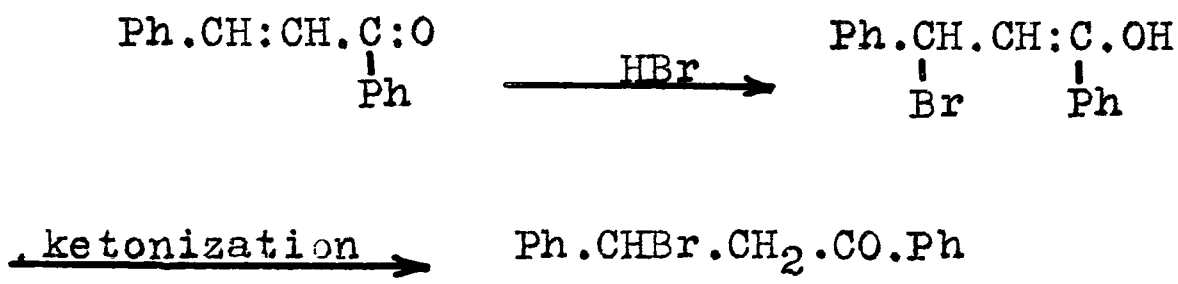
(a) The Grignard reagent will react with alpha-beta unsaturated carbonyl compounds. With the more reactive carbonyl groups the predominating reaction is 1,2 addition to the carbonyl group to give tertiary alcohols (3); however, with certain compounds, 1,4 addition can be shown to occur:

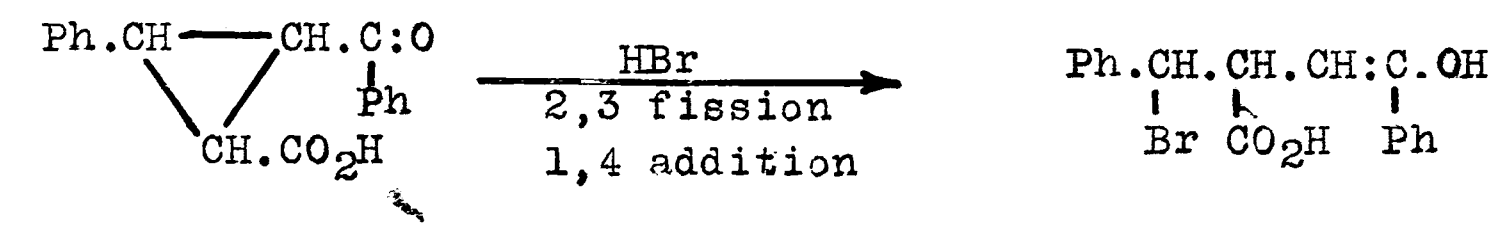


One case is known where a cyclopropane derivative reacts 1,4 with a Grignard reagent:



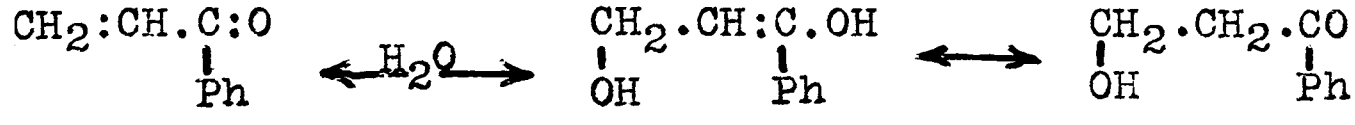
(b) Hydrogen bromide, and all unsymmetrical addends of the H-A type almost always add 1,4, the hydrogen going to the carbonyl oxygen, and the A group going to the beta carbon.





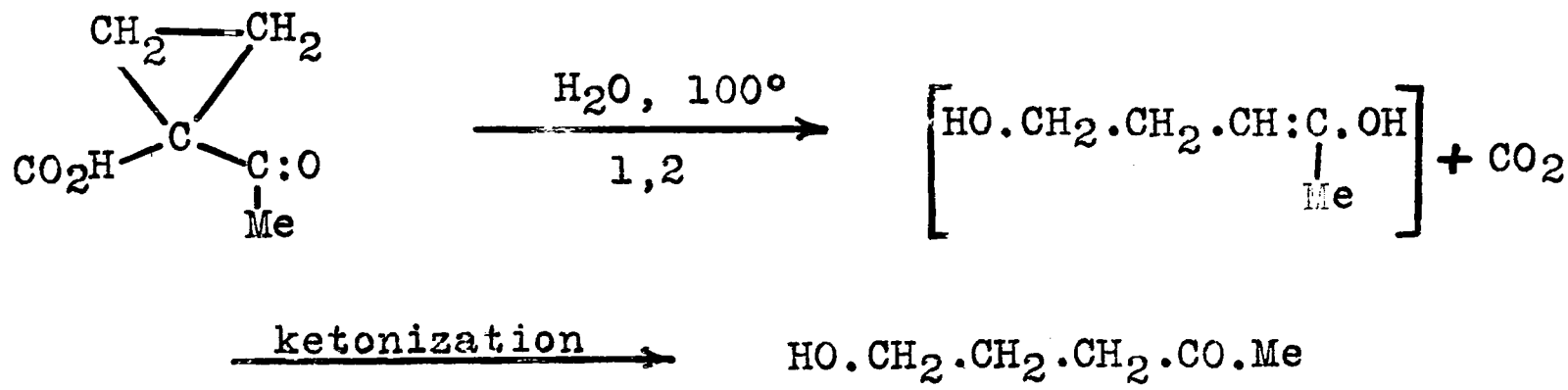
With the cyclopropane addition product, the enol often loses hydrogen bromide to form a lactone, as do most compounds with a bromine atom gamma to a carbon carrying a hydroxyl with an active hydrogen.

(c) Addition of water:



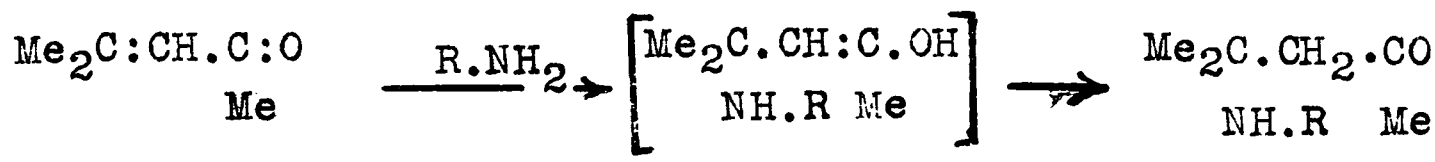
Here an equilibrium exists, but it is displaced far to the left, since the hydroxyl is adjacent to an "alpha hydrogen" activated by the carbonyl group, and water is easily lost.

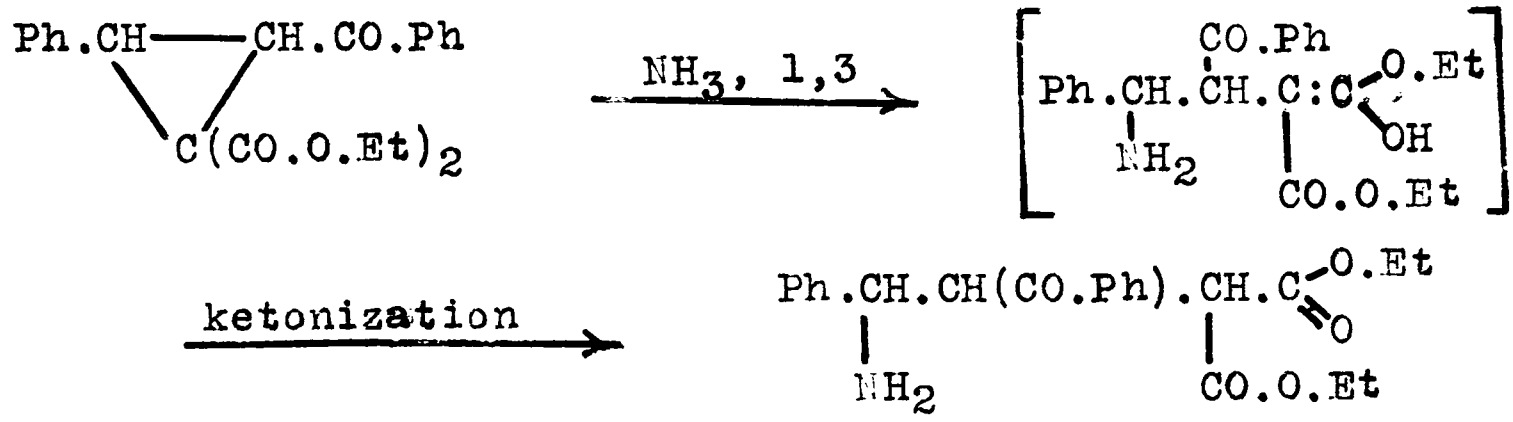
There is one very reactive cyclopropane derivative that adds water 1,4 at 100°:



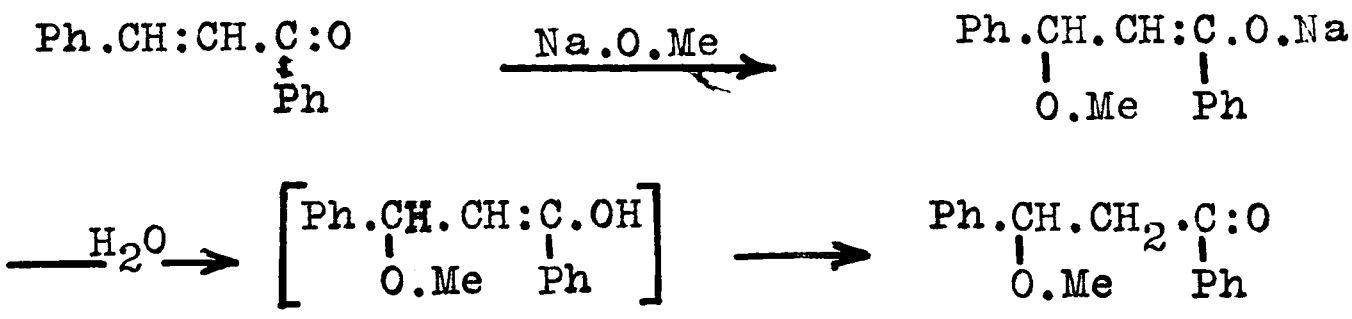
Here, the hydroxyl group is separeated from the "alpha hydrogen" by a methylene group, so interaction is not so easy,, and the reaction goes to completion.

(d) Ammonia and Amines--

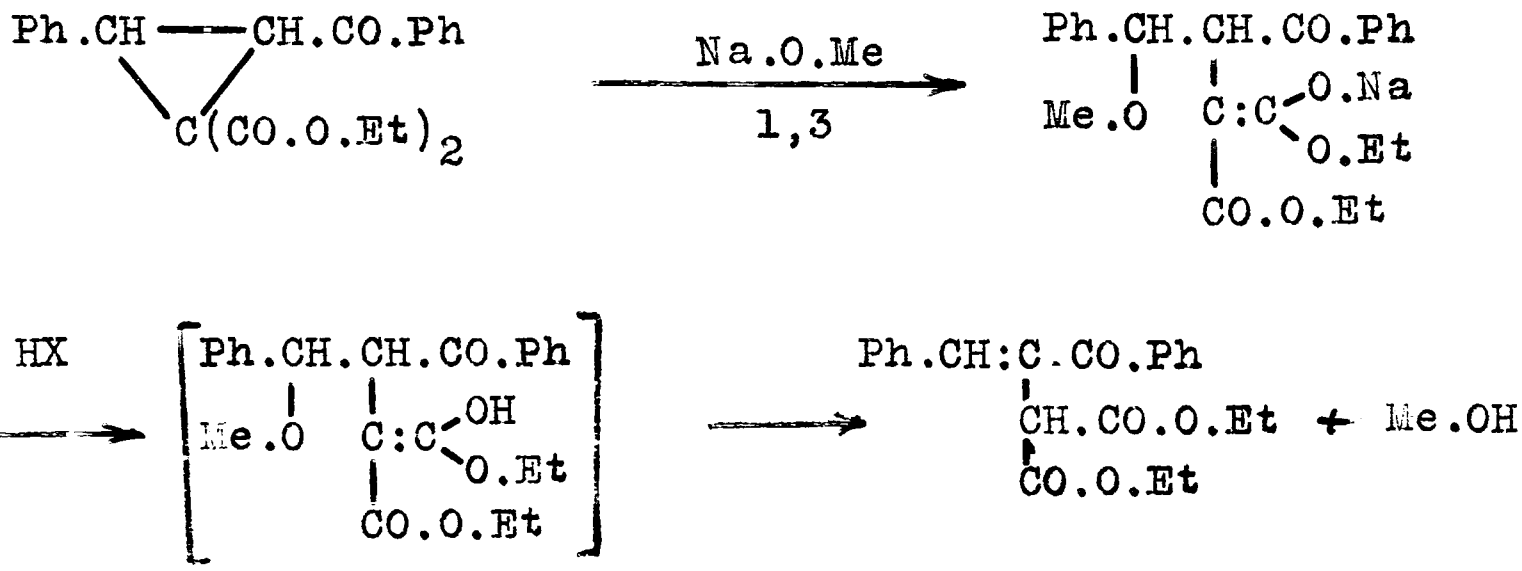




(e) Sodium methylate gives a reversible reaction similar to that with water:

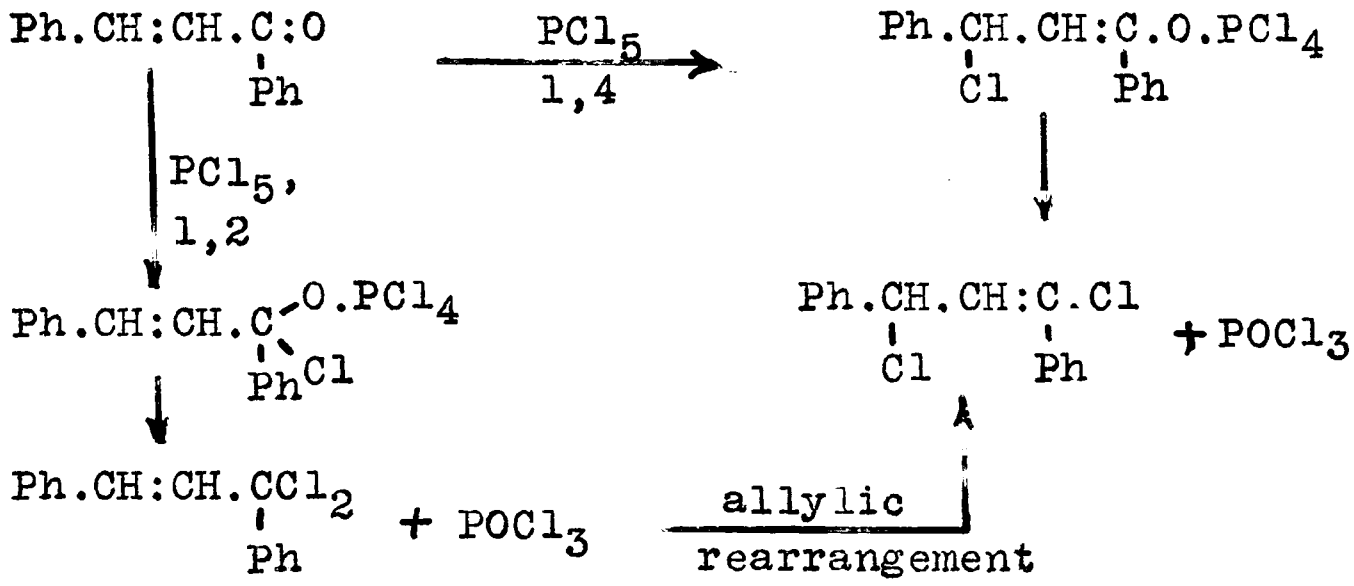


Here the methoxyl group is adjacent to an activatedhydrogen, and methyl alcohol is easily lost, so the equilibrium lies far to the left.

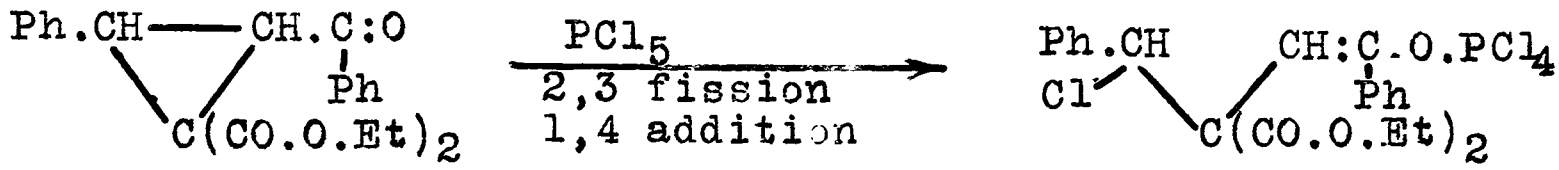


Here again the methoxyl group is adjacent to an activated hydrogen and methyl alcohol is lost; but it is not the same hydrogen that enolized and was replaced by the sodium, so the reaction goes to completion, and the product is a different compound than the starting material.

(f) Phosphorus pentachloride could react in either of two ways with an alph-beta unsaturated carbonyl compound; both are likely, and both would give the observed product:

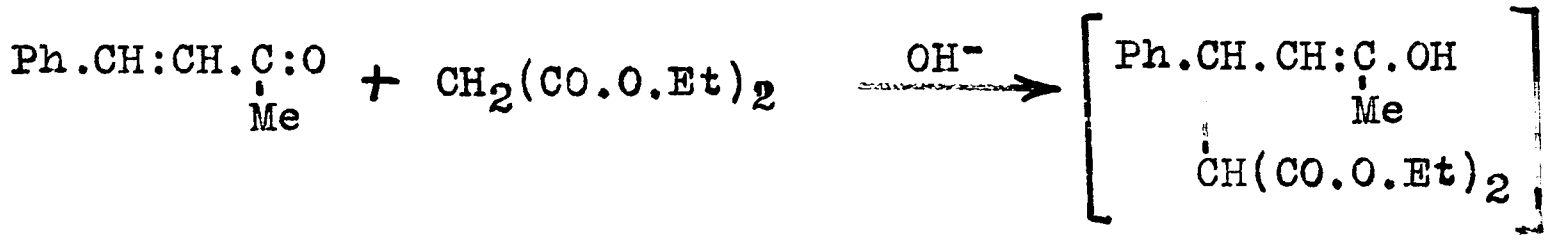


With the cyclopropane compound, the possibility of a 1,3 shift seems rather remote, since the ring is more saturated than the double bond. This indicates that the 1,4 addition mechanism is followed, and may be an indication of the course of the reaction with the ethylenic compound.

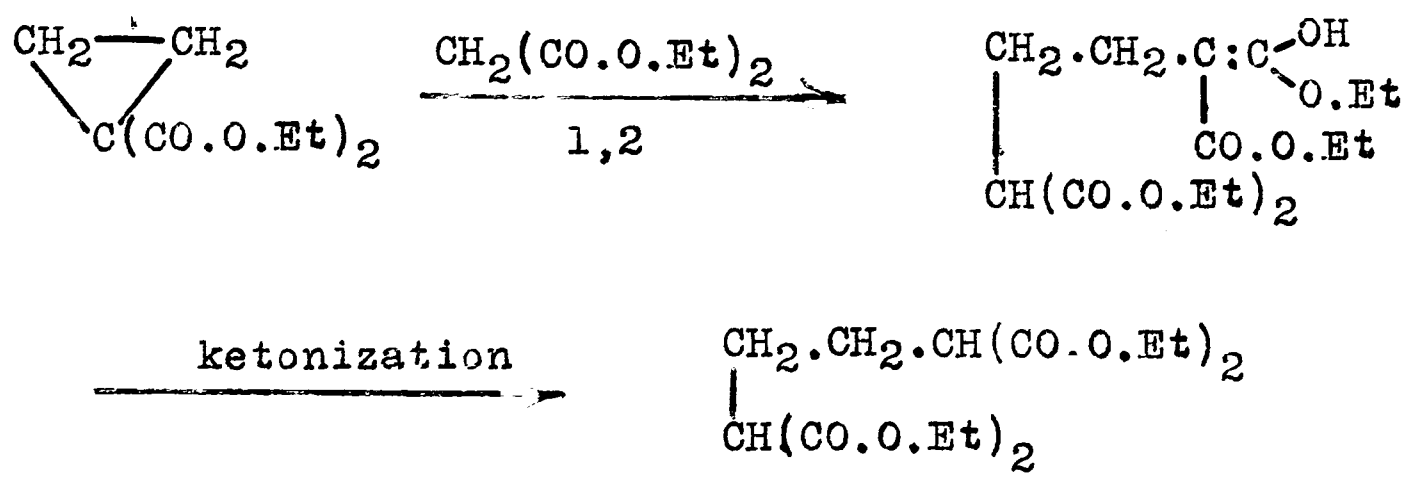


$\longrightarrow$ $Ph.CHCl.C(CO.O.Et)_2.CH:CCl.Ph + POCl_3$

(g) The addition of malonic ester to alpha-beta unsaturated carbonyl compounds in the presence of strong bases (the Michael reaction) has its counterpart in the cyclopropane series:



One case is known where a cyclopropane derivative gives the Michael reaction:



(h) There are several reagents that react primarily with one only of the two functional groups of the unsaturated carbonyl compound, and may be forced into reacting 1,4. However, they can rarely be made to open the cyclopropane ring. They include such reagents as hydrogen cyanide, and sodium bisulfite.

In the succeeding portions of this thesis, ring opening reactions of reagents of the type H-A will be indicated as 1,2 addition, though the actual mechanism is probably 1,4 addition.

(i) Hydrogen, and symmetrical reagents generally, probably add 1,2 (or 3,4).

Reduction of alph-beta unsaturated carbonyl compounds can be made selective for either the double bond or the carbonyl group. With metal combinations a 1,4 type of dimolecular reduction may occur:

$$2\ \mathrm{Ph.CH{:}CH.CO.Ph} \xrightarrow{\ H\ } \begin{matrix}\mathrm{Ph.CH.CH_2.CO.Ph}\\ |\\ \mathrm{Ph.CH.CH_2.CO.Ph}\end{matrix}$$

The mechanism here is probably addition of hydrogen to the carbonyl oxygen, followed by dimerization in the 4 position. This has not been observed with cyclopropane derivatives.

Reduction of 1,2 dicarbonyl cyclopropanes by metal combinations probably proceeds through 1,6 addition followed by ketonization, shown by the fact that it invariably (one exception) opens the ring 1,2. Catalytic hydrogenation may go 1,3; so it may be addition directly to the ring.

(j) One of the most marked differences between ethylenic and cyclopropane compounds lies in their behavior toward oxidizing agents. Ethylenic compounds almost without exception react with potassium permanganate instantaneously. The primary product is a 1,2 dihydroxy compound, but this is usually oxidized further, the end product often being an acid. With ozone, ethylenic compounds form unstable ozonides which on hydrolysis yield aldehydes and hydrogen peroxide.

In contrast, cyclopropane compounds are almost without exception stable to potassium permanganate and to ozone. One case of ring opening by oxidizing agents has been reported (electrolytic oxidation of cyclopropane monocarboxylic acid, see Historical Review), but here ring fission was a secondary reaction.

(2) Number of Substituents

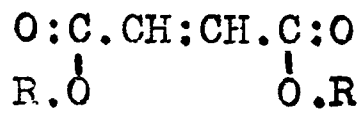
For hydrocarbons, the effect of the number of substituents has already been described in connection with the discussion of the application of Markownikoff's rule.

Increase in the number of unsaturated substituents may either increase or decrease the stability of the ring, depending on their position. See the next section.

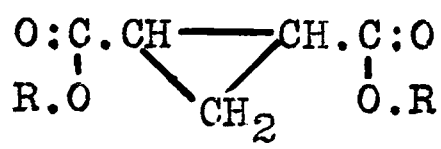
(3) Position of Substituents

The effect of unsaturated side chains on the stability of the ring depends on the relative positions of attachment. Again, close analogies can be drawn to corresponding ethylenic compounds.

(a) Substituents on Different Carbon Atoms -- 1,2 di-substituted cyclopropanes correspond to a conjugated system of three double bonds:



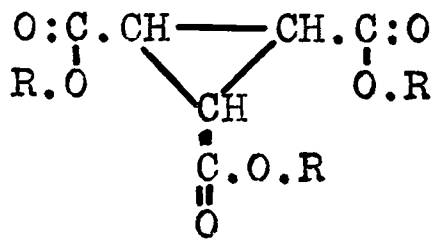
Ethylenic



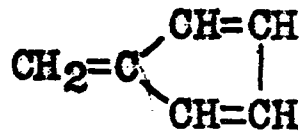
Cyclopropane

Here, the three centres of unsaturation form a continuous system, and the conjugation weakens the reactivity of the middle centre of unsaturation. Thus maleic ester will not add bromine readily; and the cyclic ester requires drastic conditions to open the ring. When it does take place, ring opening almost always occurs between the two substituted carbon atoms.

1,2,3-Trisubstituted derivatives obviously have no analogue in the ethylenic system. A careful examination shows that all three side chains are conjugated with the unsaturation of the ring, and through it with each other. Hence this is the most stable type of cyclopropane derivative known; it is almost impossible to open the ring.

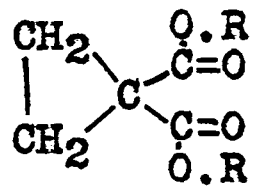


(b) Derivatives with Substituents on the Same Carbon Atom correspond to the "crossed" or "opposed" system of double bonds, best exemplified by the fulvenes:



Here there are two possible conjugated systems, each including the semicyclic double bond, and each excluding it from taking part in the other conjugated system. This "competition" of the two possible conjugated systems for the semicyclic double bond results in its being extremely reactive. These compounds are colored, polymerize and auto-oxidize readily, even take up oxygen from the air.

In the corresponding cyclopropane structure the unsaturation of the ring corresponds to the semicyclic double



bond of the fulvenes, with the two carbonyl groups competing for its participation in a conjugated system. This results in activation of the ring, so this type of structure is much more reactive than the previous example, with substituents on different carbon atoms. Indeed, Allen and Cressman have characterized this type as "unsaturated," and the previous type as "saturated."

Configuration may affect the type of ring opening obtained, especially in the more complex derivatives; e.g. 2-benzoyl-3-phenyl cyclopropane carboxylic acid-1, which exists in four stereoisomeric forms. Reduction with zinc and acetic acid cleaves the ethyl ester of the isomer melting at 174-5° 1,2; the ethyl ester of the isomer melting at 153-4° is cleaved 1,2 and 2,3 simultaneously.

Ring Opening Reagents

Many reagents will give ring opening reactions with cyclopropane derivatives; in general they are the more energetic reagents that add to the double bond.

(1) Pyrolysis-- Stability of the ring to distillation, either in vacuo or at atmospheric pressure, was formerly the principal criterion of "stability" of the ring. Now that much of the emphasis has shifted to type rather than ease of ring opening the reaction is of less interest. Cyclopropane derivatives on pyrolysis rearrange to propylene or ethylene derivatives. With the more complex molecules the reaction may be complicated by secondary reactions.

