MIXED DIMERIZATIONS OF HALOGENATED KETENES AND

CHEMISTRY OF CYCLOADDUCTS

DISSERTATION

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By

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The investigation presented is in two parts: a study of the mixed dimerizations of halogenated ketenes with non-halogenated ketenes and a study of the rearrangements of 8-chloro-8-methylbicyclo[4.2.0]oct-2-en-7-ones.

Part I describes the codimerization of alkylhaloketenes and ketoketenes to yield primarily the unsymmetrical halo-1, 3-cyclobutanediones. These mixed dimers have been prepared by several different methods. Some of the ketenes employed are methylchloro-, ethylchloro-, isopropylchloro-, <u>t</u>-butylchloro-, dimethyl-, diethyl-, pentamethylene-, <u>n</u>-propylmethyl-, isopropyl-methyl- and <u>t</u>-butylketenes. In certain systems, a β-lactone mixed dimer is formed, which probably results from a β-keto acid chloride intermediate. The mixed dimerizations appear to be quite sensitive to steric effects and the $_\pi 2_s + _\pi 2_a$ process seems more sensitive than the β-keto acid chloride pathway. Pentamethyleneketene readily cycloadds to reactive unsaturated compounds to yield spiro[5,3]nonanes.

Part II is concerned with the rearrangement of 8-chloro-8-methylbicyclo[4.2.0]oct-2-en-7-one in the presence of various bases. A substitution and ring contraction reaction

are in competition and the rearranged product is dependent

upon the nature of the base. The chemistry of the 8-chloro-

8-methylbicyclo[4.2.0]oct-2-en-7-one was not dependent

upon the stereoisomers as observed in the 7-halo-7-alkylbicyclo-

[3.2.0]hept-2-en-7-one. This is apparently due to the fact

that enolization occurs readily in the former system but not

in the latter bicyclic compound.
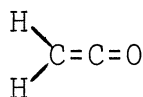
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PART I

MIXED DIMERIZATIONS OF HALOGENATED KETENES

CHAPTER I

INTRODUCTION

Ketene is a highly reactive compound with both an ole-
finic linkage and a carbonyl group in its molecular structure.

$$\begin{array}{c} H \\ \diagdown \\ \diagup \\ H \end{array} C = C = 0$$

Monosubstituted ketenes are aldoketenes, while disubstituted
ketenes are ketoketenes. Halogenated ketenes have a halogen
atom directly attached to the carbon-carbon double bond of
the ketene functionality. Some newly synthesized organometal-
lic ketenes have a silicon, germanium or tin atom directly
bonded to the ketene functionality.[1]

$$\begin{array}{c} R_3M \\ \diagdown \\ \diagup \\ H \end{array} C = C = 0 \qquad , \qquad \begin{array}{c} R_3M \\ \diagdown \\ \diagup \\ R_3M \end{array} C = C = 0$$

The first comprehensive review of the chemistry of
ketenes was published by Staudinger in 1912.[2] Staudinger
synthesized a variety of substituted ketenes, and also studied
many of the reactions of this then new class of reactive com-
pound.

Many ketenes are often generated *in situ* from stable
precursors in the presence of suitable substrates because of

the ketenes' instability with regard to dimerization and/or

homopolymerization. The simplest and most useful way to

generate ketenes is the dehydrohalogenation of appropriately

substituted acid halides. However, this method suffers from

$$R-\underset{\underset{H}{|}}{\overset{\overset{R'}{|}}{C}}-\overset{\overset{O}{\parallel}}{C}-X \;+\; NEt_3 \longrightarrow \;\; \underset{R}{\overset{R'}{>}}C=C=O \;\;+\;\; Et_3\overset{+}{N}HCl^-$$

the disadvantage of generating a reactive species in the pre-

sence of a base, which can catalyze either the dimerization

or polymerization of the ketene or can alter the course of its

reaction because of base catalysis. Therefore, pyrolysis pro-

cedures, in which the ketenes are generated in the vapor phase,

are preferred for a few specific ketenes.[3]
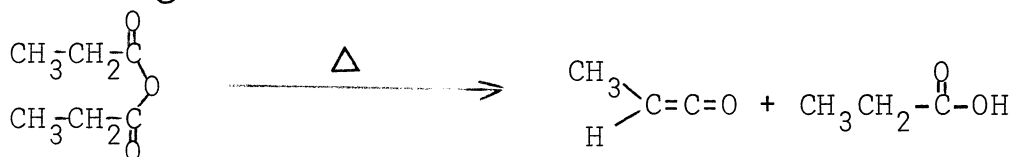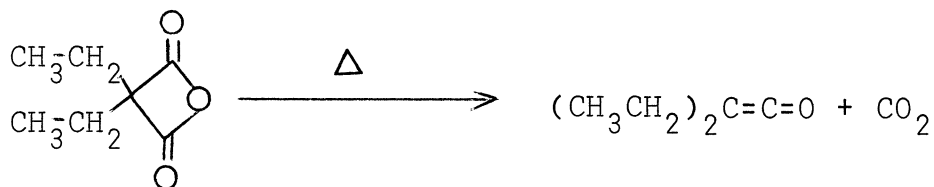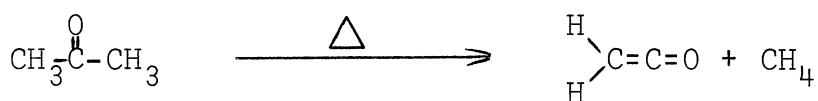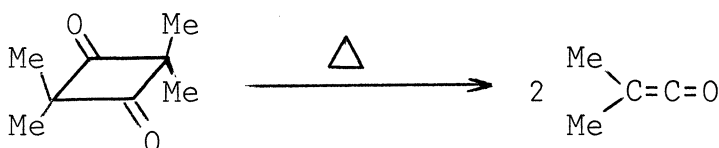
The dehalogenation of α-haloacid halides has been known since 1905 when Staudinger dechlorinated diphenylchloroacetyl chloride with zinc to yield diphenylketene.[4] A review on

$$C_6H_5-\underset{\underset{Cl}{|}}{\overset{\overset{C_6H_5}{|}}{C}}-\underset{\overset{\|}{O}}{C}-Cl \xrightarrow{\quad Zn \quad} \underset{C_6H_5}{\overset{C_6H_5}{>}}C=C=O \;+\; ZnCl_2$$
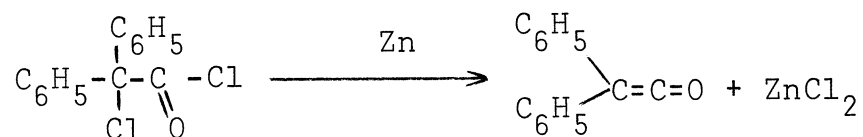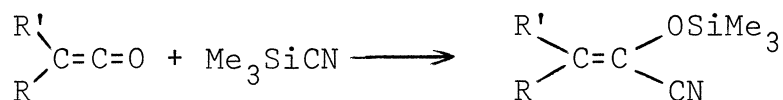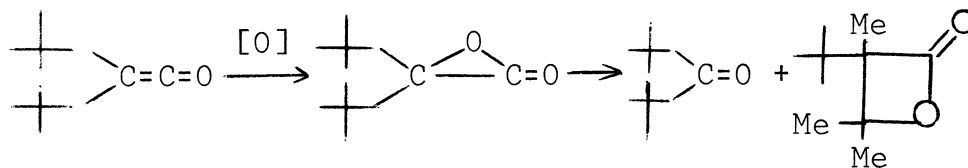
preparative ketene chemistry, including halogenated ketenes, has recently been published.[5]

