SYNTHESIS OF ALKYL CYCLOPROPYL ETHERS

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TABLE OF CONTENTS

	Page
INTRODUCTION. PART I. PHARMACOLOGY	1
Theories of Narcosis	1
Chemotherapy of Anesthetics	2
Properties of an Ideal Anesthetic	3
Properties of Inhalation Anesthetics	4
Reasons for Preparing Cyclopropyl Ethers	6
INTRODUCTION. PART II. CHEMISTRY	8
Methods of Preparing Ethers	8
Methods of Making Certain Cyclopropyl Compounds	9
Methods of Making Cyclopropyl Rings	14
Choice of a Method of Synthesis	18
EXPERIMENTAL	20
Introduction	20
Attempts to Synthesize Biscyclopropyl Ether	36
Experiments with α,γ Dichloro-β-Bromopropane	38
Synthesis of β,β'-Dichloroisopropyl Methyl Ether	39
Synthesis of β,β'-Dibromoisopropyl Methyl Ether	41
Synthesis of β,β'-Dibromoisopropyl Ethyl Ether	43
Synthesis of β,β'-Dibromoisopropyl n-Propyl Ether	44
Synthesis of β,β'-Dibromoisopropyl n-Butyl Ether	45
Synthesis of β,β'-Dibromoisopropyl Bromopropyl Ether	48
Synthesis of Methyl Cyclopropyl Ether	46
Synthesis and Properties of Ethyl Cyclopropyl Ether	64

Synthesis and Properties of Propyl Cyclopropyl Ether..... 68

Synthesis and Properties of n-Butyl Cyclopropyl Ether 71

PHARMACOLOGY OF METHYL CYCLOPROPYL ETHER 74

SUMMARY 76

REFERENCES 77

List of abbreviations 77

Literature Cited 78

LIST OF TABLES

Table No.	Title	Page
I	Average Yields of Cyclopropyl Ethers	27
II	Physical Properties of Cyclopropyl Ether	29
III	Physical Constants Reported for Allyl Ethers	30
IV	Comparison of Parachors and Molecular Refractivities of Cyclopropyl and Allyl Ethers	30
V	Physical Constants of α,γ-Dibromopropyl Alkyl Ethers	31
VI	Physical Constants of β,γ-Dibromopropyl Alkyl Ethers	32
VII	Melting Points of β-Bromopropionic Acid Obtained from Cyclopropyl Ethers	32
VIII	Physical Constants of Propylene Dibromide Obtained from the Cyclization of β,β'-Dibromoisopropyl Alkyl Ethers	35
IX	Physical Constants of Dibromopropanes	35
X	Attempts to Prepare a Metallic Alkoxide Derivative of Glycerin α,γ-Diacetate	37
XI	Synthesis of β,β'-Dichloroisopropyl Methyl Ether	39
XII	Yields of β,β'-Dichloroisopropyl Methyl Ether	40
XIII	Yields of β,β'-Dibromoisopropyl Methyl Ether	42
XIV	Methylation in the Presence of a Solvent	43
XV	Fractionation of β,β'-Dibromoisopropyl Ethyl Ether	45
XVI	Summary of Some Cyclization Experiments	47
XVII	Crude Yields of Methyl Cyclopropyl Ether from β,β'-Dibromoisopropyl Methyl Ether	49

XVIII	Reaction of Perbenzoic Acid with Methyl Cyclopropyl Ether	51
XIX	Calibration of Surface Tension Apparatus with Benzene	53
XX	Calibration of Pycnometer No. 59	54
XXI	Physical and Molecular Properties of Methyl Cyclopropyl Ether	54
XXII	Atomic and Structural Parachors	56
XXIII	Constants Used to Calculate Molecular Refractivity from Molecular and Structural Data	57
XXIV	Determination of Carbon and Hydrogen in Methyl Cyclopropyl Ether	58
XXV	Physical Properties of α,γ-Dibromopropyl Methyl Ether	58
XXVI	Calibration of Pycnometer No. 1	58
XXVII	Determination of Bromine in α,γ-Dibromopropyl Methyl Ether	59
XXVIII	Determination of Carbon and Hydrogen in β-Bromopropionic Acid	60
XXIX	Determination of Halogen in the Material Recovered from Methanol	61
XXX	Physical Properties of the Bromine Derivative of the Gaseous By-Product from the Preparation of Methyl Cyclo-Propyl Ether	61
XXXI	Determination of Halogen in the Bromine Derivative of the Gaseous By-Product from the Preparation of Methyl Cyclo-Propyl Ether	62
XXXII	Physical and Molecular Properties of Allyl Methyl Ether	63
XXXIII	Determination of Carbon and Hydrogen in Allyl Methyl Ether	63
XXXIV	Physical and Molecular Properties of Ethyl Cyclopropyl Ethers	64

XXXV	Determination of Carbon and Hydrogen in Ethyl Cyclopropyl Ether	65
XXXVI	Physical Properties of α, γ Dibromopropyl Ethyl Ether	65
XXXVII	Determination of Halogen in α, γ-Dibromopropyl Ethyl Ether	65
XXXVIII	Determination of Halogen in the Material Recovered from Ethanol	66
XXXIX	Physical Properties of the Bromine Derivative of the Gas from the Preparation of Ethyl Cyclopropyl Ether	67
XL	Determination of Halogen in the Bromine Derivative of the Gas from the Preparation of Ethyl Cyclopropyl Ether	67
XLI	Physical and Molecular Properties of n-Propyl Cyclopropyl Ether	69
XLII	Determination of Carbon and Hydrogen in n-Propyl Cyclopropyl Ether	69
XLIII	Physical Properties of α, γ-Dibromopropyl n-Propyl Ether	70
XLIV	Calibration of Pycnometer No. 2	70
XLV	Physical Properties of the Brominated Gas from the Preparation of n-Propyl Cyclopropyl Ether	71
XLVI	Physical and Molecular Properties of n-Butyl Cyclopropyl Ether	72
XLVII	Determination of Carbon and Hydrogen in n-Butyl Cyclopropyl Ether	72

SYNTHESIS OF ALKYL CYCLOPROPYL ETHERS

INTRODUCTION. PART I. PHARMACOLOGY

A Brief History of Anesthetics. Anesthetics for dulling pain have been used since antiquity. Thus, the Egyptians used narcotics; the Chinese used hashish. During the middle ages various kinds of narcotics such as opium and drugs containing hyoscine were employed.

Safe, surgical anesthesia has been known less than one hundred years. In 1799, Sir Humphrey Davy suggested the use of nitrous oxide in surgical operations, since it appeared capable of destroying pain. However, this suggestion was not acted upon at that time. Dr. Crawford W. Long administered ether as a surgical anesthetic for the first time in 1842 but he did not publish his discovery adequately. In 1844, Dr. Horace Wells, a dentist, introduced nitrous oxide into general dental practice. He gave the matter wide publicity. He also tried ether in 1845, but he thought that nitrous oxide was superior. Dr. Wm. T.G. Morton, another dentist, carried out a successful anesthesia with ether in 1846. A little later, he demonstrated its use in a surgical operation performed by Dr. J.C. Warren. Morton obtained a patent for the use of ether as an anesthetic.

Flourens used chloroform on animals in 1847. Simpson, acting on an independent suggestion by McWadie, used chloroform on man in the same year.

Hayfelder used ethyl chloride for surgical anesthesia in 1848, but this compound was not used again until 1895.

Theories of Narcosis. The Meyer-Overton hypothesis states that narcotic action depends upon the fat-water partition of a compound; the higher the coefficient, the greater is the potency of the anesthetic. Chemical composition

and purely chemical properties are not directly concerned in narcotic strength, but lipoid and surface affinities have a great deal of effect. Both of these properties tend to condense the compound on the surface of the cell, thereby altering the properties of the surface, and decreasing the permeability of the cell membrane.

There is a close parallelism between the narcotic concentration and the depression of the surface tension of water. The depression of the surface tension of water by a narcotic and the fat solubility of the compound are usually parallel. Depression of the surface tension of water is not directly concerned in narcosis, but it is a measure of the concentration of the drug at the surface.

Concentration of a narcotic at the surface of a cell tends to flocculate the colloids, alter the surface properties, change the catalytic activity, and decrease the permeability of the cell membrane. If the compound is soluble in the lipoid surface, liquifaction may play a major part in the narcosis. Narcotic concentrations of a drug decrease the permeability of the cell membrane but toxic concentrations increase the permeability.

Narcotics interfere with changes in permeability necessary for stimulation. Stimulation depends on a change in the electric polarization of the cell due to a change in concentration of ions at the surface. The change in concentration is brought about by a sudden increase in the permeability of the membrane at the moment of stimulation. This change is hindered when the permeability is decreased by narcotics.

Chemotherapy of Anesthetics. Certain empirical relations[8] hold between chemical composition and pharmacologic action. Narcotic strength and toxicity increase in each homologous series with the addition of each carbon atom while the margin of safety diminishes. A limit is soon reached, how-

ever, when the drugs become less volatile, less soluble, and less absorbable. Increased oil solubility parallels the number of carbon atoms and the narcotic strength. An increase in the excitability of the central nervous system occurs with the addition of each carbon atom in each homologous series. This generalization is revealed during deep narcosis by muscle rigidity, spasm, hyperventilation and cardiac arrhythmia which increase with the number of carbon atoms.

Double bonds increase the narcotic strength, triple bonds increase it slightly but branching the carbon chain decreases it. The introduction of halogen, especially chlorine, usually enhances the anesthetic action but is not in proportion to the number of halogens introduced. Ether linkages increase the narcotic action while carboxylic and ester groups decrease it. Certain groups such a nitrite, may be so biologically active, that introduction of such a group will completely over-shadow the narcotic properties of the rest of the molecule. Amine groups destroy the narcotic potency of hydrocarbons. More than one hydroxyl group will weaken or destroy the ability of a compound to produce narcosis. Aldehydes and ketones are more active narcotics than the corresponding alcohols.

To be a satisfactory anesthetic, a compound must be sufficiently soluble in water to be carried to the central nervous system, and must have such a high solubility in lipoids to be differentially accumulated there.

Properties of an Ideal Anesthetic. An ideal anesthetic must satisfy four groups of people.

The patient wants an anesthetic which will cause a rapid, pleasant induction. The substance should be non-irritating and without any unpleasant odor. Recovery should be devoid of discomfort.

The surgeon wants a non-explosive anesthetic which gives complete muscular relaxation and which does not increase the capillary bleeding.

Anesthetists want an anesthetic with a wide margin of safety. The compound should be eliminated from the body unchanged and should produce no functional or organic injury. It should be sufficiently potent to allow administration with a high percentage of oxygen. There should be a rapid interchange of gas between atmosphere and tissues to allow close control of the depth of anesthesia.

A compound which is simply and inexpensively produced is preferred by the manufacturers. It should be easily purified and should remain chemically unchanged during storage.

Properties of Inhalation Anesthetics.[3,4,5] Ether, chloroform, cyclopropane and certain other volatile and gaseous compounds are employed for surgical anesthesia. They depress successively the psychic centers, then probably the basal ganglia and cerebellum, then the spinal reflexes, first the sensory and then the motor functions of the cord, probably from below upward and finally, the medullary centers.

Nitrous oxide meets all the requirements of an ideal anesthetic except that it lacks potency. Satisfactory relaxation cannot be obtained without simultaneous anoxia. Nitrous oxide is frequently used for short anesthesias and for inducing anesthesia. After induction, a more potent substance is used to continue the anesthesia. Nitrous oxide is not very useful in long operations.

Diethyl ether is one of the best anesthetics available and it is used very frequently. It is probably the safest anesthetic for long operations. It gives nearly complete relaxation, causes little asphyxia and does not induce much of a rise in blood pressure. It is not toxic to the heart. Respiration ceases before the heart dies; if administration of the drug is stopped and artificial respiration is started promptly, recovery will occur

Ether, however, irritates the air passages, causes marked salivation and stimulates the production of mucus. It does not induce anesthesia very rapidly and there is a long excitement stage. In hot climates, anesthesia with ether may be difficult to induce due to rapid evaporation. Ether may cause late deaths by pulmonary edema and pneumonia. Finally, ether is inflammable.

Chloroform is another excellent anesthetic. It is quicker and less irritating than ether. When excitement must be avoided and when the air passages are irritated, chloroform is preferred over ether. Chloroform is more potent than ether and it produces more complete relaxation. It is non-inflammable.

Chloroform cannot be used in cases of fatty degeneration of the heart and in renal diseases. The concentration necessary for anesthesia is close to the concentration which seriously effects the heart. Chloroform may cause ventricular fibrillation. Late deaths can occur by fatty changes in the heart, liver and kidneys, or by diabetic coma. Marked salivation is observed although not so much as with ether. The blood pressure and the respiratory center are depressed by chloroform.

Cyclopropane is a gaseous anesthetic. The odor is not unpleasant. It is chemically stable and easily purified but it is inflammable. The compound is not altered in the body. Anesthetic concentrations are not irritating. Less salivation occurs than with any other surgical anesthetic. Induction of anesthesia is smooth and usually without excitement. Most surgical operations can be done with cyclopropane but the muscular relaxation is not so complete as with ether. Cyclopropane is the only common anesthetic agent which does not increase the respiratory rate. It produces fewer post-operative reactions than agents of similar potency, even in bad risks and cardiac cases. There is

no liver injury. However, the drug relaxes the peripheral blood vessels and increases capillary bleeding. The heart rate is reduced below the resting level. There is some controversy as to whether it produces certain cardiac disturbances.

A great many other compounds have been used as inhalation anesthetics but not so frequently as those mentioned above. Some are not sufficiently potent for general use. Others are chemically unstable. Many produce bad side effects. The following is a list of some substances which have been used as inhalation anesthetics: methane, ethane, propane, n-butane, isobutane, neopentane, ethylene, propylene, α-butylene, β-butylene, isobutylene, allene, 1,3 butadiene, acetylene, vinyl chloride, methyl chloride, ethyl chloride, methyl cyclopropane, mono and dichlorocyclopropanes, ethyl bromide, ethyl iodide, divinyl ether and dimethyl ether. Many of these substances have been tried only on animals, and some are not suitable for human anesthesia.

In addition to the volatile and gaseous anesthetics which are administered by inhalation there are many fixed anesthetics such as avertin, which are administered rectally, orally or hypodermically. All of these suffer from one great disadvantage: after an anesthetic dose has been administered it is not possible to lighten the anesthesia quickly. The only variation that can be produced is deeper anesthesia. Therefore, these substances are not so safe as inhalation anesthetics in full anesthetic doses, but they are frequently useful in conjunction with an inhalation anesthetic.

Reasons for Preparing Cyclopropyl Ethers. It can be seen from the above discussion that there are no ideal anesthetics in general use. Of those which are used, ether and cyclopropane appear to be the best. Each possesses certain advantages which the others do not.

From a pharmacologic point of view, it is interesting to see whether a combination in the same molecule of the ether and the cyclopropane structures would produce an anesthetic, and whether it would have any advantages over those anesthetics now in existence.

The synthesis of cyclopropyl ethers is an interesting chemical problem because numerous unsuccessful attempts have been made to prepare cyclopropanol. It is of interest to see whether the ethers can be made and whether they are reasonably stable compounds.

INTRODUCTION, PART II. CHEMISTRY

Methods of Preparing Ethers.[6,7] Reactions which can be used to produce ethers are indicated below.

$$RONa + R'X \longrightarrow ROR' + NaX$$

$$ROH + R'I + Ag_2O \longrightarrow ROR'$$

$$(C_6H_5)_3CCl + ROH + C_5H_5N \longrightarrow ROC(C_6H_5)_3$$
This reaction works best with primary alcohols

$$RX + Ag_2O \longrightarrow ROR$$

$$RX + R'OH \xrightarrow{200^\circ} ROR'$$
Pyridine and tertiary bases will aid this reaction.

$$ROH + \text{catalyst} \longrightarrow ROR$$
H_2SO_4, HCl, H_3PO_4, $KHSO_4$, $ArSO_3H$, $FeCl_3$, BF_3, $Al_2(SO_4)_3$, and $ZnCl_2$ are some of the catalysts which can be used.

$$ROH + R'_2SO_4 \xrightarrow{\text{alkali}} ROR'$$

$$ArSO_3R + R'OH \xrightarrow{\text{alkali}} ROR'$$

$$ROSO_3Na + ROH \xrightarrow[150-180]{\text{alkali}} ROR'$$

$$(RO)_2Mg + (CH_3)_2SO_4 \longrightarrow ROCH_3$$
This reaction can also be used with diethyl sulfate.

$$(CH_3)_2C{=}CHCH_3 + CH_3OH + H_2SO_4 \xrightarrow{25^\circ} (CH_3)_2C(OCH_3)-C_2H_5$$

$$ROH + CH_2N_2 \xrightarrow[\text{catalyst}]{\text{acid}} ROCH_3$$

$$CH_3C{\equiv}CH + C_2H_5OH + KOH \xrightarrow{75^\circ} CH_3C(OC_2H_5){=}CH_2$$

$$RCH(OR')_2 + H_2 + HI \xrightarrow[200^\circ]{\text{vapor phase}} RCH_2OR' + R'OH$$

$$RCH(OR')_2 + R''MgX \longrightarrow RCH(R'')OR' + R'OMgX$$

$$RCH_2C(R'')(OR')_2 \xrightarrow[\text{heat}]{\text{catalyst}} RCH{=}C(R'')OR' + R'OH$$

$$RCH_2O + R'OH + HCl \longrightarrow RCH_2Cl(OR')$$

$$ROCH_2X + R'MgX \longrightarrow ROCH_2R'$$

To make a cyclopropyl ether by any one of these reactions, it would be necessary to start with cyclopropanol, a cyclopropyl halide, cyclopropane or cyclopropene.

Methods of Making Certain Cyclopropyl Compounds. Despite numerous attempts to synthesize cyclopropanol none has been successful.