(2) Hydrogenation-- Zinc and acetic acid, or zinc and ethanol, are very consistent reagents for compounds that react readily. With keto acids and ester they usually give 1,2 ring opening. Sodium amalgam is a more energetic reagent, and often gives 1,3 ring opening. Catalytic hydrogen over platinum has been used, and gives 2,3 opening. Nickel catalysts at elevated temperatures and pressures do not appear to have been heretofore tried, except for hydrocarbons.

(3) Halogens-- Bromine usually reacts directly with the ring via a 1,2 cleavage to give a dibromo compound. With any but the very reactive compounds the reaction may require such drastic conditions as to be complicated by substitution, reduction of products by hydrogen halide, etc.

(4) Acids-- There are two acids that are important, hydrogen bromide and sulfuric acid.

Hydrogen bromide usually adds as H- and Br-; it may add either directly to the ring, when it follows Markownikoff's rule, or where unsaturated side chains are present it adds as H-A 1,4 to the ends of the conjugated system, giving 1,2, 1,3, and 2,3 ring openings with different compounds. In the case of esters the bromo compound is usually recovered, while acids usually lose hydrogen bromide to form a lactone. In the case of ketones the bromo compound may enolize and form a lactone, or the bromo compound may be recovered.

Sulfuric acid is usually used in water or glacial acetic acid solution. It is uncertain whether the sulfuric acid itself adds, or whether it merely catalyzes the addition of the elements of water. In any case, the product obtained is that which addition of water would give. Addition is always of the H-A type. With cyclopropane acids, the product is often the same lactone obtained from treatment with hydrogen bromide.

(5) Bases-- Only the more reactive cyclopropanes are sensitive to bases. Water, ammonia and amines, potassium hydroxide in water or alcohol solution, and sodium methylate give varying degrees of reactivity. The base usually adds 1,4 splitting to e.g. Na- and -O.Me, or H- and -NH.R. Bases give both 1,3 and 2,3 opening.

(6) Phosphorous halides-- These have the effect of adding two atoms of halogen to the ends of the conjugated system. The shifted double bond is retained, instead of being returned to its original position as in H-A addition by ketonization.

(7) Organo-Metallic compounds-- These react only with the most reactive cyclopropanes; they include Ph.Mg.Br and $Na.CH(CO.O.Et)_2$.

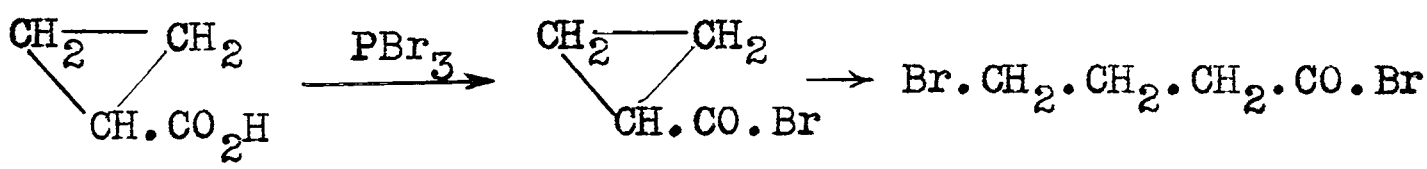
HISTORICAL

The following review will be confined to cyclopropane acids and keto-acids and to their esters, and will include ring opening reactions only. It purports to cover all such reactions that have been reported in the literature to date.

The compounds are classified as to structure and are arranged in order of increasing complexity. A discussion of the salient points with regard to ring opening is followed by a compendium of the compounds in each class.

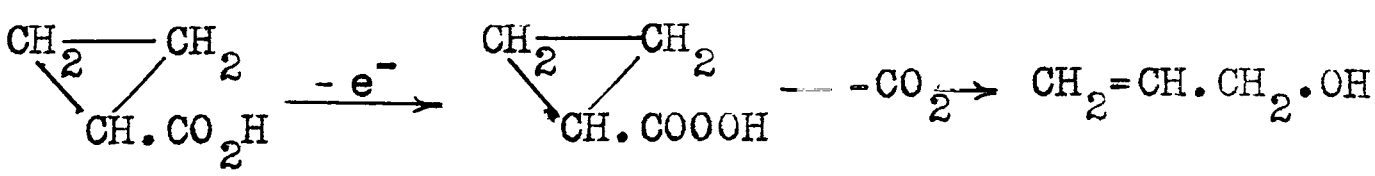
(a) Monocarboxy Cyclopropanes

For cyclopropane monocarboxylic acid (I) data is available for the action of bromine only (1): in carbon disulfide solution there is no action in the cold; warm, some substitution takes place. In the presence of red phosphorous, the acid bromide is formed, which splits 1,2:



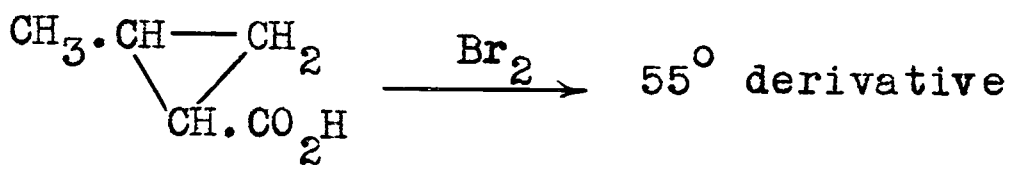
I

Electrolysis of equivalent quantities of acid and sodium salt gives allyl alcohol which forms the ester:



(b) Monoalkyl derivatives of cyclopropane monocarboxylic acid

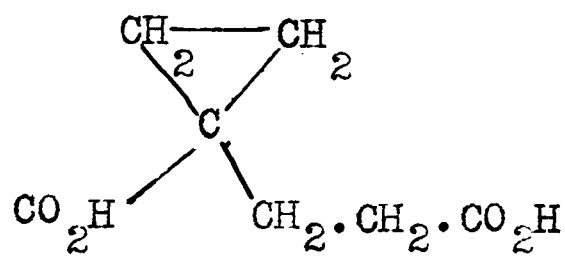
In 3-methyl cyclopropane carboxylic acid-1 (II) the substitution of a positive alkyl group increases the reactivity somewhat; bromine in the cold gives a product whose structure was not determined, melting at 55° (2)



(II)

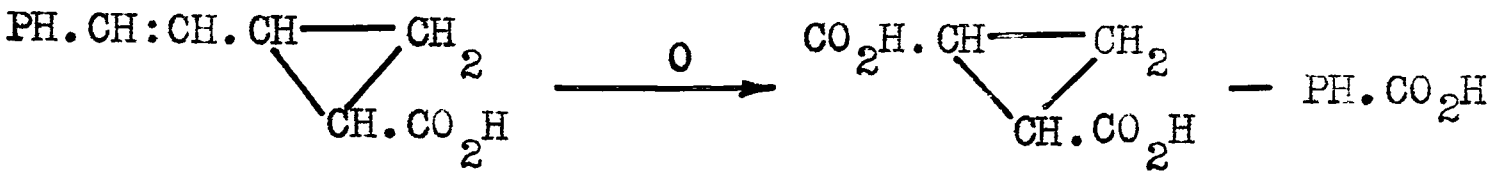
3-Isopropyl cyclopropane carboxylic acid-1 (III) is stable to heat (both acid and ester); and is not oxidized by permanganate. (3)

The molecule of 1-propionic acid cylopropane carboxylic acid-i (IV) is decomposed by concentrated sulfuric acid (78)



(IV)

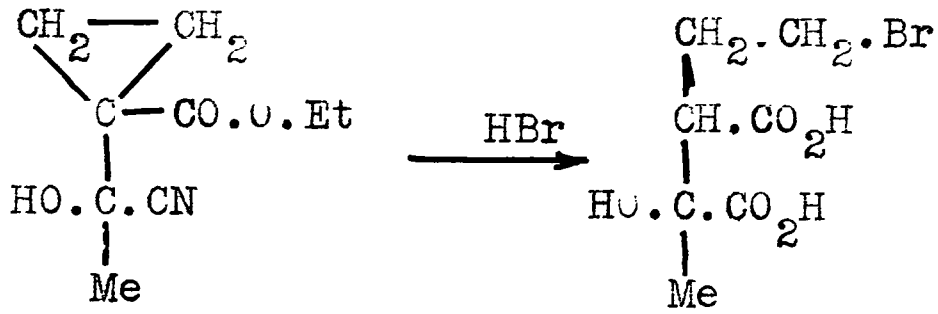
The ring of 3-styryl cyclopropane carboxylic acid-1 (V) is unaffected by permanganate, which does however oxidize the side chain to carboxyl (4):



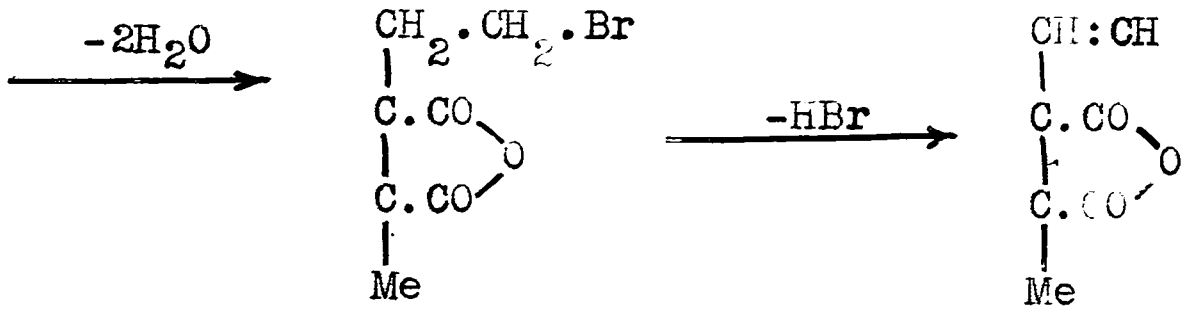
(V)

The ester is stable to heat, distilling unchanged in vacuo.

The cyclopropane (VI) is split 1,2 by hydrogen bromide, and then secondary reactions occur (5):



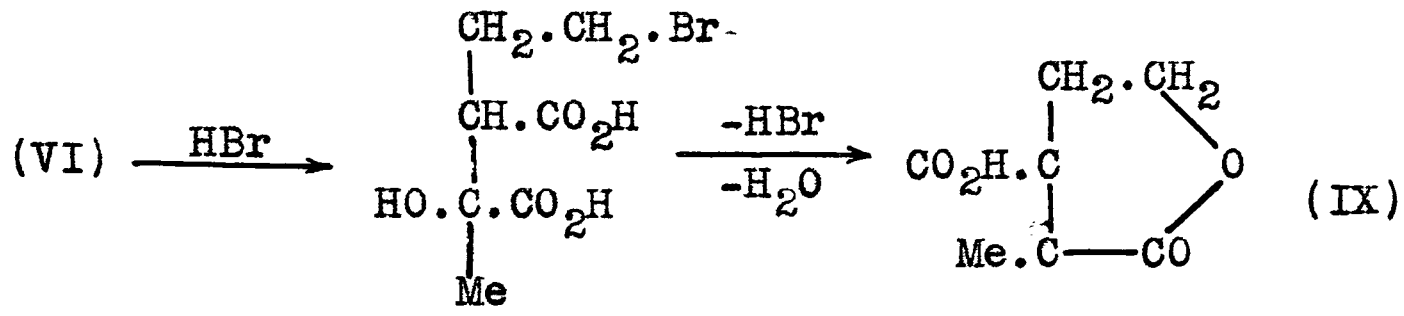
(VI)



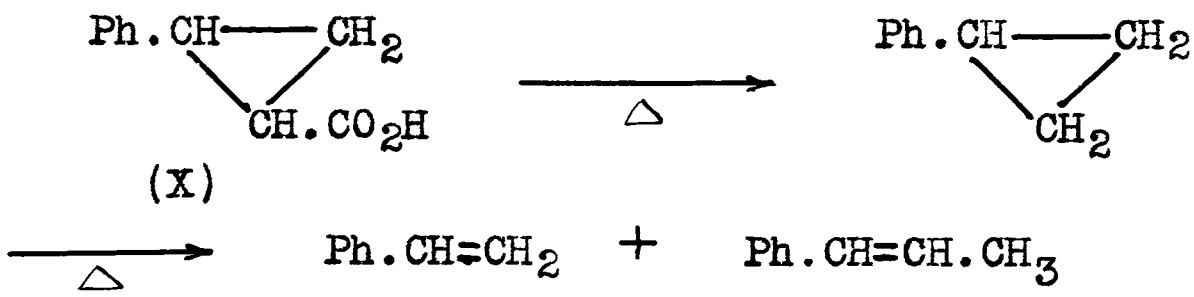
(VII) (VIII)

The compounds (VII) and (VIII) were the actual products; the 1,2 ring fission is postulate to explain their formation.

Another course of reaction was postulated (6) to explain the production of (IX): the first step is 1,2 ring fission:

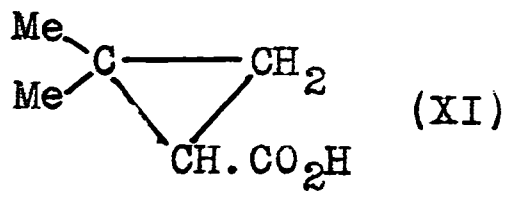


Pyrolysis of 3-phenyl cyclopropane carboxylic acid-1 (X) gives styrene and 1-phenyl propene; a possible course of reaction is through phenyl cyclopropane, which would give the usual pyrolysis type of reaction for cyclopropanes (7):

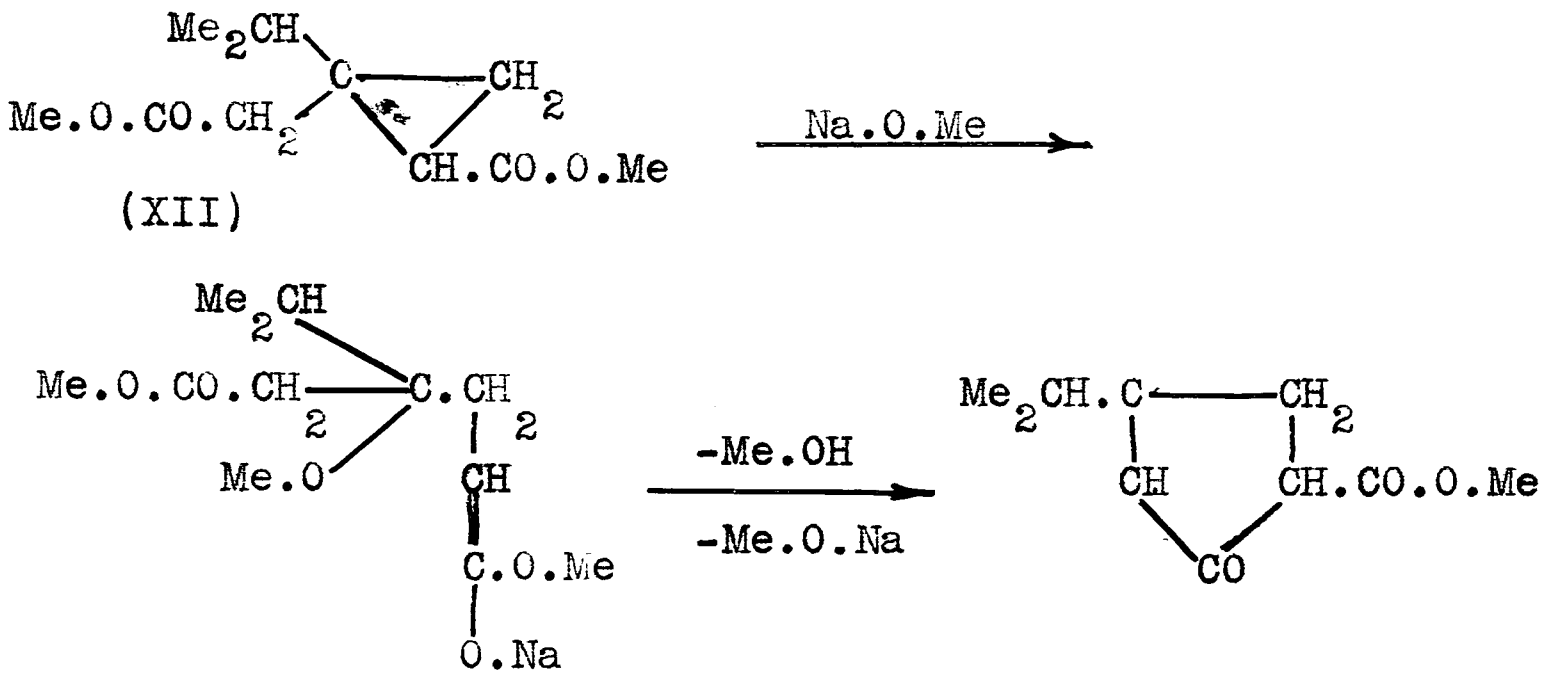


(c) <u>3,3-Dialkyl Monocarboxy Cyclopropanes</u>

Both 3,3-dimethyl cyclopropane dicarboxylic acid-1 (XI) and its ester are stable to vaccuum distillation (3, 8)



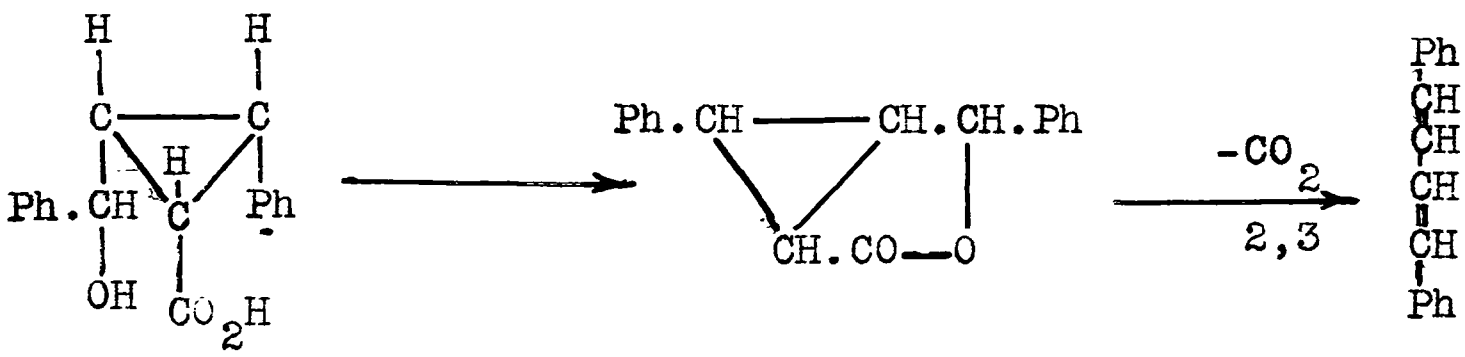
Alpha tanacetone dicarboxylic acid (XII) is stable to dilute acids (10, 11). However, it is one of the few comparatively simple compounds that open with bases (12). Sodium methylate opens the ring 1,3:



(XII)

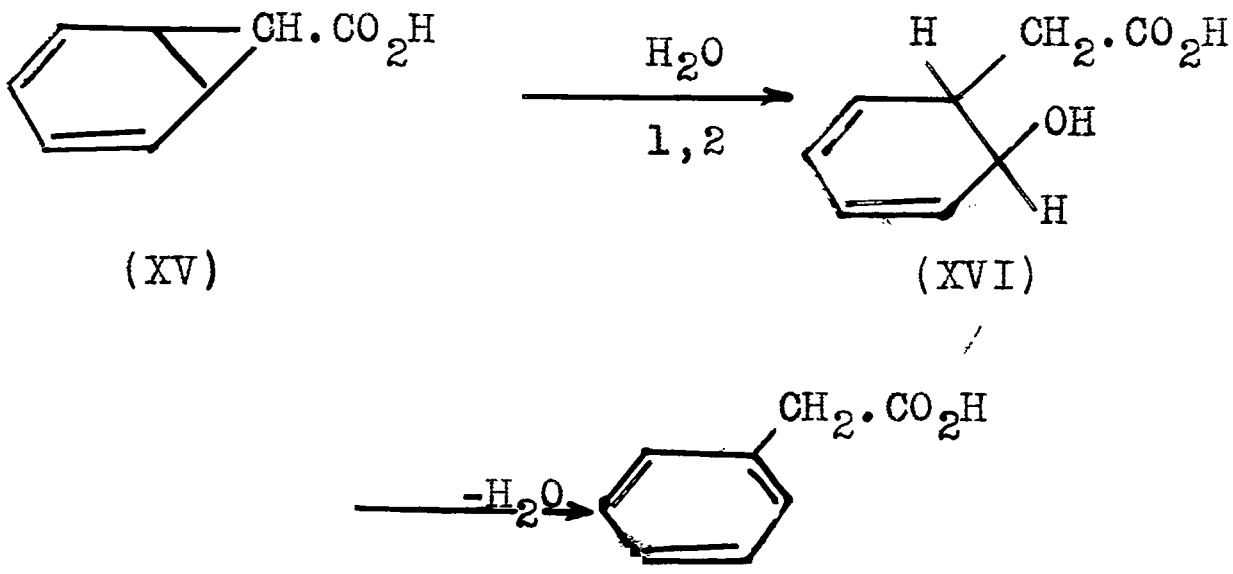
(d) <u>2,3-Dialkyl Monocarboxy Cyclopropanes</u>

Cis-3-benzoxyl-2-phenyl cyclopropane carboxylic acid-1 (XIII), isomer melting at 145-6°, is unstable to heat (13, 14, 15, 16), forming a lactone which then loses carbon dioxide, the ring opening 2,3:

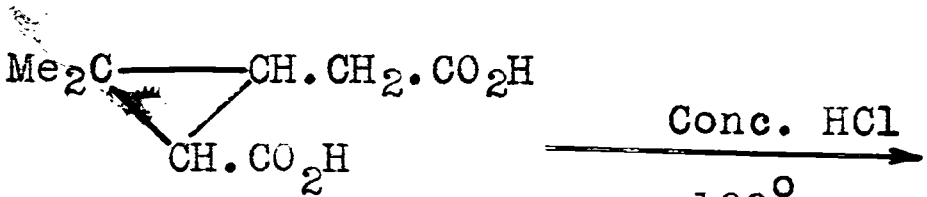


(XIII) (XIV)

"Norcaradiencarbonsaure" (XV) is converted by 50% sulfuric acid into phenyl acetic acid (72). A 1,2 fission with additon of water is postulated to explain the product; the primary product (XVI) loses water to "aromaticize" to phenyl acetic acid:

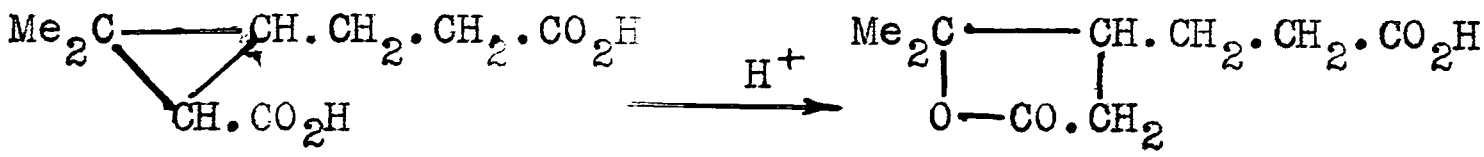


Homocaronic acid (XVII) adds water in the presence of concentrated hydrochloric acid at 100° to give an unidentified product, a lactone $C_8H_{12}O_4$ melting at 101-2° which is stable to hydriodic acid and to sodium amalgam:



(XVII)

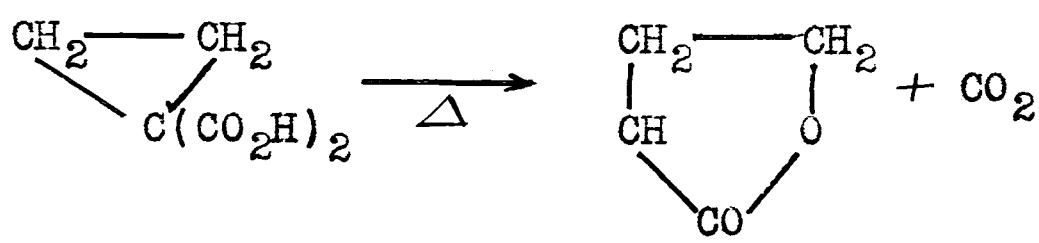
Acids cleave 3,3-dimethyl cyclopropane propionic acid-2-carboxylic acid-1, hydrobromic, hydrochloric, and sulfuric acids all cleaving 1,3 and giving the same lactone (XIX):



(e) <u>1,1-Dicarboxy Cyclopropanes</u>

These belong to the type of cyclopropane compound corresponding to the crossed system of double bonds in the ethylenic analogue. They are much more sensitive to ring opening than the monocarboxylic acids, or the 1,2-dicarboxy compounds.

Cyclopropane dicarboxylic acid-1,1 (XX) is unstable to pyrolysis (17, 75). Distillation of the acid yields butyrolactone, a 1,2 fission:

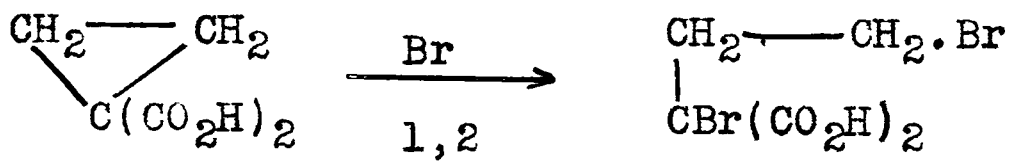


(XX)

The acid is stable to reduction by dilute sodium amalgam and water.

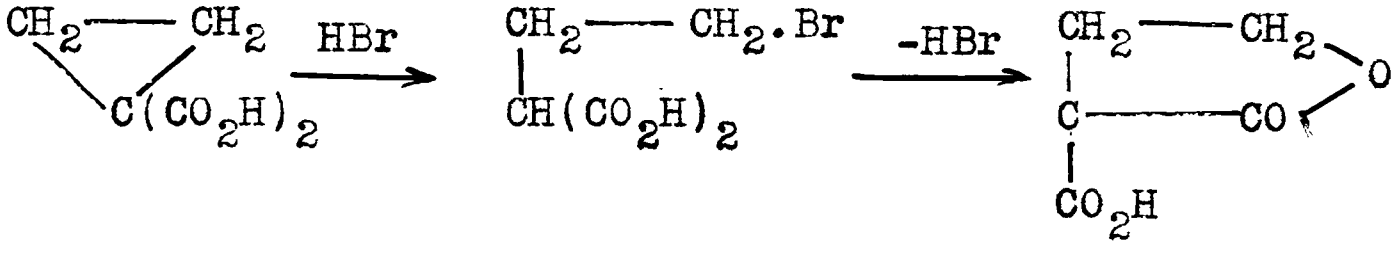
Chromic acid oxidizes the acid slightly; potassium permanganate and nitric acid are without effect (20).