Ketenes undergo nucleophilic addition reactions to yield carboxylic acid derivatives.

$$\underset{R}{\overset{R'}{>}}C=C=O \;+\; HNu \longrightarrow \underset{R}{\overset{R'}{>}}CH-\overset{\overset{O}{\|}}{C}-Nu$$
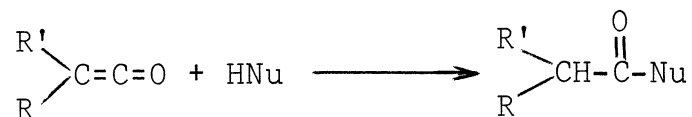
Certain ketenes have recently been shown to undergo oxidation with peracids to yield α-lactones as intermediate oxidative products. Recently, trimethylsilylcyanide has been reported to add cleanly and in good yield to the carbonyl group of ketenes to yield β-substituted α-trimethylsiloxyacrylonitrile.[6]

$$\underset{+}{\overset{+}{>}}C=C=O \xrightarrow{[O]} \underset{+}{\overset{+}{>}}C\overset{O}{\diagdown}C=O \longrightarrow \underset{+}{\overset{+}{>}}C=O \;+\; \underset{Me}{\overset{Me}{+}}\overset{O}{}$$

$$\underset{R}{\overset{R'}{>}}C=C=O \;+\; Me_3SiCN \longrightarrow \underset{R}{\overset{R'}{>}}C=C\underset{CN}{\overset{OSiMe_3}{<}}$$

The 1,2-cycloaddition of ketenes to olefins was first observed by Staudinger and co-workers. The reaction occurs most readily with activated olefins such as cyclic conjugated dienes, enol ethers and enamines. These ketenophiles are widely used for trapping highly reactive ketenes in situ to form adducts. This reaction mode constitutes one of the most useful synthetic routes to cyclobutanones,[7] and has been utilized for a high yield preparation of 2-alkyltropones[8] and as a key step in the total synthesis of several important prostaglandins.[9]

The cycloaddition of ketenes and olefins ordinarily occurs antarafacially with respect to the ketene, with a regiospecificity explicable by assuming charge separation along the reaction coordinate, and with an orientation for the ketene substituents which places the large group in the more hindered position in the product. These cycloadditions are considered as $[_{\pi}2_a + _{\pi}2_s]$ concerted reactions which require an orthogonal approach of the reactants.[10] The most sterically favored orthogonal transition state leads to the cycloadduct which places the largest ketene substituent in the endo position. This has been demonstrated with many cycloadditions
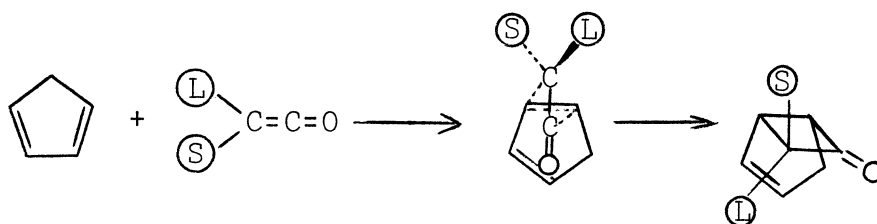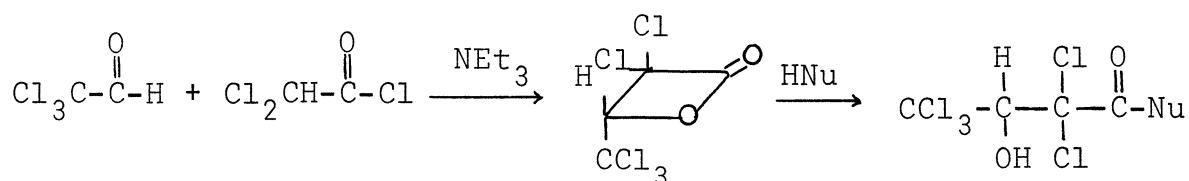
L = Large group;   S = Small group

involving alkylhaloketenes and cyclopentadiene and cyclo-hexene.[11]

The first reported cycloaddition of a ketene and a carbonyl compound was by Staudinger in 1908. The cyclo-addition of diphenylketene and benzophenone to yield the corresponding β-lactone (2-oxetanone) was described.[12]

$$\phi\!\!>\!\!C=O \;+\; \phi\!\!>\!\!C=C=O \longrightarrow$$
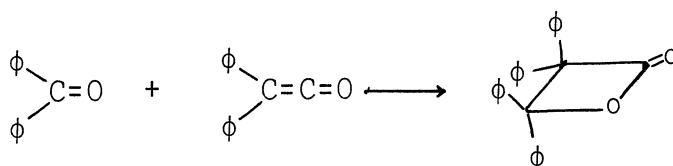
Brady and co-workers[13] have found that the cycloaddition of alkylhaloketenes with unsymmetrical carbonyl compounds pro-duces cis and trans isomers of 2-oxetanones in approximately equal amounts. Activation of the carbonyl compounds is neces-sary for cycloaddition. Electronegative substituents on the 2-oxetanone ring increase the reactivity of the 2-oxetanone towards nucleophilic addition, and only acyl-oxygen bond cleavage occurs during the nucleophilic addition reaction.

$$Cl_3C\text{-}\overset{O}{\overset{\|}{C}}\text{-}H \;+\; Cl_2CH\text{-}\overset{O}{\overset{\|}{C}}\text{-}Cl \xrightarrow{NEt_3} \xrightarrow{HNu} CCl_3\text{-}\overset{H}{\underset{OH}{\overset{|}{C}}}\text{-}\overset{Cl}{\underset{Cl}{\overset{|}{C}}}\text{-}\overset{O}{\overset{\|}{C}}\text{-}Nu$$

The tendency of ketene to undergo dimerization was noted as early as 1908 by Chick and Wilsmore and by Staudinger and

Klever.[14] The structure of dimeric ketene (diketene) was in doubt until recent investigators established its correct structure.[15,16] The dimerization of ketene can be affected

$$2 \quad \underset{H}{\overset{H}{>}}C=C=O \longrightarrow$$
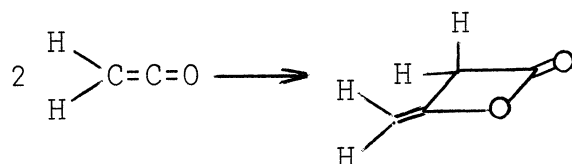
by heat,[17] acid or base catalysis; and often, diketene is formed as a by-product in ketene reactions.