Hübner and Müller [9]

$$(CH_2Cl)_2CHOH + Na \xrightarrow{\text{dry ether}} CH_2{+}CHCH_2OH$$

Nef[10]

$$CH_2(O)CHCH_2Cl + Na \longrightarrow CH_2{=}CHCH_2OH$$

Bigot[11] and Tornee[12]

$$CH_3COOCH(CH_2Cl)_2 + Na \longrightarrow CH_3COOCH_2CH{=}CH_2$$

C. Aschan[13]

$$(CH_2Br)_2CHOH + Na \longrightarrow CH_2{=}CHCH_2OH + CH_2(O)CHCH_2Br$$

Gustavson[14]

$$(CH_2Br)_2CHOH + Zn \longrightarrow CH_2{=}CHCH_2OH$$

M. Tilitschejew[15]

$$HO{-}CH(CH_2{-}OC{=}O)_2 \xrightarrow{\text{pyrolyse}} CH_2{=}CHCH_2OH$$

Gustavson[16]

$$CH_2(CH_2)CHCl + CH_3COOK + CH_3COOH \longrightarrow CH_3COOCH_2CH{=}CH_2$$

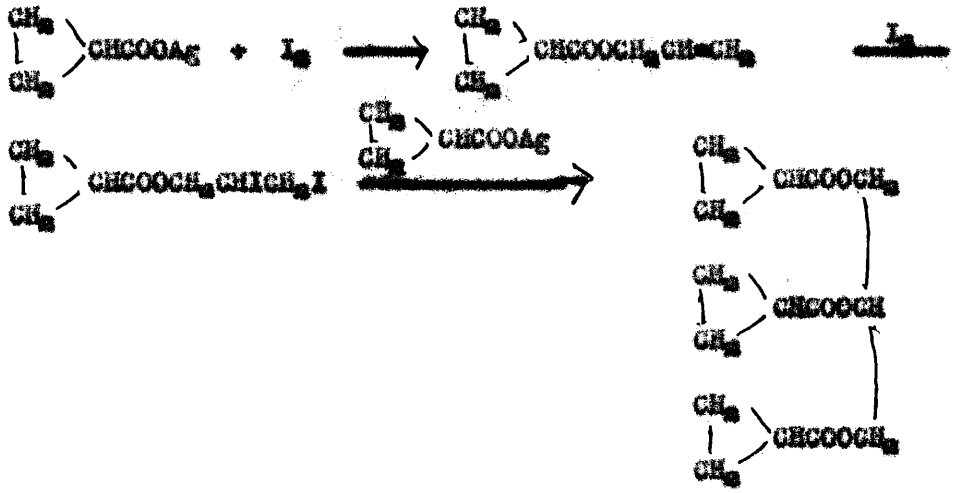
Kishner[17]



Fichter and Reeb[18]

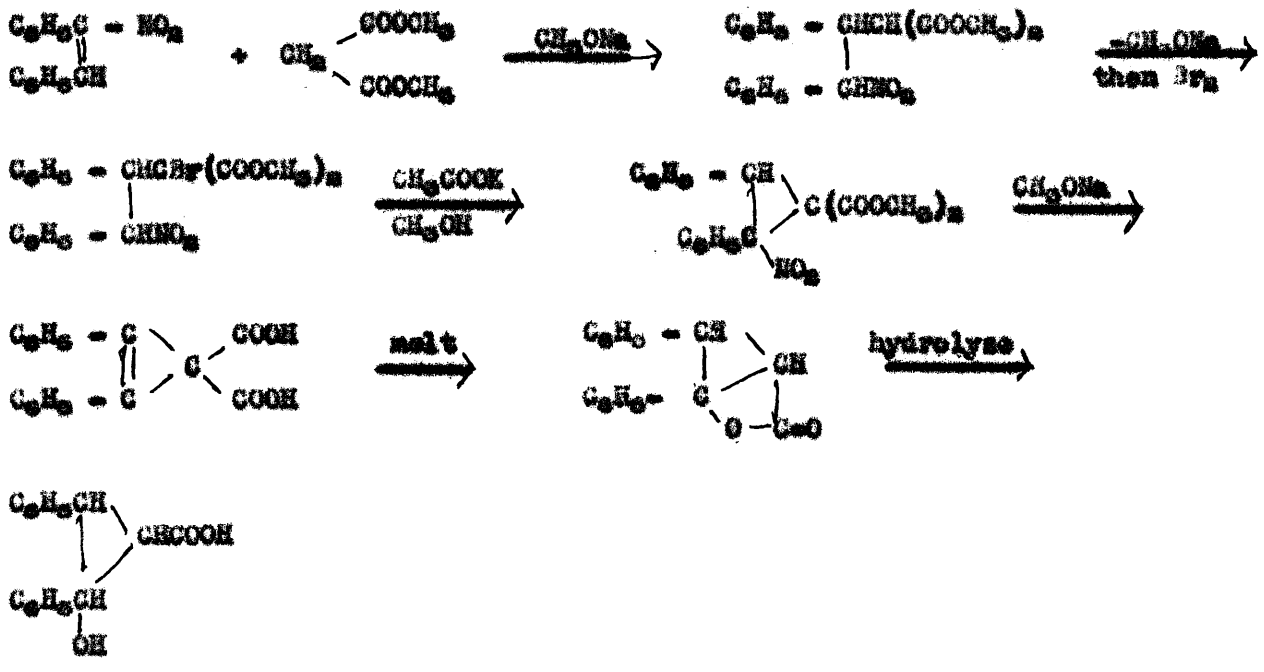


Windaus and Klanhard[19]

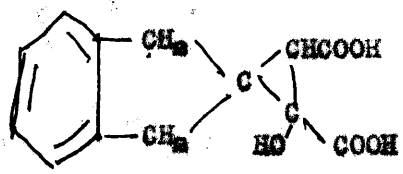


Although cyclopropanol has never been prepared, many substituted cyclopropanols are known.

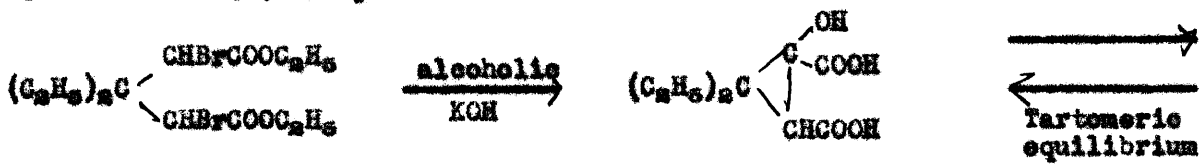
S.P. Darling and E.W. Spangel[20]

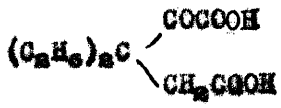


Aruppillai and Kandiah[21] made cis, 1,2-dicarboxy-1-hydroxy-cyclopropane-3 (2')-spiro-trans-hepahydroxyhydrindene.

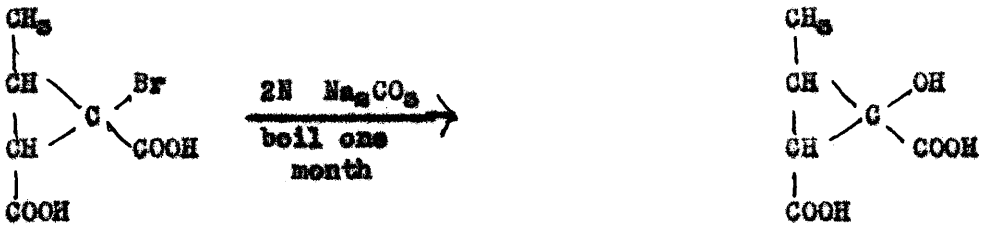


L. Bains and J.F. Thorp[22]

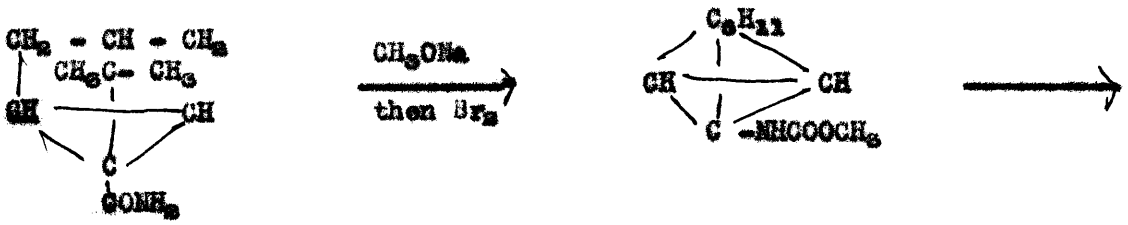




The corresponding diprepyl compound was also made



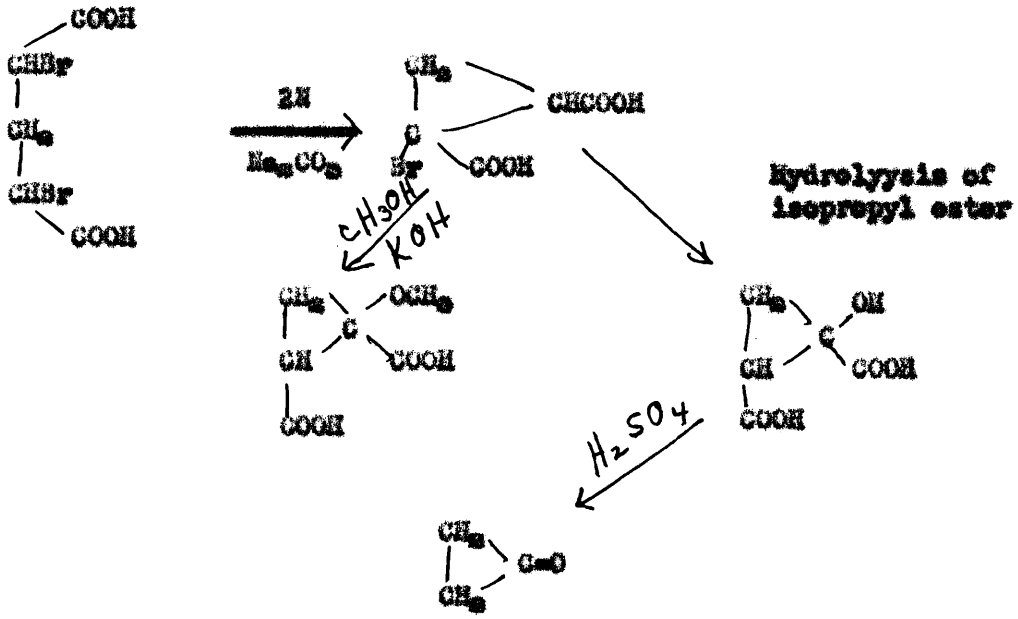
Lipp and Padberg[24]





There have been several reported syntheses of cyclopropanone.

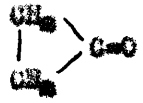
C.K. Ingold[88]



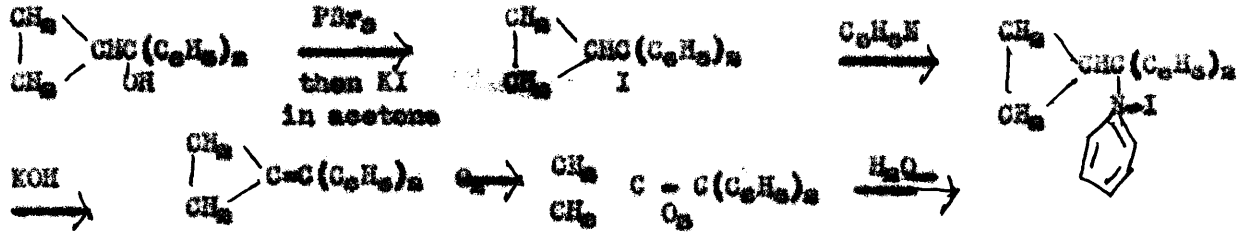
The cyclopropanone was isolated as the semicarbazone.

C.K. Ingold, S. Sako and J.F. Thorpe[88]





P. Lipp and Hans Seeles[87] do not believe that Ingold really had cyclopropanone because they say that the ring would not be stable towards sulfuric acid treatment. These investigators failed to obtain cyclopropanone by the following series of reactions.



$(C_6H_5)_2CO$.

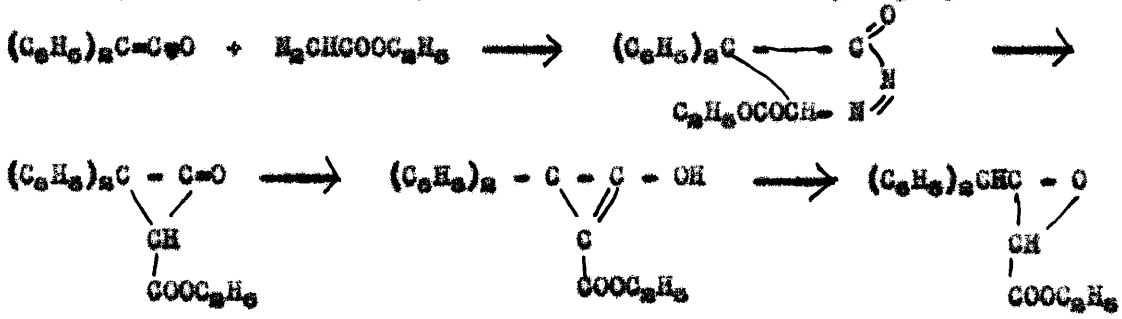
N. Demjanov and V.V. Feofilaktov[28] repeated Ingold's[26] reported synthesis of cyclopropanone without success.

P. Lipp, J. Buchkremer and H. Seeles[29] prepared the hydrate of cyclopropanone:

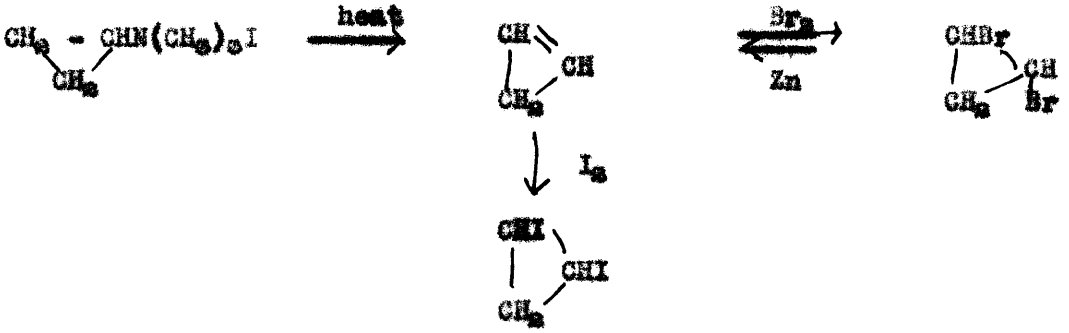


In the presence of methanol or ethanol, the hemiketal is formed instead of the hydrate

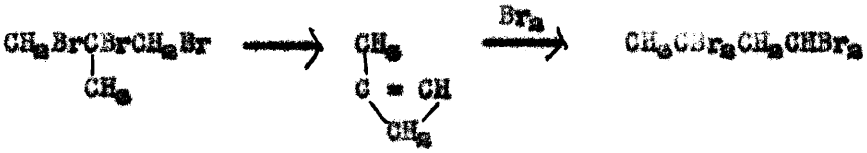
Staudinger and Reeber[30] synthesized a substituted cyclopropanone.



A number of cyclopropenes are known. N. Demjanov and M.N. Doyarenko[31]

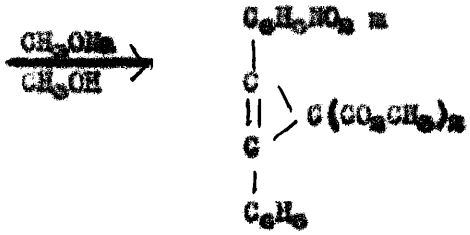


B.K. Mereshkovskii[32]



E.P. Kohler and Darling[33]





Several examples of halogenated cyclopropanes follow.

Gustavson[34]



small yield

Demjanov[35]



P. Bruylant and A. Stassens[36]



If one must start the proposed synthesis with an intermediate containing a cyclopropyl ring, these examples indicate that it would be no easy matter to make a compound which could be used for the preparation of a cyclopropyl ether. Most of the substances suitable for such a reaction have complex substitutions on the cyclopropane ring, and even the simpler ones are difficult to make and could be available in only small quantities.

Methods of Making Cyclopropane Rings. There is, however, a simpler approach to the solution of the problem. It should be possible to introduce the desired alkyl group into a compound which can then be cyclized to a cyclopropyl ether.

The methods of making cyclopropane are as follows: A. Freund[37] heated

trimethylene bromide with sodium; Wolkow and Menschutkin[38] added trimethylene bromide to sodium under boiling xylene; Gustavson[39] heated trimethylene bromide and zinc dust in 75 per cent. alcohol between 50-60°; Haehn[40] reacted trimethylene bromide with zinc wool in isoamyl alcohol; Zelinsky[41] and Gutt cyclized trimethylene bromide with magnesium in ether; Chamblay[42] prepared cyclopropane from trimethylene bromide and alkali metal ammonium compounds in liquid ammonia; Zelinsky and Schlesinger[43] heated trimethylene bromide with zinc in 50 per cent. acetic acid; Domanitzki[44] introduced magnesium into an ether solution of α-chloro-γ-bromopropane.

A very important research on the synthesis of cyclopropane was carried on by H.B. Haas, E.T. McBee, G.E. Hunds and E.W. Gluesenkamp[45]. They found that when trimethylene chloride was heated to 210° in the presence of zinc suspended in diphenyl ether, a 57 per cent. yield of cyclopropane was obtained. Trimethylene chloride, diphenyl and sodium heated to 210° gave a 64 per cent. yield of cyclopropane. Dibutyl ether, xylene, sodium iodide catalyst, magnesium and trimethylene chloride at 140° yielded after purification of the gas 60 per cent. of the theoretically possible quantity of cyclopropane.

There was no reaction with magnesium unless an iodide catalyst was used. Sodium iodide, free iodine, ethyl iodide or ethyl magnesium iodide would all serve equally well. The iodide converts the trimethylene chloride to α-chloro-γ-iodopropane or α,γ-diodopropane which then reacts with the magnesium quite readily.

Zinc iodide did not catalyze the reaction because it does not ionize sufficiently. If zinc in 95 per cent. alcohol with a little iodide catalyst

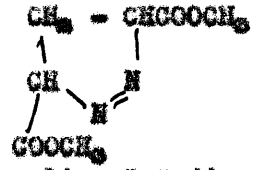
was used for the cyclization, the reaction soon stopped unless something was added to release iodide ions. Na_2CO_3 did this by forming a basic zinc carbonate; acetamide also released iodide ions by formation of a $Zn(CH_3CONH_2)_x^{++}$ complex.

The best method of making cyclopropane from trimethylene chloride according to these investigators is to add trimethylene chloride to molten, anhydrous acetamide which is maintained at a temperature of 125° and which contains 1/60 mole NaI, a slight excess of zinc and Na_2CO_3. The yield of cyclopropane is 80 per cent.

A number of examples of ring closures resulting in the formation of cyclopropane derivatives are illustrated below.

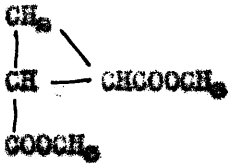
E. Buchner and A. Papendieck[46]

$$CH_2 = CHCOOCH_3 + N_2CHCOOCH_3 \longrightarrow$$



pyrazoline 3,5 dicarboxylate dimethyl ether

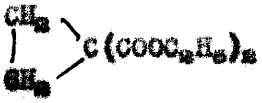
$$\xrightarrow[\text{distillation}]{\text{vacuum}} N_2 +$$



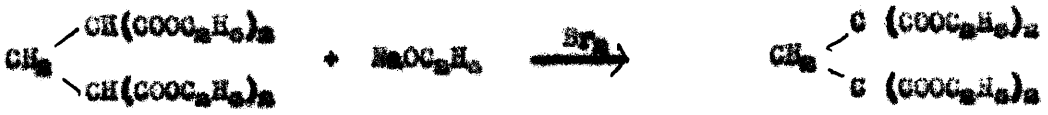
This reaction is of general application. Diazo compounds will react with unsaturates to form a pyrazoline which can be decomposed to a cyclopropane derivative. Sometimes it is necessary to use a catalyst in the decomposition of the pyrazoline. Acid, alkali and platinum have been used as catalysts.