Bromine in diffuse sunlight opens the ring 1,2 to give the bromo acid (XXII):



(XXII)

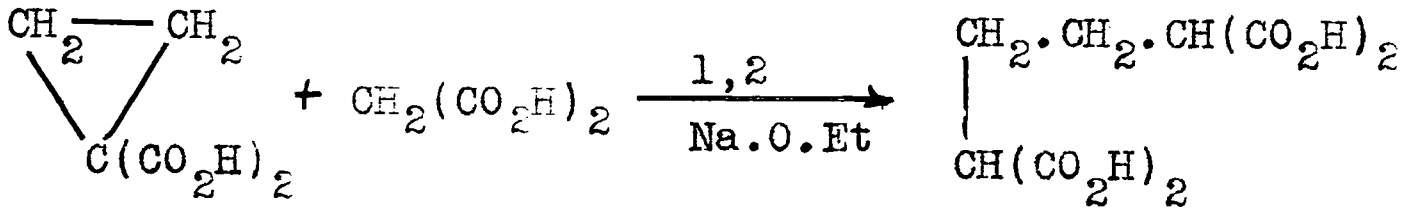
Hydrogen bromide opens the ring 1,2 at 0°. The primary product is a bromo acid, which loses hydrogen bromide to form a lactone (XXI):



(XXI)

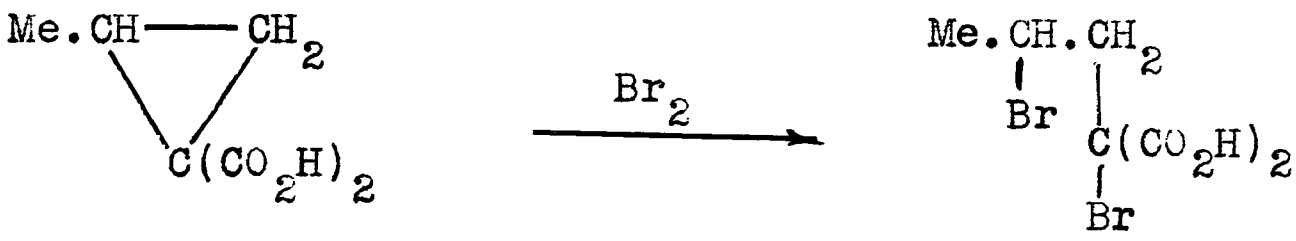
Sulfuric acid is used in 50% dilution. The ring is cleaved 1,2 as with hydrogen bromide, and the product is the same lactone (18, 19). The reaction probably goes through addition of water to the ring in the 1,2 position.

The sodium compound of malonic ester gives a reaction (21) similar to that with an alph-beta unsaturated carbonyl compound (the Michael reaction), involving a 1,2 ring split:



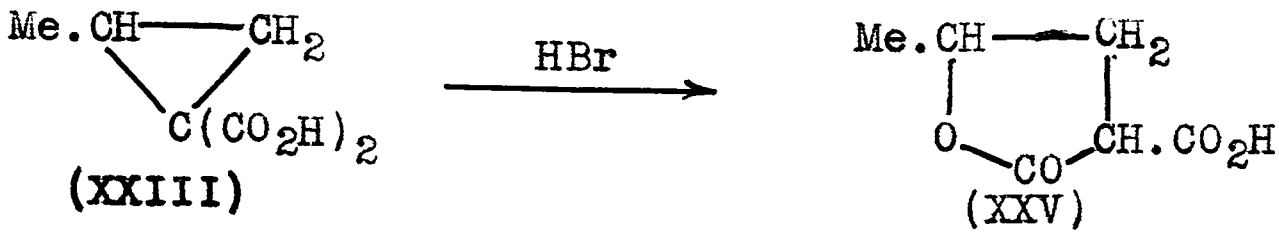
3-Methyl cyclopropane dicarboxylic acid-1,1 (XXIII) distills in vacuo undecomposed, and is stable to reduction by sodium amalgam, and to potassium permanganate.

Bromine opens the ring 1,3 to give a bromo acid (XXIV):



(XXIII) (XXIV)

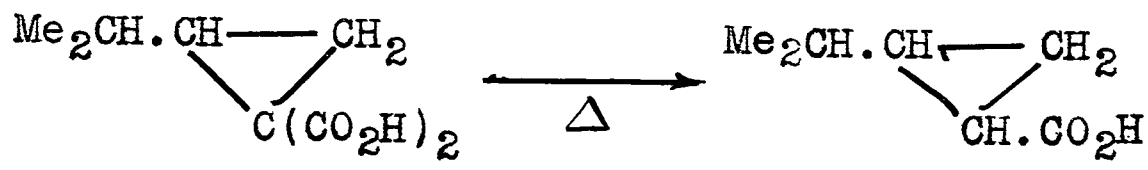
Hydrogen bromide gives a reaction similar to that of the unsubstituted cyclopropane 1,1-dicarboxylic acid, opening the ring 1,3 at 0° to give a bromo acid which loses hydrogen bromide to give a lactone (XXV):



(XXIII) (XXV)

Sulfuric acid (50%) gives the same lactone (22, 23, 24)

On pyrolysis, 3-isopropyl cyclopropane dicarboxylic acid-1,1 yields the monocarboxylic acid (III) and carbon dioxide (25):



(g) <u>1,2-Dicarboxy Cyclopropanes</u>

Cyclopropane dicarboxylic acid-1,2 as the subject of the present investigation deserves special mention (26, 27, 29, 31, 32)

It belongs to the class of cyclopropanes corresponding to the conjugated system of double bonds, the ring corresponding to the central double bond, and therefore very inactive. The ring is difficult to form, but once formed is very stable; drastic conditions are invariably required to open it.

The acid exists in two stereoisomeric forms; the cis acid melts at 135° and forms an anhydride on vaccuum distillation (81). The trans acid melts at 175° (55) and does not form an anhydride. At elevated temperatures in the presence of a dehydrating agent it gives the anhydride of the cis acid. The trans form is the more stable of the two, as shown by the conversion of cis to trans by fusion with potassium hydroxide.

The ester of cyclopropane dicarboxylic acid-1,2 (XXVII) has been reported stable to distillation in vacuo (28, 77) The trans acid distills unchanged at reduced pressure; the cis acid forms the anhydride (81).

Concentrated sodium amalgam (80) and potassium permanganate at 100° (29) do not affect the ring.

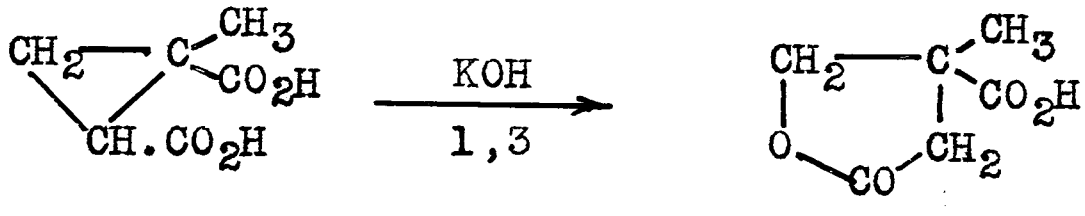
Bromine alone has no effect on the ring. In the presence of red phosphorous, heated in a bomb tube, two hydrogen atoms are replaced by bromine (30).

Concentrated hydrochloric acid could not affect the cis acid in six hours (28). Concentrated sulfuric acid at 100° has no effect; at higher temperatures, the compound is destroyed (33). Hot dilute sulfuric acid converts the cis acid into the trans (34, 35).

(h) 2-Alkyl-1,2-Dicarboxy Cyclopropanes

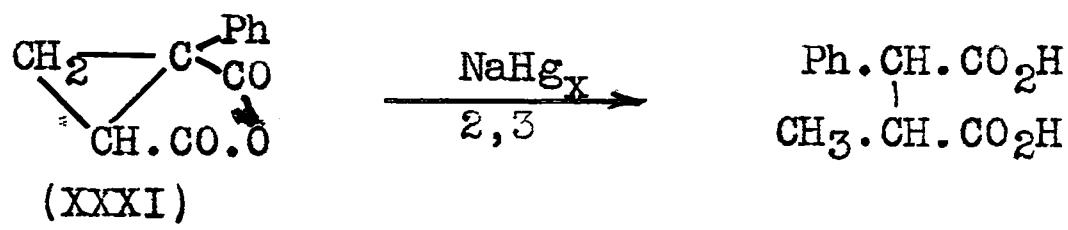
The resemblance between 2-methyl cyclopropane dicarboxylic acid-1,2 and the previous example is apparent. Distillation of the cis acid yields the anhydride. Heat in the presence of a dehydrating agent converts the trans acid into the anhydride of the cis acid.

The ring is sensitive to bases, being opened 1,3 by concentrated aqueous potassium hydroxide to form a lactone:



Hydrogen halides convert the cis acid to the trans; they do not affect the ring (36, 37).

Special interest attaches to 2-phenyl cyclopropane dicarboxylic acid-1,2 (XXX) because its anhydride (XXXI) offers the only reported case where reduction opens the ring of a 1,2-disubstituted cyclopropane 2,3 (39, 40):



(XXXI)

The compound is stable to potassium permanganate and to bromine.

The ester of 2-acetic acid cyclopropane dicarboxylic acid-1,2 distill unchanged, but the acid is decomposed slowly (41, 37).

(i) <u>1,2-Dialkyl-1,2-Dicarboxy Cyclopropanes</u>

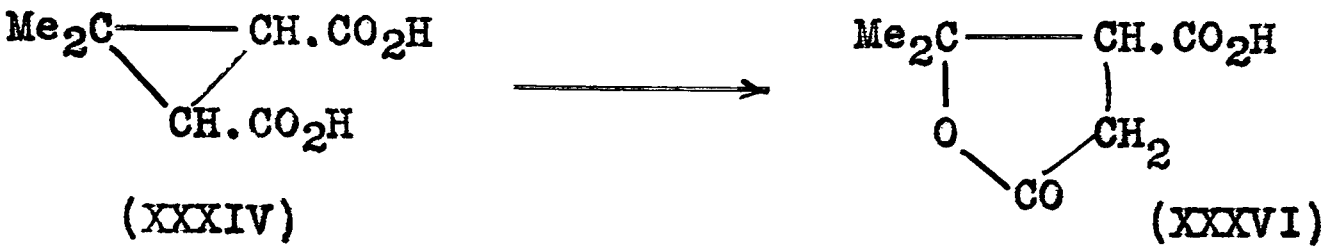
Insufficient data are available to judge the activity of this class of compounds.

1,2-Dimethyl cyclopropane dicarboxylic acid-1,2 exhibits a generally saturated character. It is stable to oxidation by potassium permanganate (43, 44, 45).

(j) <u>3,3-Dialkyl-1,2-Dicarboxy Cyclopropanes</u>

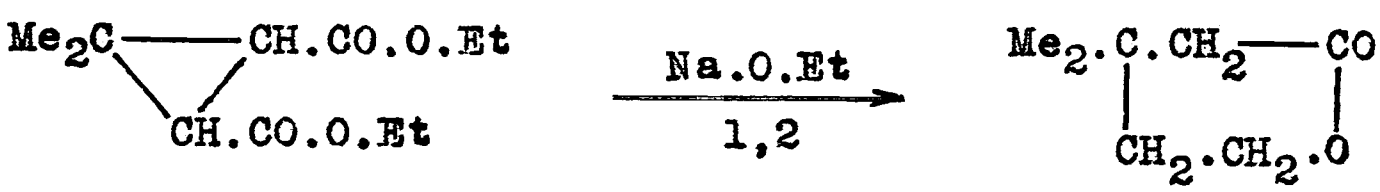
These are characterized by ease of formation, and by greater reactivity than the preceding group, the 1,2 dialkyl derivatives.

Caronic acid, 3,3-dimethyl cyclopropane dicarboxylic acid 1,2 (XXXIV) is converted by heat to terebic acid (XXXVI) via a 1,3 ring cleavage:



(XXXIV) (XXXVI)

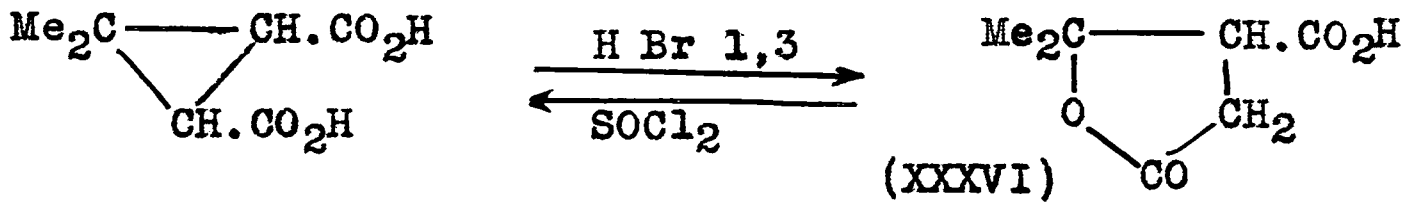
The action of sodium and ethanol on the ester gives a peculiar reaction (46) in which one of the ester groups is reduced to a primary alcohol group; the ring then splits 1,2; the final product is a lactone (XXXV):



(XXXV)

The acid has been reported stable to potassium permanganate (47).

The lability of this type of compound is shown by the ease of cleavage and re-formation of the ring in the presence of acids:

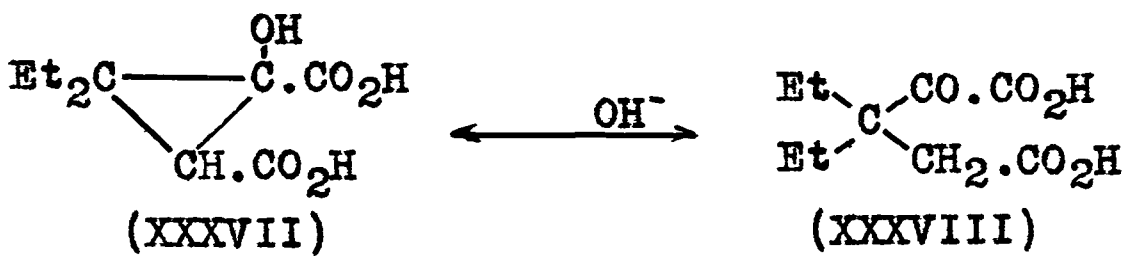


(XXXVI)

Here terebic acid (XXXVI) is formed by the 1,3 ring opening of the hydrogen bromide and subsequent lactone formation. Treatment with thionyl chloride puts a chlorine on the Me_2C carbon atom; and the C_3 ring closes spontaneously with loss of hydrogen chloride.

Sulfuric acid gives the same 1,3 cleavage.

Another example of the extreme lability of this ring is afforded by the following reaction (50):



(XXXVII) (XXXVIII)

The equilibrium is established in aqueous solution in the presence of hydroxyl ion. It is analogous to a keto-enol tautomerism, (XXXVII) corresponding to the enol, the ring corresponding to the double bond, and (XXXVIII) corresponding to the ketone. The reaction is catalyzed by hydroxyl ion; and the formation of the "enol" is promoted by strong bases in the formation of the compound from the open-chain halogen derivative, β,β-diethyl-α,α-dibromo glutaric acid.

(k) <u>Tricarboxy Cyclopropanes</u>

Cyclopropane tricarboxylic acid-1,1,2 (XXXIX) contains both the inactivating "conjugated" system of the 1,2-dicarboxy derivatives, and the activating "opposed" system of the 1,1-dicarboxy derivatives. Insufficient data are available to say which predominates; it is probably the inactivating tendency.

The ester distills unchanged, as does the 1,2-dicarboxy compound. The free acid on heating, instead of opening 1,2 as does the 1,1-dicarboxy compound, loses carbon dioxide to give the more stable 1,2-dicarboxylic acid (XXVII):

(XXXIX)

Potassium permanganate is without effect on the acid (51, 52).

Cyclopropane tricarboxylic acid-1,2,3 (XL) belongs to the most stable, most perfectly conjugated type of cyclopropane derivative (53). Cleavage of the ring has never been reported.

(1) Tetracarboxy Cyclopropanes

Cyclopropane tetracarboxylic acid-1,1,2,2 (XLI) -- This again contains both the "conjugated" and "opposed" systems; and the tendency to conjugation is probably the stronger.

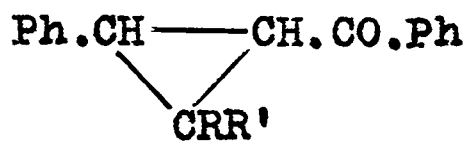
The ester is stable to heat, distilling unchanged. The acid undergoes no ring opening, merely losing two molecules of carbon dioxide to give the more stable dicarboxy compound (XXVII) (54, 55, 56, 57, 58, 59).

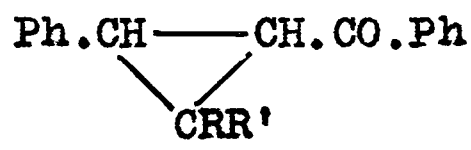
Keto Acids and Esters

These are the most reactive and the most versatile cyclopropane derivatives. They are readily propared, and react smoothly and easily with a large variety of ring opening reagents.

Kohler, who initiated the study of the unsaturation of the cyclopropane ring, used compounds of the type 2-benzoyl-3-phenyl cyclopropane dicarboxylic acid-1,1. His students, particularly C. F. H. Allen, have extended the field to include 2-benzoyl-3-phenyl cyclopropane carboxylic

acid-1, 2-benzoyl cyclopropane dicarboxylic acid-1,1, and 2-benzoyl cyclopropane carboxylic acid-1.





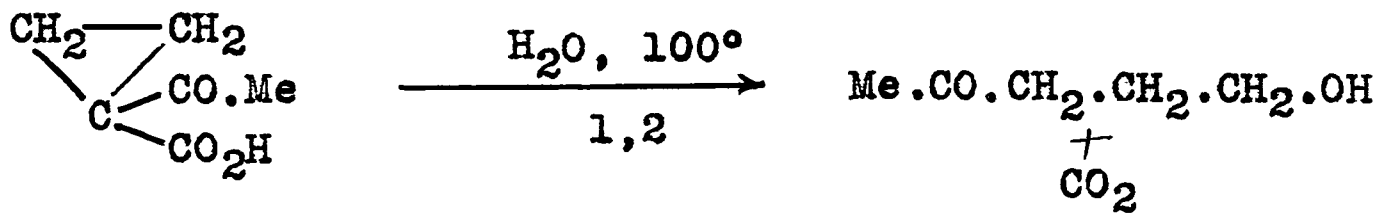
The symbols R and R' may represent -H, $-CO_2H$, or -CO.O.Et.

(m) <u>1-Acyl-1-Carboxy Cyclopropanes</u>

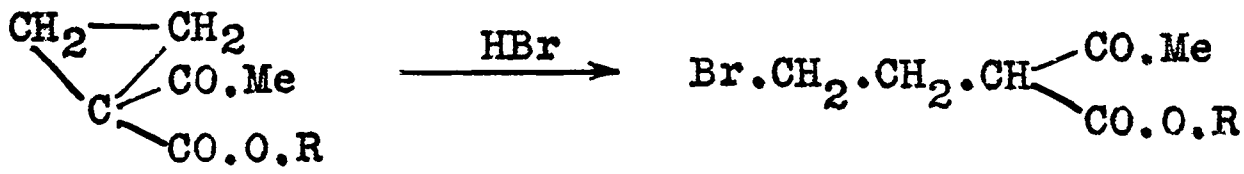
These compounds belong to the class of cyclopropanes that correspond to the opposed system of double bonds, and are accordingly very reactive.

1-Acetyl cyclopropane carboxylic acid-1 (XLII) furnishes a good example of the great reactivity of this class--greater even than that of the 1,1-dicarboxy cyclopropanes.

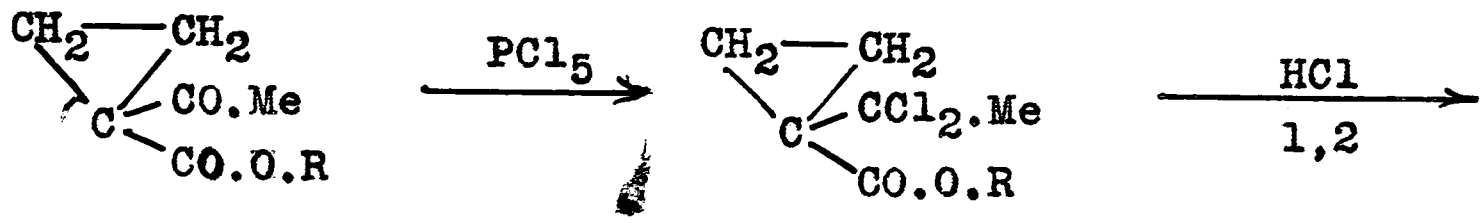
Water at 100° is sufficient to cleave the ring. Loss of carbon dioxide and 1,2 cleavage are simultaneous (60):

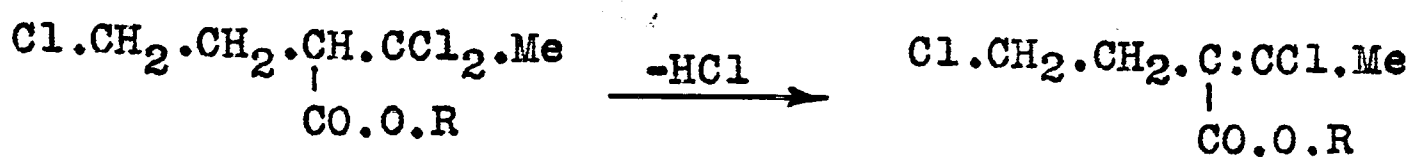


The ester is more sensitive to cleavage by acidic reagents than the acid. Hydrogen bromide cleaves the ring of the ester 1,2 (60):



Phosphorous pentachloride gives a 1,2 cleavage with the ester. (60, 61):





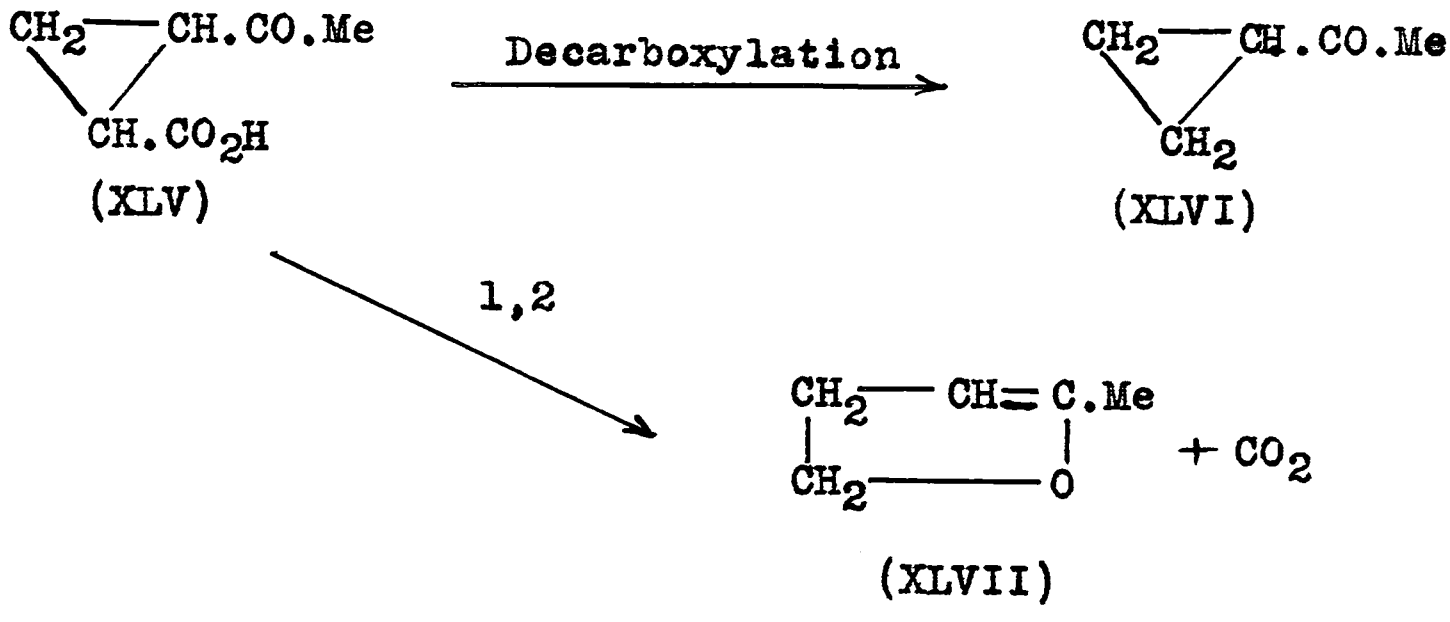
Dilute sulfuric acid causes decarboxylation, but no cleavage (62).

1-Benzoyl cyclopropane carboxylic acid-1 reacts similarly to the preceding example; water at 100° gives 1,2 cleavage followed by decarboxylation (63).

The ring of 3-methyl-1-acetyl cyclopropane carboxylic acid-1 is quite stable. Pyrolysis of the acid gives slight decarboxylation. Alcoholic potassium hydroxide has no effect on the ring (64).

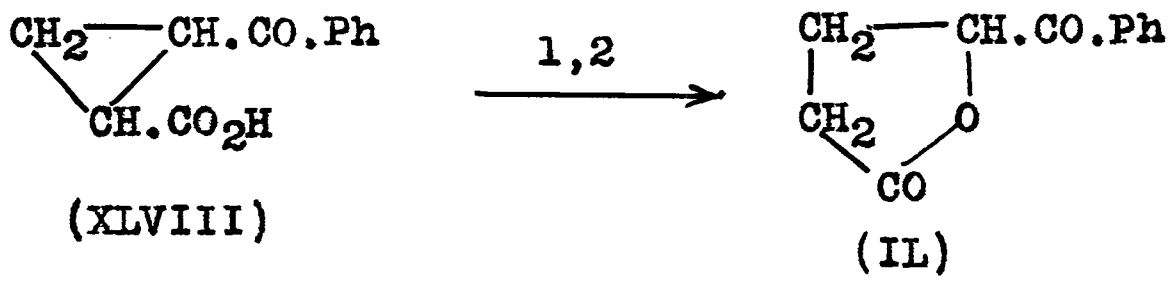
(c) <u>2-Acyl-1Carboxy Cyclopropanes</u>

The acid 2-acetyl cyclopropane carboxylic acid-1 (XLV) is unstable to heat. There are two courses of reaction, decarboxylation to give (XLVI), and a 1,2 ring split plus decarboxylation giving the anhydride of aceto-propyl alcohol, (XLVII) (60):



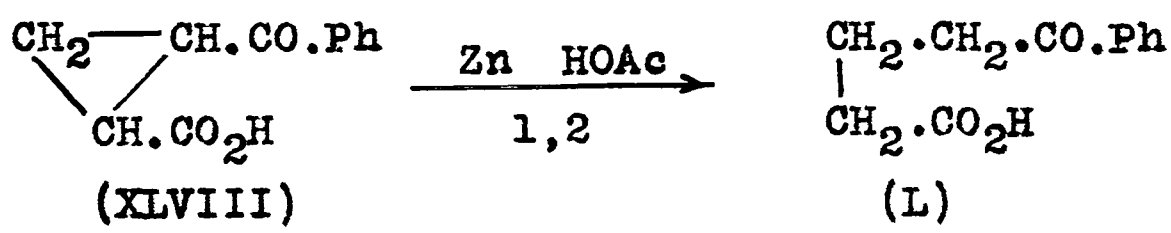
2-Benzoyl cyclopropane carboxylic acid-1 (XLVIII) exists as two geometric isomers. These will be designated as the low- and high-melting isomers; it is not known which is the cis and which the trans (66).