Methylketene forms both a liquid dimer and a crystalline dimer.[18] Woodward and Small[19] have established the structure for the solid dimer which has an acidic hydrogen.[20]

$$2 \quad \underset{H}{\overset{Me}{>}}C=C=O \longrightarrow$$
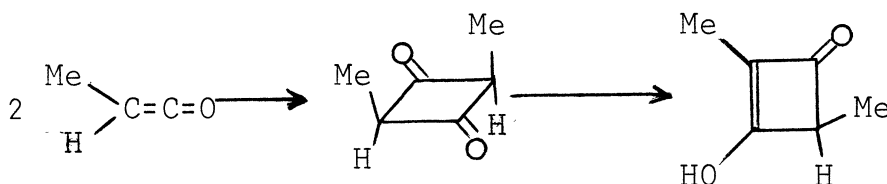
The unsymmetrical β-lactone structure, a 2-oxetanone, was confirmed for the liquid material by Johnson and Shiner[15] and others.[16,21]

$$2 \quad \underset{H}{\overset{Me}{>}}C=C=O \longrightarrow$$
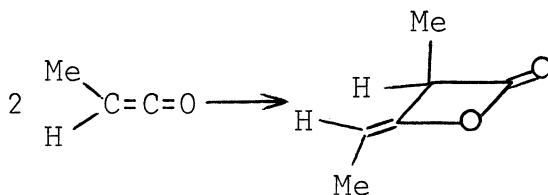
The dimeric aldoketenes are generally obtained by dehydro-chlorination of monosubstituted acetyl chlorides, and often the β-lactone dimers are formed. Upon attempted synthesis of phenylketene by dechlorination of chlorophenylacetyl chloride, Staudinger[18] obtained a neutral dimer which rearranged upon treatment with base to an acidic dimer. Baldwin and Roberts[22] established the β-lactone structure for the neutral dimer. Treatment of this dimer with sodium hydroxide causes rearrangement to the acidic dimer. The β-lactone methylketene dimer
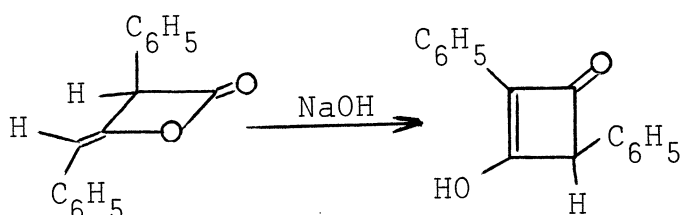
similarly rearranges to the acidic dimer upon treatment with base.[22]

Farnum and co-workers[23] attempted to generalize the dimerization sequences observed in aldoketenes. With the single exception of ketene, spontaneous dimerizations of ketenes probably afford cyclotubanediones as major primary products. The formation of β-lactone-type dimers can be facilitated by the presence of catalysts, such as triethyl-amine, triethylamine hydrochloride or zinc chloride.

Dialkylketenes dimerize spontaneously to the 1,3-cyclo-butanediones. The symmetrical dimer of dimethylketene, 2,2,4,4-tetramethyl-1,3-cyclobutanedione was first prepared by

Staudinger and Klever.[25] In addition to this solid dimer,
Staudinger and Klever[26] also isolated the β-lactone dimer and
Hasek and co-workers[27] demonstrated that this dimer can be
obtained exclusively from dimethylketene in the presence of
aluminum chloride as a catalyst. Ketoketenes therefore
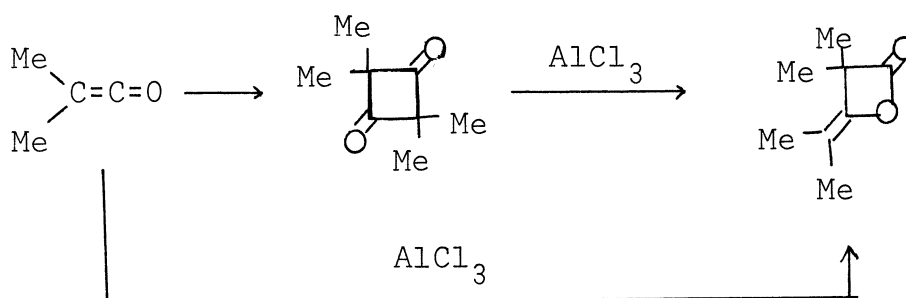
closely resemble aldoketenes with regard to their dimeriza-
tions. The dione dimer can be converted to the β-lactone
dimer by the addition of a catalytic amount of aluminum
chloride to the molton dione dimer. The β-lactone dimer can
also be obtained upon thermolysis of a polymer obtained from
dimethylketene in the presence of sodium methoxide.[27,28] The
more stable diphenylketene dimerizes to the β-lactone dimer
upon addition of a catalytic amount of sodium methoxide.[29]
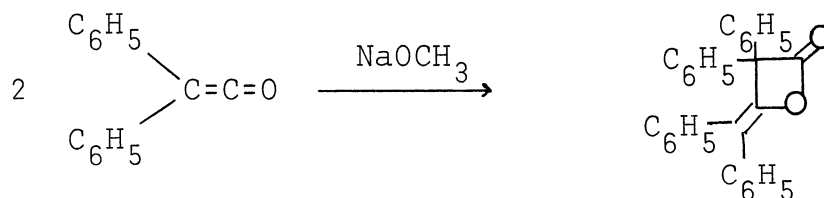
The dimerization of ketenes is also regarded as a $[_\pi 2_s +_\pi 2_a]$ concerted process with a high negative entropy of activation and little solvent polarity dependence.[30] One of the ketene molecules participates as a $_\pi 2_s$ component, while the other acts in a normal $_\pi 2_a$ fashion, whereby the transition state involves an orthogonal approach.[31] The possible transition states for the dimerization of an unsymmetrical ketene are illustrated in Scheme I. The antarafacial