W.H. Perkins[47]

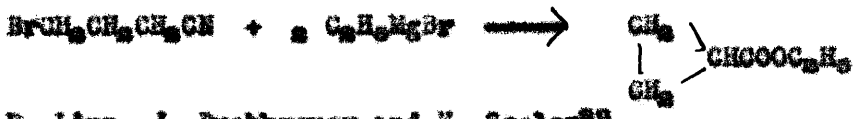
$$CH_2BrCH_2Br + CH_2(COOC_2H_5)_2 + C_2H_5ONa \longrightarrow$$



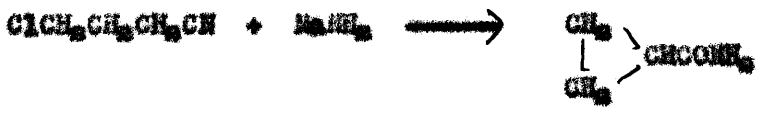
H. Guthzeit[48]



P. Bruylant[49]



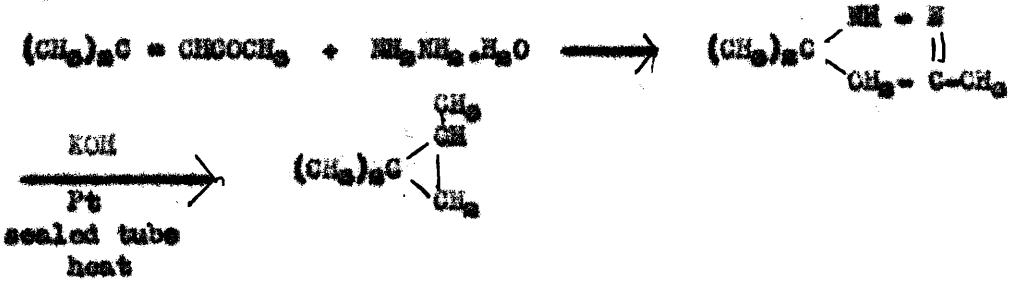
P. Lipp, J. Buchkremer and H. Seeles[50]



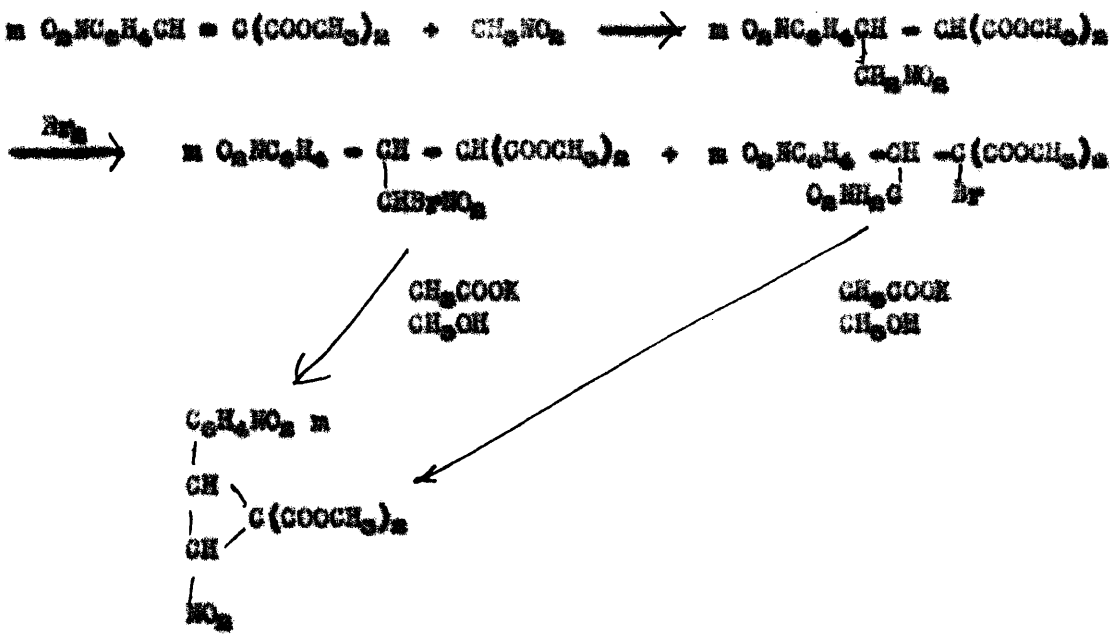
P. Bruylant and A. Stassens[46]



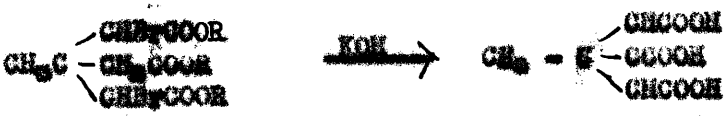
N. Kishner[51]



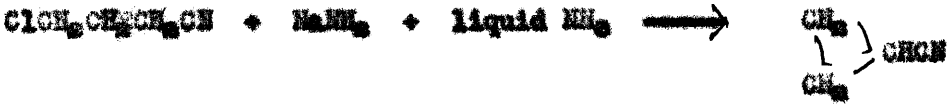
E.P. Kohler and S.F. Darling[52]



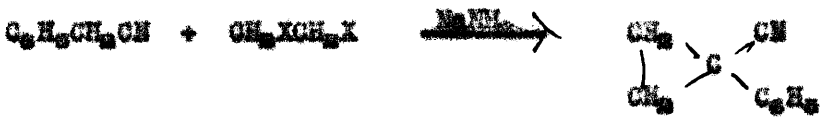
Beesley and Thorp[52]



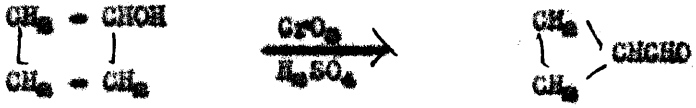
Cloke, Anderson, Lachman and Smith[53]



Case[54]



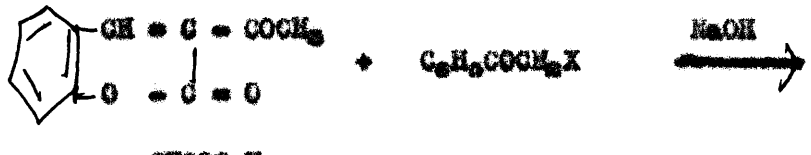
N. Demjanov and M. Dojarenko[55]

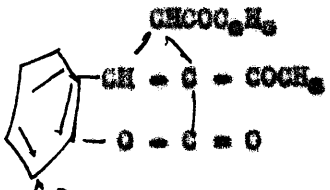


The same workers also found;[56]



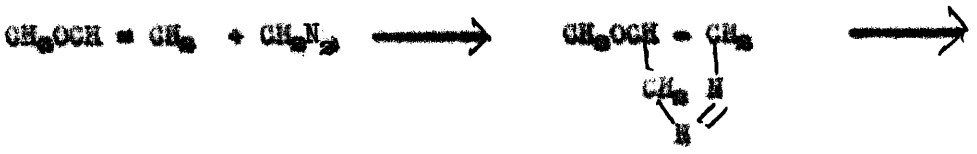
O. Widman[57]

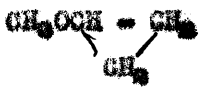




Choice Method of Synthesis. Of all the reactions useful in making cyclopropane rings the most applicable for cyclopropyl ethers are the decomposition of a pyrazoline and the cyclization of a dibromide with a metal.

For example, one series of reactions which might result in the desired product would be;

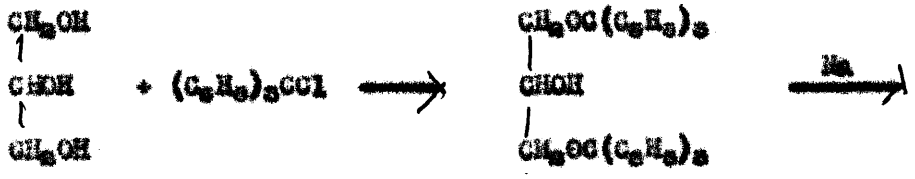




Another approach would be:

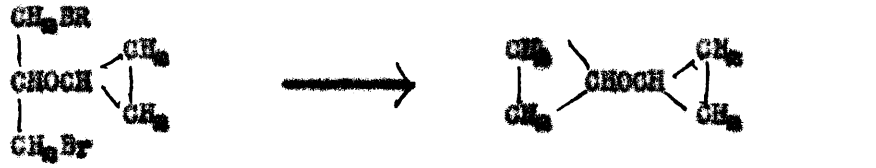


Similarly to make biscyclopropyl ether, the following plan would appear to work:









It was the latter method of attack which was used in this research because the preparation of large quantities of diazomethane would not only be troublesome, but would present serious health and explosion hazards. The intermediates for making $(CH_2X)_2CHOH$ are much more readily available.

EXPERIMENTAL

Introduction. The first synthesis which was attempted was biscycloprepyl ether by the method outlined above. Glycerin α,γ bistriphenylmethyl ether was prepared according to the method described by B. Helfrich, P.E. Speidel and W. Teeldte[60]. However, this compound could not be made to react with sodium.

Glycerin α,γ diacetate was prepared next in an effort to substitute it in the synthesis for glycerin α,γ bistriphenylmethyl ether. Glycerin α,γ diacetate has been prepared by heating glycerin and acetic acid to 200° in a sealed tube[58]; by refluxing glycerin and acetic acid[59,61]; from epichlorhydrin heated to 150° in a sealed tube with silver acetate[60]; from β,β'-diisochloropropanol and sodium acetate at 150°[59]. The glycerin α,γ diacetate was prepared by Sellig's[62] method which yields chiefly the α,γ diacetate.

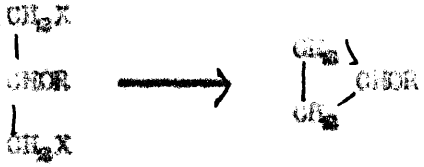
It was not found possible to prepare a metal alcoholate of this substance. Sodium or potassium decomposed the ester, magnesium would not react with it, nor would ethyl magnesium bromide react with the hydroxyl hydrogen to form an alkoxy magnesium bromide. Magnesium ethylate heated with glycerin α,γ diacetate yielded ethyl acetate. Magnesium oxide did not appear to react with the compound.

α,γ-dichloro-β-bromopropane was prepared from α,γ-dichlorohydrin and phosphorus pentabromide according to the method of Berthelot and Lucas[64], and also from α,γ-dichlorohydrin and phosphorus tribromide. The product was reacted with sodium ethylate and yielded a mixture of sodium chlorides and sodium bromide. Analysis showed that two-thirds of the sodium ethylate had reacted with the chlorides.

These experiments indicated that the proposed method of preparing biscycloprepyl ether is not at all promising. Although other methods might be tried such as the reaction of diazomethane and divinyl oxide followed by decomposition

of the dipyrazoline, this phase of the research was abandoned. It was thought more profitable to attempt the synthesis of simple alkyl cyclopropyl ethers, because if they cannot be made, the obviously more complex bis-cyclopropyl ether can certainly not be made. The converse is not necessarily true.

Since the alkyl cyclopropyl ethers might be made according to the equation;



a consideration of β,β'-dihaloisopropanol and β,β'-dihaloisopropyl alkyl ethers is pertinent at this point.

β,β'-dichloroisopropanol has been made by treating glycerin[65] with fuming hydrochloric acid at 100°C. by leading hydrogen chloride gas through glycerin[66] at 120-130°C.; by saturating a mixture of glycerin and acetic acid with hydrogen chloride gas[67]; from glycerin and gaseous or aqueous hydrogen chlorides in the presence of an organic carboxylic acid as a catalyst[68]; by heating glycerin and sulfur monochloride on a water bath[69]; by treating epichlorohydrin with fuming hydrochloric acid and allowing the mixture to stand[70]; from glycerin, hydrogen chloride and diacetin[70]; from castor oil or oxidised linseed oil, hydrogen chloride and alcohol[71]; from α-monochlorohydrin and hydrogen chloride[72]; from allyl chloride and hypochlorous acid[73]; by treating glycerin dibutyl ether with hydrogen chloride[74]. The β,β'-dichloroisopropanol used in this research was obtained from the Eastman Kodak Company.

β,β'-dibromoisopropanol has been prepared from glycerin and phosphorus tribromide[75]; from glycerin and bromine[76]; from bromine on $C_6H_{10}O_3$ resulting from the distillation of glycerin from calcium chloride[77]; from glycerin, red phosphorus and bromine[78,79]; from glycerin and hydrogen bromide at 100°C.[80] .

Most of the β,β'-dibromoisopropanol used was prepared by the method described in Organic Syntheses[78]. Some was obtained from the Eastman Kodak Company.

Other β,β'-dihaloisopropanols have been synthesized; β,β'-diiodoisopropanol has been prepared by heating β,β'-dichloroisopropanol with sodium iodide or potassium iodide and a little water[81]; β-chloro-β'-bromoisopropanol was made from epichlorohydrin and hydrogen chloride and from epibromhydrin and hydrogen chloride[82]; β-chloro-β'-iodoisopropanol has been prepared from epiiodohydrin and hydrogen chloride, from epichlorohydrin and fuming hydriodic acid[83] and from epichlorohydrin treated with ethyl magnesium iodide in the cold, followed by decomposition by water[84].

β,β'-dichloroisopropyl methyl ether has been prepared by treating an ether solution of β,β'-dichloroisopropanol and methyl iodide with silver oxide[84]. L. Blanchard[85] prepared it by heating β,β'-dichloroisopropanol with methyl para-toluenesulfonate at 150°C. for five hours. The reaction mixture must be neutralized, the product fractionated off, and the unreacted materials heated several more times in the same way. Although the method is more practical than the one described first, it is a very tedious and long-drawn out procedure. Blanchard also made β-chloro-β'-bromoisopropyl methyl ether by the same procedure but could not make the ether of β-chloro-β'-iodoisopropanol by this method. In another paper[86], he described the preparation of β,β'-dichloroisopropyl chloromethyl ether from β,β'-dichloroisopropanol, trioxymethylene and dry hydrogen chloride. The product can be reacted with alkyl magnesium halides to yield compounds whose formulas are of the type $(CH_2Cl)_2CHOCH_2R$. Blanchard made β,β'-dichloroisopropyl ethyl ether by the same method. Similarly, B.V. Allen and H.A. Mangs[87] made β,β'-dichloroisopropyl α-chloroethyl ether from β,β'-dichloroisopropanol,

paraldehyde and dry hydrogen chloride. The product could be reacted with alkyl magnesium halides to yield secondary ethers of the type $(CH_2Cl)_2CHOCHCl_2$. Finally, L. Blanchard[66] made bis-β,β'-dichloroisopropyl ether and bis-β-chloro-β'-bromoisopropyl ether from sulfuryl chloride and β,β'-dichloroisopropanol and from sulfuryl chloride and β-chloro-β'-bromoisopropanol respectively. He could not make the bis ethers of α,γ-dibromohydrin and α-chloro-γ-iodohydrin in this way.

L. Sattler, M. Altmann and S. Pganer[66] prepared the methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-amyl and isoamyl ethers of β,β'-dibromoisopropanol by the following reactions:

$$CH_2BrCH{=}CH_2 + (CH_3COO)_2Hg + ROH \xrightarrow[\text{yield}]{100 \text{ per cent.}} CH_2BrCHCH_2OHgOCOCH_3 \quad (OR)$$

$$\xrightarrow[Br_2 \quad 21\text{-}32 \text{ per cent. yield}]{H_2O,\ KBr} (CH_2Br)_2CHOR$$

Paal[66] made β-chloro-β'-iodoisopropyl alkyl ethers from epichlorohydrin and alkyl iodides by heating in a sealed tube for many hours at temperatures around 200°C. He reports the methyl, ethyl, n-propyl, and isopropyl ethers.

Of the reactions discussed only Sattler's synthesis of β,β'-dibromoisopropyl methyl ether holds any promise for the preparation of fairly large quantities of β,β'-dichloroisopropyl methyl ether and β,β'-dibromoisopropyl methyl ether. Both this synthesis and Blanchard's synthesis from β,β'-dichloroisopropyl chloromethyl ether and alkyl magnesium halides have some promise for the preparation of the higher ethers. However, Sattler's yields were not very good, and therefore another method was chosen to prepare β,β'-dichloroisopropyl methyl ether Instead of using methyl para-toluenesulfonate as Blanchard did, this reagent was replaced by the more reactive dimethyl sulfate.

After a number of unsuccessful methylation experiments, it was found

that β,β'-dichloroisopropanol could be methylated by heating it with a 20 per cent. excess of dimethyl sulfate between 120-130°C. for two or three hours. Some charring occurred, but not to an excessive extent. At 100°C. the reaction was too slow, while at 140°C. complete decomposition occurred. The reaction mixture was neutralized with aqueous sodium bicarbonate, the unreacted β,β'-dichloroisopropanol was converted with aqueous sodium hydroxide to epichlorohydrin, which could be more easily removed by fractionation and the dimethyl sulfate was destroyed with concentrated ammonia. None of these reagents will affect the methylated product at room temperature.

One experiment carried out as described above gave a 31 per cent. yield. Other experiments in which the sodium hydroxide and ammonia treatments were omitted gave yields varying from 7 to 78 per cent. The very low yield of 7 per cent. was probably due to overheating during the preparation or to decomposition during the distillation due to the presence of dimethyl sulfate. The product distilled between 159-161.5°C./760mm., between 40.5-42°C./1.5-2 mm. and at 47°C./5mm.

β,β' dibromoisopropanol was methylated in the same way except that the mixture was heated at 100°C. for twelve hours. Temperatures above 110°C. caused complete decomposition. The material was purified by the same treatment described above. The substance was distilled between 48-49°C./1.5 mm. from calcium carbonate to prevent decomposition. The yields ranged from 11 to 40 per cent., and were usually about 30 per cent.

A variation of this method was also tried in a preliminary experiment. The mixture of dimethyl sulfate and β,β'-dibromoisopropanol was diluted with xylene and slowly fractionated from an excess of calcium carbonate. The acid which was formed during the reaction was immediately neutralized by the calcium carbonate and the water produced was distilled off. After five hours,

the mixture was filtered, the xylene was removed by fractional distillation, the residue was distilled from the calcium carbonate and the product was purified as described previously, starting with the treatment with sodium hydroxide. The yield was at least as good as those obtained by the other method. The omission of the troublesome neutralization with sodium bicarbonate more than compensates for the necessity of removing the xylene.

This latter method was used in all the subsequent alkylation experiments. Purification with sodium hydroxide and ammonia was not carried out because the higher dialkyl sulfates did not react with ammonia at room temperature, and treatment with sodium hydroxide was omitted because the advantage gained by it alone was not likely to compensate for the extra trouble.

Ethyl sulfate purchased from the Eastman Kodak Company was used to make β,β'-dibromoisopropyl ether. The reaction mixture was heated and stirred for 16 hours. The yield was 44 per cent. and it could not be purified by fractionation. It distilled between 69.5-78°C./7.5-8 mm.

The β,β'-dibromoisopropyl propyl and butyl ethers were made in the same way. The propyl ether distilled between 84-88°C./9-11 mm. to give a 35 per cent. yield. The yield of butyl ether was 55 per cent. and it distilled between 86-95°C./4 mm.

Part of the dipropyl sulfate used was purchased from the Eastman Kodak Company. The rest was made from sulfuryl chloride and propyl sulfite which was made from propyl alcohol and thionyl chloride. The methods developed by Suter and Gerhart[21] were used to make these substances. The general reactions involved are represented by the following equations:

$$2\ ROH + SOCl_2 \longrightarrow R_2SO_3 + 2HCl$$

$$R_2SO_3 + SO_2Cl_2 \longrightarrow ROSO_2Cl + RCl + SO_2$$

$$ROSO_2Cl + R_2SO_3 \longrightarrow R_2SO_4 + RCl + SO_2$$

All of the butyl sulfate was made in this way.

None of these alkylation experiments were very satisfactory. The yields were low in all of them, and, with the exception of the methyl ethers, could not be obtained pure. Only methyl and ethyl sulfates are easily available. Blanchard's[66] method of making the ethers from β,β'-dichloroisopropyl chloromethyl ether and alkyl magnesium halides may be preferable. β,β'-dibromoisopropyl bromomethyl ether was prepared in 55 per cent. yield from β,β'-dibromoisopropanol, trioxymethylene and dry hydrogen bromide. The material distilled between 129-135°C./12 mm., almost all of it coming over at 131°C./12 mm. No attempt has been made to prove the identity of this product, but the author intends to study the compound further. Hydrogenation experiments will be carried out in an effort to selectively replace the bromine on the methyl group without disturbing the other bromines.