The esters both distill under reduced pressure unchanged. The acids show a difference in behavior towards heat. The high-melting acid is stable; and the low-melting acid is slightly affected (66), probably cleaving 1,2 to give gamma-benzoyl butyrolactone (IL):



(XLVIII) (IL)

Reduction with zinc and acetic acid (66) cleaves the ring 1,2 to give benzoyl butyric acid (L):

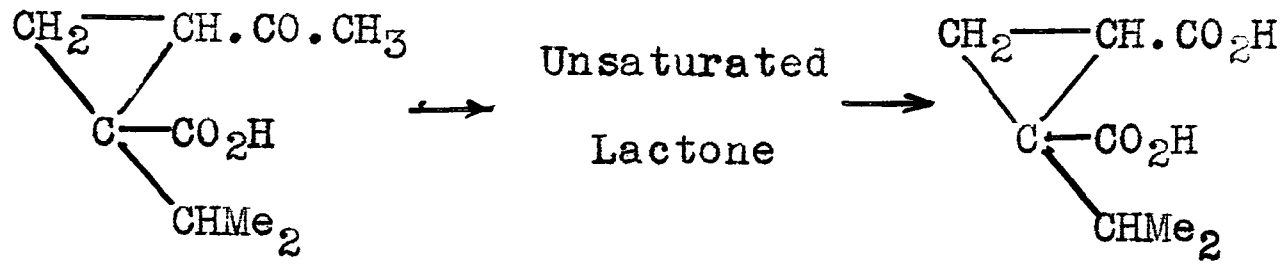


(XLVIII) (L)

The compound is stable to bromine in chloroform at room temperature, to potassium permanganate in acetone, and to concentrated sulfuric acid at room temperature (67).

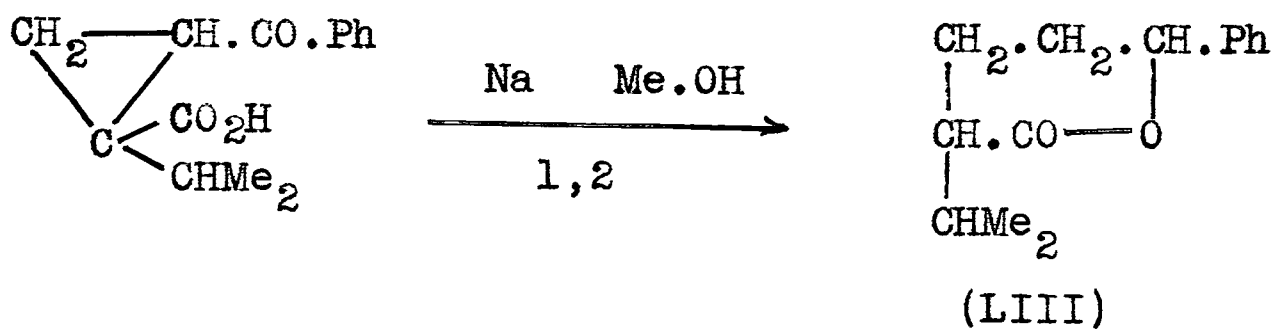
(p) <u>1-Alkyl-1-Carboxy-2-Acyl Cyclopropanes</u>

The derivative 1-isopropyl-2-acetyl cyclopropane carboxylic acid-1 (LI) is not cleaved by heat (70, 71); however, pyrolysis gives an unsaturated lactone which on oxidation gives 1-isopropyl cyclopropane dicarboxylic acid-1,2 (LII):



(LI) (LII)

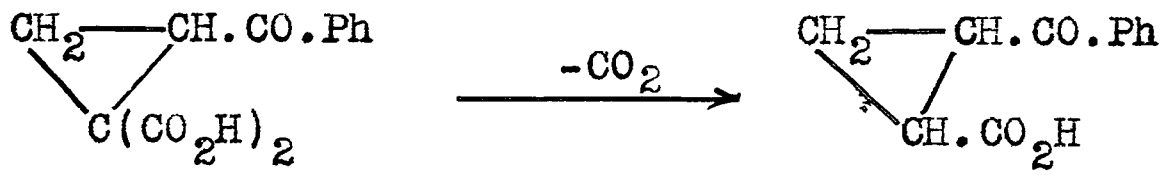
Reduction opens the ring 1,2 (69), and the final product is the saturated lactone (LIII):



(LIII)

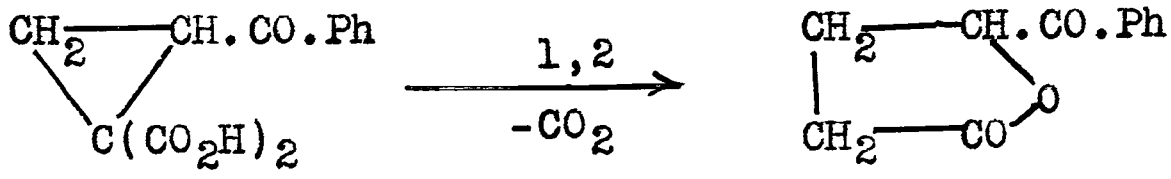
(q) <u>1,1-Dicarboxy-2-Acyl Cyclopropane</u>

On pyrolysis, 2-benzoyl cyclopropane dicarboxylic acid-1,1 (LIV) decarboxylates (66, 90) to yield both possible stereoisomers of 2-benzoyl cyclopropane carboxylic acid-1 (LV):



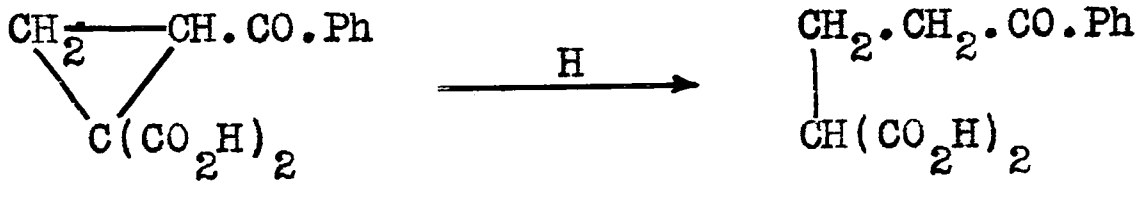
(LIV) (LV)

1,2 Cleavage occurs simultaneously to yield gamma-carboxy butyrolactone (LVI):



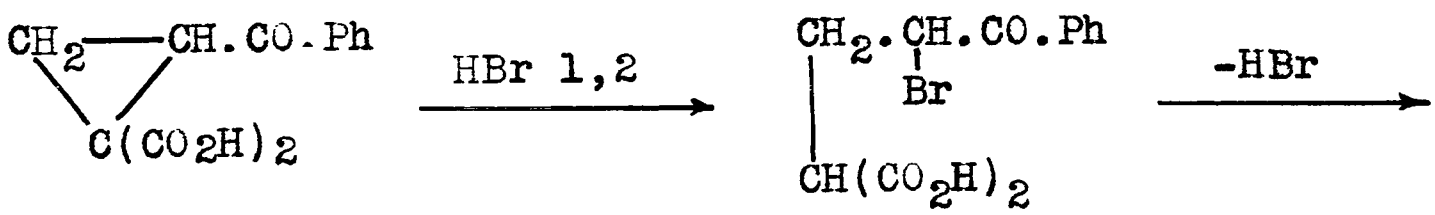
(LIV) (LVI)

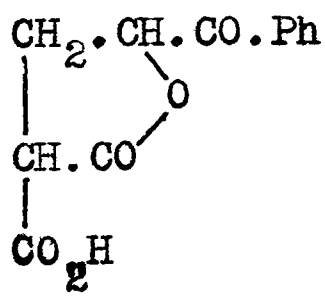
Reduction by zinc and acetic acid opens the ring 1,2:



Neither permanganate nor bromine in chloroform open the ring.

Hydrogen bromide in glacial acetic acid solution reacts at room temperature, cleaving the ring 1,2. With the acid, the final product is the lactone (LVII), whereas with the ester the reaction stops after the addition of HBr:





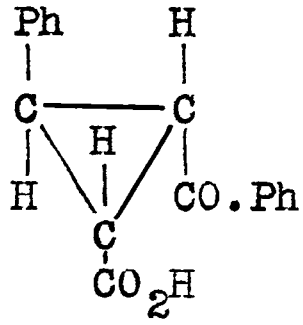
(LVII)

Sulfuric acid, concentrated at room temperature, or 20% at 100° has no effect on this acid. Concentrated, at 190°, it decomposes the molecule.

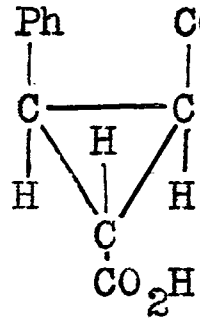
The ring is resistant to bases, dry sodium and magnesium methylate having no effect.

(r) 1-Carboxy-2-Acyl-3-Alkyl Cyclopropanes

There are four possible stereoisomers of 2-benzoyl-3-phenyl cyclopropane carboxylic acid-1 (LVIII), and all are known (89). They melt at (a) 174-5°, (b) 157-157.5°, (c) 153-4°, (d) 136-7°. Stoermer and Schenk (13) represent the configuration of two of them as follows:

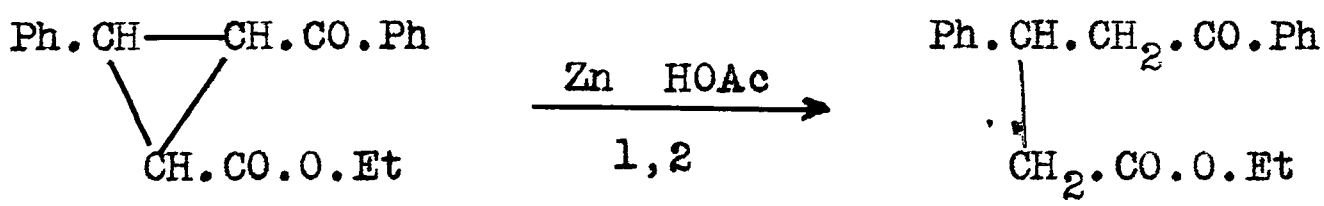


(a)



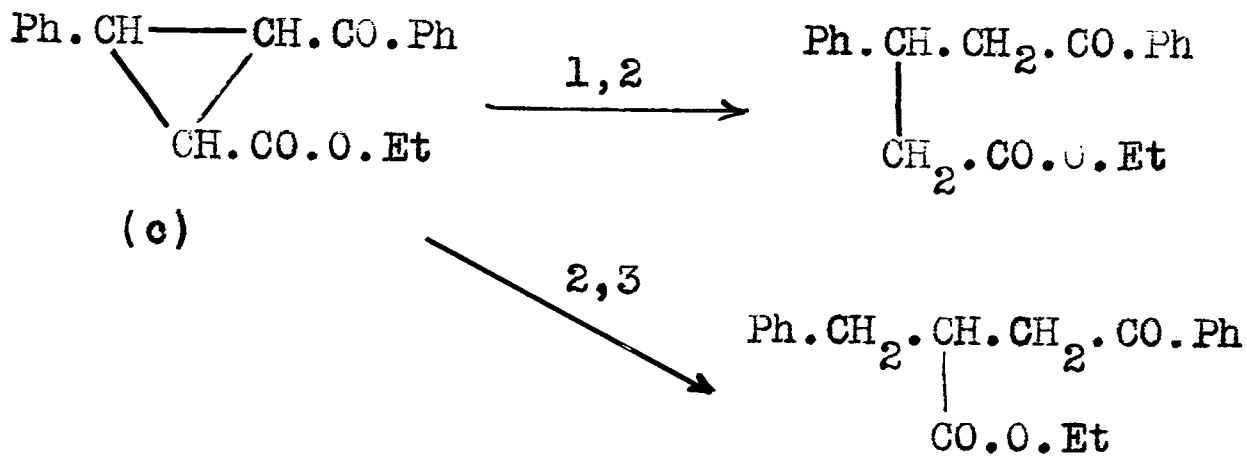
(c)

Reduction of this compound is an example of a reaction where the configuration affects the type of ring opening; the ethyl esters are used, and the reducing agent is zinc and acetic acid; the ethyl ester of isomer (a) cleaves 1,2:



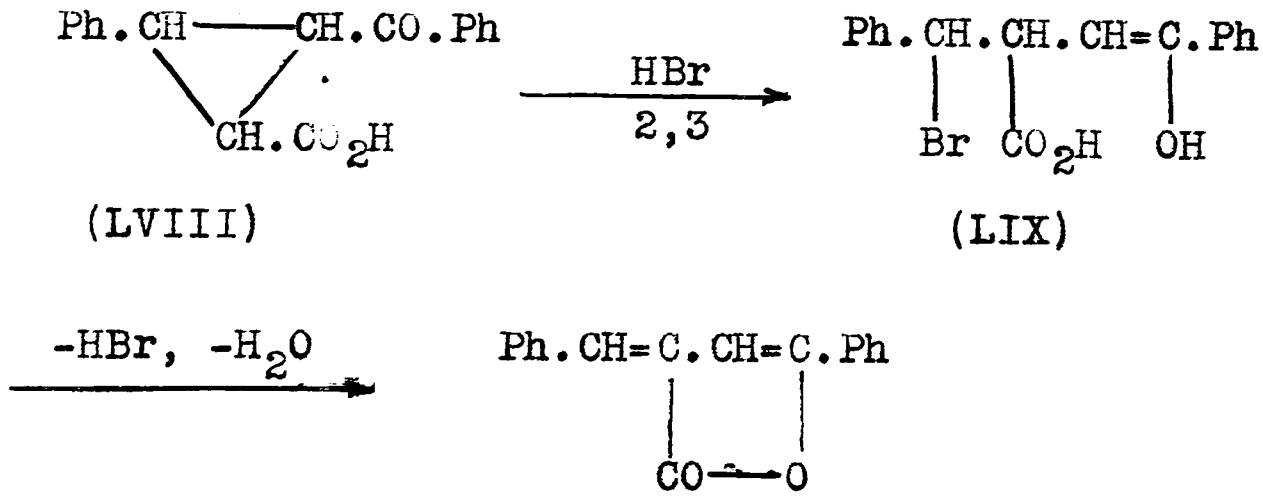
(LVIII) (a)

The ethyl ester of the isomer (c) cleaves 1,2 and 2,3 simultaneously:



Catalytic hydrogen cleaves the acids (b), (c), and (d) 2,3. The mechanism of catalytic hydrogenation is not certain; but that for reduction by metal combinations is probably 1,6 addition to the ends of the conjugated system, followed by ketonization.

Both the acid and the ester react with hydrogen bromide as readily as do alpha-beta unsaturated ketones. The ring is opened 2,3; in the case of the ester, the reaction stops there, and treatment with potassium acetate regenerates the ring.



It is interesting to follow the secondary reactions, the loss of water and of hydrogen bromide from the unstable bromoacid or ester first formed. The first step is 1,4 addition of hydrogen bromide to give an enol (LIX). The enol form will be partially stabilized by the conjugation of the phenyl group; so this gamma hydroxy acid forms the lactone. Since the ester group has a greater activating influence on the alpha hydrogen than the carboxyl group and since Ph-C=C- is also an activating group the hydrogen adjacent to the bromine is now active enough that hydrogen bromide is lost spontaneously with formation of a double bond.

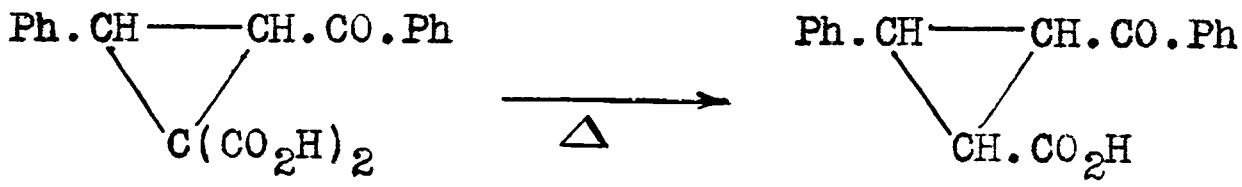
In the case of the ester, no lactone can be formed; so ketonization occurs. Then, when hydrogen bromide is eliminated, there are two active hydrogens that might react. But the ketone group is a stronger activating group than the ester group, so its alpha hydrogen is lost, and the ring is re-formed. Since only one activating group is acting on the hydrogen, hydrogen bromine is not lost spontaneously, as it is with the acid (above); but the presence of the weakly basic potassium is sufficient to remove it.

Dry alcoholates have no reaction on the ring; aqueous alkalis give the usual very rapid hydrolysis of the ester group.

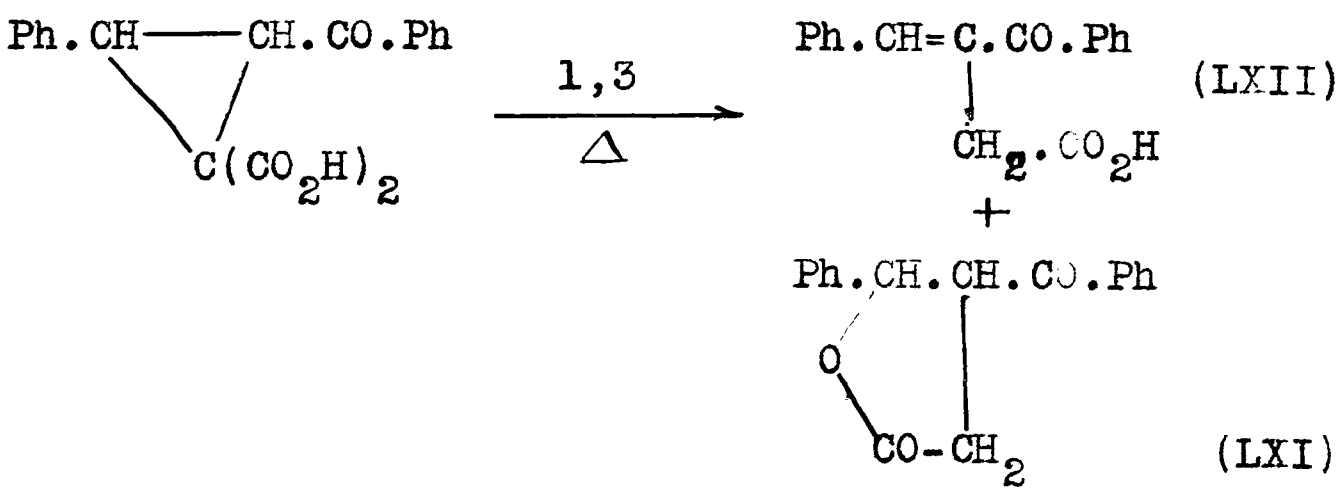
(s) 1,1-Dicarboxy-2-Acyl-3-Alkyl Cyclopropanes

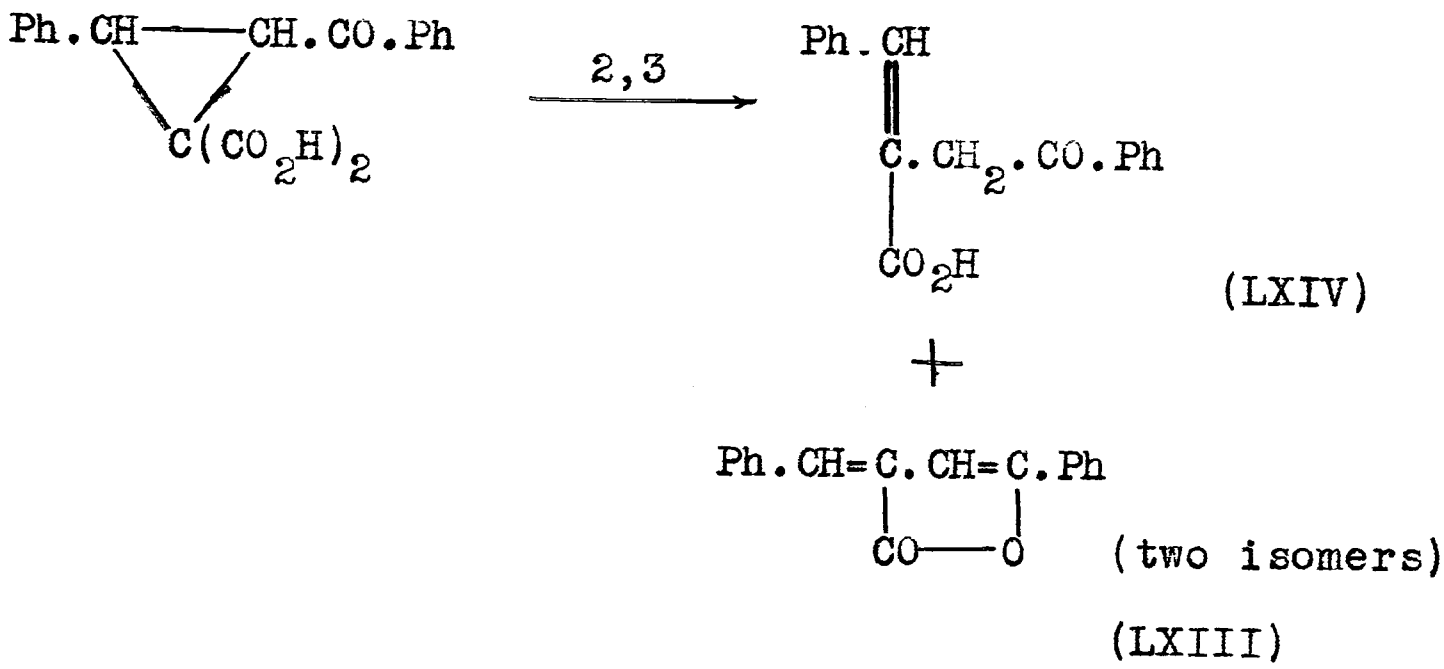
These are Kohler's compounds. He and his students have worked out and verified mechanisms for many reactions, both by choosing suitable derivatives to allow the intermediates to be isolated, and by putting in blocking groups at appropriate places, thereby stopping the reaction. The compounds can be opened on any side, giving the most rigid proof of the existence of a three membered ring.

The ester of 2-benzoyl-3-phenyl cyclopropane dicarboxylic acid-1,1 (LX) is stable at high temperatures. The free acid decarboxylates at about 150°; however, the ring becomes unstable at about this temperature, opening 1,3 and 2,3, and little of the monocarboxy acid (LVIII) is recovered.



(LX) (LVIII)

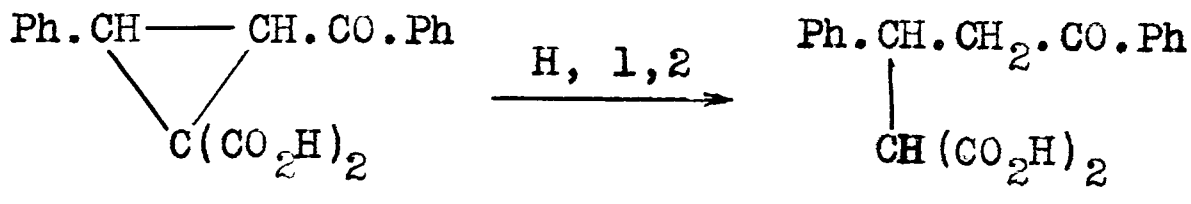




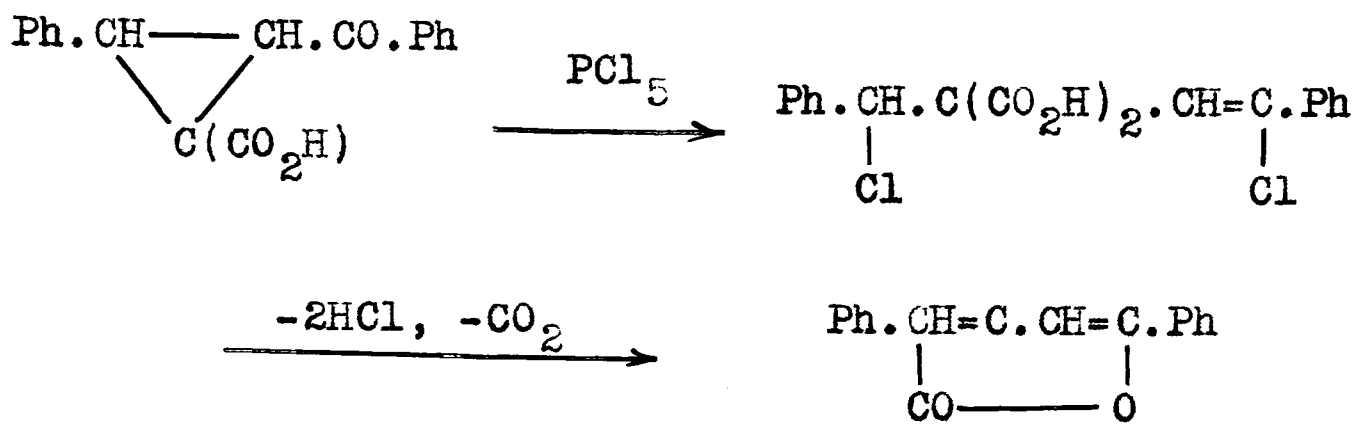
These ring cleavages are the usual ring isomerizations to propene derivatives; lactone (LXI) formation in the case of the 1,3 cleavage may be considered to be the result of water adding to the double bond of (LXII) to give a gamma-hydroxy acid, and subsequent lactone formation. Since this would require the addition of the water contrary to Markownikoff's rule, it seems more probable that at the high temperature of the reaction the carboxy group is able to add to the double bond, probably simultaneously with its formation.

In the case of the 2,3 cleavage, the lactone (LXIII) is simply that of the enol form of (LXIV).