Scheme I
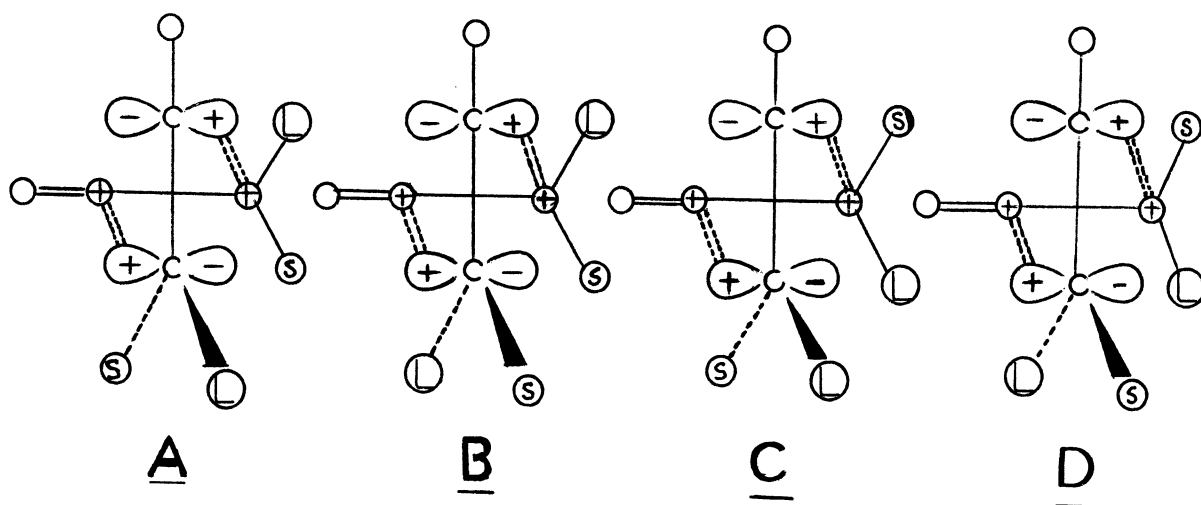
components are perpendicular to the suprafacial components which lie on the paper. The approach represented in A has the least sterically hindered approach and D has the most sterically hindered approach. Therefore, A leads to cis-cyclobutanedione as the preferential product.

Dehmlow found that the thermal dimerization of some isolated unsymmetrical ketoketenes such as phenylmethyl-, benzylmethyl- and benzyl phenylketenes produced the cis-

cyclobutanediones.[32] The same dimerization of benzylphenyl-
ketene by the dehydrochlorination of 2,3-diphenylpropanoyl
chloride with either triethylamine or by heating above 230°C
produced both cis- and trans-cyclobutanediones.[33,34] The
proposed mechanism to produce the trans-isomer was considered
to be through the β-keto acid chloride, 2-benzyl-3-keto-2,4,5-
triphenylpentanoyl chloride.
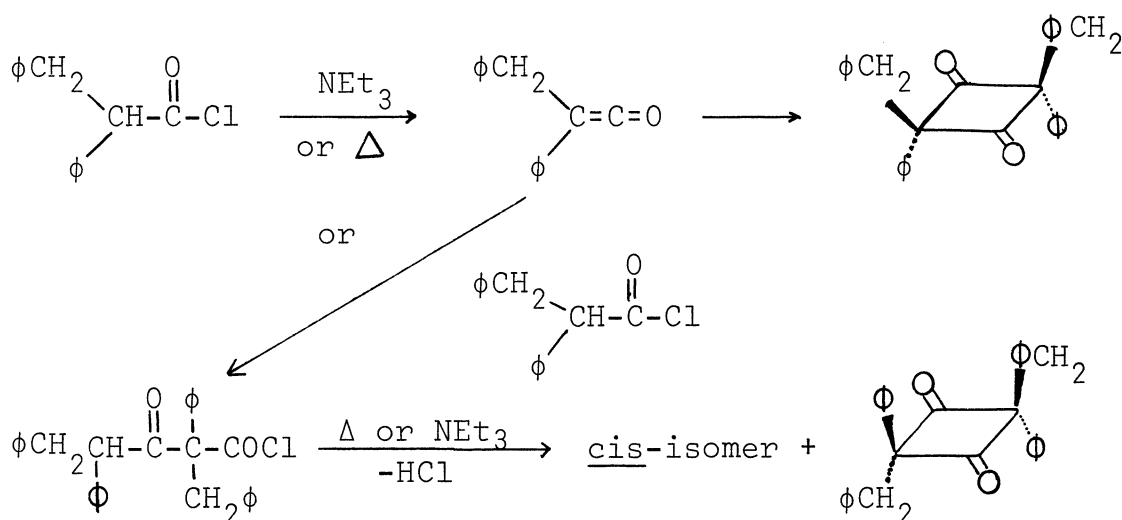
Staudinger and co-workers were the first to describe the
addition of an acid halide to a ketene to produce a β-keto
acid halide.[35] While this reaction has been investigated, the
β-keto acid halide was not isolated but converted into an ester.
Brady and Smith have found that the addition of acid halides
to ketenes is of limited synthetic value and less than general
in that the scope of the reaction is limited by the reactivity
of the ketenes, reactivity of the acid halides, and to ketenes
which can be isolated.[36,37]

Halogenated ketenes are extremely labile and to date no halogenated ketene has been isolated. Methylbromo-, t-butyl-bromo- and t-butylchloroketenes have been observed in solution by infrared absorption near 2000-2121 cm^{-1}.[38] Even though dimerization is a characteristic reaction of most ketenes, no dimers of halogenated ketenes have been reported. Attempts to form dimers of halogenated ketenes in the dehydrohalo-genation reaction mixture have resulted in the formation of α-halovinyl esters.[39]

$$2 \ R\text{-}\overset{X}{\underset{|}{C}}H\text{-}\overset{O}{\overset{\parallel}{C}}\text{-}X + NEt_3 \longrightarrow R\text{-}\overset{X}{\underset{|}{C}}H\text{-}\overset{O}{\overset{\parallel}{C}}\text{-}O\text{-}\underset{\underset{X}{|}}{C}\text{=}\underset{\underset{X}{|}}{C}\text{-}R + Et_3\overset{+}{N}HCl^{-}$$
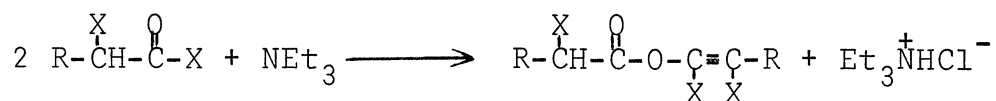
Mixed dimerizations of ketenes have rarely been studied, because in addition to the low yield of mixed dimers, the two homodimers are produced. However, recently England and Krespan have described mixed dimers of bis(trifluoromethyl)-ketene.[40] This ketene does not thermally homodimerize and forms mixed dimers with various other ketenes in good yield. Bis(trifluoromethyl)ketene is generated in 90% yield by heating a mixture of hexafluoroisobutyric acid and excess phos-phorus pentaoxide.[41] Since this ketene is prepared by such a simple process and is thermally stable, there is no problem of the ketene reacting with the precursor or substrate in the reaction mixture.