Experiments on the cyclization of the β,β'-dihaloisopropyl alkoxy ethers to alkyl cyclopropyl ethers were similar to the experiments reported by Hass et al.[46] on the synthesis of cyclopropane. The most successful results were obtained when molten acetamide was used as the solvent medium for the reaction. Two moles of sodium iodide were used for each mole of β,β'-dihaloisopropyl alkyl ether, although no experiments were carried out to see whether this quantity could be reduced or whether the sodium iodide could be omitted entirely. A large excess of zinc dust, which is the cyclizing agent, and a plentiful amount of sodium carbonate to prevent formation of [illegible] due to hydrolysis of the zinc salts, were the other reagents used. The reaction mixture was stirred efficiently. The temperature was never allowed to fall below 137°C. because crystallization occurred to a considerable extent below this point. On the other hand, unnecessarily high temperatures were avoided because of the danger of pyrolysis. Since the reaction was exothermic, the

halogenated ethers had to be added slowly. Also there was some chance of two molecules coupling in a concentrated solution and thereby reducing the yield.

Table I lists the average yields obtained from the cyclization of β,β'-dihaloisopropyl alkyl ethers. The estimation of the per cent. purity was made after a consideration of the point in the purification process at which the yield calculated.

Table I

Average Yields of Cyclopropyl Ethers

Halide	Alkyl Group	Per cent. Yield	Estimated per cent. Purity
Cl	CH_3	22	90-95
Br	CH_3	60	90-95
Br	C_2H_5	64	90-95
Br	n-C_3H_7	22.5	95
Br	n-C_4H_9	1	99

The only chloride which was cyclized gave a low yield. With bromides, the yields appear to decrease sharply with the increase in size of the alkyl group, but in reality this data does not justify such a conclusion because, with the exception of the methyl ether, the products used in the cyclization experiments were suspected of being very impure.

Cyclopropane rings and olefinic double bonds are so similar in reactivity that detection and removal of unsaturates from cyclopropyl ethers presented a problem. O. Filipow[28] reports that cyclopropane compounds give a yellow color with tetranitromethane. Therefore, this reagent could not be used to detect olefines. Comparison of the ease of addition of bromine to allyl methyl ether and methyl cyclopropyl ether showed that the former added bromine more rapidly than the latter, but addition of bromine to the cyclopropyl ethers studied in this research was not a difficult reaction at all. No very precise bromine

titration of unsaturates could be obtained in the presence of methyl cyclopropyl ether.

Perbenzoic acid in toluene solution gave very good results in the titration of unsaturates. It reacts only very slowly, if at all, with the cyclopropyl ethers.

This same reagent concentrated as much as possible in toluene was very successful in removing unsaturates from methyl and ethyl cyclopropyl ethers. The closely related monoperphthalic acid in the solid state was used on the propyl and butyl cyclopropyl ethers with success.

After treatment of a cyclopropyl ether with either of these reagents, the purified ether will still decompose perbenzoic acid over a period of many days. There are two possibilities; either the perbenzoic acid removes the last traces of unsaturates only very slowly, or the perbenzoic acid reacts slowly with the cyclopropyl ether. The latter is probably true, because if an ether which has been treated with perbenzoic acid is titrated for unsaturates, a perbenzoic acid titration after the second purification will give the same result as the first titration. Also, silica gel which is reported to be a selective adsorbant of unsaturates and aromatic compounds, failed to change appreciably the perbenzoic acid titration of a purified methyl cyclopropyl ether.

Bromine may also be used to remove unsaturates, but this reagent destroys a considerable quantity of the cyclopropyl ether, and introduces small amounts of halogen which is difficult to remove. Methyl cyclopropyl ether treated in this way still gave the usual small titration value with perbenzoic acid which is obtained with the cyclopropyl ethers purified by either of the two methods which were used.

Halogens were detected by a modification[28] of the Beilstein test. The compound was burned with illuminating gas over a copper screen in a dark room.

Ruigh claims that 30 parts of halogen per million can be detected by the green color which it will impart to the flame. Halogens were almost completely removed from certain samples of methyl cyclopropyl ether by refluxing first over sodium hydroxide and then over zinc dust. Either of these treatments alone seemed to be very effective. Usually, methyl cyclopropyl ether was quite free of halogen if purification was carried out by the perbenzoic acid method.

Peroxides can be detected in cyclopropyl ether by the well known method of shaking a portion with neutral potassium iodide.

Sodium hydroxide was the best reagent for drying these cyclopropyl ethers. Sodium or potassium metal attacks the ethers with the production of unsaturates, and therefore they cannot be used as drying agents.

The physical properties of the cyclopropyl ethers are listed in Table II and the constants reported in the literature for allyl ethers are recorded in Table III.

All densities, refractive indices and surface tensions reported in this research were determined at 25°C. under thermostatic control, unless special mention is made to the contrary. Refractive indices were determined with respect to the D line of sodium. Surface tension is reported in dynes per centimeter.

Table II

Physical Properties of Cyclopropyl Ethers

Ether	Boiling Range °C.	Density	Refractive Index	Surface Tension
Methyl	44.5-46	0.796	1.3742	19.98
Ethyl	67 -68	0.780	1.3838	20.36
n-Propyl	94 -96	0.790	1.3933	21.17
n-Butyl	121 -122.5	0.799	1.4043	

Table III

Physical Constants Reported for Allyl Ethers

	Boiling Range °C.	Refractive Index (D line)	Density
Methyl[94,98]	46, 42.5–45	1.3778–1.3803	$^{11}_{11}$0.77
Ethyl[96,97,98]	62.5, 64, 66–67	1.38810	$^{20}_{4}$0.7651
n-Propyl	90–91		^{0}0.8004 ^{20}0.787

These constants were used to calculate the parachors and the molecular refractivities which were compared with the values obtained by calculations involving the atomic and structural values. In all cases the experimental results obtained from the cyclopropyl ethers were closer to the values calculated for the cyclopropyl ethers than to the values calculated for the corresponding allyl ether, although in every instance these experimental results were between the constants calculated for the two isomeric compounds.

The next table compares the various molecular data. These physical data are important corroborations of the chemical proof of the presence of the cyclopropyl ring.

Table IV

Comparison of Parachors and Molecular Refractivities of Cyclopropyl and Allyl Ethers

	Molecular Refractivities				Parachors			
	Cyclopropyl		Allyl		Cyclopropyl		Allyl	
	Expt.	Calc.	Expt.	Calc.	Expt.	Calc.	Expt.	Calc.
Methyl	21.00	20.85	22.05	21.72	194.0	192.7	200.4	199.2
Ethyl	25.77	25.64	26.60	26.53	234.7	231.7	—	238.2
n-Propyl	30.31	30.06	—	30.96	272.0	270.7	—	277.2
n-Butyl	34.99	34.68	—	35.37	—	—	—	—

The literature contains sufficient data for the calculation of an experimental molecular refractivity for allyl ethyl ether only. Allyl methyl ether was prepared from allyl iodide and sodium methylate. The allyl iodide was prepared[88] from allyl alcohol, phosphorus and iodine. The physical constants determined on the allyl methyl ether are; boiling range 43-45°C.; density, 0.757; refractive index, 1.3799; and surface tension, 19.66 dynes/cm. Combustion analyses for carbon and hydrogen indicate that the compound is not pure. The physical constants obtained from it, are, nevertheless, valuable for comparison with those determined on methyl cyclopropyl ether.

Combustion analyses were carried out on all of the cyclopropyl ethers, and the experimental values obtained for the percentages of carbon and hydrogen were so close to the calculated values that there can be no doubt that the compounds have the empirical formulae attributed to them and that the liquids are reasonably pure.

All of the cyclopropyl ethers reacted readily with bromine. The ring was opened to form α,γ-dibromopropyl alkyl ethers whose alkyl group corresponded to the alkyl group present in the cyclopropylalkyl ether. The dibromides resulting from the methyl and ethyl ethers were analysed for bromine. The results were sufficiently close to the calculated values to leave little doubt as to the empirical formulae. Although the butyl ether reacted with bromine, a sufficient quantity was not available to characterize the bromine derivative.

Table V.

Physical Constants of α,γ-Dibromopropyl Alkyl Ethers

	Boiling range	Density	Refractive Index
Methyl	68-70°C./9 mm.	1.790	1.5060
Ethyl	75.7-77.5°/9.5 mm.	1.666	1.4930
n-Propyl	96-98°C./18.5 mm.	1.594	1.4898

A. Kirmann, M. Goudard and M. Chahidozeh[100] reported the following constants for α,γ-dibromopropyl methyl ether: boiling point, 75°C./16 mm.; density d_4^{19} 1.806.

The constants of β,γ-dibromopropyl alkyl ethers which are known are listed in the next table.

Table VI

Physical Constants of β,γ-Dibromopropyl Alkyl Ethers

	Boiling Range	Density	Refractive Index
Methyl[94,98,101]	185°/760 mm. 83–84°/17 mm. 84°/18 mm.	d_4^{15} 1.8330	1.5134
Ethyl[100,103]	193–195°/760 mm. 103.5°/35 mm. 199°/760 mm.		

These values are not very useful for comparison with the α,γ dibromopropyl ethers.

All of the α,γ dibromopropyl alkyl ethers were oxidized with nitric acid to -bromopropionic acid. The derivative which was obtained starting from methyl cyclopropyl ether prepared from β,β'-dibromoisopropyl methyl ether was analyzed for carbon and hydrogen, and the empirical formula was thereby established. Mixed melting points of the acids obtained from the methyl ether prepared from β,β'-dichloroisopropyl methyl ether and from the ethyl and *n*-propyl ether were taken with the acid whose analysis for carbon and hydrogen had been determined. These results are exhibited in Table VII.

Table VII

Melting Points of β-Bromopropionic Acid Obtained from Cyclopropyl Ethers

Ether	Melting Point	Remelting Point	Mixed Melting Point	Mixed Remelting Point
Methyl (from Br)	60.5–61.5	60.0–61.0	—	—
Ethyl (from Cl)	59.0–60.0	59.0–60.0	59.5–61.5	60.0–61.5
Ethyl	58.0–60.0	58.0–59.0	60.0–61.0	59.0–61.0
n-Propyl	56.0–57.0	55.5–57.0	57.5–59.5	57.5–59.5

The substances sintered for several degrees before any actual liquid could be seen in the capillary

The column listed "remelting point" is the temperature at which the acid melted after it had been melted once and allowed to crystallize again.

The literature records the following melting points for β-bromopropionic acid: 60-61[104], 62[105], 62-63[106,107], 62.5[108]. The isomeric[109] dl α-bromopropionic acid melts at 25°C.

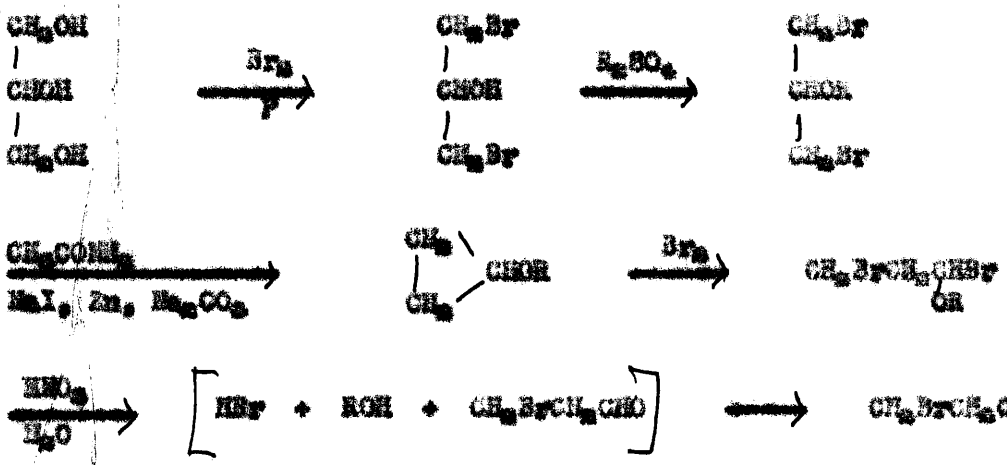
The methods used to prepare the β bromopropionic acid were adaptations of Lederer's[108] and of Hajèhn's[107] methods of preparing it from γ-bromopropanol. The yields were usually poor, and it was not always possible to isolate the -brome propionic acid in a pure condition although the conditions of the reaction were kept the same in each attempt. Repeated attempts produced some of the acid in every case except one. The bromine derivative of α,γ-dibromopropyl-n-butyl ether from n-butyl cyclopropyl ether reacted with nitric acid, but the β-bromopropionic acid could not be isolated due to the small quantity with which it was necessary to work.

β,γ-dibromopropyl methyl ether made by brominating allyl methyl ether did not react with fuming nitric acid heated in oil bath at 100°C.

The evidence for the structure of cyclopropyl ethers which have been prepared can now be summarized. The combustion analyses have established the empirical formulae. The physical constants differ to some extent from the constants of the corresponding allyl ethers which are known. The experimentally determined molecular refractivities and parachors are closer to those calculated for cyclopropyl ethers than to those calculated for the corresponding allyl ethers. Methyl cyclopropyl ether is less reactive towards bromine in dilute, cold solution than methyl allyl ether. The cyclopropyl ethers will not react very readily with perbenzoic or monoperphthalic acid but unsaturated compounds react quite readily under the usual conditions. Bromine adds readily to cyclopropyl ethers causing the ring to open and α,γ-dibromopropyl alkyl ethers to form. α,γ-dibrome products would be

impossible to obtain by addition to a double bond. Proof of the α,γ-position of the halogen in these derivatives was obtained by oxidation with nitric acid to β-bromopropionic acid which was identified by melting points and combustion analyses. β,γ-dibromopropyl methyl ether does not appear to react even with fuming nitric acid, and even if it did, it could never yield β-bromopropionic acid.

The more important reactions involved are illustrated below.



In all of the preparations of the cyclopropyl ethers, a gas was obtained along with the desired liquid. The cyclization of β,β'-dichlorisopropyl methyl ether yielded a gas which was the principal product. In this reaction over 100 cc. of liquified gas was collected in the spiral condenser cooled in the carbon dioxide ice and alcohol bath. Unfortunately, the gas was not saved. In the preparation of n-butyl cyclopropyl ether, there was not enough gas obtained to identify it. However, in the cyclization of the β,β'-dibromisopropyl methyl, ethyl and n-propyl ethers, the gas was identified in each case as propylene. The gas was bubbled through bromine cooled in ice water and the liquid products were identified by their physical constants to be propylene dibromide. The halogen analyses of the liquids from the methyl and ethyl ethers

showed that the empirical formula must be that of propylene dibromide. The liquid obtained from the propyl ether was not analysed for halogen.

It is reasonable to assume, therefore, that in the cases where the gas was not identified, it was also propylene.

The densities and refractive indices of the samples of propylene dibromide were obtained at room temperature which was approximately 25°C.

Table VIII

Physical Constants of Propylene Dibromide Obtained from the Cyclisation of β,β'-dibromoisopropyl Alkyl Ethers

Ether	Boiling Range	Density	Refractive Index
Methyl	139-141	1.925	1.514
Ethyl	139-140.5	1.918	1.514
n-Propyl	140-142	1.919	1.517

Table IX

Physical Constants of Dibromopropanes

Position of Br	Boiling Range	Density	Refractive Index
α,α [110]	about 130°		
α,β [111]	141.6°, 141.5-141.9°	d_4^{17} 1.9463 d_4^{18} 1.9307 d_4^{20} 1.93326	1.5203
α,γ [112]	165°, 164.5°-165.5°, 165.25°	$d_4^{16.7}$ 1.956 $d_4^{17.6}$ 1.9228, 1.967 d_4^{0} 2.017, d_4^{20} 1.979	1.523
β,β [113]	114-114.5	d_0 1.9149, d_4^{19} 1.875 d_4^{20} 1.7825	

A mechanism by which propylene might be obtained from a β,β'-dibromoisopropyl ether is illustrated below.

$$CH_2BrCHOCH_2Br + Zn \longrightarrow CH_2BrCHOCH_2ZnBr \xrightarrow{\text{active H}}$$
(OR) (OR)

$$CH_2BrCHOCH_2 \xrightarrow{Zn\ Br_2} CH_2BrCHBrCH_3 \xrightarrow{Zn} CH_2{=}CHCH_3$$
(OR)

Attempts to Synthesize Diacrylopropyl Ether.

Preparation of glycerin α,γ bistriphenyl methyl ether. 4 gms. of anhydrous glycerin, 80 cc. of pyridine dried over sodium hydroxide and 28 gms. of triphenylmethyl chloride were mixed in a flask and heated on a boiling water bath for half an hour. The solution was poured into water and a gummy material separated which crystallized after several hours. The product was recrystallized, first, from methanol and acetone, then from absolute ethanol. The yield was 6 gms. of material which melted between 174-175°C. An additional quantitiy could probably be obtained from the mother liquors. The melting point reported by Helfrich et al.[58] was 170-171°C.

Attempt to react glycerin α,γ bistriphenyl methyl ether with sodium. 6.8gms. (0.01 mol.) of the ether previously dried in vacuum was dissolved in 100 cc. of dry benzene. 0.23 gms. of sodium was added and the mixture was refluxed. No reaction occurred. The benzene was distilled off and replaced by 50 cc. of xylene. This mixture was refluxed 50 hours but very little reaction occurred.

Preparation of glycerin α,γ diacetate[61].

255 gms. of glycerin and 660 cc. of glacial acetic acid were refluxed for 8 hours. 175 gms. of acetic acid and water were fractionated off before the temperature of the distilling vapors reached 117°C. 175 gms. of glacial acetic acid were added and the mixture was refluxed 15 hours longer. Acetic acid and water were then fractionated off until the temperature in the

distilling flask reached 165°C. The residual liquid was fractionated in vacuum. The fraction distilling between 155-157°C./16-17 mm. weighed 406 gms. (85 per cent.). The product was miscible with water. Although it gave an acid reaction to litmus, it did not react with sodium bicarbonate.

400 gms. of glycerin was converted to glycerin α,γ diacetate in one other experiment in the same way.

Table X

Attempts to Prepare a Metallic Alkoxide Derivative of Glycerin α,γ Diacetate

Expt. No.	Reagent	Solvent	Conditions	Results
1	Na	Benzene	Refluxed	No reaction
2	Na	Xylene	Refluxed	Decomposition
3	Na	None	25°	No reaction
4	Na	None	80°	Decomposition
5	K	Benzene	Reflux 24 hrs.	K disappeared
6	$(C_2H_5O_2)Mg$	None	150-160°	$CH_3COOC_2H_5$ formed
7	Mg, I_2	None	150-160°	No reaction
8	Mg, I_2	None	220°	Decomposition
9	MgO	None	150-160°	No reaction
10	Mg, $HgCl_2$, I_2	Xylene	Reflux	No reaction
11	C_2H_5MgBr	Et_2O	25°	Reacts with ester group

In experiment 5, the potassium disappeared but the glycerin α,γ diacetate seemed to have decomposed to a syrupy substance insoluble in benzene.