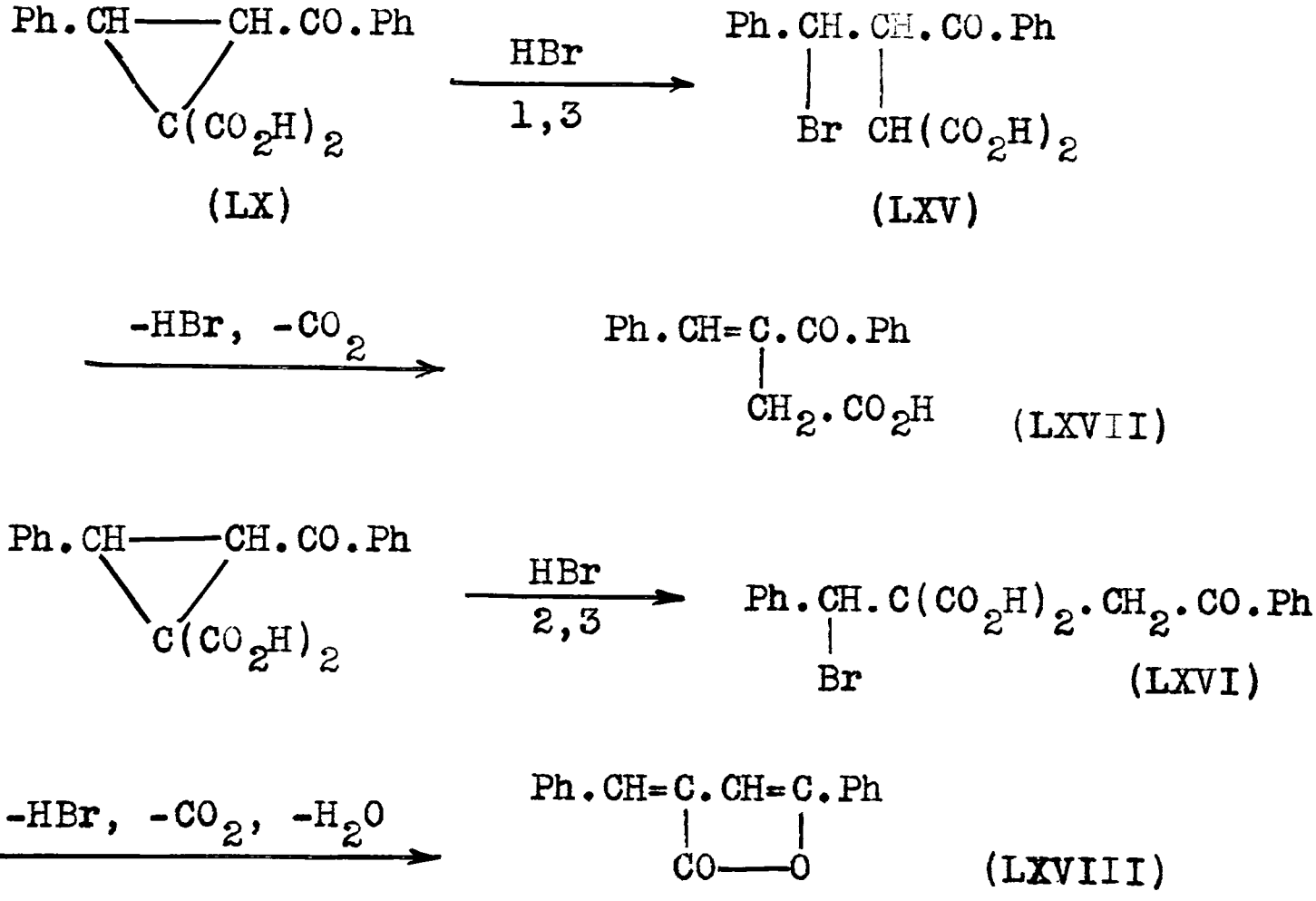
Zinc and acetic acid cleaves the compound 1,2 to give an open-chain compound:



Phosphorous pentachoride cleaves the ring 2,3 at room temperature in chloroform solution. The mechanism is probably 1,4 addition:



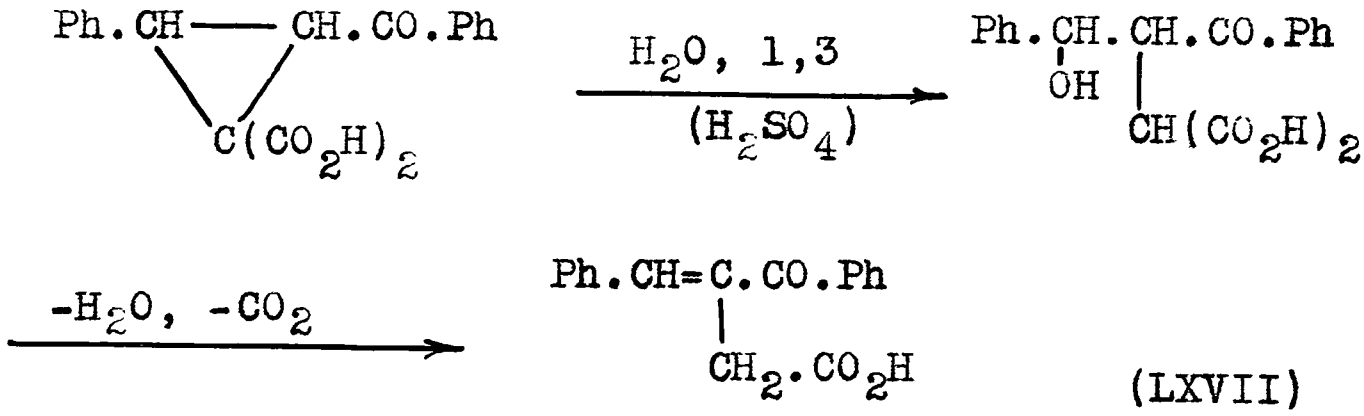
Hydrogen bromide solution in glacial acetic acid reacts in two ways, opening the ring 1,5 and 2,3.



(LX) (LXV) (LXVII) (LXVI) (LXVIII)

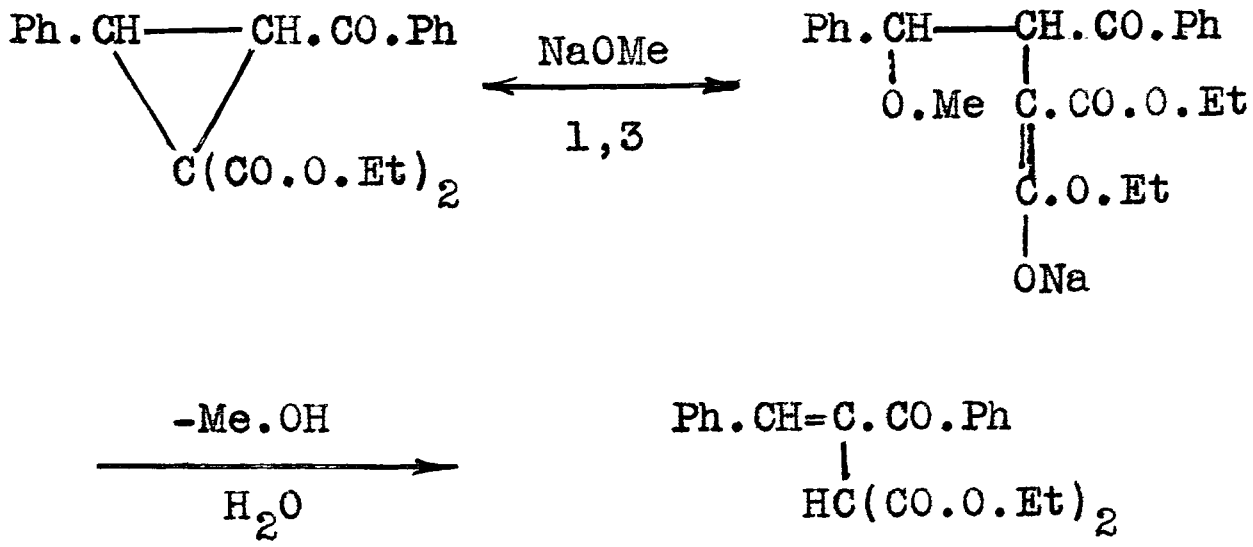
The bromo acid intermediates (LXV) and (LXVI) are postulated to explain the production of the substances isolated, (LXVII) and (LXVIII). Further evidence was that when the reaction was carried out in alcohol, some of the bromo acid was esterified, preventing the secondary reactions occurring. This oily bromo ester could then be treated with potassium acetate, hydrogen bromide abstracted, and the cyclopropane ester regenerated. Final proof was furnished by putting substituents on the phenyl groups, making the intermediates less soluble, whereby they could be isolated and identified.

Sulfuric acid opens the ring 1,3, giving the same product as the 1,3 reaction of hydrogen bromide; this suggests that the 1,3 reaction may be due to the catalytic effect of strong acids causing the addition of water.



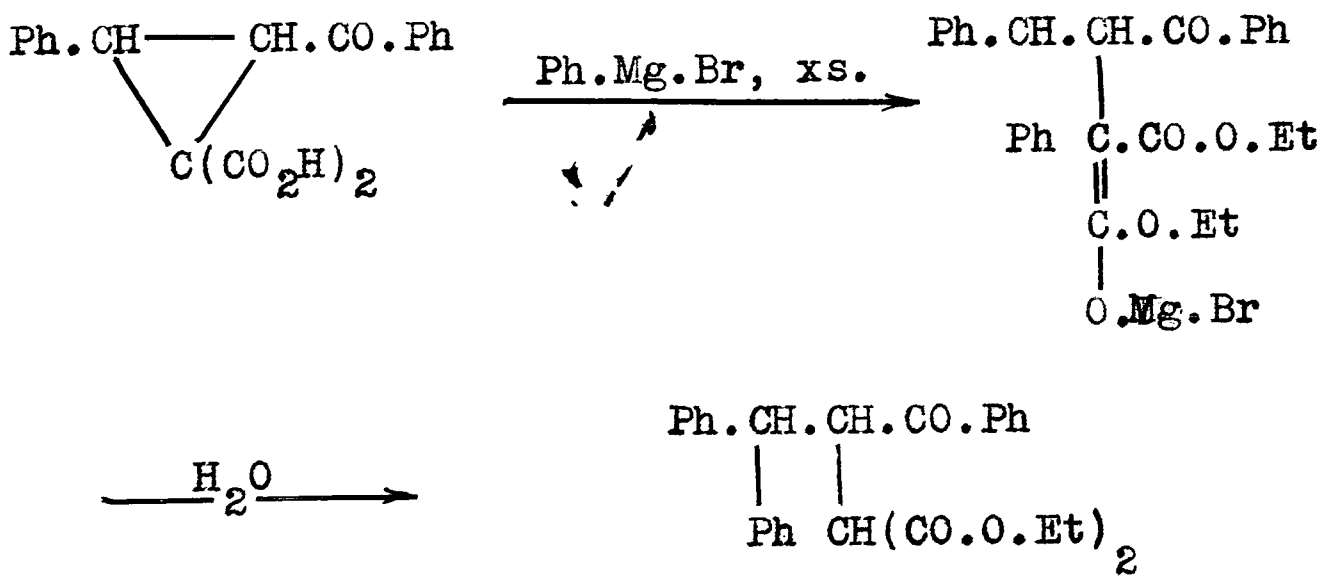
(LXVII)

This compound differs from the previously described ones in being very sensitive toward bases. Dry alcoholates, ammonia, or amines open the ring (of the ester) 1,3:



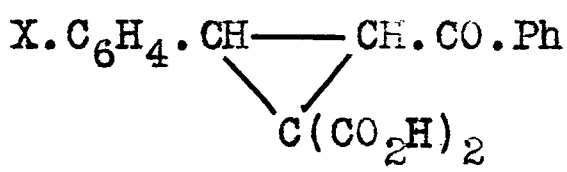
This mechanism has been verified by replacing the hydrogen on carbon atom-2 by a methyl group, thus blocking the loss of methyl alcohol.

This compound is one of the few cyclopropane derivatives that react with the Grignard reagent. The reaction is analogous to the 1,4 addition of the Grignard reagent to alpha-beta unsaturated carbonyl compounds. Under normal conditions, the reagent gives the usual ester reactions, with resulting complex gums. However, it is possible to force the reaction, by using a large excess of Grignard reagent, to go by 1,4 addition.

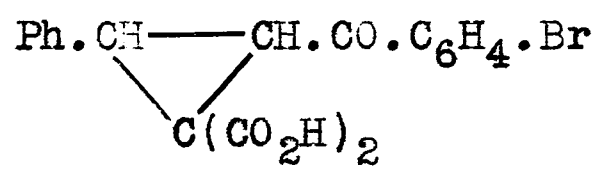


This reaction is of special interest, because it affords a final proof that 1,4 addition does occur.

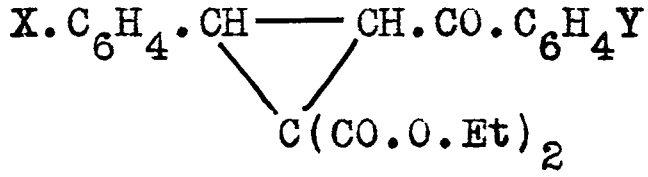
To verify the mechanism proposed for the reaction of (LX) with hydrogen bromide, Kohler made use of various compounds with substituents on the phenyl groups which would make the intermediates less soluble, and so separable by precipitation from the reaction medium. The four compounds below were tried:



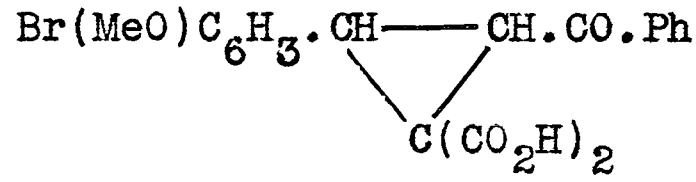
(LXIX)



(LXX)



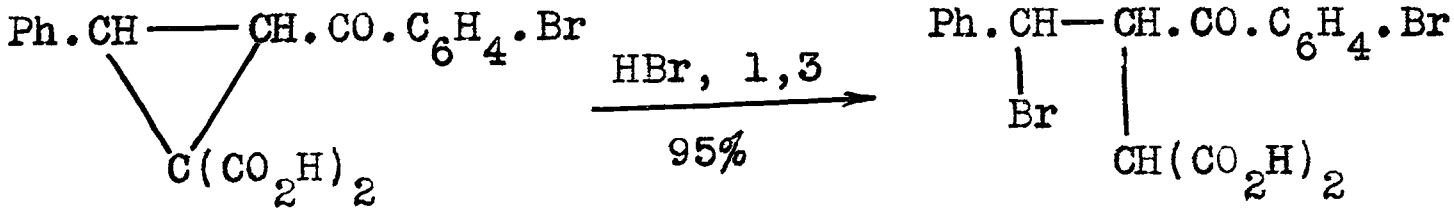
(LXXI)



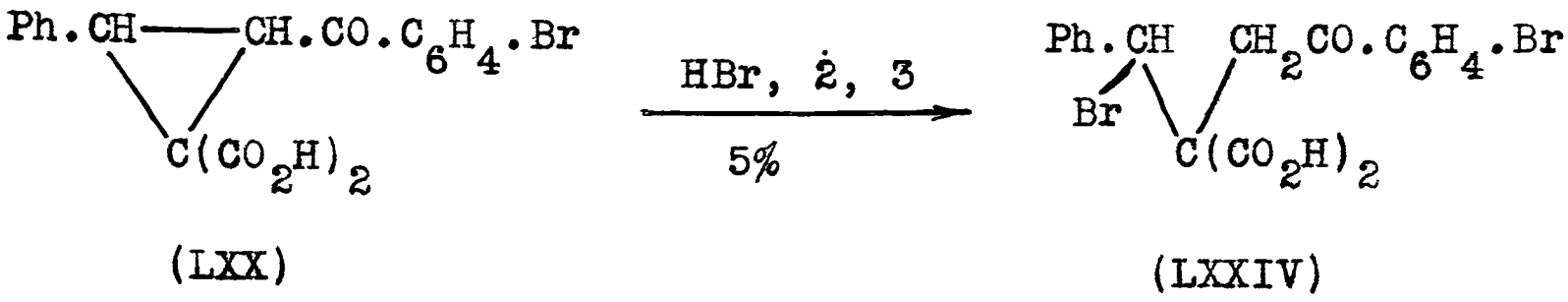
(LXXII)

With (LXX) the products of both 1,3 and 2,3 addition of hydrogen bromide to the ring could be isolated. Apart from this, the substituents seem to have no effect on the ring opening reactions of the compounds.

Hydrogen bromide in glacial acetic acid opens the ring of (LXX) both 1,3 (95%) and 2,3 (5%), and the bromo acids produced may be isolated.

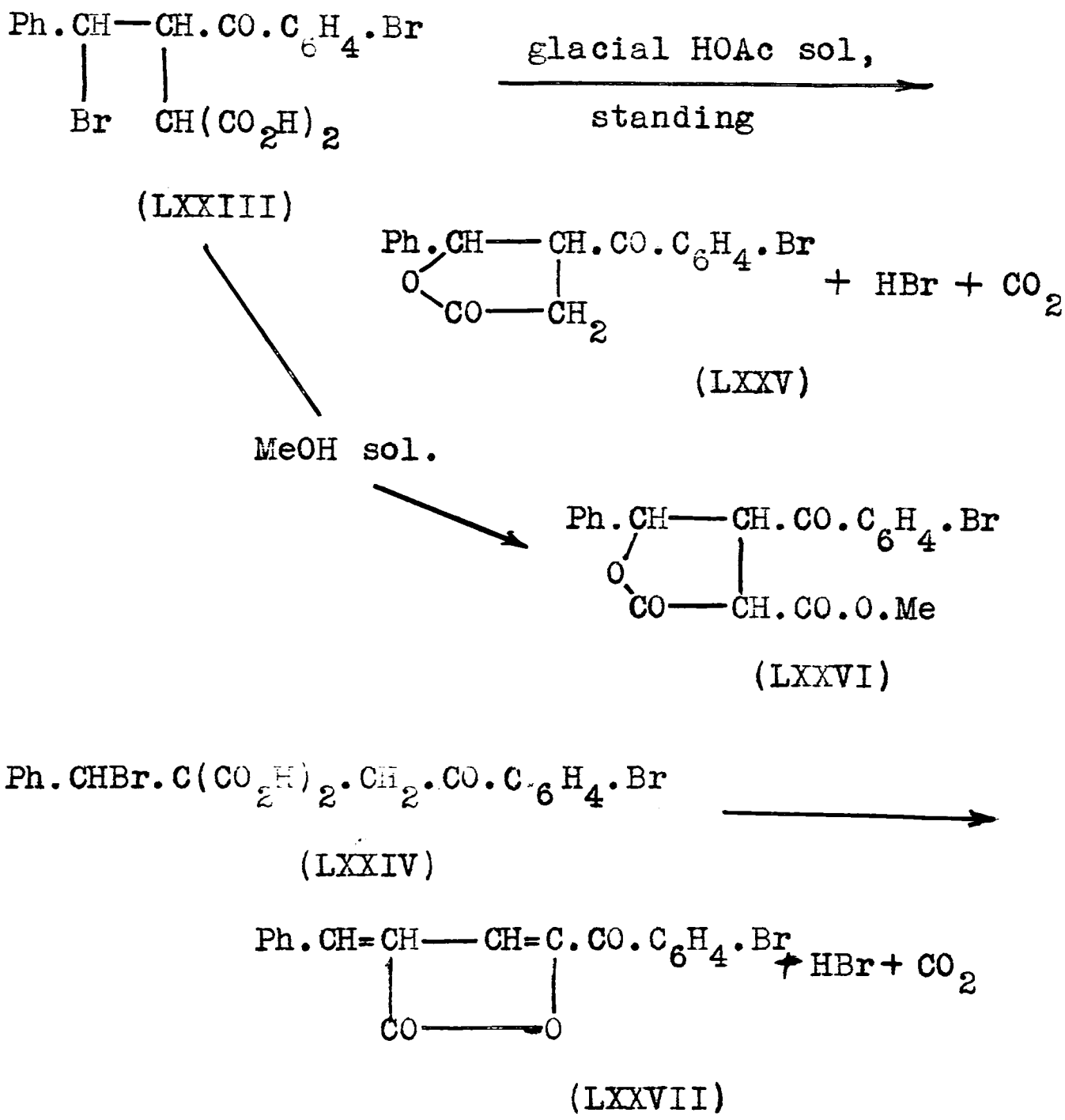


(LXX) (LXXIII)



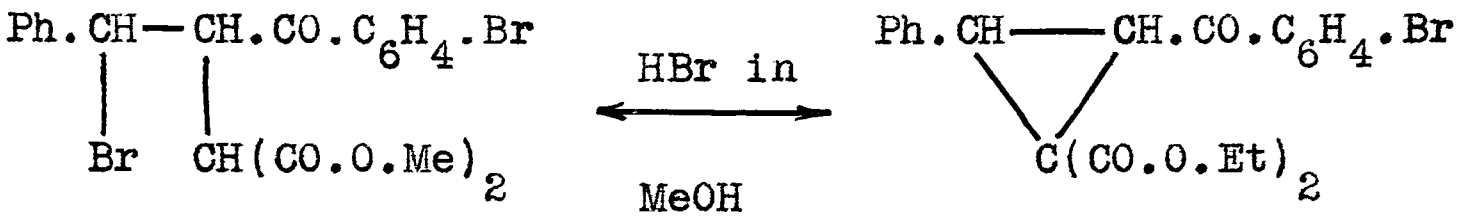
(LXX) (LXXIV)

Both bromo acids are unstable, losing hydrogen bromide spontaneously on standing:



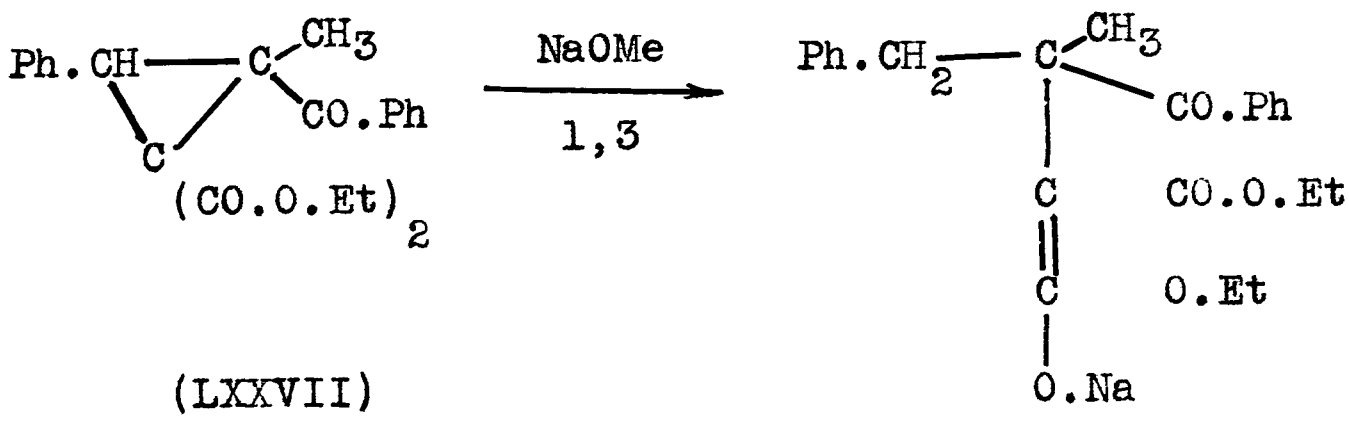
In methyl alcoholic solution, the stable lactone-ester (LXXVI) is formed. Removal of hydrogen bromide to

regenerate the cyclopropane ring takes place less readily than lactone formation. But in alcoholic hydrogen bromide, the bromo acid (LXXIII) yields a little of the cyclopropane ester, suggesting the equilibrium:



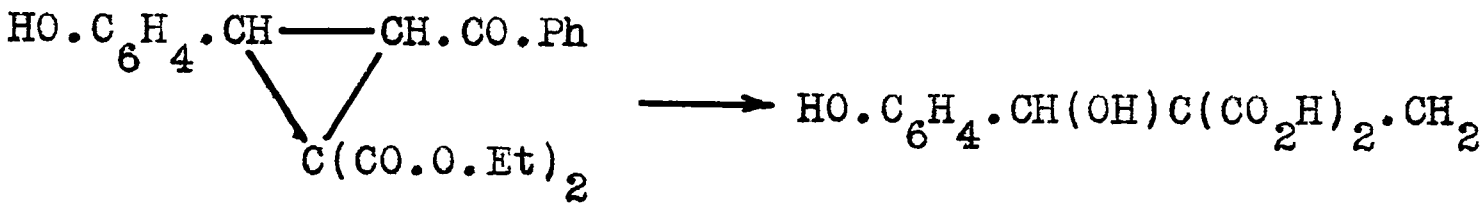
(LXXIII) (LX)

In an attempt to verify the proposed mechanism for the reaction of alcoholates, the compound 2-methyl 2-benzoyl cyclopropane dicarboxylic acid-1,1 (LXXVII) was investigated. It does not react to any perceptible extent with alcoholates, indicating that the 2-methyl group blocks the splitting off of methyl alcohol, so the series of reactions cannot go to completion. Kohler suggests the existance of the equilibrium, which is displaced far to the left:



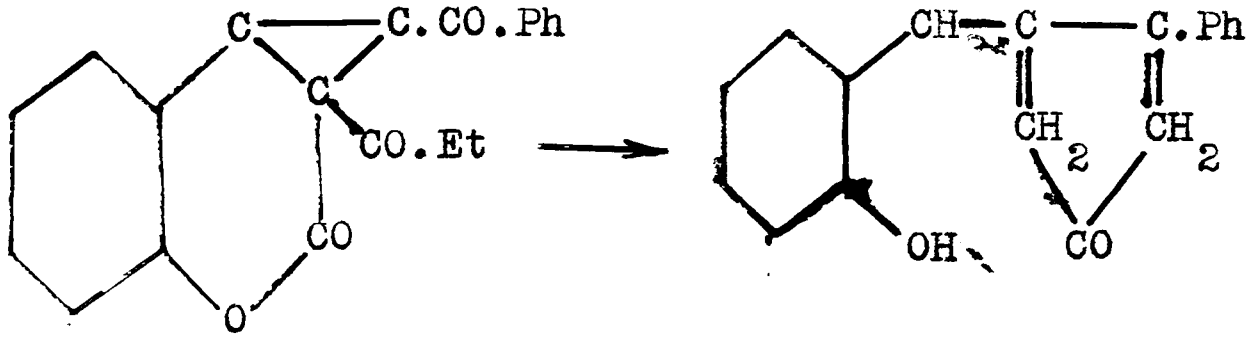
(LXXVII)

While halogen and methoxyl groups on the phenyl groups do not appear to affect the chemical properties of the ring, hydroxy groups have the effect of rendering the ring more sensitive to bases. Dilute sodium hydroxide gives a 2,3 opening with (LXXVIII):



(LXXVIII)

A similar compound, (LI), gives 1,3 cleavage with dilute sodium hydroxide:



(LXXIX)

TABLE I

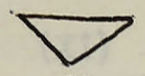
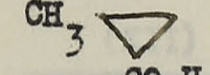
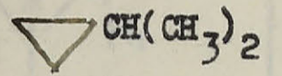
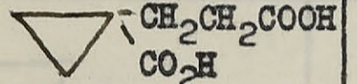
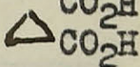
COMPOUND	PYROLYSIS	REDUCTION	ACIDS	BASES	BROMINE	REFERENCES REMARKS
 (I)					Cold, stable; warm HBr evolved + red P → 1,2	(1) Electrolysis of acid + Na salt → $CH_2=CH-CH_2OH$ → ester
 (II)					Br_2 in $CHCl_3$ → 55° derivative	(2)
 (III)	Stable (Acid and ester)					(3) Stable to $KMnO_4$
 (IV)			Conc. H_2SO_4 decomp.			(78)
 (V)	Stable (ester)					(4) $KMnO_4$ →  + $Ph.CO_2H$
Ph  (X)	2,3					(7)

Table I, continued

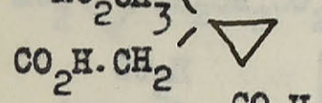
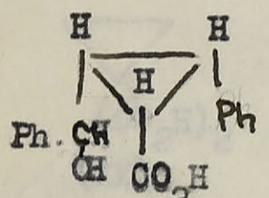
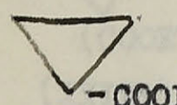
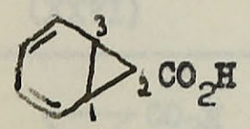
COMPOUND	PYROLYSIS	REDUCTION	ACIDS	BASES	BROMINE	REFERENCES REMARKS
$(CH_3)_2$  COOEt (H) (XI)	Unstable to vac. distillation (acid and ester)					(3, 8)
Me_2CH  $CO_2H.CH_2$ CO_2H (XII)				Me ester NaOMe → C_3H_2-C = CH-CO / CH_2-CH \ COOMe		(10, 11, 12)
 Ph. CH CH CO_2H Ph (XIII)	2,3					(13,14,15,16)
 -COOEt HO . C . CN Me (XIV)			HBr, 1,2 H_2SO_4, 1,2			(5,6)
 CO_2H (XV)			Dilute H_2SO_4 cleaves 1,2 → $Ph.CH_2CO_2H$			(72)