$$(CF_3)_2CH\overset{\overset{\displaystyle O}{\|}}{C}-OH \xrightarrow{\quad P_2O_5 \quad} \begin{matrix} CF_3 \\ \diagdown \\ \diagup \\ CF_3 \end{matrix} C=C=O$$
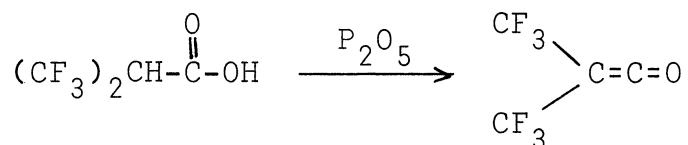
Bis(trifluoromethyl)ketene reacts with a ketoketene such as dimethylketene to produce both 1,3-cyclobutanedione and β-lactone dimers. Methylketene reacts with bis(trifluoromethyl)-ketene to produce only a β-lactone dimer.
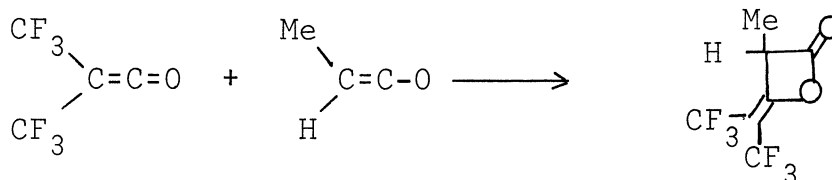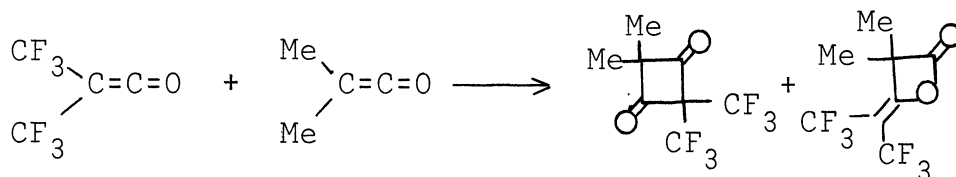
Halogenated ketenes are ideally suited for mixed dimerization studies because these ketenes do not homodimerize, are highly reactive and undergo in situ cycloaddition reactions to produce a variety of cycloadducts. Therefore, the objective of this research problem is to study mixed dimerizations of halogenated ketenes with nonhalogenated ketenes.

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CHAPTER II

EXPERIMENTAL

Proton nuclear magnetic resonance (n.m.r.) spectra were recorded on a Jeolco PS-100 Spectrometer employing tetramethyl-silane as an internal standard and carbon tetrachloride as the solvent. Gas chromatography was performed on an F. & W. Scientific model 700 instrument with a 10 ft x 1/4 in column packed with 10% SE-30 on acid washed Chromosorb W (60/80).

The infrared spectra were obtained using a Perkin-Elmer model 237 Grating Infrared Spectrometer. The cell used for sample handling was 0.1 mm fixed thickness sodium chloride cell.

Mass spectra of samples were obtained on a Hitachi Perkin-Elmer RMU-6E Mass Spectrometer.

Elemental analyses were performed by Midwest Microlab. Ltd., 6000 East 46th Street, Indianapolis, Indiana 46226

Preparation of Reagents

Solvents were dried and purified by distillation from metallic sodium or calcium hydride prior to use.

Triethylamine was commercially available and was dried over sodium metal and distilled prior to use.

Dimethylketene was prepared by pyrolysis of the ketene dimer, tetramethyl-1,3-cyclobutanedione, which was also syn-thesized by dehydrochlorination of isobutanoyl chloride in

17

the presence of triethylamine in benzene.[1] Diphenylketene
was obtained by the dehydrochlorination of diphenylacetyl
chloride with triethylamine.[2]

Tetramethylallene was obtained by the $AlCl_3$-catalyzed
rearrangement of the tetramethyl-1,3-cyclobutanedione dimer
of dimethylketene followed by pyrolysis over a hot wire.[3]

N-tert-Butylbenzylimine was prepared from benzaldehyde
and t-butylamine according to standard procedures.

The acid halides were prepared from the appropriate
carboxylic acids and thionyl chloride or phosphorous penta-
chloride. The α-haloacid chlorides were obtained by α-halo-
genation of the corresponding acid chlorides by sulfuryl chlo-
ride or bromine. The acid chlorides prepared from commercially
available acids are listed in the Table. The structures

TABLE

ACID CHLORIDES PREPARED FROM COMMERCIALLY AVAILABLE ACIDS

Acid Chloride	Boiling Range (°C)
2-Chloropropanoyl chloride[4]	110-112
2-Chlorobutanoyl chloride[5]	129-131
2-Chloro-3-methylbutanoyl chloride[4]	149-150
α-Bromocyclohexanecarboxyl chloride[6]	105-107 (15 mm)
Dichloroacetyl chloride[7]	108-110
2-Methylpropanoyl chloride	92
2-Ethylbutanoyl chloride	140
2-Methylpentanoyl chloride	45-47 (15 mm)
Cyclohexanecarboxyl chloride[8]	75-77 (15 mm)
Propanoyl chloride	80

TABLE--Continued

Acid Chloride	Boiling Range (°C)
Butanoyl chloride	102
3-Methylbutanoyl chloride	114.5-115.5

of the resulting acid halides were confirmed by the n.m.r.
spectra, and by agreement of observed boiling points with
those reported in the literature.

Preparation of Acid Chlorides

Acid chlorides which were not commercially available were
prepared from readily available starting materials as described
below.

3,3-Dimethylbutanoyl Chloride

The reaction of t-butyl alcohol with 1,1-dichloroethene
in the presence of sulfuric acid was used to produce 3,3-di-
methylbutanoic acid.[9] Thus 200 ml of 90% sulfuric acid was
placed in a three-neck flask equipped with an additional funnel
and mechanical stirrer. The flask was maintained at 0-5°C in
an ice bath as a mixture of 75 grams of t-butyl alcohol and
145 grams of 1,1-dichloroethene was added dropwise with rapid
stirring. After hydrogen chloride gas ceased to evolve, the
mixture was poured over crushed ice. The resulting acid was
purified by forming the potassium salt with potassium hydroxide
and freeing the acid by addition of dilute hydrochloride acid.
The resulting acid was dissolved in ether and dried over

magnesium sulfate, filtered, and the ether removed by rotatory evaporation. The acid was then used without further purification. The acid chloride was prepared by refluxing with thionyl chloride and distilling at 128-130°C in 78% yield.

2-Chloro-3,3-dimethylbutanoyl Chloride

The α-chlorination was achieved by refluxing 3,3-dimethylbutanoyl chloride with a 50% excess of sulfuryl chloride in the presence of a catalytic amount of iodine overnight. The α-chloro acid chloride was distilled at 90-92°C mm.[10]

2-Bromo-3,3-dimethylbutanoyl Chloride

To one mole of the acid chloride in a one-neck flask equipped with a reflux condenser was added 1.0 mole of bromine and 10 ml of phosphorous trichloride. The reaction mixture was then heated at 70-80°C until the color of bromine had appeared, usually about 24 hours. The reaction mixture was then cooled and distilled at 108-110°C at 30 mm. The structure was confirmed by analysis of its n.m.r. spectrum and mass spectrum.