In experiment 6, the liquid which was distilled off was not miscible with water. Its density at 27°C. was 0.865 and its boiling point was 74°C. The density of ethyl acetate at 20°C. is reported[115] to be 0.900 and its

boiling point is 77.1 C. Therefore the liquid is probably impure ethyl acetate.

The magnesium ethylate was prepared[134] by refluxing absolute ethanol with 10 gms. of magnesium, 50 gms. of xylene, a crystal of iodine and a little mercuric chloride. The liquid was filtered from the solid and the latter was dried in vacuum.

In experiment 11, the object was to prepare an alkoxy magnesium bromide. No gas was evolved during the reaction, which indicated that the ester group had reacted instead of the hydroxyl.

Experiments with α, γ -Dichloro-β Bromopropane

α, γ -dichloro-β-bromopropane was prepared from 26 gms. of α, γ -dichlorohydrin and 40 gms. of phosphorus pentabromide. The reaction mixture was washed with water, extracted with concentrated sulfuric acid and centrifuged to break the emulsion. The product was next washed with water and then with sodium bicarbonate solution and dried over calcium chloride. The yield was 6 gms. boiling at 176°C.

This preparation was later modified.

150 gms. of α, γ -dichlorohydrin was reacted with 410 gms. of phosphorus tribromide by adding the latter slowly to the former. The flask was then heated to 130°C and allowed to cool. Water was added to decompose the reaction mixture. The product was extracted with 50 per cent. sulfuric acid washed with water and dried over magnesium sulfate.

17 gms. of α, γ -dichloro-β-bromopropane was added to the reaction mixture between glycerin α, γ diacetate and potassium, described previously in experiments and heated for 8 hours. No reaction occurred.

20 gms. of α, γ -dichloro-β- bromopropane was dissolved in 100 cc. of absolute ethanol. A solution containing 1 gm. of sodium was dissolved

in 100 cc. of absolute ethanol was added slowly. After 2 hours the solution was neutral to litmus. The salts were filtered off and the alcohol was removed by fractionation through a short column. The material in the flask was filtered and the two protions of salts were combined. The salts were dissolved in water, filtered and evaporated to dryness. 1 gm. was dissolved in exactly 100 cc. of water and 10 cc. portions were titrated with tenth-normal silver nitrate using sodium chromate as the indicator. 13.6 cc. of silver nitrate was required in each of two titrations.

Let x = mols of NaBr
Let y = mols of NaCl
$x + y = 0.00135$
$102.9x + 58.46y = 0.1000$
$y = 0.000677$ mols
$x = 0.000473$ mols

Therefore, about twice as much reacts with the alpha halogen as with the beta halogen. Consequently this reaction is not very useful for making β,β'-dichlorisopropyl ethers.

Synthesis of β,β'-Dichlorisopropyl Methyl Ether.

Table XI.

Summary of Unsuccessful Experiments on the Methylation of β,β'-Dichlorisopropanol with Dimethyl Sulfate

Expt.	Temp.	Alkali	Time in hrs.	Results
1	70°	30 per cent. NaOH	—	No methylation. NaOH reacts with the dihalide
2	25°	aq. $NaHCO_3$	20	No methylation
3	50-60°	aq. $KHCO_3$	5	No methylation
4	100°	none	3	Not much reaction
5	140-145°	none	3	Decomposition

In experiment 1 the alkali and the dimethyl sulfate were added from separate funnels. More than the equivalent amount of NaOH was required, indicating a reaction with β,β'-dichlorisopropanol.

In another experiment 0.4 mol of β,β'-dichloroisopropanol was heated with 1 mol of dimethyl sulfate between 120-130°C. for 2 hours. The mixture was cooled, poured into water and neutralized with sodium bicarbonate. The aqueous portion was extracted with ether, mixed with the water insoluble part and dried over calcium chloride. The ether was distilled off at 50°C. The residual liquid was distilled at 4 mm. from a boiling water bath. The distillate was then fractionated at atmospheric pressure. Almost all of it boiled at 160°C. which is the boiling point reported for β,β'-dichloroisopropanol[84].

Yields from four additional experiments carried out in the same way are listed in Table XII.

Table XII.

Yields of β,β' Dichloroisopropyl Methyl Ether

Mols	Yield in Gms.	Per cent. of Theoretical Yield
1	68	47.5
2	144	50
4	40	7
4	447	78

The ether boiled between 40.5-42/1.5-2 mm. and 47°/3 mm.

The last methylation experiment with β,β'-dichloroisopropanol was carried out with 5 mols of this alcohol and 18 mols of dimethyl sulfate. The mixture was heated at 125° for 3.5 hours. After neutralizing with sodium bicarbonate and drying over magnesium sulfate the product was heated again for 3 hours. Neutralization with sodium bicarbonate showed that very little additional reaction had occurred. The product was shaken with 50 per cent. sodium hydroxide to convert any unreacted β,β'-dichloroisopropanol to the lower boiling, more easily separated epichlorhydrin. The liquid was shaken successively with concentrated ammonia to remove dimethyl sulfate, water and calcium chloride solution. It was dried over magnesium sulfate and then dis-

tilled in vacuum to remove the tarry material always present. Redistillation under atmospheric pressure between 159-161.5°C. yielded 690 gms. (31 per cent.).

Synthesis of β,β'-Dibromoisopropyl Methyl Ether.

Preparation of β,β'-dibromoisopropanol[79]

2000 gms. of glycerin and 260 gms. of red phosphorus were placed in a 5 liter flask equipped with a stirrer, dropping funnel reaching to the bottom, and a gas trap. 5500 gms. of bromine were added while the temperature was maintained between 80-100°C. When the heat of the reaction could no longer hold the temperature between these limits, external heat was applied by means of a water bath. After all the bromine had been added, the water bath was heated to 100°C. for 3.5 hours. The reaction mixture was distilled in vacuum. The distillate was neutralised with aqueous sodium bicarbonate and the liquid was fractionated under reduced pressure. The yield was 2500 gms. (46 per cent.) boiling at 108°C./21 mm.

Two additional preparations were carried out in a 12 liter flask using 7000gms. of glycerin, 875 gms. of red phosphorus, and 12250 gms. of bromine in each batch. After the first distillation, the yield was neutralised and dried over $MgSO_4$ but not distilled again. The yields were 9660 gms. (50 per cent.) and 9220 gms. (48 per cent.) Distillation of 500 gms. of one of the yields showed that 90 per cent. boiled in the desired range.

Methylation of β,β'-dibromoisopropanol

Expt. 1. 22 gms. (0.1 mol) of β,β'-dibromoisopropanol and 15 gms. (0.12 mol) of dimethyl sulfate heated between 120-125° for several hours decomposed.

Expt. 2. The same quantities of materials heated between 105-110°C. for several hours caused considerable decomposition, but some product was

obtained. The substance was neutralized with aqueous sodium bicarbonate, dried over calcium chloride and distilled in vacuum.

Expt. 3. 2.5 mols of β,β'-dibromoisopropanol and 3 mols of dimethyl sulfate were heated for 12 hours on a boiling water bath. The solution was neutralized with aqueous sodium bicarbonate and then shaken with 50 per cent. sodium hydroxide while the mixture was cooled with tap water. The lower layer was shaken with concentrated ammonia added 10 cc. at a time, and the mixture was kept cold by an ice water bath.

The product was washed with water, and with 30 per cent. calcium chloride. The yield distilled between 66-69°/1.8 mm. and weighed 162 gms. (28 per cent.)

Table XIII gives the yields obtained in six similar experiments.

Table XIII

Yields of β,β'-Dibromoisopropyl Methyl Ether

Moles of $(CH_2Br)_2CHOH$	Yield in Gms.	Per cent. of Theoretical
5	360	29
11	1042	40
13	1140	35
18	1120	29
18	377	11
18.5	976	25

The methylated product did not react with 50 per cent. sodium hydroxide or concentrated ammonia at room temperature.

Magnesium sulfate was used as the drying agent in most of the experiments above. Calcium carbonate prevented decomposition during distillation.

Expt. 4. 2 mols of β,β' dibromoisopropyl methyl ether, 2.4 mols of dimethyl sulfate, and 3 mols of calcium carbonate were heated in a water bath and stirred. The calcium carbonate caked, and the experiment was abandoned.

Other methylation experiments were tried using the same proportions of reagents employed in experiment 4, but diluted with a solvent and heated at the reflux temperature. The reaction mixtures were filtered, the solvent distilled off under diminished pressure and the residue was distilled in vacuum from calcium carbonate. The distillate was treated with 50 per cent. sodium hydroxide and with concentrated ammonia as described in experiment 3. The conditions and yields, at this point of the procedure are given in the next table.

Table XIV

Methylation in the Presence of a Solvent

Moles of $(CH_2Br)_2CHOH$	Solvent	Heating time in hours	Yield in Gms.	Per cent.
1.25	1000 cc. benzene	15	87	30
0.5	500 cc. toluene	8	31	27
0.5	500 cc. xylene	5	43	38

Synthesis of β, β'-Dibromoisopropyl Ethyl Ether.

3 mols of β, β'-Dibromoisopropanol, 3.6 mols of diethyl sulfate, 6 mols of calcium carbonate and 2100 cc. of xylene were stirred and fractionated for 18 hours. The xylene which distilled off was replaced with fresh material from time to time. 59 cc. of water was collected in the distillate. After filtration, the liquid was distilled from 100 gms. of calcium carbonate through a twenty inch, jacketed column packed with helices.

Table XV

Fractionation of β, β'-Dibromoisopropyl Ethyl Ether

Fraction No.	Boiling range	Sp. Gr.	Weight
1	69.5°/7 mm. to 76°/7.0 mm.	1.82	165 g.
2	76°-77°/7 mm.	1.80	107 g.
3	77-78°/8 mm.	1.78	67 g.

It does not seem likely that these fractions can be nearly pure compounds. The specific gravities are higher than the specific gravity of diethyl sulfate and lower than that for β,β' dibromoisopropanol. They all probably contain some of the desired product and for that reason they were mixed. The total yield was 329 gms. (44 per cent.).

Synthesis of β,β'-Dibromoisopropyl n-Propyl Ether.

Preparation of dipropyl sulfite[91]

640 gms. of n-propanol were placed in a flask equipped with a stirrer, condenser, thermometer and dropping funnel. 660 gms. of thionyl chloride was added with stirring in the course of about 2 hours. The temperature was kept between 35-45° by immersion in a cold water bath during the first half of the addition and by the application of heat during the second half. The mixture was slowly heated to boiling to complete the reaction. The product was fractionated in vacuum and the yield distilled between 82-85°C./21 mm. It weighed 368 gms. (50 per cent.).

Preparation of dipropyl sulfate[92]

250 gms. of dipropyl sulfite was placed in a flask equipped with a dropping funnel, stirrer condenser and thermometer. 100 gms. of sulfuryl chloride was added in half an hour with rapid stirring while the flask was cooled with water. The temperature was raised gradually until the refluxing became vigorous. The condenser was then replaced by a fractionating column, and the flask was heated until no more propyl chloride or sulfur dioxide came off. After the residue had cooled to room temperature, it was stirred with saturated sodium carbonate for 10 minutes, filtered with suction, separated from the aqueous portion and dried over magnesium sulfate. The yield distilled between 90.5-97°C./2.5 mm. and weighed 60 gms. (44 per cent.).

Preparation of β, β'- dibromoisopropyl Propyl Ether.

3 mols of β, β'- dibromoisopropanol were reacted with 3.6 mols of di-n-propyl sulfate in the same way that the ethylation experiment was conducted. Fractionation from calcium carbonate through a 20 inch, helix packed column yielded 258 gms. (33 per cent.) of material having a boiling range of 84-86°C./9-11 mm. and a specific gravity of about 1.84.

Synthesis of β, β' Dibromoisopropyl n-Butyl Ether.

Preparation of dibutyl sulfite[91].

647 gm. of n-butanol were reacted with 480 gms. of thionyl chloride exactly as described for the preparation of diprepyl sulfite. The product which was fractionated from 10 gms. of calcium carbonate, distilled between 99-104°/7.6 mm. and weighed 470 gms. (65 per cent.).

Preparation of di-n-butyl sulfate[91].

470 gms. of dibutyl sulfite were reacted with 163 gm.s of sulfuryl chloride exactly as described for the preparation of di-n-propyl sulfate. The product was fractionated from 5 gms. of calcium carbonate. The yield was collected between 110-115°C./4.5-5 mm. and it weighed 256 gm. (92 per cent.).

Preparation of β, β'- dibromoisopropyl-n-butyl ether.

0.81mol of di-n-butyl sulfate, 0.6 mol of β, β'- dibromoisopropanol, 1.6 mols of calcium carbonate and 700 cc. of xylene were stirred and fractionated for 17 hours. The reaction mixture was treated in the same way as in the preparation of β, β'- dibromoisopropyl ethyl ether. The yield weighed 119 gms. (58 per cent.) and distilled between 86°-95°C./4 mm.

Synthesis of β, β'- Dibromoisopropyl Bromomethyl Ether.

656 gms. (3 mols) of β, β'- dibromopropanol and trioxymethylene (9 mols of formaldehyde) were mixed and cooled in an ice water bath. 756 gms. of dry hydrogen bromide was passed into the suspension. The hydrogen bromide was

made by direct combination of hydrogen and bromine[116]. Hydrogen was bubbled through a flask of bromine heated in a water bath, and the mixed gases were burned in a silica tube heated by a gas burner. At the end of the absorption, all of the trioxymethylene had dissolved, and the reaction mixture had separated into two layers of which the upper one was water soluble. The lower layer was fractionated. The forerun was cut at 129°C./12 mm. The yield distilled between 129-135°C./12 mm. and weighed 775 gms. (63 per cent.) No attempt has been made as yet to prove the identity of the product.

Synthesis of Methyl Cyclopropyl Ether.

Table XVI summarises some preliminary cyclisation experiments.

Experiment 2 did not always work. Apparently pure, dry reagents are necessary, and it was not always possible to obtain the β,β'- dichloropropyl methyl ether in such a condition. In one experiment which did work, a liquid was obtained. The fraction boiling up to 57°C. decolorised potassium permanganate, reacted slowly with bromine in carbon tetrachloride, was soluble in concentrated sulfuric acid, gave a precipitate with silver nitrate, was insoluble in water and had a specific gravity greater than 1. In other similar experiments no liquid products could be isolated.

Experiment 5 yielded a liquid which boiled at about 47°C. reacted with potassium permanganate but not with silver nitrate. This product may have been methyl cyclopropyl ether. It was not investigated any further.

One objection to the use of butyl ether as a solvent in the cyclisation is that sodium iodide and magnesium salts in general are insoluble in it.

The β,β'- dibromoisopropylmethyl ether was much more reactive than the

Table XVI

Summary of Some Preliminary Cyclization Experiments with β, β'-Dibromoisopropyl Methyl Ether and β, β'-dichloroisopropyl Methyl Ether

Expt.	Halide	Metal	Solvent	Temp.	Time in hrs.	Catalyst	Results
1	Cl	Mg	Bu_2O, Xylene	Reflux	20	CH_3MgI	No reaction
2	Cl	Mg	Bu_2O	Reflux	24	EtMgI EtI	Reacts
3	Cl	Mg	80% EtOH	Reflux	45	NaI	Very slow and incomplete
4	Cl	Mg	$AcNEt_2$	Heat	—	NaI Na_2CO_3	No reaction
5	Cl	Na	Biphenyl	260°	—	none	Reacts
6	Cl	Zn	80% EtOH	Reflux	45	KI	No reaction
7	Cl	Zn	Bu_2O	Reflux	—	NaI, Na_2CO_3	No reaction
8	Br	Zn	70% EtOH	Reflux	8	NaI, Na_2CO_3	Reacts
9	Br	Zn	Bu_2O	Reflux	3	NaI, CH_3MgI	Reacts
10	Br	Mg	Bu_2O	Reflux	2	NaI, CH_3MgI	Reacts
11	Br	Mg	$AcNEt_2$	Heat	—	NaI, Na_2CO_3	Reacts

corresponding chloro compound. In experiment 8, the reaction was too slow. No attempt was made to isolate any products from experiments 8 -11.

None of these experiments was so satisfactory as the ones which are described below.

1000 gm. of acetamide, 4 mols of sodium carbonate, 8 mols of sodium iodide and 12 mols of zinc dust were placed in a flask equipped with a stirrer, thermometer, dropping funnel and a short fractionating column. A flask with a sidearm was attached to the sidearm of the distilling column. The flask was kept in the ice water bath. Attached to this sidearm was a glass spiral which was sealed to the top of a 100 cc. flask. A straight outlet tube was also sealed to this flask and led to a gas holder. A tube sealed to the bottom of this flask was bent along the side of the flask, up the center of the spiral and then bent down again. A glass stopcock was sealed to the end of this tube. This tube could serve as a siphon. The entire flask and spiral fitted in a 500 cc. Dewar flask which was filled with carbon dioxide snow and ethyl alcohol.

The reaction flask was heated by an oil bath kept between 120-135°C. 3 mols of β,β' dichloroisopropyl methyl ether was added slowly. The internal temperature rose to about 150°C. The carbon dioxide trap condensed more than 100 cc. of a liquid which was a gas at room temperature. In addition, a great deal of gas was collected in the gas holder. 60 gms. (23 per cent.) of liquid was obtained from the flask immersed in ice water.

Another experiment involving one mol of the chloro ether yielded 15 gms. (21 per cent.) of liquid which distilled between 46-49°C.

1250 gms. of acetamide, 5 mols of sodium carbonate, 10 mols of sodium iodide and 15 mols of zinc were placed in the reaction flask of the apparatus described previously. The temperature within the flask was kept between 110-120°C. since the reaction was exothermic. After all the bromide

had been added, the temperature was raised to 155°. The liquid condensed in the flask cooled in ice water was fractionated and yielded 275 gms. (76 per cent.) of crude methyl cyclopropyl ether boiling between 41.5–44.5°C. In addition, some gas was collected in the gas holder.

Table XVII gives the yields from experiments carried out in the same way.

Table XVII

Crude Yields of Methyl Cyclopropyl Ether from Cyclization of β,β-Dibromoisopropyl Methyl Ether

Moles	Yield gms.	Yield per cent.
2	120	83
5	300	83

Dry reagents were used in these successful cyclization experiments.

Determination of unsaturates.

Bromine method. The sample was added to 50 cc. of carbon tetrachloride in an Erlenmeyer flask which was kept in an ice water bath throughout the determination. 0.2 N bromine in carbon tetrachloride was added slowly until an excess was present which did not decolorize completely in 10 minutes. Aqueous potassium iodide was then added and the liberated iodine was titrated with sodium thiosulfate. The latter titration was subtracted from the bromine titration. This method was not very precise because the endpoint was not definite. Although bromine reacts more readily with an unsaturated compound such as methyl allyl ether, the rate of reaction with methyl cyclopropyl ether is by no means negligible.

Perbenzoic acid method. 10 cc. of a solution of perbenzoic acid in toluene was diluted with 1 cc. of toluene. To another 10 cc. portion was added 1 cc. of methyl cyclopropyl ether. The two solutions were kept

in the refrigerator in similar well stoppered bottles. After 24 hours the solutions were analyzed by adding 1 cc. of each to aqueous, acidified potassium iodide and titrating the liberated iodine with tenth-normal sodium thiosulfate using starch as an indicator. The difference between the titrations was representative of the amount of unsaturates present.

Preliminary fractionation. Crude methyl cyclopropyl ether was fractionated to remove gases and high boiling materials. The desired fraction was not cut sharply at this time.

Methods of removing unsaturates.