Table I, continued

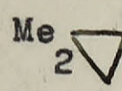
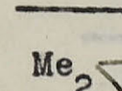
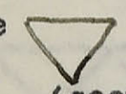
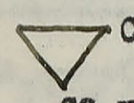
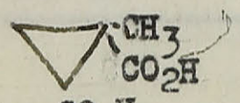
COMPOUND	PYROLYSIS	REDUCTION	ACIDS	BASES	BROMINE	REFERENCES REMARKS
Me_2  CH_2CO_2H CO_2H (XVII)			Conc. HCl → unidentified lactone			(76)
Me_2  $CH_2CH_2CO_2H$ CO_2H (XVIII)			HBr, 1,3 HCl, 1,3 H_2SO_4, 1.3			(73, 74)
 $(CO_2H)_2$ (XX)	1,2	$NaHg_x$ Stable	HBr, 1,2 H_2SO_4, 1,2 HNO_3, stable	$NaCH(COOEt)_2$ 1,2	1,2	(17,18,19,20,75) Stable to $KMnO_4$, almost to CrO_3
Me  $(COOEt)_2$ (XXIII)	Stable (ester) 1,2 (acid	$NaHg_x$ Stable (acid and ester)	HBr, 1,2 H_2SO_4 50%, 1,3		1,2	(22, 23, 24)
Me_2CH  $(CO_2H)_2$ (XXVI)	Loses CO_2					(25)
 CO_2H CO_2H (XXVII)	Trans-stable Cis → anhydride	Stable $NaHg_x$	Cis, stable to HCl aq. H_2SO_4-stable	Stable to {NaOMe / KOH}	Red P + Br_2 substitution only	(26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 79) Stable to $KMnO_4$ at 100°
 CH_3 CO_2H CO_2H (XXVIII)	Cis → anhydride Trans - stable			Conc. KOH 1,3		(36,37)

Table I, continued

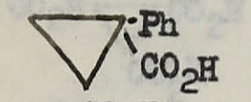
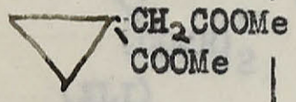
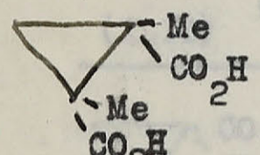
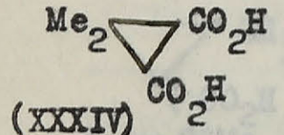
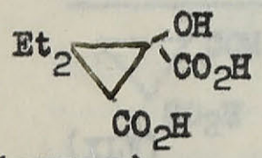
COMPOUND	PYROLYSIS	REDUCTION	ACIDS	BASES	BROMINE	REFERENCES REMARKS
 (XXIX)			Conc. HCl stable			(38)
 (XXX)		$NaHg_x$ 2,3			Stable to Br_2	(39, 40)
 (XXXII)	Ac.-decomp. Ester - stable					(41, 42)
 (XXXIII)						(43, 44, 45) Generally saturated character
 (XXXIV)	1,3		WBr - 2,3 H_2SO_4, 1, 3(?)			(46, 47, 48, 49) Stable to $KMnO_4$
 (XXXVII)				1,2 Reversible		(50)

Table I, continued

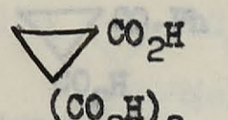
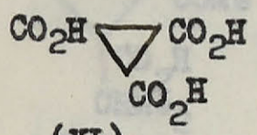
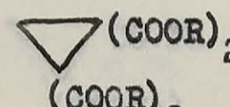
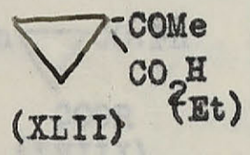
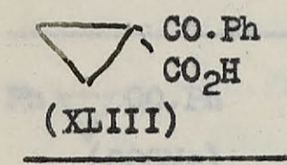
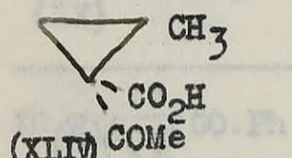
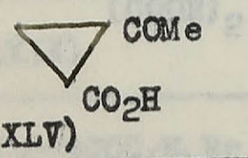
COMPOUND	PYROLYSIS	REDUCTION	ACIDS	BASES	BROMINE	REFERENCES REMARKS
 (XXXIX)	Ester - stable Acid - loses CO_2 and H_2O					(51, 52) Stable to $KMnO_4$
 (XL)			H_2SO_4 dil. 150° → unidentified product			(53) Extremely stable
 (XLI)	Acid loses $2CO_2$					(54, 55, 56, 57, 58, 59) Stable to $KMnO_4$
 (XLII)			HBr, 1,2 H_2SO_4, $-CO_2$	H_2O, 1,2		(60, 61, 62) PCl_5 cleaves ester, not acid
 (XLIII)				H_2O, 1,2		(63)
 (XLIV)	$-CO_2$			Stable to alc. KOH		(64)
 (XLV)	$-CO_2$, Cleavage					(60)

Table I, continued

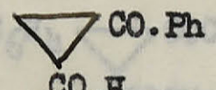
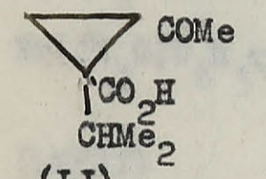
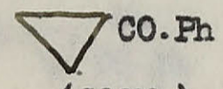
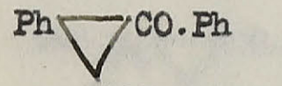
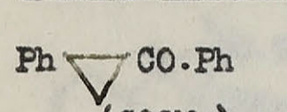
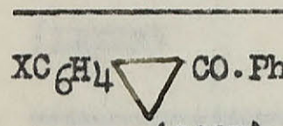
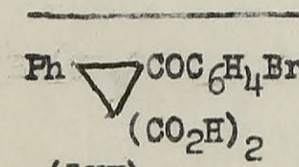
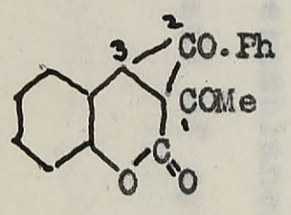
COMPOUND	PYROLYSIS	REDUCTION	ACIDS	BASES	BROMINE	REFERENCES REMARKS
 (XLVIII)	Stable	Zn + HOAc, 1,2	H_2SO_4, conc. Stable at room temp.		Stable to Br_2 in $CHCl_3$	(66)
 (LI)	unsat. lactone	Na + CH_3OH → sat. lactone				(69, 70, 71)
 (LIV)	$-CO_2$ Also 1,2	Zn + HOAc 1,2	H_2SO_4, decomp. at 190° HBr, 1,2	Stable to $NaOCH_3$ $Mg(OCH_3)_2$	Stable to Br_2 in $CHCl_3$	(66, 90)
		174° Et ester, 1,2 153° Et ester, 1,3 Cat. H, 1,3	HBr, 1,3(?)	Stable		(13,86,87,88,89,90)
 (LX)	Acid 1,2; (2,3?)	Zn + HOAc 1,2	HBr, 1,3 2,3 H_2SO_4, 1,3	$NaOCH_3$) NH_3) 1,3 $NaNH_2$)		(86,87,88,90,91,92) PCl_5, 2,3 Grignard, 1,3
 (LXIX)	1,3 2,3		HBr, 1,3 2,3			(86,87,88,89,94)
 (LXX)			HBr 1,3 95% 2,3 5%			(88)

Table I, continued

COMPOUND	PYROLYSIS	REDUCTION	ACIDS	BASES	BROMINE	REFERENCES REMARKS
XC_6H_4 ▽ COC_6H_4Y (COOMe)$_2$ (LXXI)		1,2	HBr 1,3 1,3; 2,3	NaOMe 1,3 1,2(?)	Stable	(86,87) (88,89)
$Br(CH_3O)C_6H_3$ ▽ CO.Ph (COOMe)$_2$ (LXXII)			HBr, 1,3			(63, 88, 92) PCl_5 cleaves acid 2,3 Ester stable
Ph ▽ Me CO.Ph (COOR)$_2$ (LXXVII)				1,3 Reversible Imperceptible		(94)
HOC_6H_4 ▽ CO.Ph (COOR)$_2$ (LXXVIII)			Hot dil. NaOH 2,3			(95)
 (LXXIX)				Hot dil. NaOH 1,3		(95)

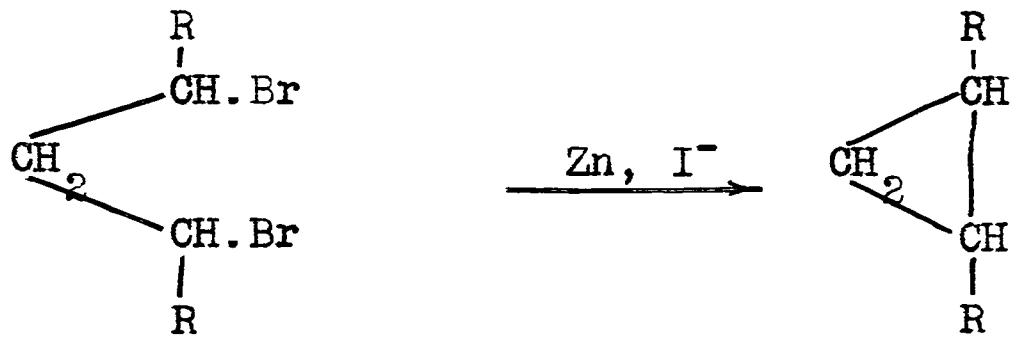
Methods of Ring Formation Applied to Cyclopropane Derivatives

There are six general methods for the synthesis of the three-membered carbocyclic ring. Some are open chain reactions for the formation of a carbon-carbon bond modified to give a ring structure; some are peculiar to ring formation.

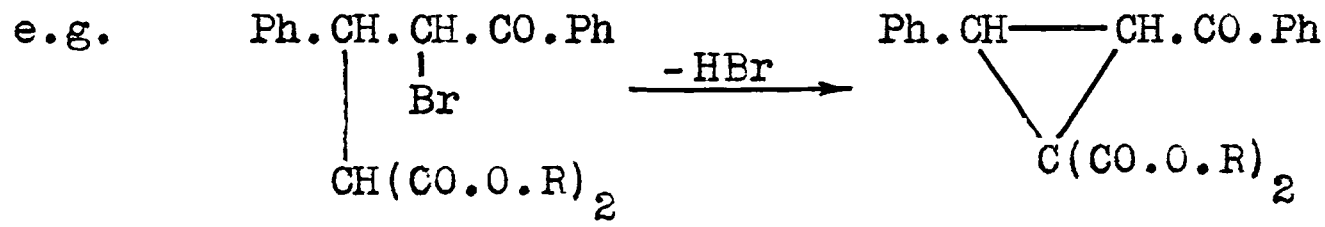
(1) The Wurtz reaction may be modified to give a ring by putting both the halogen atoms on the ends of one chain (96, 97); removal of halogen by sodium, zinc, or "molecular" silver gives ring closure. This method has been used principally for the preparation of hydrocarbons, but will also yield derivatives.

Ease of ring closure is the reverse of that predicted by Baeyer's strain theory-- the ethylenic double bond is formed more readily than the three membered ring. The reaction does not give practical yields of the larger rings. This may be due to steric effects-- in the 1,2 and 1,3 dibromo compounds the two bromine atoms are close enough to react readily, whereas with a larger separation side reactions predominate.

The action of sodium iodide in promoting the reaction affords an example of the close resemblance between the chemistry of ethylenic compounds and of cyclopropane compounds.



(2) Removal of the elements of hydrogen bromide with bases is a general reaction for preparation of a variety of cyclopropane derivatives, especially ketones and esters.

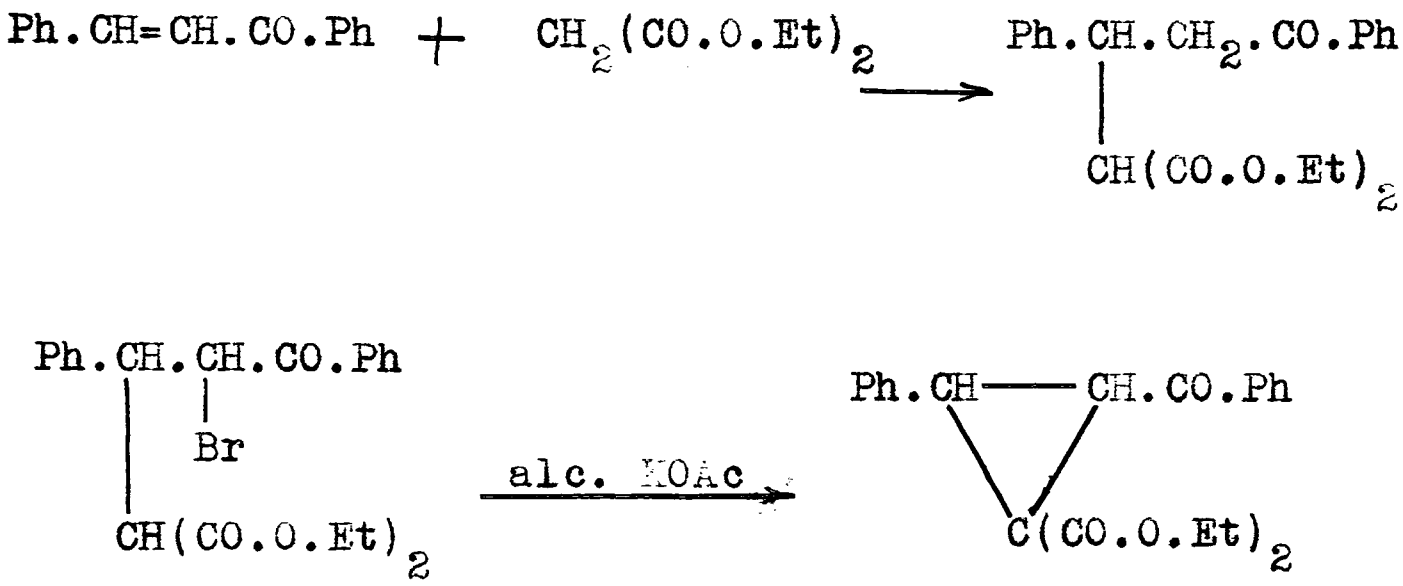


The preference of ring formation to double bond formation is due to the activating effect of the two ester groups on the hydrogen alpha to them. When only one activating group is present, alkaline reagents give hydrolysis and lactone formation. (100)

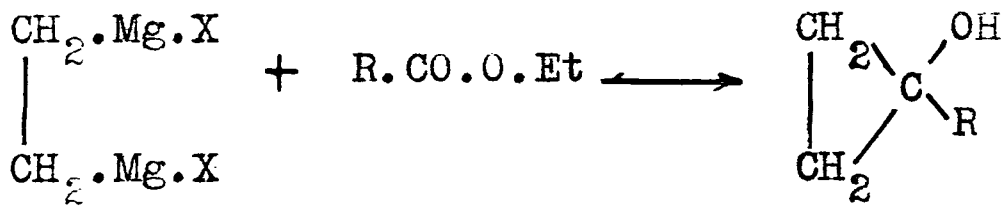
The base used to extract the hydrogen halide may be alcoholic potassium acetate for substances that cyclicize readily, e.g. ketones; or alcoholic or aqueous potassium hydroxide, e.g. for esters. Organic bases may be used where it is desired to abstract hydrogen halide without hydrolyzing ester groups; dimethyl aniline and quinoline are used.

The method is most useful for preparation of cyclopropanes with activating groups on both 1 and 2 carbon atoms.

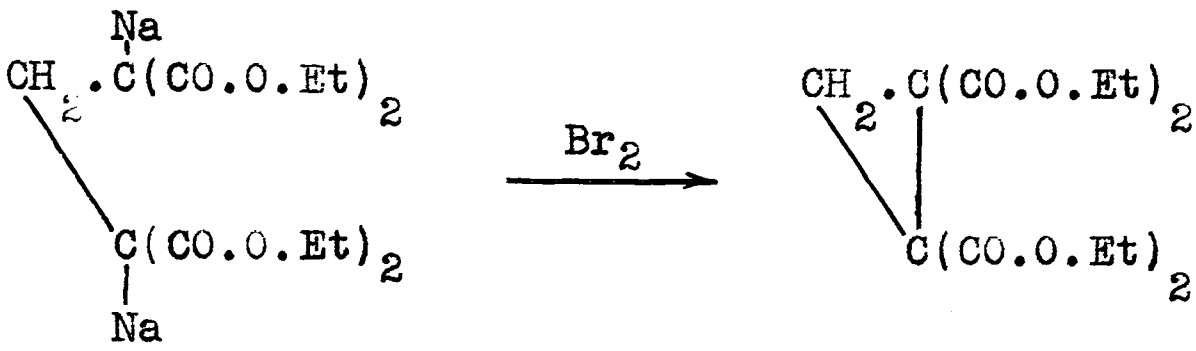
This allows easy bromination of the open-chain compound and abstraction of hydrogen bromide. For example a synthesis due to Kohler(86):



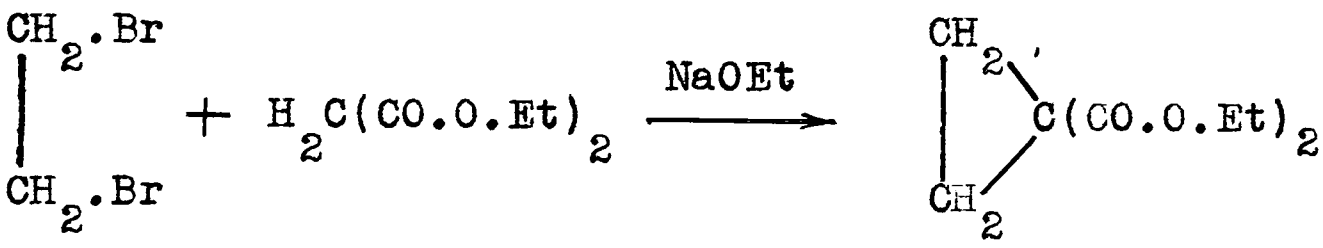
(3) Use of metallo-organic derivatives can be modified in much the same manner as the Wurtz synthesis to give ring compounds. The di-Grignard reagent with an ester gives a cyclic alcohol, and the method could be adapted for cyclopropane derivatives.



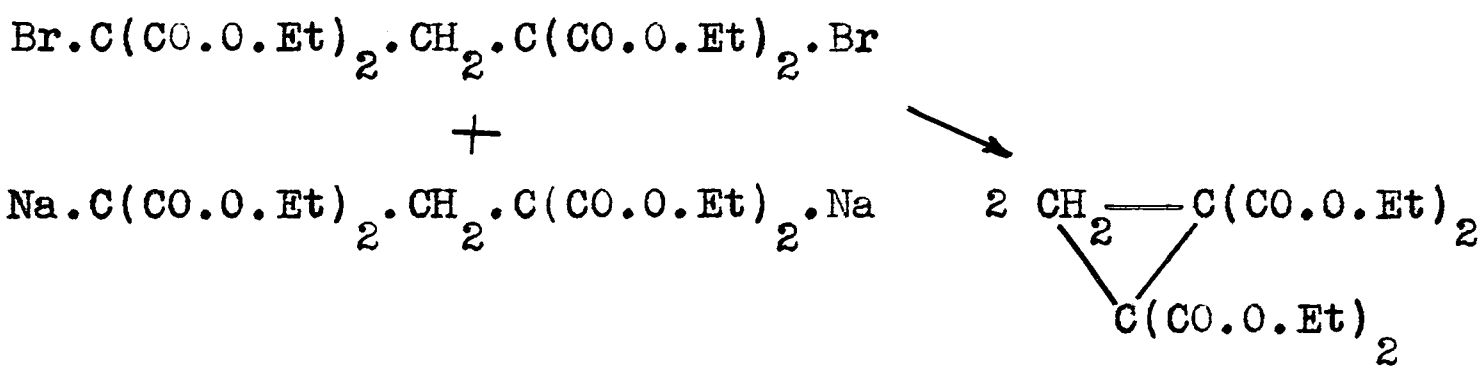
Sodio derivatives of compounds with active methylene groups can be used in different ways. Where there are active methylene groups on either end of the chain, the di-sodio compound may be made and the sodium abstracted with bromine (82):



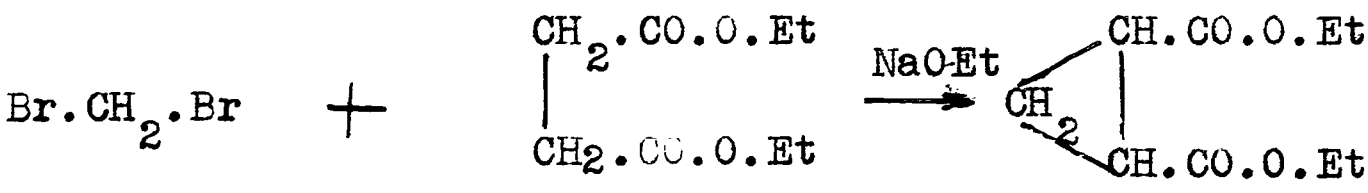
The reaction of malonic ester with 1,2 dibromo compounds in the presence of sodium ethylate is a general method for 1,1 dicarboxylic acids (51):



Combining methods (1) and (3) (82):

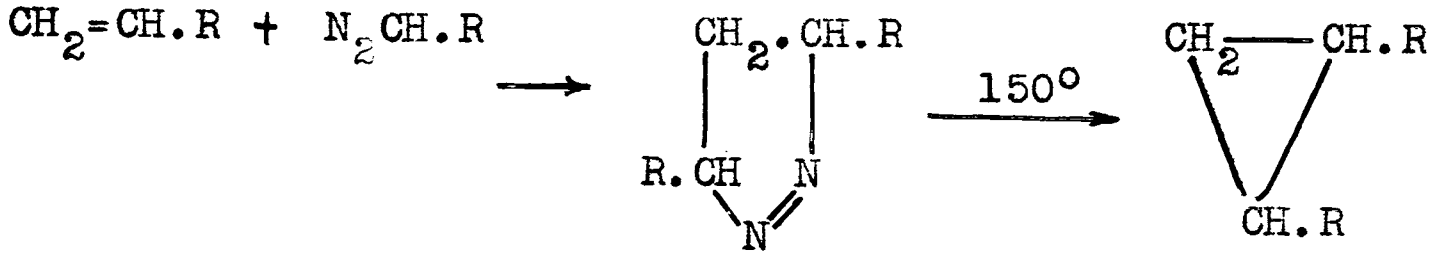


Even succinic ester forms a sodio compound and reacts (58) with methylene halides:



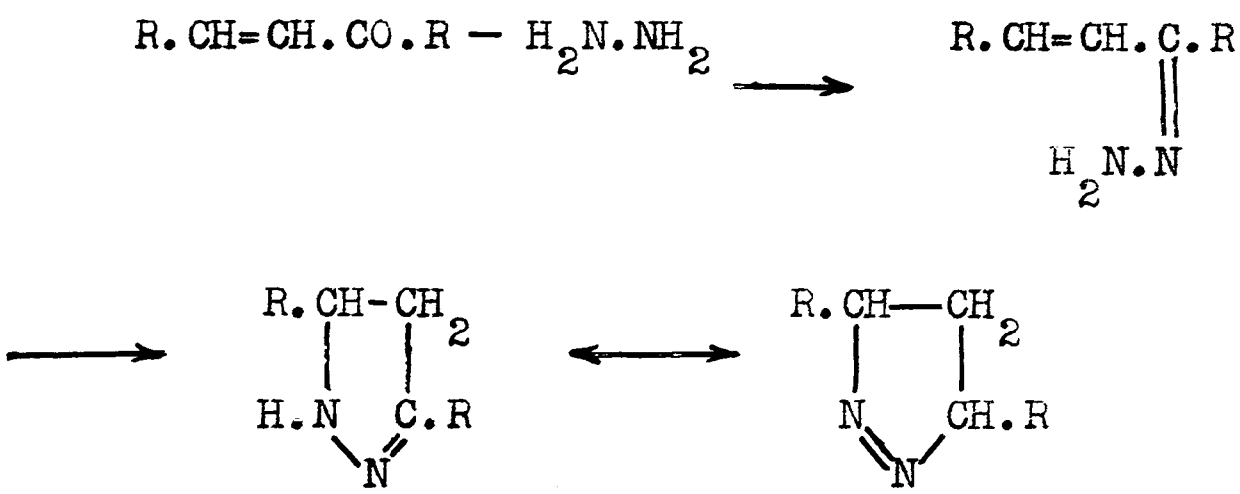
(4) Synthesis via the Pyrazoline Ring deserves

special mention (28, 37, 4, 77, 41, 79, 83) since it was used in the present research. It is useful for preparation of compounds where the open chain does not brominate readily or lose hydrogen bromide in a suitable way to form a ring, or form sodio compounds; and hence is specially valuable for acids. The general course of the reaction is:

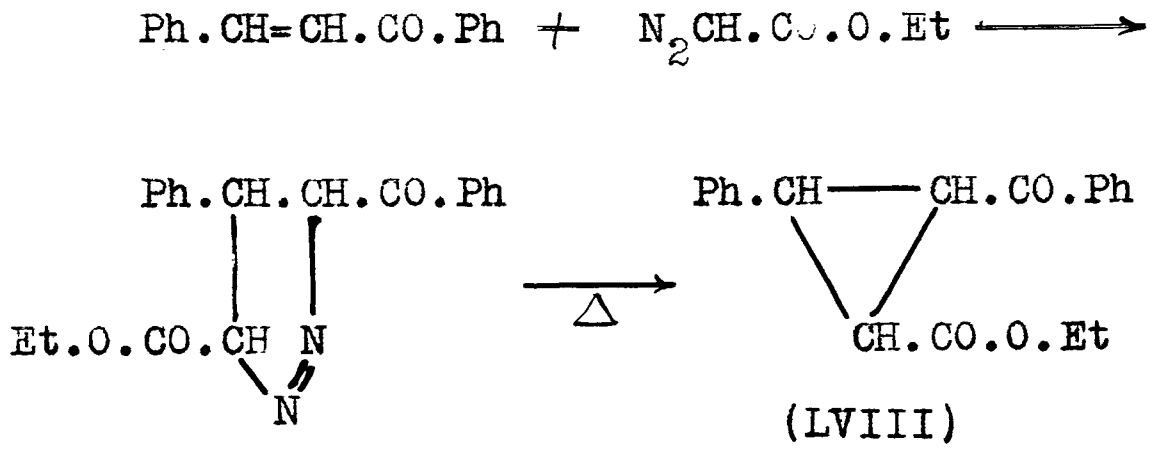


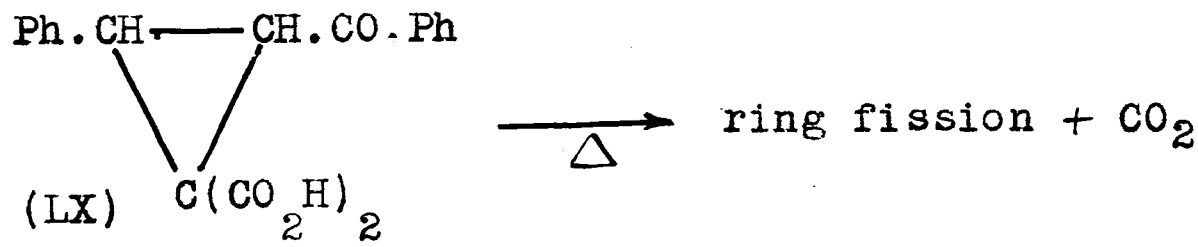
An unsaturated compound reacts with am aliphatic diazo compound to give the pyrazoline derivative, which loses nitrogen on heating. Some of the ethylenic isomer is always produced in addition to the cyclopropane derivative. (R) may be CO.O.R, or negative groups in general.