2,3-Dimethylbutanoyl Chloride

To a solution of 1.0 mole of cyclohexylisopropylamine in 200 ml of THF was added 1.2 mole of n-butyllithium at -78°. A 0.95 mole portion of isopentyl isovalerate was added to this solution and stirred for 15 min. at -78°. The dry ice-acetone bath was removed and 1.0 mole of methyl iodide was added and

stirring continued at room temperature for 2 hr. An equal volume of water was added to the reaction mixture, the organic layer was separated and the aqueous layer extracted with ether. The combined extracts were dried over magnesium sulfate, filtered and concentrated, and then distilled to give a 50% yield of the α-methylated ester. The ester was hydrolyzed by refluxing for 24 hr in a sodium hydroxide solution of ethanol-water. The reaction mixture was acidified with 6N hydrochloric acid and extracted with ether. The ether extracts were washed with a sodium chloride solution and dried over magnesium sulfate. Removal of the ether by evaporation and distillation at 192° afforded a 20% yield of 2,3-dimethyl-butanoic acid.[11]

This acid can be synthesized by another procedure which follows. To a solution of the sodium enolate of diethyl malonate, prepared from 23 grams of sodium, 300 ml of absolute ethanol and 1.0 mol of diethyl malonate, 1.0 mol of methyl iodide was added dropwise. After the reaction mixture was boiled under reflux with stirring for 15 hr, most of the ethanol was distilled from the mixture and water was added. The product was extracted with ether, and the ether solution was dried over magnesium sulfate and vacuum distilled to afford an 87% yield of diethyl methylmalonate at 80-82°C at 3 mm. This diethyl methylmalonate was alkylated with iso-propyl bromide in the same manner as described above to produce a 55% yield of diethyl isopropylmethylmalonate. This

ester was hydrolyzed in aqueous potassium hydroxide; acidification, extraction with ether, drying and evaporation of the ether afforded the crude acid. This was refluxed at 170-220°C for 2 hr until carbon dioxide ceased to be evolved. The residue was distilled at 192°C to give an 80% yield of 2,3-dimethylbutanoic acid. This acid was refluxed with thionyl chloride for 4 hr to give a 50% yield of the 2,3-dimethylbutanoyl chloride at 135-138°C.[12]

Synthesis of α-Halovinyl Esters

To a stirred solution of 0.1 mol of the α-halo acid halide in 100 ml hexane at room temperature was added 0.05 mol of triethylamine in 20 ml hexane. The addition was made dropwise over a 30 minute period. Stirring was continued at room temperature for 12 hrs. The triethylammonium salt was filtered and the filtrate concentrated on a rotatory evaporator and vacuum distilled to yield the vinyl ester.[13]

1,2-Dichloropropenyl 2-Chloropropanoate

To a solution of 0.1 mol of 2-chloropropanoyl chloride in 100 ml hexane was added a 0.05 mol of triethylamine in 20 ml of hexane at room temperature. A 65% yield was obtained and the physical properties, ir and n.m.r. spectra were identical to those in the literature.[13]

1,2-Dichlorobutenyl 2-Chlorobutanoate

To a solution of 0.1 mol of 2-chlorobutanoyl chloride in 100 ml hexane was added, dropwise, 0.05 mol of triethylamine in 20 ml hexane at room temperature. A 55% yield was obtained and the physical properties, ir and n.m.r. spectra were identical to those in the literature.[13]

Synthesis of β-Keto Acid Chlorides

To a solution of 0.2 mol of the α-haloacid chloride in hexane was added an excess of dimethylketene which was generated directly from tetramethylcyclobutanedione by pyrolysis. After standing under nitrogen for two days at 0°C or room temperature, the solvent was removed under reduced pressure and the residue was vacuum distilled.

4,4-Dichloro-2,2-dimethyl-3-ketobutanoyl Chloride

To a solution of 0.2 mol of dichloroacetyl chloride in hexane was added an excess of dimethylketene at room temperature. A 53% yield was obtained and the physical properties, ir and n.m.r. spectra were identical to those in the literature.[14]

4-Chloro-2,2-dimethyl-3-ketopentanoyl Chloride

To a solution of 0.2 mol of 2-chloropropanoyl chloride in hexane was added an excess of dimethylketene at 0°C. A 35% yield was obtained and the physical properties, ir and n.m.r. spectra were identical to those in the literature.[14]

General Methods for Mixed Dimerizations

Method A.--To a stirred solution of 0.05 mol of dimethyl-
ketene and 0.05 mol of triethylamine in 50 ml of ether was
added a solution of 0.05 mol of α-chloroacid chloride in 10 ml
of ether at room temperature. Stirring was continued for 2 hr
and then the amine salt was removed by filtration. The sol-
vent was removed from the filtrate with a rotatory evaporator
and the residue vacuum distilled.

Method B.--To a refluxing solution of 0.1 mol of α-halo-
acid chloride and 0.1 mol of isobutyryl chloride, or 2-methyl-
pentanoyl chloride, or 2,3-dimethylbutanoyl chloride, or 2-
ethylbutanoyl chloride, or cyclohexanecarboxyl chloride in
150 ml of benzene, was added, dropwise with stirring, 0.25 mol
of triethylamine in 15 ml benzene. The reaction mixture was
stirred from 1 hr to 4 days and the salt removed by filtration,
the filtrate concentrated with a rotatory evaporator and
vacuum distilled. Other solvents which can be used include
hexane, acetonitrile, chloroform and ether.

Method C.--To a refluxing solution of 0.05 mol of 1,2-
dichloropropenyl 2-chloropropanoate or 1,2-dichlorobutenyl
2-chlorobutanoate and 0.10 mol of triethylamine in 100 ml of
benzene was added dropwise 0.05 mol of cyclohexanecarboxyl
chloride in 15 ml of benzene. Refluxing was continued for
several days as the reaction was monitored by vapor phase
chromatography until the reaction was complete. The amine

salt was removed by filtration, the solvent was removed by evaporation on a rotatory evaporator and the mixed dimer vacuum distilled.

2-Chloro-2-t-butyl-4,4-dimethyl-1,3-cyclobutanedione (I)

Method A.--A 50% yield of mixed dimer was produced.

Method B.--The reaction mixture was stirred for 24 hr and a 56% yield of dione was produced and a 13% yield of β-lactone.

This mixed dimer was also prepared directly from the two ketenes as described below: A solution of 0.05 mol of 2-chloro-3,3-dimethylbutanoyl chloride in 10 ml of chloroform was added dropwise to a stirred solution of 0.05 mol of tri-ethylamine in 100 ml of chloroform at 0-5°C. The ketene band in the infrared at 2110 cm^{-1} reached a maximum intensity within about 4 hr. At this time, a solution of 0.07 mol of dimethylketene in 10 ml of ether was added over a period of about 3 hr. The solution was concentrated on a rotatory eva-porator and 100 ml of hexane was added to precipitate the amine salt. After removal of the salt by filtration, the filtrate was concentrated and the mixed dimer distilled at 39-40°C at 0.025 mm to give a 40% yield; ir, 1750 cm^{-1}, n.m.r., δ, 1.19 (s, 9 H), 1.28 (s, 3 H), 1.60 (s, 3 H).