Bromine method. The approximate quantity of unsaturates was determined by a bromine titration. The methyl cyclopropyl ether (21 gms.) was chilled in an ice and salt bath and stirred vigorously while the quantity of bromine (12 gms.) in excess of that indicated by the titration was distilled over the liquid. The methyl cyclopropyl ether was fractionated from the higher boiling bromides. The distillate was shaken with powdered sodium hydroxide (3 gms.) and fractionated from it.

Perbenzoic acid method. The ether was titrated with perbenzoic acid to determine the quantity of unsaturates present. 35 cc. of a 1.5 molar perbenzoic acid solution in toluene (an excess) was mixed with 100 cc. of methyl cyclopropyl ether. The solution was allowed to stand in the refrigerator for several days. 1 cc. was titrated to make certain that a sufficient excess of perbenzoic acid was still present. The peroxide and benzoic acid were removed with sodium hydroxide solution. The liquid was then washed with water and calcium chloride solution and dried over a little magnesium sulfate and fractionated. The portion which distilled between 42.0°-43.5°C. was dried over powdered sodium hydroxide and refractionated. The pure methyl cyclopropyl ether distilled between 43.5 -44.0°C.

Methyl cyclopropyl ether reacts slowly with perbenzoic acid, or the unsaturates react slowly in very dilute solutions.

A series of titrations carried out over a number of days is listed in Table XVIII. The data represent cc. of a tenth-normal sodium thiosulfate solution required in a perbenzoic acid titration carried out as described previously.

Table XVIII

Reaction of Perbenzoic Acid with Methyl Cyclopropyl Ether

Days	Standard	Ether	Difference
1	2.90	2.50	.40
6	2.75	1.35	1.40
7	2.75	1.20	1.55
8	2.70	1.15	1.55
9	2.70	1.00	1.70
10	2.70	.95	1.75
30	2.35	.15	2.20
1	4.45	4.05	.40
2	4.40	3.70	.70
3	4.35	3.45	.90
4	4.30	3.20	1.10
5	4.25	3.00	1.25

The perbenzoic acid solution in toluene was prepared by a slight modification of the method described by Tiffeneau, R. Adams and F.D. Kendall[11e]. 121 gms. of benzoyl peroxide was dissolved in 1.5 liter of dry toluene cooled below -5°C. 19 gms. of sodium dissolved in 500 cc. of absolute ethanol and chilled to -5°C. was added with mechanical stirring. 2 liters of ice water were added and stirring was continued until solution of the sodium perbenzoate was complete. The toluene layer was removed, and the aqueous layer was extracted 5 times with 100 cc. portions of toluene. The aqueous layer was placed in the flask in the ice and salt bath and a solution of 54 gms. of concentrated sulfuric acid in 50 cc. of water cooled to 0°C. was added with stirring. The perbenzoic acid was extracted with three 250 cc. portions of toluene. The portions were kept separate. They were dried over $MgSO_4$ and stored in the refrigerator.

An attempt was made to remove any residual unsaturates from methyl cyclopropyl ether by filtering repeatedly through a column of activated silica gel. The value of a perbenzoic acid titration before the filtration was 1.60 cc. tenth-normal sodium thiosulfate and after the filtration was 1.55. The standard required 1.81 cc. Therefore, the silica gel has little, if any effect.

Test for peroxides. A small portion of the ether was shaken with neutral aqueous potassium iodide in a well stoppered test tube. A yellow color did not develop within a half hour. This indicated that no peroxides were present.

Test for halogen. A modified Beilstein test as developed by Ruigh[93] was used. Illuminating gas was passed through a warmed flask to a burner which was placed under a copper gauze. The gauze was heated on both sides until no green color could be seen in the flame. The methyl cyclopropyl ether was added to the flask by means of a dropping funnel. The ether purified by the perbenzoic acid method gave a negative test.

Methyl cyclopropyl ether which gave a strong test for halogen was stripped of all except a trace by refluxing first over powdered sodium hydroxide and then over zinc dust. Either of these treatments alone did not remove the halogen effectively.

Drying agents.

Methyl cyclopropyl ether was refluxed over sodium metal. The ether reacted with the metal and produced unsaturated compounds.

Potassium metal reacted in the same way.

The ether was stable towards sodium hydroxide even during a long reflux period. Powdered sodium hydroxide was the best drying agent used on this compound.

Physical properties.

Density, refractive index, and surface tension measurements made during the research were carried out at 25°C. by means of a thermostat set at this temperature. The refractive indices were taken with respect to the D line of sodium by means of an Abbe refractometer. Surface tension measurements were made by the bubble method described by Sugden[117]. The equations used to calculate the surface tensions and parachors were taken from Sugden's book. The pressure necessary to produce a bubble in a liquid from a capillary and from a larger tube was measured by means of alcohol in a manometer. The pressure is given in the tables in cms. of alcohol opposite the words "Capillary" or "larger tube." The surface tensions are given in dynes/cm. Densities were measured by means of pycnometers. The weights are not corrected for air buoyancy in the tables but the densities are given in gms./cc. in vacuum[118]. Volumes are given in cc. Any exceptions to these general rules will be noted. Sufficient data will be provided to permit the calculation of any of the constants which are given, but data listed in a table will not be repeated in subsequent tables.

Table XIX

Calibration of Surface Tension Apparatus with Benzene

Wt. of ethyl alcohol + pycnometer No. 39	26.732
Wt. of ethyl alcohol	7.806
Density of ethyl alcohol	.788
Capillary	9.65
Larger tube	.84
Diameter of larger tube	.2998
Density of benzene[119]	.873
Surface tension of benzene[117]	28.22

The immediately adjacent section of the tubing from which the larger tube was made was measured under a microscope by means of a calibrated micrometer eyepiece. The value given in the table is the average of eight

measurements on four diameters.

$$\phi = 1 + .69 r_2 \, g \, D/P$$

$$A = \gamma/P\phi$$

ϕ is a correction factor

r_2 is the radius of the larger tube

g is 981

D is the density of the liquid

P is the difference between the pressure on the capillary tube and the larger tube expressed in dynes/sq. cm.

A is a constant characteristic of the surface tension apparatus

γ is the surface tension

$$\phi = 1 + .69 \times \frac{.2996}{2} \times 981 \times .873/ 8.81 \times .788 \times 981$$

$$\gamma = 1.013$$

$$A = 28.22/ 8.81 \times .788 \times 981 \times 1.013$$

$$A = .004090$$

Table XX

Calibration of Pycnometer No. 39

Pycnometer + water	28.774
Pycnometer	19.276
H_2O	9.498
Density of $H_2O^{11°}$	.9970
Volume of pycnometer	9.557

Table XXI

Physical and Molecular Properties of Methyl Cyclopropyl Ether

Distilling range	43.5-44.0
Vapor pressure at 26°C.	414
Pycnometer No. 39 + ether	26.755
Methyl cyclopropyl ether	7.459
Density	.788
Capillary	7.04
Larger tube	.85
Surface tension	19.92
Refractive index	1.3749
Parachor (experimental)	194.0
Parachor (calculated)	192.7
Molecular refractivity (experimental)	21.00
Molecular refractivity (calculated)	20.83

The methods of calculating the surface tension, parachor and molecular refractivities from the experimental values is illustrated below using the data on methyl cyclopropyl ether. Calculations of the parachor and molecular refractivity from the atomic and structural constants is also shown.

Calculation of surface tension:

$\gamma = AP\phi$

$\phi = 1 + .69\ r_m\ \xi\ D/P$

$\phi = 1 + .69 \times .150 \times 981 \times .786/6.91 \times .788 \times 981$

$\phi = 1 + .0168 = 1.017$

$\gamma = .00609 \times .788 \times 961 \times 6.19 \times 1.017$

$\gamma = 19.92$ dynes / cm.

Calculation of parachor from experimental data:

$$P = \frac{M\gamma^{1/4}}{D - d}$$

P is the parachor

γ is the surface tension

D is the density of the liquid

d is the density of the vapor

$d_b = .0122\ M/T_b$

d_b = density of vapor at boiling point

T_b = absolute temperature of the boiling point

$d_b = .0122 \times 72.1/317$

$d_b = .00278$

$\log_{10}\ d/d_b = 5\ (T/T_b - 1)$

d is density of the vapors at any desired temperature

T is absolute temperature at which the density is desired

$\log_{10}\ d/.00278 = 5(295/317 - 1)$

$d = .0013$

$$P = \frac{72.1 \times 19.92^{1/4}}{.786 - .001}$$

$$P = 194.0$$

The following table of values was used to calculate the parachors of cyclopropyl ethers and the isomeric allyl ethers.

Table XXII[117]

Atomic and Structural Parachors

C	4.8
H	17.1
O	20.0
3 membered ring	16.7
Double bond	23.2

The calculations of the parachor of methyl cyclopropyl ether using these values is shown below:

$$P = 4 \times 4.8 + 8 \times 17.1 + 20.0 + 16.7$$

$$P = 192.7$$

The calculation of the molecular refractivity from experimental data was done as follows:

$$M = \frac{n^2 - 1}{n^2 + 2} \times \frac{M.W.}{D}$$

M = molar refractivity

n = refractive index

M.W. = molecular weight

D = density

$$M = \frac{1.3749^2 - 1}{1.3749^2 + 2} \times \frac{72.1}{.786}$$

$$M = 21.00$$

Table XXIII[lat, lmm]

Constants Used to Calculate Molecular Refractivity from Molecular and Structural Data

C	2.418
H	1.100
Ether oxygen	1.643
Cyclopropane ring	.71
Double bond in $RCH=CH_2$	1.60

The calculation follows:

$$M = 4 \times 2.418 + 8 \times 1.100 + 1.643 + .71$$

$$M = 20.83$$

The vapor pressure of methyl cyclopropyl ether at 26°C. was determined by adding an excess of the liquid to a known volume of air in a nitrometer. Dry mercury was the confining liquid. 10 cc. of air increased in volume to 22.0 cc. The volume then remained constant. Assuming that atmospheric pressure was 760 mm. of mercury, the vapor pressure at 26°C. was 414 mm.

Lower explosive limit.

The lower explosive limit of methyl cyclopropyl ether was determined by mixing the vapor with oxygen in a Hempel explosion pipette and sparking the gas by means of an induction coil. Small amounts of the ether were added to known volumes of oxygen. From the increase in volume, the percentage of the vapor in the gas was known. Such mixtures, which were never near saturation, were used as stock mixtures and diluted with oxygen to give any desired concentration. 1.86 per cent. of methyl cyclopropyl ether in oxygen did not explode, while 2.09 per cent. exploded.

Combustion analyses for carbon and hydrogen were carried out by the micro method developed by Pregl[lan].

Table XXIV

Determination of Carbon and Hydrogen in Methyl Cyclopropyl Ether

Analysis Numbers	I	II	III	IV
Sample and sample tube	35.285	16.675	23.941	16.984
Sample tube	20.467	12.668	19.907	12.852
Sample	4.758	4.007	4.034	4.132
H_2O + H_2O tube	24.082	7.854	11.815	16.929
H_2O tube	19.342	3.886	7.854	11.815
H_2O	4.690	3.968	3.961	4.114
CO_2 + CO_2 tube	45.205	11.958	21.805	31.080
CO_2 tube	33.676	2.191	11.958	21.805
CO_2	11.527	9.767	9.847	10.075
per cent. H	11.07	11.06	10.98	11.08
per cent. C	66.39	66.52	66.61	66.22

Calculated for C_4H_6O: H, 11.18; C, 66.63

Preparation of α,γ-dibromopropyl methyl ether from methyl cyclopropyl ether prepared from β,β'- dibromoisopropyl methyl ether.

5 gms. of methyl cyclopropyl ether was mixed with 50 cc. of chloroform and immersed in an ice bath. 11 gms. of bromine dissolved in 50 cc. of chloroform which was similarly cooled, was added slowly. After the bromine had reacted, the chloroform was evaporated in vacuum and the residue fractionated. The fraction distilling between 68-70°C./9 mm. was the desired product.

Table XXV

Physical Properties of α,γ-dibromopropyl methyl ether

Pycnometer No. 1 + liquid	6.0346
Liquid	4.287
Density	1.730
Refractive index	1.5060

Table XXVI

Calibration of Pycnometer No. 1

Pycnometer No. 1 + H_2O	4.1372
Pycnometer No. 1	1.7482
H_2O	2.3890
Volume	2.395

Determination of halogen. Halogen was determined by the micro Parr bomb Method. 15 gms. of sodium peroxide, 0.4 gms. of sucrose, 1.3 gms. of potassium nitrate and the liquid sample weighed out in a tared gelatin capsule were placed in the bomb. The top was screwed tight, the charge was mixed and the bomb was ignited until the water on the top of the bomb boiled for one minute. The fused mass was dissolved in 200 cc. of water, and heated to boiling. The solution was cooled and 35-40 cc. of concentrated nitric acid was added. The solution was heated to boiling again, the burner was removed and 1 gm. of hydrazine sulfate was added cautiously.

The solution was heated to boiling and the halogen was precipitated with 10 cc. of 5 per cent silver nitrate. The contents of the beaker was boiled gently until the silver halide coagulated. The mixture was cooled and filtered into a tared, fritted glass crucible, and washed with 0.01 molar nitric acid and 95 per cent. alcohol. The crucible was dried for 1 hour at 120-130°C., cooled in a dessicator for half an hour, placed in a balance case for 15 minutes and weighed with a similar crucible used as a tare.

Table XXVII

Determination of Bromine in α,γ-dibromopropyl Methyl Ether

Analysis Number	I	II
Blank	.0005	.0005
Capsule and sample	1.8858	1.9009
Capsule	1.7136	1.7132
Sample	.1723	.1877
Crucible and AgBr	1.2146	1.3344
Crucible	.9365	1.0819
AgBr	.2781	.3025
Per cent. Br	68.51	68.47

Calculated for $C_4H_8Br_2O$; Br, 68.91

Preparation of β-bromopropionic acid from α, γ-dibromopropyl methyl ether. 0.7 gms. of this ether was added, drop by drop, to 1 gm. of nitric acid having a specific gravity of 1.5. The reaction test tube was shaken during the addition and cooled in a beaker of tap water. After the most vigorous reaction has quieted, the tube was heated at 100°C. until the reaction was complete. The nitric acid was distilled off in vacuum. The residue was crystallized from petroleum ether until the product melted constantly between 60.5-61.5°C. after a little SINTERing. It was allowed to solidify and it remelted between 60.0-61.0°C.

Table XXVIII

Determination of Carbon and Hydrogen in β-Bromopropionic Acid

Analysis Number	I	II
Sample and boat	6.489	7.375
Boat	.839	1.159
Sample	5.650	6.216
H_2O tube + H_2O	7.273	9.128
H_2O tube	5.580	7.273
H_2O	1.693	1.855
CO_2 tube and CO_2	9.579	14.947
CO_2 tube	4.697	9.579
CO_2	4.882	5.368
per cent. H	3.35	3.34
per cent. C	23.58	23.57

Calculated for $C_3H_5BrO_2$: C, 23.55; H, 3.29

β-bromopropionic acid was prepared from the methyl cyclopropyl ether synthesized from β, β'- dichloroisopropyl methyl ether by the same series of reactions. It melted and remelted between 59.0-60.0°C. after a little sintering. A mixture of this sample with the analyzed sample melted between 59.5-61.5°C and remelted between 60.0°-61.5°C.

Attempt to prepare α, α- dimethoxy- γ -bromopropane.

2 gms. of α, γ-dibromopropyl methyl ether was refluxed with 10 cc. of absolute methanol for two hours. The methanol was removed by distillation and the residual liquid was distilled in vacuum. Only a small quantity of distillate was obtained.

Table XXIX

Determination of Halogen in the Material Recovered from Methanol

Analysis Number	I	II
Capsule and sample	1.9000	1.8623
Capsule	1.7103	1.7126
Sample	.1897	.1497
Crucible and AgBr	6.4206	1.0133
Crucible	6.1618	.8051
AgBr	.2588	.2082
Per cent Br	60.23	59.10

Calculated for $C_3H_{11}BrO_2$: Br, 43.63

Calculated for $C_4H_6Br_2O$: Br, 68.91

Identification of the gaseous by-product.

The gas obtained from β, β' dibromoisopropyl methyl ether during the preparation of methyl cyclopropyl ether was bubbled through bromine cooled in ice water. Only a small part of the gas was absorbed. The reaction mixture was poured into water and the excess bromine was destroyed with sodium sulfite. The insoluble liquid which remained was dried over magnesium sulfate and fractionated in the small fractionating apparatus described below. The product distilled between 138-141°C. Only one component seemed to be present. 0.1 cc. of the liquid was measured out in a pipette and weighed to determine the density. The density and refractive index were determined at room temperature, which was 25°C. without the use of a thermostat.

Table XXX

Physical Properties of the Bromine Derivative of the Gaseous By-Product from the Preparation of Methyl Cyclopropyl Ether

Container and liquid	10.2526
Container	10.0401
Density	1.[illegible]
Distilling range	138-141°
Refractive index	1.514

Table XXXI

Determination of Halogen in the Bromine Derivative of the Gaseous By-Product from the Preparation of Methyl Cyclopropyl Ether

Analysis Number	I	II
Capsule and sample	1.8862	1.8336
Capsule	1.7120	1.7086
Sample	.1742	.1252
Crucible and $AgBr$	.4867	.4370
Crucible	.2012	.1965
$AgBr$	.2873	.2335
Per cent. Br	79.15	79.19

Calculated for $C_3H_6Br_2$: Br, 79.15

The liquid was unquestionably propylene dibromide, proving that the gas was propylene.

A small fractionating apparatus was used to distill the liquid. The bulb was 20 mm. in diameter with a glass jacketed column 4 x 100 mm. At the head of the column was a 7.5 x 60 mm. tube into which the thermometer bulb fitted and onto which the sidearm was sealed. A capillary tube sealed at one end served as an ebullator tube.

Preparation of allyl iodide[99].

260 gms. of allyl alcohol and 32.5 gms. of red phosphorus in a flask equipped with a reflux condenser were treated with 414 gms. of iodine added 25 gms. at a time. The allyl iodide was distilled in an atmosphere of carbon dioxide. The distillate was washed with water, sodium bicarbonate solution, sodium sulfite solution and again with water. It was dried over magnesium sulfate and distilled between 100-102.5°C. The yield was 458 gms. (82 per cent.).

Preparation of allyl methyl ether[99].

550 gms. of methanol was reacted with 75 gms. of sodium. 450 gms. of allyl iodide was added at a rate such that the mixture refluxed. After refluxing for 1-1/2 hours longer, the solution was filtered and fractionated. The

portion distilling at 42°C. was collected, washed with 40 per cent. calcium chloride solution, dried over a mixture of 10 gms. of calcium chloride and 10 gms. of magnesium sulfate and then refluxed over 18 gms. of sodium and potassium alloy. A reaction occurred, apparently between the allyl methyl ether and the alkali metal. The fraction distilling between 43–45°C. was collected as the yield.

Table XXXI

Physical and Molecular Properties of Allyl Methyl Ether

Distilling range	43–45°
Pycnometer No. 39 and liquid	27.497
Liquid	7.211
Density	.757
Capillary	6.35
Larger tube	.30
Surface tens[illegible] (experimental)	19.46
Refractive i[illegible] (calculated)	1.3755
Parachor (experimental)	200.4
Parachor (calculated)	199.2
Molecular refractivity (experimental)	22.06
Molecular refractivity	21.72

Table XXXII

Determination of Carbon and Hydrogen in Allyl Methyl Ether

Analysis Number	I	II
Sample and sample tube	60.932	28.065
Sample tube	58.513	18.570
Sample	2.419	9.495
H_2O and A_2O tube	29.359	33.952
A_2O tube	24.956	29.309
H_2O	4.433	4.643
CO_2 and CO_2 tube	84.347	79.429
CO_2 tube	83.425	84.347
CO_2	10.922	11.082
Per cent. H	11.22	11.31
Per cent. C	67.40	67.30

Calculated for C_4H_8O : H, 11.18; C, 66.63

Allyl methyl ether reacts quantitatively with perbenzoic acid.