The aliphatic diazo compounds that are most useful are diazo methane and ethyl diazo-acetate. Or hydrazine may be allowed to react with an alpha-beta unsaturated carbonyl compound to give the pyrazoline (98):



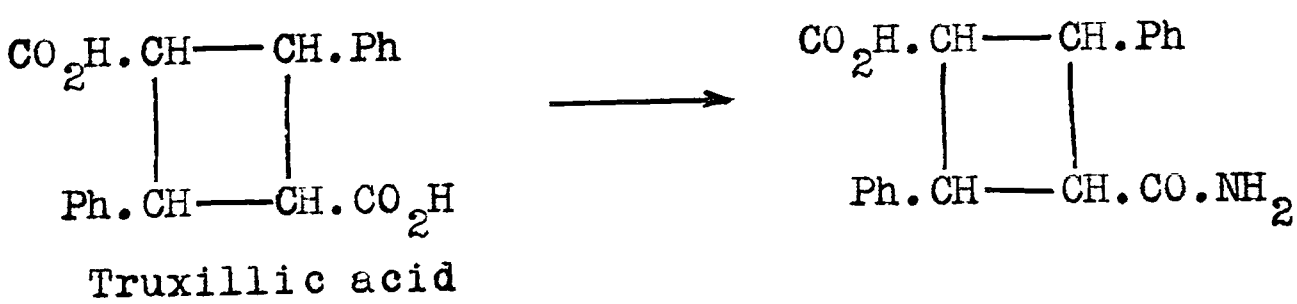
Kohler (89) used this method for preparing the compound (LVIII). The alternative method of decarboxylating the di-carboxylic acid (LX) gave ring fission at the temperature of decarboxylation.

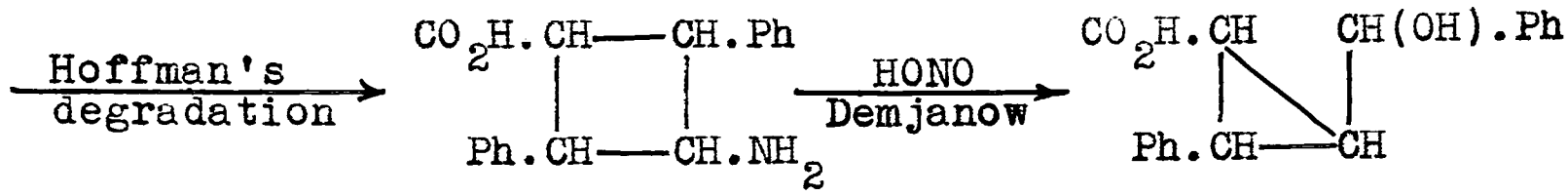




Various catalysts have been used to promote the pyrolysis of the pyrazoline. Kohler used polished platinum scrap (89); Simonsen used copper bronze (76).

(5) The Demjanow ring contraction method has a limited application to cyclopropane syntheses. A good example is the degration of truxinic and truxillic acids to give (XIII) (13, 15):

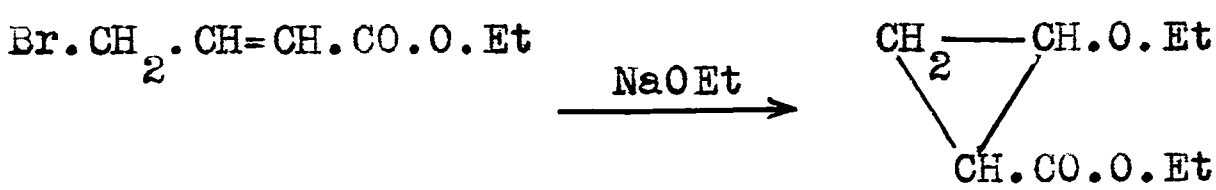




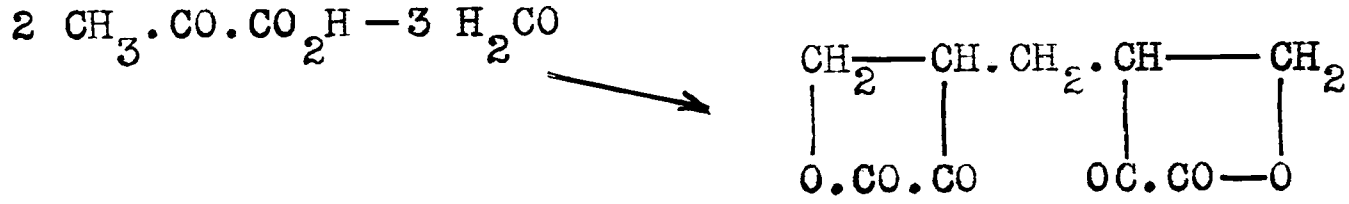
(XIII)

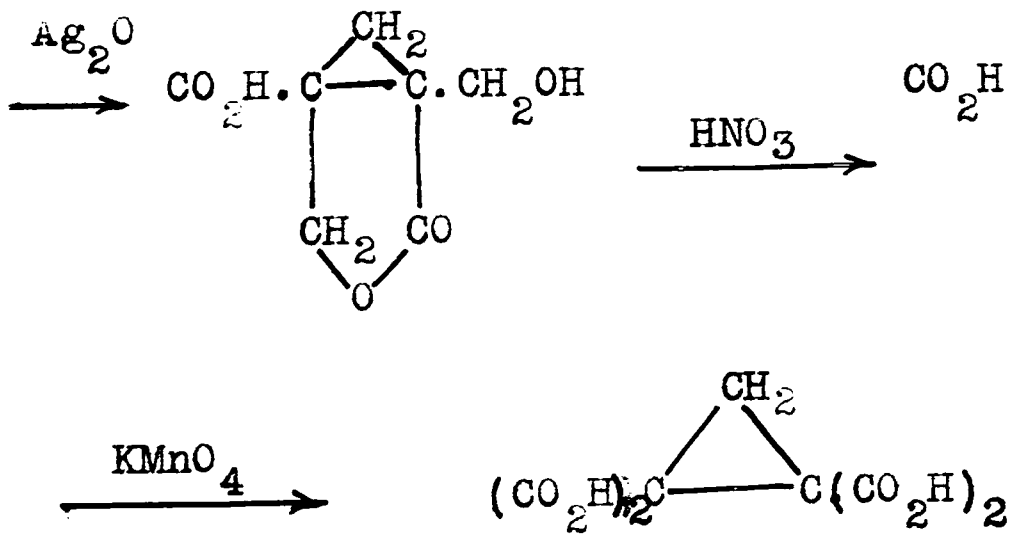
(6) Special methods-- A few examples follow of reactions applicable only to one compound.

2-Ethoxy Cyclopropane Carboxylic Ester--



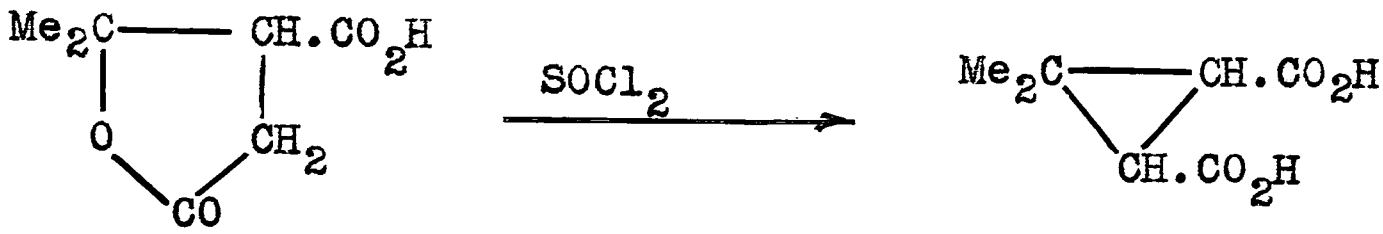
Cyclopropane tetracarboxylic acid-1,1,2,2 (99)



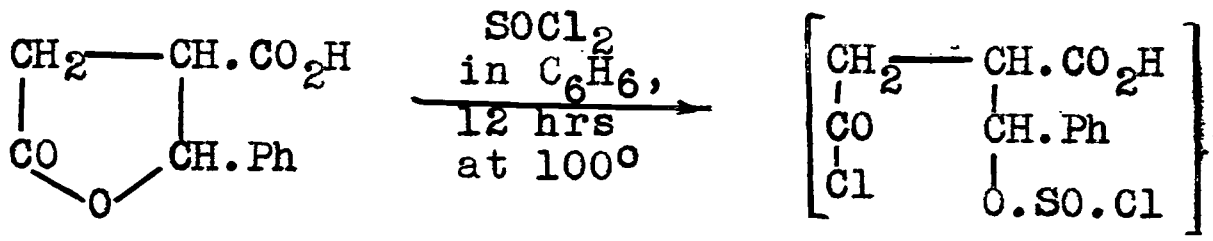


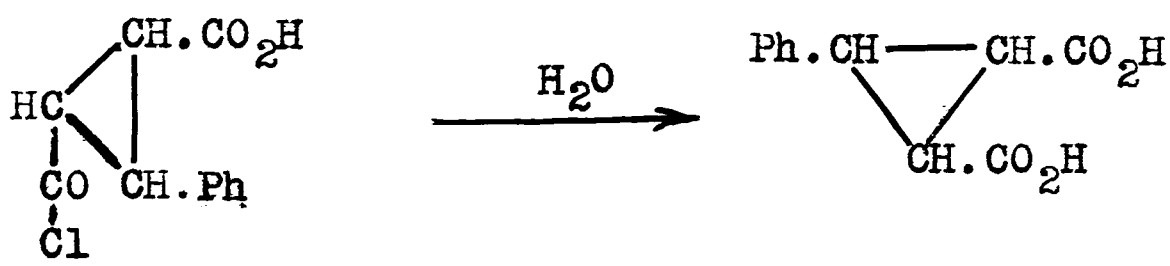
Ring closure is apparently due to the removal of the two hydrogens alpha to the carbonyls by the oxidizing action of the Ag_2O.

The reversal of ring fission and lactone formation seems to be possible when carbon atom-3 is alkyl substituted. Thus terebic acid gives caronic acid:



and phenyl paraconic acid gives 3-phenyl cyclopropane dicarboxylic acid-1,2:



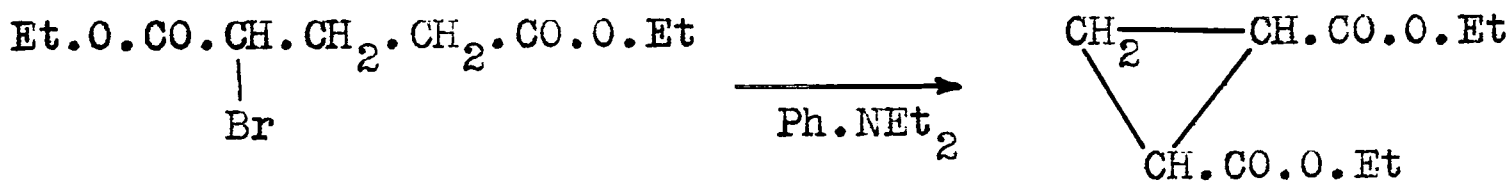


THEORETICAL

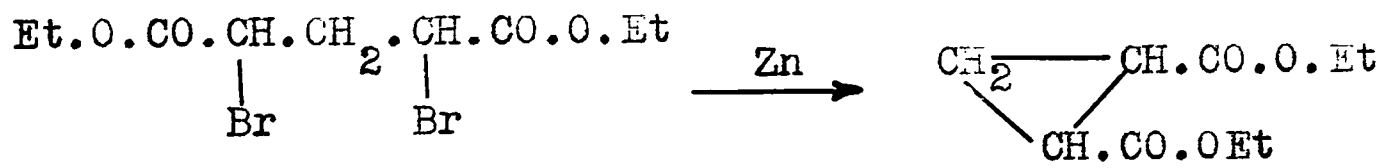
Synthesis of Cyclopropane Dicarboxylic Ester-1,2

Though this compound is very stable, the ring is not very readily formed. Several synthetic methods are available and indeed all the methods previously outlined (except perhaps (5), ring contraction) may be adapted to produce this substance. Possible schemes are:

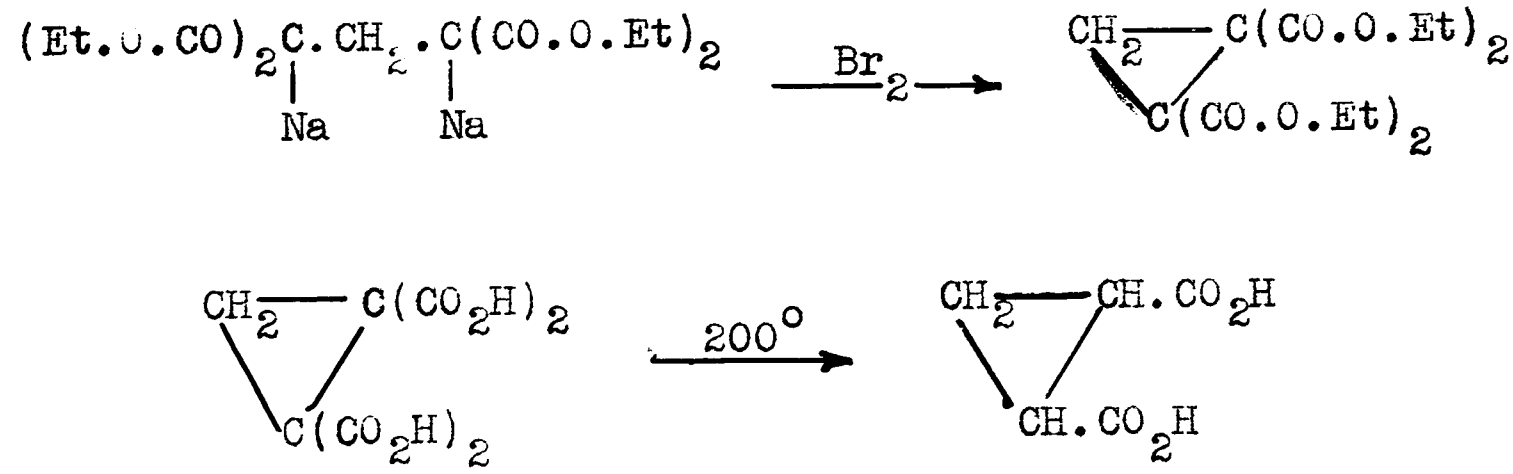
(1) Removal of hydrogen bromine from alpha bromo glutaric ester (26, 27):



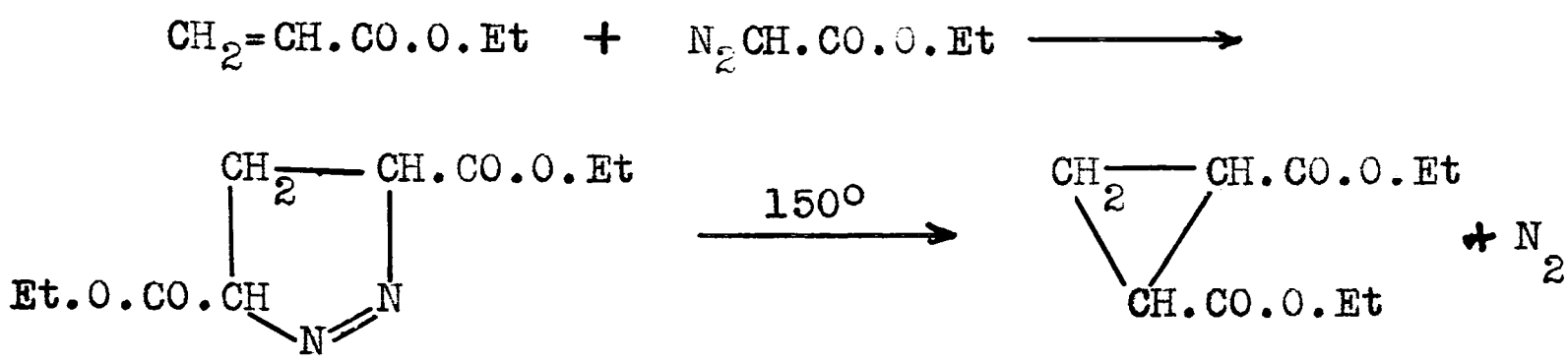
(2) Removal of bromine from $\alpha\alpha'$dibromo glutaric ester:



(3) Removal of sodium from the ends of 1,1,3,3-tetra-carboxy propane, and subsequent decarboxylation (82):



(4) Synthesis via the pyrazoline compound (28):



The last method was the one finally decided upon. It has the advantage that the ester is formed directly, and that no operations are necessary after the ring is formed. The principal disadvantage is the simultaneous production of the ethylenic isomer glutaric ester. The boiling points of the two lie within 5° of each other so separation by fractional distillation was difficult. The method finally used was to obtain a partial separation by fractional distillation, using a column of the Whitmore type, and to remove the last traces of glutaric ester by washing the product, in benzene solution, with aqueous potassium permanganate. This gave a product that did not decolorize permanganate in two minutes. Complete freedom from ethylenic compounds was essential, as these might well give reactions with the ring opening reagents similar to those of the ring compound, thus invalidating the results.

Auwers and König have made a study of the effect of substituents on the pyrazoline ring on the production by pyrolysis of ethylenic or cyclopropane compounds. Their findings are that the more complex pyrazoline derivatives

give a larger proportion of cylic compounds; that monocarboxy pyrazolines give principally ethylenic compounds, while dicarboxy pyrazolines give principally cyclopropane compounds, though mixtures may be obtained; and that pyrazolines tend to form ethylenic isomers, while pyrazolines tend to form cyclic derivatives.

Accordingly, a reasonable yield of the cyclopropane isomer should be obtained from the dicarboxy pyrazoline.

The action of various catalysis on the pyrolysis of the pyrazoline was investigated in an effort to increase the amount of the cyclopropane compound formed at the expense of the ethylenic compound. Copper powder, nickel powder, and polished platinum were used. Copper alone had any effect, causing the reaction to go at a lower temperature; no effect on the relative yields was noticed.

Both the condensation of the diazoacetic ester with the acrylic ester, and the pyrolysis of the resulting pyrazoline are exothermic reactions. A run must be made in small batches, and the temperature closely controlled, both heating and cooling. A modification was introduced to allow large runs to be made in one batch, and to combine the two operations. It also had the effect of improving the yield. Instead of mixing the reactants in equimolecular quantities and allowing the reaction to proceed, the diazoacetic ester was passed slowly, through a long hair-capillary, into an excess of boiling ethyl acrylate.

Condensation and elimination of nitrogen took place simultaneously, giving a crude mixture of the cyclopropane ester and glutaconic ester, which was distilled directly.

Cleavage of Cyclopropane Dicarboxylic Ester-1,2

Since the compound is so stable, drastic conditions were required to open the ring. Every reaction was carried out in a bomb tube, and the ring still resisted some reactants.

The reactions tried were pyrolysis on the ester; catalytic reduction on the free acid; bromine on the ester; hydrogen bromide both on the acid and on the ester; sulfuric acid (50%), both on the acid and on the ester; and sodium ethylate in ethanol on the sodium salt.

Pyrolysis

The ester was reported to be stable to vaccuum distillation (28, 77). A micro boiling point determination at atmospheric pressure showed the boiling point to be unchanged after boiling for 15 minutes. This was taken to indicate that the ester was stable to distillation at atmospheric pressure.

Reduction

The ester was known to be stable to reduction by concentrated sodium amalgam (80). It was not felt necessary to repeat this reaction.

Catalytic reduction over colloidal platinum at one

atmospheric pressure and room temperature failed to affect the ring. With a view to obtaining more drastic conditions, the acid was treated with hydrogen over Raney nickel at varying pressures and temperatures.

The nickel catalyst was prepared by the method of Homer Adkins, and in a test run catalyzed the reduction of benzene to cyclohexane in the usual manner.

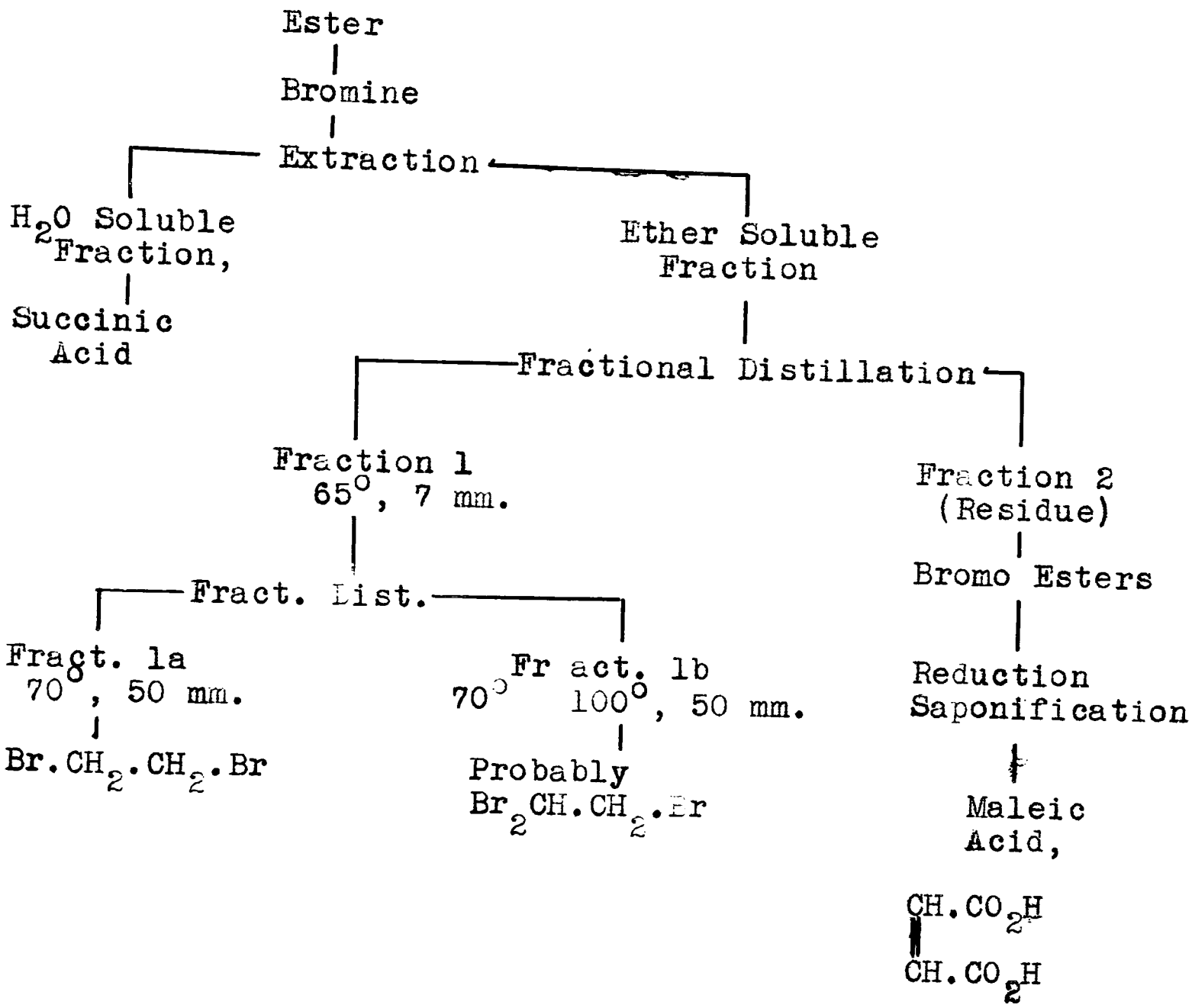
The run was made on the free acid in absolute ethanol solution. The pressure and temperature were gradually raised, until at 200° C. and 200 atmospheres an apparent inflection point was noted. After 20 minutes under these conditions the product was removed, but no reduction products could be isolated from the reaction mixture; the bulk of the original acid was recovered unchanged either as the acid or the ester.

Bromine

Previous reports indicate that bromine is without effect on our compound, but that in the presence of red phosphorus it gives substitution. (30)

The ester was treated with bromine at elevated temperatures. The best results were obtained with high temperatures (200 - 250° C.) for a short time ($\frac{1}{2}$ - 1 hour). No derivatives containing all three of the carbon atoms of the original ring were obtained, but only C_2 derivatives. These included succinic acid, more or less heavily brominated succinic esters, and brominated ethanes.

Flow Sheet, Bromine fission



Outline of a run: The reaction mixture was heated in a bomb tube under varying conditions of time and temperature. On opening the tube, much hydrogen bromide escaped. The reaction mixture was dissolved in ether and the solution extracted with an equal quantity of water, dividing the products into two fractions , ether soluble and water soluble.

The water solution was evaporated, and the residual solid identified by neutral equivalent and mixed melting point determinations as succinic acid.

The ether soluble fraction was fractionally distilled. Early runs showed that it contained brominated ethanes and brominated succinic esters, so the distillation was run so as to effect a rough separation of these two classes, the distillate (Fraction 1) containing the brominated hydrocarbons, and the residue (Fraction 2) the brominated esters. Fraction 1 was fractionally distilled again, and separated into two fractions, 1a and 1b. Only very small amounts of these fractions were obtained, so a complete purification was not possible, making identification difficult. Elementary analysis, boiling point, melting point, and refractive index, showed that these fractions were probably 1,2-dibromo ethane and 1,1,2-tribromo ethane.

Fraction 2, the bromo esters, was reduced with zinc-copper couple and saponified. The product was identified by melting point and mixed melting point determinations as maleic acid.

The occurence of succinic and maleic acids among the products of the reaction with bromine seemed to indicate a 1,3 ring fission, going through the intermediate methyl succinic acid. This is a rather unexpected result, as experience shows that with 1,2-disubstituted cyclopropanes

the ring is almost always open between the two substituted carbon atoms. This unusual result may be due to the unusually drastic conditions employed. Also, with this procedure, it is impossible to distinguish between effects of the bromine and of the hydrogen bromide which is present as a result of substitution.

To test the possiblity of methyl succinic ester as an intermediate, a run was made on methyl succinic ester under the same conditions as with the cyclopropane ester. Similar treatment of the reaction mixture gave the same products as were obtained from the cyclopropane ester. The water-soluble fraction consisted of succinic acid; of the ether soluble fraction, fraction 1 was brominated hydrocarbons, and was not further treated. Fraction 2 was brominated ester, and was reduced with zinc-copper couple, the product being a mixture of maleic and succinic acids.