Analysis: Calculated for $C_{10}H_{15}ClO_2$: C, 59.25; H, 7.47; Cl, 17.44. Found: C, 59.09; H, 7.20; Cl, 17.29

2-Chloro-2-ethyl-3,3-dimethyl-1,3-cyclobutanedione (II)

Method A.--A 55% yield.

Method B.--The reaction mixture was refluxed for 3 hr and then stirred for an additional 3 hr to produce a 41% yield of the dione and a 13% yield of the vinyl ester, 1,2-dichloro-butenyl 2-chlorobutanoate; bp 54-55° at 0.25 mm; ir, 1755 cm^{-1}; n.m.r., δ, 1.14 (t, 3 H), 1.34 (s, 3 H), 1.54 (s, 3 H) and 2.40 (q, 2 H).

Analysis: Calculated for $C_8H_{11}ClO_2$: C, 55.01; H, 6.30; Cl, 20.34. Found: C, 55.20; H, 6.39; Cl, 20.06.

2-Chloro-2-methyl-4,4-dimethyl-1,3-cyclobutanedione (III)

Method A.--A 42% yield was obtained along with a small amount of 1,2-dichloropropenyl 2-chloropropanoate.

Method B.--As soon as the addition was completed at reflux, the reaction mixture was cooled over a period of 1 hr. Vacuum distillation afforded the mixed dimer at 70° at 0.25 mm which crystallized from ether giving a 34% yield and a small amount of the vinyl ester; mp, 78-80°; ir, 1750 cm^{-1}, n.m.r., δ, 1.36 (s, 3 H), 1.52 (s, 3 H), 1.70 (s, 3 H).

Analysis: Calculated for $C_7H_9ClO_2$: C, 52.34; H, 5.61; Cl, 22.12. Found: C, 52.52; H, 5.75; Cl, 21.63.

2-Chloro-2-methylspiro[3.5]nona-1,3-dione (IV)

Method B.--Refluxed for 24 hr; bp 67-70° at 0.025 mm; recrystallized from alcohol, mp 67-69° in 62% yield.

Method C.--After 48 hr, the reaction was completed in 63% yield; ir, 1750 cm^{-1}, n.m.r., δ, a multiplet centered at 1.80 out of which there was a singlet at 1.70.

Analysis: Calculated for $C_{10}H_{13}ClO_2$: C, 59.85; H, 6.48; Cl, 17.70. Found: C, 59.60; H, 6.65; Cl, 17.45.

2-Chloro-2-ethylspiro[3.5]nona-1,3-dione (V)

Method B and Method C.--Refluxed for 2-3 days, 35% yield of dione and 14% yield of α-chlorovinyl ester; bp 60-62° at 0.1 mm; ir, 1750 cm^{-1}; n.m.r., δ, 1.16 (t, 3 H) and 1.84 (m, 12 H).

Analysis: Calculated for $C_{11}H_{15}ClO_2$: Cl, 16.55. Found: Cl, 16.72.

2-Chloro-2-methyl-4,4-diethyl-1,3-cyclobutanedione (VI)

Method B.--The reaction mixture was refluxed for 24 hr and a yield of 63% of mixed dimer was obtained; bp 43° at 0.05 mm; ir, 1750 cm^{-1}; n.m.r., δ, 1.08 (2 t, 6 H), 1.72 (s, 3 H), 1.96 (m, 4 H).

Analysis: Calculated for $C_9H_{13}ClO_2$: C, 57.29; H, 6.90; Cl, 18.83. Found: C, 57.44; H, 7.04; Cl, 18.71.

2-Chloro-2-ethyl-4,4-diethyl-1,3-cyclobutanedione (VII)

Method B.--Refluxed for 4 days, 51% yield of dione and 7% yield of α-chlorovinyl ester; bp 41-43° at 0.025 mm; ir, 1750 cm^{-1}; n.m.r., δ, 1.04 (m, 9 H), 1.84 (m, 6 H).

Analysis: Calculated for $C_{10}H_{15}ClO_2$: C, 59.26; H, 7.41; Cl, 17.53. Found: C, 59.17; H, 7.46; Cl, 17.29

2-Chloro-2-isopropyl-4,4-dimethyl-1,3-cyclobutanedione (VIII)

Method B.--Refluxed for 20 hr, 40% yield, bp 40-43° at 0.05 mm; ir, 1750 cm^{-1}; n.m.r., δ, 1.20 (d, 6 H), 1.34 (s, 3 H), 1.52 (s, 3 H) and 2.40 (hept., 1 H).

Analysis: Calculated for $C_9H_{13}ClO_2$: C, 57.29; H, 6.90; Cl, 18.83. Found: C, 57.63; H, 7.03; Cl, 18.36.

2-Chloro-2-t-butyl-4,4-diethyl-1,3-cyclobutanedione (IX)

Method B.--Stirred for 2 days at room temperature in chloroform to yield 43% of dione, bp 52° at 0.1 mm and mp 43-45°; ir, 1750 cm^{-1}; n.m.r., δ, 1.08 (t, 6 H), 1.16 (s, 9 H), 1.80 and 2.10 (2 q, 4 H).

Analysis: Calculated for $C_{12}H_{19}ClO_2$: C, 62.47; H, 8.24. Found: C, 62.10; H, 8.46.

2-Bromo-2-t-butylspiro[3.5]nona-1,3-dione (X)

Method B.--Refluxed for 2 days and obtained a mixed dimer in 36% yield, bp 32-34° at 0.25 mm; recrystallized from ethanol, mp 77-78°; ir, 1760 cm^{-1}; n.m.r., δ, 1.10 (s, 9 H) and 1.60 (m, 10 H).

Analysis: Calculated for $C_{13}H_{19}BrO_2$: C, 54.55; H, 6.64; Br, 27.62. Found: C, 54.33; H, 6.82; Br, 27.45.

2-Chloro-2,4-dimethyl-4-n-propyl-1,3-cyclobutanedione (XI)

Method B.--Refluxed for 1.5 days, 57% yield; bp 42-45° at 0.05 mm; ir, 1761 cm^{-1}; n.m.r., δ, a multiplet centered at 1.60 out of which there were 4 singlets at 1.36, 1.52, 1.64 and 1.72.

Analysis: Calculated for $C_9H_{13}ClO_2$: C, 57.29; H, 6.90; Cl, 18.83. Found: C, 57.23; H, 6.87; Cl, 18.62.

2-Chloro-2,4-dimethyl-4-i-propyl-cyclobutanedione (XII)

Method B.--Refluxed for 2 days to yield 42% of dione, bp 47-50° at 0.8 mm; ir, 1754 cm^{-1}, n.m.r., δ, 1.10 (d), 1.27 (s), 1.46 (s), 1.60 (s), 1.66 (s) and 2.40 (m); M$^+$, 188 (m/e).

Analysis: Calculated for $C_9H_{13}ClO_2$: C, 57.29; H, 6.90. Found: C, 57.52; H, 6.92.