Preparation of β,γ-dibromopropyl methyl ether.

5 gms. of methyl allyl ether were dissolved in 20 cc. of chloroform and treated with a slight excess of bromine. The solution was washed with potassium carbonate solution and dried over magnesium sulfate. After the chloroform had been removed by distillation, the product distilled at 81°C./ 17 mm. This material did not react with nitric acid (sp. gr. 1.5) heated in an oil bath at 100°C.

Synthesis and Properties of Ethyl Cyclopropyl Ether.

Cyclization of β,β'-dibromoisopropyl ethyl ether.

246 gms. (1 mol.) of β,β'-dibromoisopropyl ethyl ether was cyclized in the same way that methyl cyclopropyl ether was prepared from β,β'-dibromoisopropyl methyl ether. 67 gms. of crude ethyl cyclopropyl ether was obtained along with some gas.

Purification of ethyl cyclopropyl ether.

The crude product was fractionated through a short, helix filled column. The portion which distilled between 63-68°C. weighed 55 gms. Unsaturates were removed by the perbenzoic acid method described previously.

Table XXIV

Physical and Molecular Properties of Ethyl Cyclopropyl Ether

Distilling range	67-68°
Pycnometer No. 39 and liquid	26.708
Liquid	7.624
Density	.783
Capillary	7.29
Larger tube	.30
Surface tension	20.34
Refractive index	1.3880
Parachor (experimental)	254.7
Parachor (calculated)	251.7
Molecular refractivity (experimental)	25.77
Molecular refractivity (calculated)	25.44

Table XXXV

Determination of Carbon and Hydrogen in Ethyl Cyclopropyl Ether

Analysis Number	I	II	III	IV	V	VI
Sample and sample tube	26.212	19.935	16.421	31.036	24.227	26.459
Sample tube	21.225	16.277	13.690	25.880	20.817	21.702
Sample	4.988	3.718	4.731	5.176	3.810	4.757
H_2O tube and H_2O	21.089	24.978	29.678	12.462	16.284	7.232
H_2O tube	16.929	21.089	24.978	9.115	12.462	2.310
H_2O	5.160	5.889	4.900	3.348	3.772	4.922
CO_2 tube and CO_2	44.660	53.997	66.935	44.351	44.[illegible]	25.132
CO_2 tube	31.886	44.559	56.097	27.068	34.931	12.978
CO_2	12.699	9.438	11.998	7.278	9.127	12.154
Per cent. H	11.57	11.76	11.58	11.80	11.69	11.64
Per cent. C	69.27	69.42	69.21	69.69	68.98	69.29

Calculated for $C_6H_{10}O$: H, 11.70; C, 69.72

Preparation of α,γ-dibromopropyl ethyl ether.

5 gms. of ethyl cyclopropyl ether was brominated by the same method used to prepare methyl cyclopropyl ether.

Table XXXV

Physical Properties of α,γ-Dibromopropyl Ethyl Ether

Distilling range	76.6- 77.3°C./9.8 mm.
Pycnometer No. 1 and liquid	8.7391
Liquid	3.201
Density	1.666
Refractive index	1.4939

Table XXXVI

Determination of Halogen in α,γ-Dibromopropyl Ethyl Ether

Analysis Number	I	II
Sample and capsule	1.9391	1.9011
Capsule	1.7170	1.7099
Sample	.2221	.1912
Crucible and AgBr	4.8365	6.0619
Crucible	4.5037	5.7941
AgBr	.3328	.2678
Per cent. Br	63.07	63.96

Calculated for $C_6H_{10}OBr_2$: Br, 64.30

Preparation of β-bromopropionic acid from α,γ-dibromopropyl ethyl ether.

2 gms. of this ether and 7 cc. of 45 per cent. nitric acid were shaken in a test tube. The reaction was allowed to proceed without application of heat for about 20 hours. The aqueous portion was extracted 5 times with diethyl ether, the diethyl ether was extracted with dilute sodium hydroxide, taking care to prevent a rise in temperature. The sodium hydroxide was made distinctly acid to methyl orange with dilute sulfuric acid and the solution was extracted 6 times with diethyl ether. The diethyl ether was evaporated to dryness on the steam bath and the residual syrup was extracted twice with warm petroleum ether. The petroleum ether was concentrated and the β-bromopropionic acid was crystallized repeatedly from this solvent, until it melted and remelted constantly between 58.0-59.0°C. A mixture of this acid melted between 60.0-61.0°C. and remelted between 59.0-61.0°C.

Attempt to prepare α,α-diethoxy-β-bromopropane.

3 gms. of α,γ-dibromopropyl ethyl ether were refluxed with 10 cc. of absolute ethanol for two hours. After the excess ethanol had been removed, the residual liquid distilled between 73-74°C./8 mm.

Table XXXVIII

Determination of Halogen in the Material Recovered from Ethanol

Analysis Number	I	II	III
Capsule and sample	1.9506	1.9700	1.8143
Capsule	1.7144	1.7142	1.7145
Sample	.2362	.2558	.0998
Crucible and AgBr	.6640	.2548	0.1018
Crucible	.3301	- .1267	0.0083
AgBr	.3339	.3595	.1435
Per cent. Br	61.37	59.75	61.06

Calculated for $C_7H_{15}BrO_2$: Br, 37.06
Calculated for $C_6H_{13}Br_2O$: Br, 64.96

Identification of the gaseous by-product from the cyclization of β,β'-dibromoisopropyl ethyl ether.

The gas was brominated and the product was treated exactly as in the identification of gas from the preparation of methyl cyclopropyl ether.

The density and refractive index were taken at room temperature which was 25°C. A thermostat was not used.

Table XXXIX

Physical Properties of the Bromine Derivative of the Gas from the Preparation of Ethyl Cyclopropyl Ether

Boiling range	139-140.5°C.
Refractive index	1.5154
Pycnometer 10.1 and liquid	6.5418
Liquid	4.624
Density	1.918

Table XL

Determination of Halogen in the Bromine Derivative of the Gas from the Preparation of Ethyl Cyclopropyl Ether

Analysis Number	I	II
Capsule and sample	1.8857	1.8600
Capsule	1.7119	1.7155
Sample	.1418	.1445
Crucible and AgBr	4.3057	5.7041
Crucible	4.0428	5.5254
AgBr	.2629	.2687
Per cent Br	78.76	78.98

Calculated for $C_3H_6Br_2$ Br, 79.15

The data show that the liquid was propylene dibromide and one component of the gas must have been propylene. The gas which remained was analyzed for carbon dioxide and oxygen. 40 per cent. was absorbed by 50 per cent. potassium hydroxide. The quantity of the residual gas absorbed by sodium hydrosulfite and potassium hydroxide indicated that 2.4 per cent. oxygen was in the gas after bromine treatment.

Synthesis and Properties of Propyl Cyclopropyl Ether.

Cyclization of β,β' dibromoisopropyl n-propyl ether and purification of the product.

1.07 mols of β,β' dibromoisopropyl n-propyl ether was converted to n-propyl cyclopropyl ether under the same conditions used to prepare methyl cyclopropyl ether. The crude yield was 77 gms. This liquid was washed with water three times and twice with calcium chloride solution to remove allyl alcohol, acetonitrile and acetamide. 46 gms. was left after this treatment. The material was dried over magnesium sulfate, filtered and fractionated with a small Vigreux column. The fraction which distilled between 89-98°C. weighed 22.5 gms. (22.6 per cent. yield) and was chiefly n-propyl cyclopropyl ether.

After the unsaturates were determined by a perbenzoic acid titration, an excess (18 gms.) of finely powdered monoperphthalic acid was added to the liquid. The solid did not dissolve completely, but the mixture began to warm up a little and thus indicated that a reaction was taking place. The material was placed in the refrigerator and shaken from time to time. After standing in the cold over night, the reaction mixture was allowed to stand at room temperature for 24 hours. It was then extracted with 10 per cent. sodium hydroxide washed with water and calcium chloride solution and dried over powdered sodium hydroxide. The liquid was filtered and fractionated.

0.1 cc. of the product was allowed to react with 2 cc. of perbenzoic acid solution for two days and then titrated. 1 cc. required 2.70 cc. tenth-normal sodium thiosulfate while the undiluted standard solution required 3.66 cc. Therefore, there is still a little unsaturated material present.

Table XLI

Physical and Molecular Properties of n-Propyl Cyclopropyl Ether

Distilling range	94-96°C.
Pycnometer No. 39 and liquid	26.796
Weight of liquid	7.520
Density	.790
Refractive index	1.3933
Bubbles from capillary	7.64
Bubbles from larger tube	1.05
Surface tension	21.17
Parachor (experimental)	272.0
Parachor (calculated)	270.7
Molecular refractivity (experimental)	30.31
Molecular refractivity (calculated)	30.06

Table XLII

Determination of Carbon and Hydrogen in n-Propyl Cyclopropyl Ether

Analysis Number	I	II
Sample and sample tube	57.970	19.867
Sample tube	53.121	15.341
Sample	4.849	4.526
H_2O and H_2O tube	4.347	9.219
H_2O tube	-.845	4.347
H_2O	5.192	4.872
CO_2 and CO_2 tube	15.079	27.053
CO_2 tube	2.272	15.079
CO_2	12.807	11.974
per cent H	11.98	12.04
per cent C	72.08	72.19

Calculated for $C_6H_{12}O$: H, 12.08; C, 71.94

Preparation and physical properties of α,γ-dibromopropyl n-propyl ether.

n-Propyl cyclopropyl ether was brominated in the same way that methyl cyclopropyl ether was brominated.

Table XLIII

Physical Properties of α,γ Dibromopropyl n-Propyl Ether

Distilling range	96-98°C./18.6 mm.
Pycnometer No. 2 and liquid	2.4384
Weight of liquid	.3998
Density	1.594
Refractive index	1.4998

Table XLIV

Calibration of Pycnometer No. 2

Pycnometer No. 2 and H_2O	2.2886
Pycnometer No. 2	2.0388
H_2O	.2498
Volume	.2508

β-Bromopropionic acid was obtained from α,γ-dibromopropyl n-propyl ether in the same way that it was prepared from α,γ-dibromopropyl ethyl ether. It melted between 56.0-57.0°C. and remelted between 55.6-57.0°C. A mixture of this product with the analysed product melted and remelted between 57.6-59.6°C.

Identification of the gaseous by-product from the cyclization of β,β'-dibromoisopropyl propyl ether.

Most of the gas resulting from the cyclization of β, β'-dibromoisopropyl ether was absorbed by 50 per cent. potassium hydroxide. The remaining gas was treated with bromine and the product was purified in the same way that this phase of the work was done on methyl cyclopropyl ether. The density and refractive index were taken at room temperature which was 25°C. A thermostat was not used.

Table XLV

Physical Properties of the Brominated Gas from the Preparation of n-Propyl Cyclopropyl Ether

Boiling range	140-142°C.
Pycnometer No. 2 and liquid	2.5197
Liquid	.4809
Density	1.919
Refractive index	1.5166

These physical constants show that the liquid is propylene dibromide and the gas must have been propylene.

Preparation of monoperphthalic acid.[124]

275 gms. of 15 per cent. sodium hydroxide in a liter Erlenmeyer flask was cooled in an ice and salt bath. 115 gms. of 30 per cent. hydrogen peroxide similarly cooled was added all at once. 375 gms. of phthalic anhydride powdered to pass 100 mesh was added as quickly as possible with vigorous stirring. After a minute or two the entire mixture was added all at once to 250 cc. of 20 per cent. sulfuric acid chilled to -10°C. The solution was passed through a fritted glass filter, and extracted once with 500 cc. of ether and then three times with 250 cc. of ether. The combined ether extracts were shaken with three 250 cc. portions of 40 per cent. ammonium sulfate and dried over 20 gms. of magnesium sulfate. The ether was evaporated off in vacuum without the use of heat. 66 gms. of solid remained. 0.2 gm. of the solid added to an acidified potassium iodide solution required 13.2 cc. of tenth-normal sodium thiosulfate for the titration of the iodine liberated. Therefore, the material was about 60 per cent. monoperphthalic acid and represents a yield of 43.5 per cent.

Synthesis and Properties of n-Butyl Cyclopropyl Ether.

123 gms. (0.45 mol) of β,β'-dibromoisopropyl n-butyl ether was cyclized to n-butyl cyclopropyl ether in the same way that methyl cyclopropyl etherwas made. The product was fractionated and the portion boiling up to 145°C. was

treated in the same way that n-propyl cyclopropyl ether was treated. About 0.5 gm. of liquid distilling between 121-122.5°C. was obtained as the yield (1 per cent.).

Table XLVI

Physical and Molecular Properties of n-Butyl Cyclopropyl Ether

Distilling range	121-122.5°C.
Pycnometer No. 2 and liquid	2.2389
Liquid	.2001
Density	.799
Refractive index	1.4043
Molecular refractivity (experimental)	34.99
Molecular refractivity (calculated)	34.68

Table XLVII

Determination of Carbon and Hydrogen in n-Butyl Cyclopropyl Ether

Analysis Number	I	II
Sample and sample tube	20.264	27.923
Sample tube	17.757	24.569
Sample	2.507	3.354
H_2O and H_2O tube	18.994	2.310
H_2O tube	16.234	−1.399
H_2O	2.760	3.709
CO_2 and CO_2 tube	50.844	12.978
CO_2 tube	44.058	3.886
CO_2	6.786	9.092
per cent. H	12.32	12.37
per cent. C	73.87	73.98

Calculated $C_7H_{14}O$: H, 12.36; C, 73.63

Reactions of butyl cyclopropyl ether.

0.2 gms. of butyl cyclobutyl ether was brominated to α, γ-dibromopropyl butyl ether. The quantity obtained was not sufficient to determine the physical constants. The product was oxidized with 45 per cent. nitric acid in the same way that α, γ-dibromopropyl ether was treated. A reaction was evidenced by the formation of gas and by the production of a brown color in the water immiscible layer. These signs were characteristic of all the

previous nitric acid oxidations of this type of compound. It was not possible to isolate the β-bromopropionic acid, although the odor could be detected.

Gaseous by-products from the cyclization of β,β'-dibromoisopropyl butyl ether.

The gas obtained from the cyclization reaction was treated the same way that the gas from the propyl cyclopropyl synthesis was treated. A small amount of water insoluble liquid was obtained with a specific gravity greater than that of water. The quantity was too small to characterize.

PHARMACOLOGY OF METHYL CYCLOPROPYL ETHER

John C. Krantz, Jr., C. J. Carr, E.M. Forman and W.B. Evans, Jr.[1a,b] have studied the pharmacology of methyl cyclopropyl ether which is referred to as "Cyprane Ether" in the above reference. The summary and conclusions are quoted below.

1. The union of the molecule of cyclopropane through an ether linkage with the alkyl radical, methyl, results in the formation of a volatile liquid possessing anesthetic properties in many species of animals.
2. Cyprane ether is a more potent anesthetic than ethyl ether, although it is not so potent as chloroform. The concentration producing surgical anesthesia in the blood of the dog averages 0.10 per cent. Its anesthetic index as measured on the dog is 2.31, that of ethyl ether is 1.76. It should be emphasized that this difference arises mainly from the short induction period of cyprane ether compared with that of ethyl ether.
3. In the monkey, cyprane ether produces no liver damage as shown by the bromsulfophthalein test. In the rat, histopathological changes are not found in the liver or kidneys after repeated anesthesias.
4. The cardiac toxicity upon perfusion of the frog's heart *in situ* is of the order of magnitude of that of ethyl ether, possibly slightly more toxic. In concentrations required to produce surgical anesthesia in the blood of the dog, the

frog's myocardium did not differentiate between Howell-Ringer's solution and that containing cyprone ether.

5. The explosive range of concentrations of cyprone ether and ethyl ether with oxygen and air appear to be about the same. The oil/water coefficient of cyprone ether is 49 per cent. greater than that of ethyl ether. The concentration in air required to produce anesthesia is one-half to two-thirds that of ethyl ether.
6. Cyprone ether boils 9.6° higher than does ethyl ether.
7. The blood pressure remains high and the pulse good under deep surgical anesthesia in the dog with cyprone ether.
8. The authors wish to emphasize that many of the studies reported in this communication are still in their incipiency. More extensive investigations are in progress. This first approximation of the pharmacology of cyprone ether, in our opinion, warrants its careful and judicial trial in man by skilled anesthetists.

This compound has been used successfully in three surgical anesthesias on humans.

SUMMARY

1. An attempt to make biscyclopropyl ether was unsuccessful.
2. The β,β'-dichloroisopropyl methyl ether and β,β'-dibromoisopropyl, methyl, ethyl, n-propyl and n-butyl ethers were prepared by alkylation of the corresponding dihaloisopropanol with the proper dialkyl sulfate.
3. Cyclization of these β,β'-dihaloisopropyl ethers in acetamide with zinc in the presence of sodium iodide and sodium carbonate resulted in the formation of methyl, ethyl, n-propyl and n-butyl cyclopropyl ethers.
4. Many of the physical properties of these cyclopropyl ethers have been determined.
5. All of these cyclopropyl ethers can be brominated to the corresponding α,γ-dibromopropyl alkyl ether any one of which can be oxidized to β-bromopropionic acid.
6. The structure attributed to the cyclopropyl ethers has been proved by physical and chemical evidence.
7. Propylene is a by-product in all of the cyclization reactions described in Conclusion 3.
8. β,β'-dibromoisopropyl bromomethyl ether has been synthesized from β,β'-dibromoisopropanol, trioxymethylene and dry hydrogen bromide.
9. The anesthetic action of methyl cyclopropyl ether has been studied by J.C. Krantz, Jr. et al.[126].

REFERENCES

List of Abbreviations

Abbreviation	Name of Journal
Ann.	Justis Liebig's Annalen der Chemie
Ann. chim. phys.	Annales der chimie et de physique
Ber.	Berichte der deutschen chemischen Gesellshaft
Bull. soc. chim.	Bulletin de la societe chimique de France
Cent.	Chemisches Centralblatt
C.A.	Chemical Abstracts
J. Am. Chem. Soc.	Journal of the American Chemical Society
J. Chem. Soc.	Journal of the Chemical Society
J. prakt. Chem.	Journal für praktische Chemie
J. Russ. Phys. Chem.	Journal of the Russian Physical Chemical Society
Zeit.	Zeitschrift für Chemie

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(Contribution from the University of Maryland)

caps. → Alkyl Cyclopropyl Ethers[1]

1. From the Ph.D. dissertation of Sylvan E. Forman, June, 1940. Presented before the Organic Division at the Detroit meeting of the American Chemical Society, September, 1940.

by.

Nathan S. Drake and Sylvan E. Forman.

Cyclopropane has found considerable favor as an anesthetic, and it seemed of interest to synthesize various alkyl cyclopropyl ethers and to test their usefulness as anesthetics.[2]

2. The pharmacology of methyl cyclopropyl ether has been reported elsewhere: Krantz, Carr, Forman and Evans, J. Pharmacol. Exp. Therap. 69, 207 (1940); Black, Shannon and Krantz, Anesthesiology (in press).