The brominated hydrocarbons might have two scources. They might be the product of the reactions of the methylene residues, carbon atom number three of the ring which was lost during the reaction or they might come from bromination and decarboxylation of succinic acid. To test the first possibility, a run was made using succinic ester under the same experimental conditions. Fraction 1 of the ether soluble portion was obtained as before, characterized by mode of separation, insolubility in concentrated sulfuric acid, density range, and

odor as a mixture of brominated hydrocarbons. This indicates that the source of the brominated ethanes is bromination and decarboxylation of succinic acid.

From the evidence presented above, we concluded that bromine opens the ring of cyclopropane dicarboxylic ester-1,2 between carbon atoms 1 and 3 (or 2 and 3), the reaction going through the intermediate methyl succinic ester. The experimental conditions necessary are so drastic that the ring is broken up, carbon atom number 3 of the ring being lost and not accounted for in the products.

In a run at a lower temperature (150°) the ring was not broken. The water soluble fraction was cyclopropane dicarboxylic acid-1,2; the ether soluble fraction consisted of brominated esters which on reduction and saponification gave an acid which could not be identified, but which had some of the properties of an unsaturated cyclopropene carboxylic acid.

Hydrogen Bromide

The reaction with hydrogen bromide was very sensitive to temperature, either little reaction occurring, or tar formation being the predominating reaction. The best temperature was found to be 170°. The time for all runs was six hours. Anhydrous acetic acid saturated with dry hydrogen bromide was the reagent.

At the temperature used, some tar was formed. Little gas was formed during the reaction. The reaction mixture was fractionally distilled directly. After removal of hydrogen bromide and acetic acid a bromine containing oil distilled, which solidified on standing. The solid was acidic, contained no bromine, melted at 80 - 140°. Crystallization from benzene-acetone mixture gave a precipitate which after purification was shown by melting point and mixed melting point determinations to be succinic acid.

The mother liquor from the crystallization yielded an acid which melted in the range of glutaric acid, but which was shown by a mixed melting point not to be glutaric acid, and which could not be identified.

Water extraction of the tar gave an oil which solidified on standing. The solid was identified by melting point and mixed melting point determinations as glutaric acid.

From the evidence presented above we concluded that hydrogen bromide gives both 1,2 and 1,3 ring fission with cyclopropane dicarboxylic acid-1,2.

Sulfuric Acid

It was known from previous reports that the acid was stable to concentrated sulfuric acid at 100° and that above this temperature the compound was destroyed (33, 34, 35).

Dilute acid (50%) at 150° was used in the present investigation, and runs were made both on the acid and the ester. The product from the reaction of the ester consisted of an aqueous layer and an oily layer. The aqueous layer contained unchanged cyclopropane dicarboxylic acid-1,2. The oily layer was distilled, and two fractions were separated. The saponification equivalents were determined, and were slightly above the theoretical for cyclopropane dicarboxylic ester-1,2. The acids were recovered from the saponification reaction mixtures, and consisted principally of cyclopropane dicarboxylic acid-1,2.

With the free acid, 50% sulfuric acid at 150° for six hours gave a solid tar. Water extraction yielded only a small quantity of the starting material.

Sodium Methylate

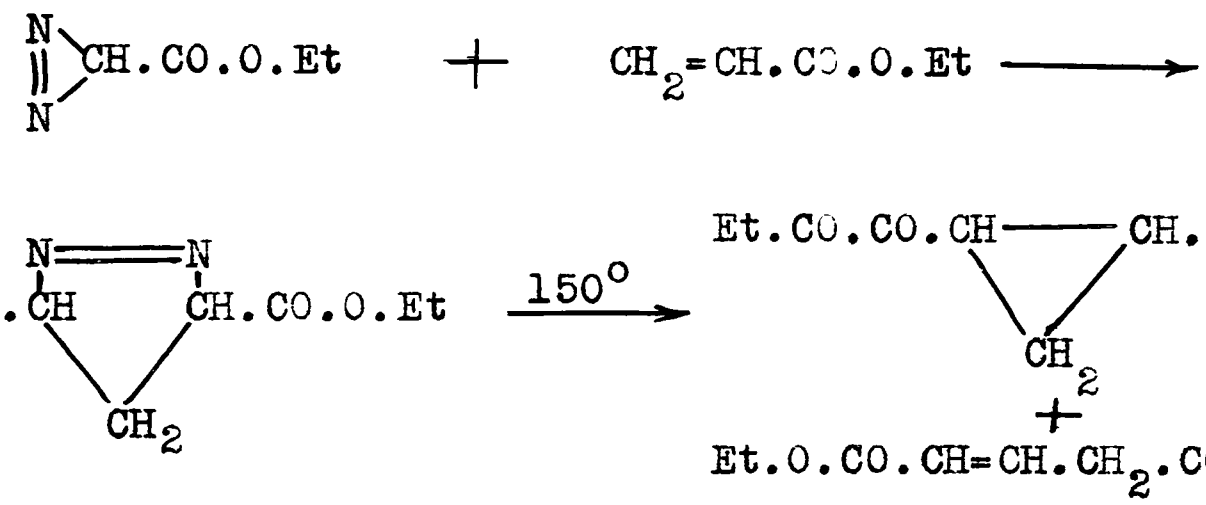
It had been previously reported that aqueous bases were without effect on the ring (31). The present run was made with anhydrous alcoholic sodium methylate at 150° for six hours. The sodium salt of the cyclopropane acid was used to avoid neutralization of part of the methylate by the acid or the products of saponification.

After treatment, no change was observable in the appearance of the reaction mixture, and the bulk of the acid was recovered unchanged. It was accordingly concluded that dry sodium methylate had no effect on the compound under the experimental conditions used.

EXPERIMENTAL

The Preparation of Cyclopropane Dicarboxylic Ester-1,2

The method employed was Büchner's pyrazoline method. Diazoacetic ester reacts with acrylic ester to give pyrazoline dicarboxylic ester-3,5, which loses nitrogen at 150° to give a mixture of cyclopropane dicarboxylic ester-1,2 and glutaconic ester:



The diazoacetic ester was made by the directions of Gatterman, Laboratory Methods of Organic Chemistry, McMillan, London, 1937. The acrylic ester was generously donated by Rohm and Haas, Philadelphia, Pa.

The first run was made by the batch method (77). The quantity of reaction mixture must be kept down to 50 g., otherwise temperature control becomes difficult. Equimolecular quantities of the reactants (27 g. diazoacetic ester and 23 g. ethyl acrylate) were mixed, and the

temperature allowed to rise spontaneously to a maximum of 50°, where it was held for 2 hours. Some nitrogen was evolved during this process.

The pyrazoline compound could be isolated by cooling the reaction mixture, when partial solidification took place. Filtering and crystalization from water yielded pyrazoline dicarboxylic acid-3,5-diethyl ester, melting point 57° C.

Since the separation gave a poor yield, it was not attempted in most cases, but the reaction mixture was subjected to pyrolysis directly.

By preference the reaction mixture from the condensation was heated cautiously under a reflux condenser to 150° C. A warm water bath was kept at hand to quench the reaction if necessary. Evolution of nitrogen continued for 3 hours. The products from several such reactions, using in all 100 g. of diazoacetic ester, were distilled in vacuo, the portion (about 100 cc.) passing over at 100-150° C. at 14mm. being collected. It was dissolved in 300 cc. benzene, and shaken in a flask, while cooling, with 10% potassium permanganate solution until a permanent excess was present (about 1500 cc. required). The benzene-water mixture was then filtered with suction, and the precipitated MnO_2 washed with benzene and with water. The two layers of the filtrate were separated; the solvent was distilled from the benzene layer, and

the residual ester distilled in vacuo, the bulk (about 45 cc.) passing over at 115 0. 5° C. at 14 mm. A sample was tested for ethylenic compounds by treatment with potassium permanganate in acetone. No change took place for 1 minute; the ester always gave decolorization on standing.

An attempt was made to prepare the cyclopropane dicarboxylic ester-1,2 by diazotizing the glycine ester hydrochloride in solution in ethyl acrylate, using amyl nitrite as a scource of nitrous acid. At the boiling point (100°) nitrogen was evolved, but no cyclopropane dicarboxylic ester could be isolated from the reaction mixture. At 0° a reaction occurred, the glycine ester hydrochloride, which is insoluble at that temperature, slowly dissolving. But again no cyclopropane ester could be isolated.

The di-ethyl ester has not been reported. So the compound was characterized by the physical constants of the acid. The ester boiled at 115° C. at 14 mm., 230° C. at 1 atmosphere with no apparent decomposition; saponification equivalent 93.0 (theoretical 93.0); density $^{20°}_{20°}$, 1.070; the acid (crude, extracted from saponification reaction mixture) melted at 174° C. (Büchner, 175° C.).

On the <u>second run</u>, an innovation was introduced enabling the first two steps, condensation of the diazoacetic ester and acrylic ester and elimination of nitrogen,

to be combined. It also improved the yield. Instead of mixing the reactants in equimolecular proportions and allowing the reaction to proceed, diazoacetic ester was passed slowly through a long hair capillary into an excess of boiling ethyl acrylate (B. P. 100° C.) under reflux. Condensation and elimination of nitrogen took place simultaneously. The reaction mixture was then distilled directly in vacuo, using a column of the Whitmore type. The first fraction contained principally cyclopropane dicarboxylic ester-1,2 and some glutaconic ester. The second fraction boiled about 4° higher, and consisted principally of glutaconic ester with about 20% cyclopropane ester.

The first fraction was washed with permanganate and distilled, boiling at 115° at 14 mm. Yield from 125 g. diazoacetic ester, 50 g. of the purified material (24%, based on diazoacetic ester). No attempt was made to recover the cyclopropane ester contained in the second fraction, which would have raised the yield above that from the first run (28%).

Ring Opening Reactions of Cyclopropane Dicarboxylic Acid-1,2 and Ester

Pyrolysis

A boiling point determination was made on the ester by the semi-micro method. After boiling for 30 minutes the boiling point was unchanged, so it was concluded that

the ester was stable to distillation at atmospheric pressure.

Reduction

Catalytic reduction was attempted both over platinum at atmospheric pressure and room temperature, and over Raney nickel at elevated temperatures and pressures.

The platinum catalyst was prepared by the method of Adams (101), and on a test run catalysed the reduction of cinnamic acid. A run on the cyclopropane ester gave no absorption of hydrogen. The apparatus used was that described by Shriner (102) for quantitative catalytic hydrogenation.

The nickel catalyst was prepared by the method of Adkins, and on a test run catalysed the reduction of benzene to cyclohexane in the expected manner. The free cyclopropane acid was used instead of the ester, since the carboxyl group is more resistant to reduction than the ester group, and under the drastic conditions employed even Raney nickel, which is ordinarily inactive in the reduction of carbonyl groups, might have attacked the ester groups. The run was made on 3 g. of the acid, dissolved in 25 cc. absolute ethanol, using 1.5 g. catalyst.

The bomb was filled with hydrogen at room temperature to a pressure of 1160 lbs./in.^{2}, and heated to 100°, when the pressure had risen to 1390 lbs./in.^{2} (95 atmos.) and held there for 30 minutes. Since no inflection point was

observed, the temperature was raised to 150° (109 atmos.) for 30 minutes, where no inflection point was observed. The bomb was allowed to cool to 100°, and more hydrogen added to 182 atmospheres pressure. It was kept at 100° for 30 minutes, then raised to 150° (206 atmos.) for 30 minutes, then to 200° (242 atmos.), when an apparent inflection point was observed. After 20 minutes the bomb was cooled and the reaction mixture removed. The sample was so small that absorption of the theoretical amount of hydrogen would have been barely perceptible on the pressure guage.

No reduction products could be recovered from the reaction mixture; the bulk of the starting material was recovered either as the acid or as the ester. Hence cyclopropane dicarboxylic acid-1,2 is stable to catalytic reduction under the conditions of the experiment.

We wish gratefully to acknowledge the loan of the Adkins high pressure hydrogenation apparatus by the Department of Industrial and Cellulose Chemistry and the assistance rendered by Mr. L. Cooke.

Bromine

In all four runs were made, in order to determine the optimum conditions. The following outline describes the most successful one, the third.

The reaction mixture consisted of 4 cc. cyclopropane dicarboxylic ester-1,2, and 6 cc. bromine in a sealed tube.

The temperature of the bomb furnace rose to 250° for 30 minutes, and was then reduced to 150° for 6 hours. We believe that most of the reaction occurred at the high temperature, and that this (purely fortuitous) temperature rise gave the clue to the best conditions. On opening the tube, much gaseous products escaped, mostly hydrogen bromide.

The reaction mixture was dissolved in ether, and washed with an equal quantity of water. The water soluble fraction after evaporation of the solvent, gave a solid residue and some oil, which was removed by pressing on porous plate. The solid, amounting to about 0.2 g., was crystalized once from water, and melted at 186-8° C. A mixture with succinic acid (m. p. 188° C.) melted at 187°C., whereas a mixture with cyclopropane dicarboxylic acid-1,2 (m. p. 175° C.) melted at about 158° C. The neutral equivalent was determined as 60 (theoretical for succinic acid, 59). Thus the substance was identified as succinic acid.

The ether soluble fraction after removal of solvent was distilled in vacuo, the distillate (Fraction 1) being taken off up to 65° C. at 7 mm. The residue will be designated Fraction 2.

Fraction 1 was separated from any esters by washing with concentrated sulfuric acid, in which it was insoluble. It was separated into two fraction, 1a and 1b, by fraction-

al distillation at 50 mm.

Fraction 1a, amounting to about 0.1 cc., distilled up to 70° C. at 50 mm. It was identified as 1,2-dibromo ethane. The properties of the two follow:

	Fraction 1a	$Br.CH_2.CH_2.Br$
Boiling point, 1 at.	126° C.	131° C.
Melting point	about -10°	7°
Density	>1.8*	2.2
$n_D^{20°}$	1.5348	1.5378

*Greater than that of sulfuric cid

Fraction 1b, amounting to about 0.1 cc., distilled at 70-100° C. at 50 mm. It was identified as 1,1,2-tribromo ethane. The properties of the two follow:

	Fraction 1b	$Br_2CH.CH_2.Br$
Boiling point, 1 at.	182° C.	186° C.
Melting point	--	-26°
Density	>1.8*	2.6
$n_D^{20°}$	1.5836	1.5890

*Greater than that of sulfuric acid.

Fraction 2 was dissolved in 40 cc. of 50% ethanol, and refluxed for 1 hour with 10 g. zinc-copper couple. The reaction mixture was filtered, the zinc ion precipitated from the filtrate with just sufficient sodium hydroxide, and the zinc hydroxide filtered off. The filtrate was boiled for a few minutes to insure complete saponification, made acid, and the acids extracted with ether. Evaporation gave a solid and some oil, from which it was freed by pressing on

porous plate. The solid, amounting to about 0.5 g., melted at 124-9° C. A mixture with maleic acid (m. p. 130° C.) melted at 127° C. Thus the substance was identified as maleic acid.

It should be noted here that the products isolated accounted for only a small portion of the starting material.

Another run at a lower temperature (150° for 6 hours) failed to open the ring. The water soluble fraction was shown to be cyclopropane dicarboxylic acid-1,2. The bulk of the ether soluble fraction distilled at 145° at 8 mm. On reduction with zinc-copper couple and saponification, a solid was obtained, acidic, bromine-free, very soluble in water, unstable to permanganate, melting at 154-6°. It was felt that it might be cyclopropene dicarboxylic acid-1,2. Since this substance has not been reported, and insufficient time was available to synthesize it, further identification was not attempted.

Hydrogen Bromide

Four runs were made to determine the optimum temperature. This was found to be 170° C., at which temperature only a little tar was formed.

The reaction mixture consisted of 4 g. cyclopropane dicarboxylic acid-1,2, 10 cc. fuming hydrogen bromide in glacial acetic acid (0.36 g. hydrogen bromide per cc. of solution). It was heated at 170° C. for 6 hours. On opening the tube little gas escaped. The reaction mixture was distilled directly, first at atmospheric pressure until the solvent

was removed, then at 15 mm., when a bromine-containing oil distilled at 115-160° C., the bulk at 145° C. After standing over night the oil partially solidified; the solid was freed from adhering oil by pressing on porous plate. It contained no bromine; on attempting to determine the melting point, about half the sample melted around 80° C., the rest around 140° C.

Fractional crystalization from acetone-benzene gave a precipitate melting at 165° C. A mixture with cyclopropane dicarboxylic acid-1,2 melted at 150° C. Recrystalization from acetone-benzene gave a product (about 0.02 g.) melting at 175° C. A mixture with succinic acid (m. p. 185° C.) melted at 182-4° C. A neutral equivalent determination gave a value of 64 (theoretical for cyclopropane dicarboxylic acid-1,2, 65; for succinic acid, 59). The acid recovered from the neutral equivalent reaction mixture melted at 180-3° C. Thus the acid was identified as succinic acid.

The mother liquors from the crystalization yielded an acid melting at 95° C. A mixture with glutaric acid melted at 65-75° C., proving the acid not to be glutaric. The acid could not be identified.

Water extraction of the solid tar from the reaction mixture gave a small quantity of an oil which on long standing solidified. The solid was pressed on porous plate, melted at 93-4° C, A mixture with glutaric acid melted at 94-5° C., proving the substance to be glutaric acid (m.p. 99° C.). There was not enough recovered to determine the

neutral equivalent.

From the evidence presented above we concluded that hydrogen bromide cleaves the acid both 1,2 and 1,3.

Sulfuric Acid

Run 1 was made on the ester. The reaction mixture consisted of 5 cc. cyclopropane dicarboxylic ester-1,2, and 5 cc, 50% sulfuric acid. It was heated at 150° C. for 6 hours.

On opening the sealed tube, little gas escaped. The reaction mixture consisted of two layers, slightly brown, otherwise unchanged in appearance. The contents of the tube were extracted with ether, the ether solution washed with sodium carbonate solution, evaporated, and the residual oil (about 0.4 cc.) distilled by a micro method. Two fractions were collected.

Fraction 1 came over below 170° (bath temperature) at 45 mm. The boiling point at 1 atmosphere was 230° C.; the saponification equivalent was determined as 95; the acid recovered from the saponification equivalent reaction mixture melted at 165-70° C., and a mixture with cyclopropane dicarboxylic acid-1,2 geve no depression. So the product was identified as cyclopropane dicarboxylic ester-1,2(b. p. 230° C., saponification equivalent 93, acid melts at 175° C.)

Fraction 2 came over at 170-210° (bath temperature) at 45 mm. Its saponification equivalent was determined as 113. The acid extracted from the saponification reaction mixture melted at 160-65° C., and a mixture with cyclopro-

pane dicarboxylic acid-1,2 gave no depression. So the product was cyclopropane dicarboxylic ester-1,2 containing impurities that could not be identified.

Acidification and ether extraction of the sodium carbonate washings yielded no product.

Run 2 was made on the free acid. After 6 hours at 200° C. a solid black tar resulted. On opening the sealed tube much gas escaped, with only a slight odor of SO_2. Water extraction of the solid tar gave a small amount of an acid melting at 170° C. a mixture of which with cyclopropane dicarboxylic acid melted at 170-2° C. So the product was identified as cyclopropane dicarboxylic acid-1,2.

From the data presented above we concluded that cyclopropane dicarboxylic ester was stable to sulfuric acid under the conditions of the experiment, and that the acid was stable under conditions insufficiently drastic to form a tar.

Sodium Methylate

The cyclopropane dicarboxylic ester-1,2 (5 cc.) was saponified with 3 g. potassium hydroxide, the reaction mixture evaporated to dryness, and the potassium salt used directly. It was mixed intimately with 8cc. of a suspension of sodium methylate in anhydrous methyl alcohol (15% sodium) and heated for 6 hours at 200° C.

The reaction mixture was dissolved in water, made acid, some silica which precipitated was filtered off, and the solution was extracted with ether. The ether solution was

evaporated to about 10 cc., chloroform added until a precipitate appeared, warmed until the precipitate dissolved, and crystalized by cooling. Further crops were obtained by evaporating to smaller volumes and cooling. Each fraction contained 0.4-0.6 g. The melting points follow:

Fraction	1	172-5° C.
"	2	172-5
"	3	173-4
"	4 (Residue)	165-9

Mixtures of these samples with cyclopropane dicarboxylic acid-1,2 gave no depression of the melting point.

So it was concluded that the product consisted mainly of unchanged cyclopropane dicarboxylic acid-1,2 (m. p. 175° C.), and that the acid was stable to sodium methylate under the conditions employed.

SUMMARY

(1) Cyclopropane dicarboxylic acid-1,2-diethyl ester was prepared by Buchner's pyrazoline method. The method was examined, and innovations introduced which increased its usefulness and raised the yield slightly.

(2) The behavior of the compound toward ring opening reagents was investigated. The reactions tried were pyrolysis on the ester, catalytic hydrogenation, both over platinum at atmospheric pressure and room temperature on the ester, and over Raney nickel at elevated temperatures and pressures on the acid, bromine on the ester, hydrogen bromide on the acid and the ester, sulfuric acid on the acid and the ester, and sodium methylate on the potassium salt.

The compound was found to be very stable. All reactions were carried out in bomb tubes at high temperatures, and the only reagents that succeeded in opening the ring were bromine, giving 1,3 cleavage, and hydrogen bromide, giving both 1,2 and 1,3 cleavage.

REFERENCES

1. Beilstein, 9, 4; 9', 3
2. Beilstein, 9, 6
3. Blanc and Haller, Compt. rend., 145, 78, (1907)
4. Carl von der Heide, Ber., 37, 2101, (1904)
5. Kuster, Z. physiol. Chem., 145, 53, (1925)
6. Kuster, May, Wolf, Eberle and Mandry, Z. physiol. Chem., 172, 232, (1927)
7. Buchner and Geronimus, Ber., 36, 3782, (1903)
8. Kishner, J. Russ. Phys. - Chem. Soc., 45, 957, (1913); through Brooks, "The Chemistry of Non-benzenoid Hydrocarbons," 1922 edition, page 250.
9. Wallach, Ann., 272, 99, (1892)
10. Semmler, Ber., 33, 273, (1900)
11. Wallach, Ann., 388, 50, (1912)
12. Toivonen, Ann. Acad. Sci. Fenn., 28, 8, (1928)
13. Stoermer, Ber., 60, 2573
14. Stoermer, Ber., 61, 2312
15. Stoermer, Ber., 64, 2785
16. Schenk, J. pr. 134, 230
17. Perkin, J. Chem. Soc., 47, 801, (1885)
18. Fittig and Roeder, Ann., 227, 21, (1885)
19. Perkin and Bone, J. Chem. Soc., 67, 111, (1895)
20. Franchimont, Rec. Chim., IV, 398, (1885)

21. Perkin and Bone, J. Chem. Soc., 67, 108

22. Marburg, Ann., 294, 112, (1897)

23. Fittig and Hjelt, Ann., 216, 56, (1882)

24. Marburg, Ann., 294, 125, (1897)

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

26. Perkin Jr. and Bowtell, Proc. J. Chem. Soc., 15, 241, (1899)

27. Perkin Jr. and Tatterstall, J. Chem. Soc., 87, 362, (1905)

28. Buchner, Ber., 23, 701, (1890)

29. Buchner, Ann., 284, 197, (1895)

30. Buchner and Wedemann, Ber., 38, 1599, (1905)

31. Ingold, J. Chem. Soc., 119, 305, (1921)

32. Beilstein, 9, 723; 9', 314

33. Feist, Ber., 26, 761, (1893)

34. Buchner, Ann., 284, 200, (1895)

35. Ingold, J. Chem. Soc., 119, 320, (1921)

36. Ingold, J. Chem. Soc., 127, 387, (1925)

37. Auwers and König, Ann., 496, 252, (1932)

38. Semmler, Ber., 40, 5022, (1907)

39. Ruhemann, J. Chem. Soc., 81, 1215, (1902)

41. Buchner, Ber., 27, 878, (1894)

42. Semmler, "Handbuch" III, s. 205.

43. Paolini, G. (30) II, 501, (1900)

44. Henstock and Woolley, J. Chem Soc., 91, 1955, (1907)

45. Reference 37.

46. Simonsen, J. Chem. Soc., 28, 431-8

47. Baeyer, Ber., 29, 2799

48. Barbier, Compt. rend., 153, 188

49. C. A., 23, 2427

50. Ken. Stevenson and Thorpe, J. Chem. Soc., 121, 650

51. Guthzeit and Conrad, Ber., 17, 1186, (1884)

52. Michael, A. C. S. IX, 120, (1887)

53. Reference 34.

54. Perkin Jr., Ber., 19, 1056, (1886)

55. Guthzeit and Dressel, Ann., 256, 197, (1889)

56. Perkin Jr. and Gregory, J. Chem. Soc., 87, 358, (1905)

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

58. Koetz and Stalmann, J. pr. Chem. (2), 68, 156, (1903)

59. Koetz and Sielisch, J. pr. Chem. (2), 75, 476, (1907)

60. Freer, P. C. and Perkin, W. H., J. Chem. Soc., 51, 820-849, (1887)

61. Kohler, E. P. and Steele, L. L., J. A. C. S., 41, 1093-1105, (1919)

62. Perkin, J. Chem. Soc., 47, 833, (1885)

63. Freer, P. C. and Perkin, W. H., J. Chem. Soc., 51, p. 838, (1887)

64. Perkin Jr., J. Chem. Soc., 47, 850, (1885)

65. Reference 60.

66. Cressman, H. W. J., Thesis, McGill U., 1933

69. Tutin, J. Chem. Soc., 89, 1104, (1906)

70. Lees, J. Chem. Soc., 85, 645, (1904)

71. Semmler, Ber., 40, 5022, (1907)

72. Buchner and Braren, Ber., 34, 985, (1901)

73. Simonsen, J. Chem. Soc., 121, 2292, (1922)

74. Owen and Simonsen, J. Chem. Soc., 1932, 1428

75. Reference 18.

76. Owen and Simonsen, J. Chem. Soc., 1933, 1225-7

77. Buchner and Papendieck, Ann., 273, 234, (1893)

78. Fecht, Ber., 40, 3883, (1907)

79. Pechmann, Ber., 27, 1891, (1894)

80. Reference 77.

81. Reference 55.

82. Reference 56.

83. Buchner and Weigand, Ber., 46, 763, (1913)

84. Semmler, Ber., 36, 4368, (1903)

85. Wallach, Ann., 275, 180, (1893)

86. Kohler and Conant, J. A. C. S., 39, 1409, (1917)

87. Kohler and Conant, J. A. C. S., 39, 1669, (1917)

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

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

90. Synthetic Organic Chemicals published by Eastman Kodak Company, X, no. 3, (1937)

91. Kohler, Am. Chem. J., 46, 474, (1911)

92. Kohler, J. A. C. S., 44, 840, (1922)

93.

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

95. (a) Widman, O., Ber., 51, 523, (1918)

(b) idem. Ber., 51, 907, (1918)

(c) idem. Ber., 52B, 1652, (1919)

96. Lespieau and Wakeman, Bull. Soc. Chem., 51, 384, (1932)

97. Haas, McBee and Glusenhamp, Ind. Eng. Chem., 28, 1178, (1936)

98. Kishner, C., 1913, II, 2133

99. Feofilaktov, C., 1930, I, 1471

100. Nicholls, R. V. V., Thesis, McGill U. 1936, (pg. 23)

101. Organic Syntheses, Collective Volume I

102. Shriner, Quantitative Analysis of Organic Compounds; Edwards Brothers, Inc., Ann Arbor, Mich., (1938)