This paper describes the preparation and properties of the first four members of the series of alkyl cyclopropyl ethers.

A general method used in the synthesis of these compounds was the following.

not

a 1,3-dihalo-2-propanol was heated in xylene in the presence of calcium carbonate with the desired dialkyl sulfate. The resulting ether was cyclized at about 140° in acetamide solution by means of zinc.[3] (2)

3. Haas, McBee and Glessenbarn, Ind. Eng Chem. 28, 1178 (1936), have used this method for cyclizing 1,3-dichloropropane

~~was used, however, in the~~ a different method of preparation of 1,3-dibromo-2-propyl n-butyl ether. ~~1,3-Dibromo-2-propanol, was suspended in excess of trioxymethylene, was treated with dry hydrogen bromide until the solid had dissappeared.~~

Dry hydrogen bromide was bubbled into a suspension of an excess of trioxymethylene in 1,3-dibromo-2-propanol until the solid had disappeared; the resulting ether was then coupled with n-butyl magnesium bromide. ~~Due to the~~ Coupling ~~was~~ involves first the extremely reactive halogen of the bromomethyl group ~~if excess of reagent is used~~ in the absence of an excess of Grignard reagent. This method of synthesis is an adaptation of one used earlier to prepare the corresponding 1,3-dichloro-2-propyl ethyl ether.[4]

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The removal of unsaturates from the crude ethers was accomplished by ~~distillation~~ treatment with perbenzoic acid in toluene solution, or by the addition of solid monoperphthalic acid. The ethers were subsequently distilled.

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October 14, 1940

Dr. Nathan L. Drake,
Department of Chemistry,
University of Maryland,
College Park, Md.

Dear Dr. Drake,

I am mailing you "Alkyl Cyclopropyl Ethers" for your revision.

There are a few differences between this paper and my thesis. The constants for n-butyl cyclopropyl ether were determined on a sample made since my thesis was completed. Also, Mumford and Philips parachor values, as reproduced in Gilman's Organic Chemistry, pg. 1733, were used to calculate the parachors since these values are more recent than Sugden's values.

Yours truly,

Sylvan E. Forman

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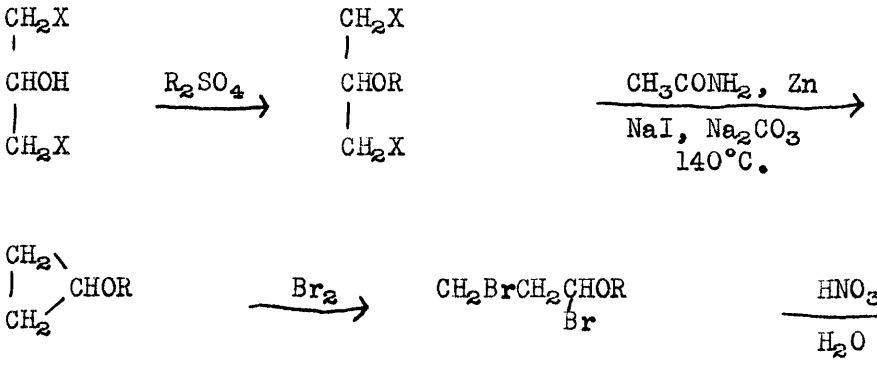
Alkyl Cyclopropyl Ethers[1]

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Cyclopropyl alcohol has never been synthesized despite many attempts to do so. It was therefore of interest to see whether or not ethers of cyclopropyl alcohol could be made. Also, since diethyl ether and cyclopropane are both good anesthetics, it was of interest to determine whether or not a combination of the ether and cyclopropane structure in the same molecule would result in a valuable anesthetic. Consequently, the methyl, ethyl, n-propyl and n-butyl ethers of cyclopropanol were prepared and the pharmacology[3] of methyl cyclopropyl ether has been studied.

The method of synthesis and the proof of the structure of these compounds are represented by the following series of reactions:



Although all of the β,β'-dihaloisopropyl alkyl ethers which were used in this research had been prepared previously, attempts were made to devise better methods of preparation. β,β'-dichloroisopropyl methyl ether had been prepared from β,β'-dichloroisopropanol by treatment with methyl iodide

and silver oxide[4], by heating the former with methyl p-toluenesulfonate[5] at 150°C. The material used in the experiments described in this paper was prepared from 3,3'-dichloroisopropanol by heating it at 125°C for 3.5 hours with an excess of dimethyl sulfate. A general method for the preparation of ethers of 3,3'-dibromoisopropanol form allyl bromide, mercuric acetate and an alcohol and subsequent treatment of the resulting product with bromine and aqueous potassium bromide had already been described[6]. However, we chose to prepare the methyl, ethyl, n-propyl and n-butyl ethers from 3,3'-dibromoisopropanol and the corresponding dialkyl sulfates. The methyl ether was prepared in the same way that 3,3'-dichloroisopropyl methyl ether was made, except that a lower temperature and a longer heating period were required. The ethyl, n-propyl and n-butyl ethers were prepared in xylene solution at the boiling temperature in the presence of calcium carbonate.

Only the halogenated isopropyl methyl ethers were obtained in pure condition. It was not possible to apply chemical methods of purification to the others, nor was it possible to successfully fractionate by distillation the mixtures which resulted after the removal of the xylene. The use of these impure mixtures in the preparation of the cyclopropyl ethers caused the yields of the cyclization ~~experiments~~ experiments to appear lower than they really were.

Pure 3,3'-dibromoisopropyl n-butyl ether was prepared according to the following equations:

$$\begin{array}{l} CH_2Br \\ | \\ CHOH \\ | \\ CH_2Br \end{array} + (HCHO)_x + HBr \longrightarrow \begin{array}{l} CH_2Br \\ | \\ CHOCH_2Br \\ | \\ CH_2Br \end{array} \xrightarrow{n\text{-}C_3H_7MgBr} \begin{array}{l} CH_2Br \\ | \\ CHOC_4H_9\text{-}n \\ | \\ CH_2Br \end{array}$$

An excess of trioxymethylene was suspended in β,β'-dibromoisopropanol and dry hydrogen bromide was led in until the solid disappeared. The β,β'-dibromoisopropyl bromomethyl ether was purified by fractional distillation and reacted with n-propyl magnesium bromide in ether solution to obtain β,β'-dibromoisopropyl n-butyl ether. This procedure is an adaptation of the method used to prepare β,β'-dichloroisopropyl ethyl ether[7], wherein a suspension of trioxymethylene in β,β'-dichloroisopropanol was treated with dry hydrogen chloride, and the chloromethyl ether which results was treated with a methyl magnesium halide.

Cyclization of β,β'-dihaloisopropyl alkyl ethers to alkyl cyclopropyl ethers was accomplished by an adaptation of a method described for the preparation of cyclopropane from trimethylene dichloride[8]. Sodium iodide, sodium carbonate and an excess of zinc dust were stirred in molten acetamide maintained at 140°. The halogenated ether was slowly added, and the product was allowed to distill off through a short fractionating column. Unsaturates were removed from the products by means of perbenzoic acid in toluene solution or by solid monoperphthalic acid. Table I gives the yields of cyclopropyl ethers obtained and the results of micro combustion analyses for carbon and hydrogen.

Table I

Yields and Combustion Analyses of Cyclopropyl Alkyl Ethers

Alkyl Group	Per cent. Yield	Empirical Formula	Calc. C	Calc. H	Found C	Found C	Found H	Found H
CH_3 [a]	22	C_4H_8O	66.63	11.18	-	-	-	-
CH_3 [b]	80	C_4H_8O	66.63	11.18	66.39,	66.52	11.07,	11.08
C_2H_5	64	$C_5H_{10}O$	69.72	11.70	69.42,	69.29	11.70,	11.64
$n\text{-}C_3H_7$	22	$C_6H_{12}O$	71.94	12.08	72.08,	72.19	11.98,	12.04
$n\text{-}C_4H_9$ [c]	1	$C_7H_{14}O$	73.63	12.36	73.87,	73.98	12.32,	12.37
$n\text{-}C_4H_9$ [d]	70	$C_7H_{14}O$	73.63	12.36	-	-	-	-

a. From β,β'-dichloroisopropyl methyl ether
b. From β,β'-dibromoisopropyl methyl ether
c. Impure starting material prepared by dibutyl sulfate method
d. Pure starting material prepared from propyl magnesium bromide

The distilling range under atmospheric pressure, density in vacuo, refractive index and surface tension in dynes/cm. ~~were determined~~ of each of the cyclopropyl ethers were determined. The surface tension was determined by the well known bubble method[9]. The physical constants are listed in Table II.

Table II

Physical Constants of Cyclopropyl Ethers

Ether	Distilling Range	D_4^{25}	n_D^{25}	γ at 25°C.
Methyl	43.5- 44	0.786	1.3749	19.92
Ethyl	67 - 69	0.780	1.3830	20.34
n-Propyl	94 - 96	0.790	1.3933	21.17
n-Butyl	122 -124	0.807	1.4026	22.76

The molecular refractivity and the parachor of each compound were calculated from physical constants and from atomic and structural values. The experimental values were always in better agreement with the values calculated for cyclopropyl

ethers than for the isomeric allyl ethers. Table III contains the atomic and structural values used in the calculations and Table IV contains the parachors and molecular refractivities.

Table III

Atomic and Structural Refractivities and Parachors

	Refractivities [10,11]	Parachors [12]
C	2.418	9.2
H	1.100	15.4
O	1.643	20.0
3 membered ring	.71	12.5
Double bond	1.60	19.0

Table IV

Molecular Refractivities and Parachors of Cyclopropyl and Allyl Ethers

Alkyl Group	Molecular Refractivities				Parachors			
	Cyclopropyl		Allyl		Cyclopropyl		Allyl	
	Calc.	Expt.	Calc.	Expt.	Calc.	Expt.	Calc.	Expt.
Methyl	20.83	21.00	21.72	22.05	192.5	194.0	199.0	200.4
Ethyl	25.44	25.77	26.33	26.60	232.5	234.7	239.0	-
n-Propyl	30.06	30.31	30.95	-	272.5	272.0	279.0	-
n-Butyl	34.68	34.49	35.57	-	312.5	309.0	319.0	-

The experimental molecular refractivity of ethyl allyl ether was calculated from physical constants obtained from the literature[13]. Allyl methyl ether prepared from allyl iodide and sodium methoxide[14] had the following physical constants: b. 43-45°C, D_4^{25} 0.757 gms./cc. in vacuo, γ (at 25°C.) 19.46 dynes/cm., n_D^{25} 1.3799. Combustion analyses indicated that the sample was not completely pure, but the physical data obtained is probably not far from the correct values and is valuable for comparison with the data obtained from methyl cyclopropyl ether.

The cyclopropyl ethers were reacted with bromine in chloroform solution to obtain the α, γ-dibromopropyl alkyl ethers. Table V gives the constants obtained for these compounds.

Table V

Physical Constants of α, γ Dibromopropyl Alkyl Ethers

Ether	Boiling range	D_4^{25}	n_D^{25}
Methyl	68 - 70°/9	1.790	1.5060
Ethyl	75.5-77.5°/9.5	1.666	1.4939
n-Propyl	96 - 98°/18.5	1.594	1.4898

These compounds were oxidized with nitric acid to β-bromopropionic acid. One sample of this acid obtained from methyl cyclopropyl ether was identified by its melting point and by combustion analyses for carbon and hydrogen. The other samples were identified by their melting points and by mixed melting points with the analyzed sample.

n-Butyl cyclopropyl ether reacted with bromine to yield a product which reacted with nitric acid. Although the odor of β-bromopropionic acid was much in evidence, it was not possible to isolate the crystalline material. This is not surprising, because, in the case of the other ethers, this derivative was isolated and purified only with difficulty. All other properties of the n-butyl ether were consistent with those of a cyclopropyl ether.

The following melting points were obtained from the literature[15] for β-bromopropionic acid: 60-61°C., 62°C., 62.5°C. and 62-63°C. The isomeric dl α-bromopropionic acid[16] melts at 25°C. The melting points and the mixed melting points of the compound obtained are given in Table VI.

Table VI

Melting Points of β-Bromopropionic Acid from Cyclopropyl Ethers

Ether	M.P.	Mixed M.P.
Methyl (from Br)	60.5 - 61.5	(analyzed sample)
Methyl (from Cl)	59.0 - 60.0	60.0 - 61.5
Ethyl	58.0 - 59.0	59.0 - 61.0
n-Propyl	56.0 - 57.0	57.5 - 59.5

Thus, it can be seen that the cyclopropyl ethers differ from the isomeric allyl ethers. The parachors and molecular refractivities are different. Cyclopropyl ethers react only very slowly with perbenzoic acid, while allyl methyl ether reacts quantitatively in about 24 hours. Bromine reacts a little less readily with cyclopropyl ethers than with allyl ethers. The bromination product of allyl methyl ether does not react with fuming nitric acid even when heated in a bath at 100°C. The bromination products from the cyclopropyl ethers are oxidized by nitric acid to β-bromopropionic acid which cannot result from the bromination and subsequent oxidation of an allyl ether.

Experimental

β,β'-Dibromoisopropyl Bromomethyl Ether. 9 mols of formaldehyde in the form of trioxymethylene was suspended in 3 mols of β,β'-dibromoisopropanol and cooled in an ice water bath. 755 gms. of dry hydrogen bromide was led in, whereupon, all the solid dissolved. The upper layer of the reaction mixture was removed and the lower layer was fractionated by distillation. The fraction which distilled between 129-135°C./12 mm. weighed 775 gms. (83 per cent.). The product fumes in air and is very hygroscopic. Determination of halogen by means of a Parr bomb indicated that this sample was not pure. Anal. Calcd. for $C_4H_7Br_3O$: Br, 77.12. Found : Br, 75.39, 75.40.

β,β'-Dichloroisopropyl Methyl Ether. 5 mols of β,β'-dichloroisopropanol and 18 mols of dimethyl sulfate were heated at 125° for 3.5 hours. The mixture was cooled, poured into water, and neutralized by the addition of solid sodium bicarbonate. The lower layer was shaken with 50 per cent. sodium hydroxide to convert the unreacted alcohol to the lower boiling, more easily separated epichlorohydrin. Dimethyl sulfate was removed by shaking with conc. ammonia. The liquid was then washed with water and dried over magnesium sulfate. It was distilled under diminished pressure to remove tarry products and then fractionated under atmospheric pressure. The fraction which distilled between 159-161.5°C. weighed 660 gms. (31%).

β,β'-Dibromoisopropyl Methyl Ether. 2.5 mols of β,β'-dibromoisopropanol and 3 mols of dimethyl sulfate were heated for 12 hours on a boiling water bath. The purification procedure was the same as described for the chlorine analog. The product distilled from calcium carbonate between 46-49°C./1.5 mm. The yields varied from 11 to 40 per cent. and were usually about 30 per cent.

β,β'-Dibromoisopropyl Ethyl Ether. 3 mols of β,β'-dibromoisopropanol, 3.6 mols of diethyl sulfate, 6 mols of calcium carbonate and 2100 cc. of xylene were mechanically stirred and fractionated for 15 hours to remove water formed during the reaction. The liquid was filtered and fractionated from 100 gms. of fresh calcium carbonate. The xylene was removed, but it was not possible to further purify the product which distilled 69.5-78°C./8mm. and weighed 329 gms. (44 per cent.).

β,β'-Dibromoisopropyl n-Propyl Ether. This compound was prepared in the same manner as the ethyl ether. The impure product from a 3 mol batch distilled between 84-88°C./9mm. and weighed 258 gms. (33 per cent.).

was removed by extraction with 10 per cent. sodium hydroxide. Sodium and potassium metals reacted with the cyclopropyl ethers and could not be used as drying agents. The purification was completed by a fractional distillation.

Tests for Impurities in Cyclopropyl Ethers. Perbenzoic acid in toluene solution was used to determine the unsaturates present in cyclopropyl ethers. However, the perbenzoic acid reacted very slowly with the methyl ether over the course of many days. Persumably the same slow reaction occurs with the other cyclopropyl ethers.

Halogens were detected by means of a modified Beilstein test[17].

Peroxides were detected by shaking a small portion of the ether with a neutral solution of aqueous potassium iodide. Absence of a yellow color within half an hour indicated absence of peroxides.

α,γ-Dibromopropyl Alkyl Ethers. 5 gms. of each alkyl cyclopropyl ether was dissolved in 50 cc. of chloroform and immersed in an ice water bath. Slightly less than an equivalent amount of bromine in 50 cc. of cold chloroform was added slowly. The chloroform was evaporated and the residue was fractionated under diminished pressure.

Anal. of methyl ether: Calcd. for $C_4H_8Br_2O$: Br, 68.91. Found: Br, 68.51, 68.47.

Anal. of ethyl ether: Calcd. for $C_5H_{10}Br_2O$: Br, 64.96. Found: Br, 63.67, 63.98.

β-Bromopropionic Acid. 2 gms. of α,γ-dibromopropyl alkyl ether was reacted with 7 cc. of 45 per cent. nitric acid in a test tube immersed in tap water. The tube was shaken from time to time and allowed to react for 20 hours. The aqueous portion was extracted 5 times with diethyl ether and the ether was extracted with dilute sodium hydroxide, taking care against a rise in temperature. The solution was made acid to methyl orange with sulfuric acid and was extracted with ether as before. The ether was evaporated and the residue was extracted with hot petroleum ether. The β-bromopropionic acid was recrystallized from this solvent until further recrystallization did not change the melting point.

The product obtained from methyl cyclopropyl ether which was prepared from

β,β'-dibromoisopropyl methyl ether was analyzed. Anal. Calcd. for $C_3H_5BrO_2$: C, 23.55; H, 3.29. Found: C, 23.58, 23.57; H, 3.35, 3.34.

Physical Properties. All density, refractive index and surface tension measurements were made under thermostatic control at 25°C. Density measurements were made by a pyknometer and were corrected for air bouyancy. Refractive index measurements were made with an Abbé refractometer. Surface tension measurments were determined by the well known bubble method[9].

The vapor pressure of methyl cyclopropyl ether at 26°C. was found to be 414 mm. An excess of this ether was introduced into a gas burette containing a measured volume of air. The vapor pressure was calculated from the increase in volume.

Allyl Methyl Ether. This compound was prepared from allyl iodide and sodium methoxide[14]. Anal. Calcd. for C_4H_8O: C, 66.63; H, 11.18. Found: C, 67.40,67.30; H, 11,22, 11,31.

Summary

1. β,β'-dichloroisopropyl methyl ether, β,β'-dibromoisopropyl methyl,ethyl, n-propyl and n-butyl ethers were prepared by alkylation of the corresponding dihaloisopropanol with the proper dialkyl sulfate.
2. β,β'-dibromoisopropyl bromomethyl ether was prepared from β,β'-dibromoisopropanol, trioxymethylene and hydrogen bromide.
3. β,β'-dibromoisopropyl n-butyl ether was prepared from β,β'-dibromoisopropyl bromomethyl ether and propyl magnesium bromide.
4. Cyclopropyl methyl, ethyl, n-propyl and n-butyl ethers were prepared by cyclization of β,β'-dihaloisopropyl alkyl ethers in acetamide with zinc in the presence of sodium iodide and sodium carbonate at 140°C. The distilling range, density, refractive index and surface tension of each cyclopropyl ether was determined.

Footnotes

1. Abstract presented before the Organic Division at the 100th meeting of the American Chemical Society, Detroit, Michigan, September 12, 1940.

2. Abstracted from the thesis submitted by Sylvan E. Forman to the Faculty of the Graduate School of the University of Maryland in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June,1940.

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