2-Chloro-2-t-butyl-4-methyl-4-n-propyl-cyclobutanedione (XIII)

Method B.--Refluxed for 2 days to yield 48% of dione, bp 64-65° at 0.25 mm; ir, 1754 cm^{-1}, n.m.r., δ, 0.95 (m), 1.15 (s, 9 H), 1.28 (s) and 1.56 (s) out of a multiplet, 1.85 (m); M$^+$, 230 (m/e).

Analysis: Calculated for $C_{12}H_{19}ClO_2$: C, 62.47; H, 8.24; Cl, 15.84. Found: C, 62.67; H, 8.69; Cl, 15.99.

General Procedure for the Preparation and Cycloaddition Reactions of t-Butylketene

A solution of 0.1 mol of 3,3-dimethylbutanoyl chloride in 20 ml of benzene was added dropwise to a refluxing solution of

0.15 mol of triethylamine and 0.20 mol of unsaturated compound in 150 ml of benzene. After completion of the addition, refluxing was continued for about 24 hr. The amine salt was removed by filtration and washed with benzene. Concentration of the filtrate afforded the crude cycloadduct. Vacuum distillation resulted in the pure cycloadduct.

3-t-Butyl-1-isopropyl-4-isopropyliminoazetidin-2-one (XIV) (β-lactam)

This cycloadduct of t-butylketene and diisopropylcarbodiimide was obtained in 42% yield; bp 50° at 0.25 mm; ir, 1812 cm^{-1} (C=O) and 1684 cm^{-1} (C=N); n.m.r., δ, 1.07 (singlet with a buried doublet, 15 H), 1.32 (d, 6 H), 3.24 (s, 1 H) and 3.60 (m, 2 H).

Analysis: Calculated for $C_{13}H_{24}N_2O$: C, 69.64; H, 10.71; N, 12.50. Found: C, 69.74; H, 10.83; N, 12.30.

7-t-Butylbicyclo[3.2.0]hept-2-en-6-one (XV)

This cyclopentadiene adduct of t-butylketene was obtained in 40% yield at 45-47° at 0.2 mm; ir, 1767 cm^{-1} (C=O) and 1601 cm^{-1} (C=C); n.m.r., δ, 0.96 (s, 9 H), 2.60 (m, 2 H), 3.22 (m, 3 H) and 5.68 (m, 2 H); endo-t-butyl/exo-t-butyl = 3 as determined by vapor phase chromatography; mol. wt. 164 by mass spect., theory 164.

General Procedure for Mixed Dimerization of Halogenated Ketenes and t-Butylketene

A solution of 0.1 mol of α-haloacid chloride and 0.1 mol of 3,3-dimethylbutanoyl chloride was added to a refluxing

solution of 0.25 mol of triethylamine in 150 ml benzene.
The reaction mixture was refluxed from 8 hr to 2 days and
the salt removed by filtration. The filtrate was concentrated
on a rotatory evaporator and the residue vacuum distilled.

3-Chloro-3-methyl-4-(2,2-dimethyl)propylidene-2-oxetanone (XVI) (β-lactone)

This mixed dimer of $\underline{t}$-butylketene and methylchloroketene
was obtained by refluxing for 8 hr to give a 32% yield of β-
lactone with a small amount of α-chlorovinyl ester: bp 45-48°
at 0.08 mm; ir, 1887, 1818 cm^{-1} (C=O) and 1724 cm^{-1} (C=C);
n.m.r., δ, 1.18 (s, 9 H), 1.88 (s, 3 H) and 4.84 (s, 1 H).

Analysis: Calculated for $C_9H_{13}ClO_2$: C, 57.29; H, 6.89;
Cl, 18.83. Found: C, 56.72; H, 6.91; Cl, 18.74.

3-Chloro-3-ethyl-4-(2,2-dimethyl)propylidene-2-oxetanone (XVII) (β-lactone)

This mixed dimer of $\underline{t}$-butylketene and ethylchloroketene
was obtained by refluxing for 24 hr to give a 10% yield of
β-lactone along with α-chlorovinyl ester. This compound was
characterized by ir at 1887, 1773 cm^{-1} (C=O) and 1724 cm^{-1}
(C=C) and converted to the methylketoester (XXI).

3-t-Butyl-4-(1-chloro-2,2-dimethyl)propylidine-2-oxetanone (XVIII) (β-lactone)

The mixed dimer of $\underline{t}$-butylchloroketene and $\underline{t}$-butylketene
was obtained by refluxing for 2 days, 20% yield; bp 54-57° at
0.1 mm; ir, 1923-1852 cm^{-1} (broad, C=O) and 1695 cm^{-1} (C=C);
n.m.r., δ, 1.16 (s, 9 H), 1.32 (s, 9 H) and 3.86 (s, 1 H).

This compound was further characterized by conversion to the methyl ketoester (XXII).

3-t-Butyl-4-(1-bromo-2,2-dimethyl)propylidene-2-oxetanone (XIX) (β-lactone)

This cycloadduct of t-butylbromoketene and t-butylketene was obtained after refluxing for 2 days, 10% yield, and an unidentified compound was found; the β-lactone: bp 77-80° at 0.15 mm; ir, 1908, 1852 cm^{-1} (C=O) and 1681 cm^{-1} (C=C); n.m.r., δ, 1.23 (s, 9 H), 1.32 (s, 9 H) and 3.80 (s, 1 H).

Analysis: Calculated for $C_{12}H_{19}BrO_2$: C, 52.36; H, 6.91; Br, 29.10. Found: C, 52.10; H, 7.19; Br; 29.14.

General Procedure for Methanolysis of 2-Oxetanones

Methanolysis of the 2-oxetanones from the mixed dimerizations of halogenated ketenes and t-butylketene was accomplished by refluxing for 6-8 hr in methanol to give a quantitative yield of the β-ketoester. The 2-oxetanones could not be easily separated from the diones of mixed dimerizations of halogenated ketenes and dialkylketenes but were observable by ir bands at 1887, 1828 cm^{-1} (C=O) and 1712 cm^{-1} (C=C). Methanolysis of the mixture of dione and 2-oxetanone was accomplished by refluxing this mixture with methanol for 1.5 hr. The β-ketoester revealed bands in the ir at 1748 and 1718 cm^{-1} (C=O). Methanolysis of the 1,3-cyclobutanediones required a much longer (1-3 days) reflux time.

Methyl 2-Chloro-2,5,5-trimethyl-3-keto-
2-methylhexanoate (XX)

The 2-oxetanone derived from $\underline{t}$-butylketene and methyl-chloroketene upon methanolysis gave bp 47-50° at 0.25 mm; n.m.r., δ, 1.06 (s, 9 H), 1.52 (s, 3 H), 2.50 (2 s, 2 H) and 3.78 (s, 3 H).

Analysis: Calculated for $C_{10}H_{17}ClO_3$: Cl, 14.76. Found: Cl, 14.91.

Methyl 2-Chloro-5,5-dimethyl-2-ethyl-
3-ketohexanoate (XXI)

The 2-oxetones from ethylchloroketene and $\underline{t}$-butylketene gave the methyl ester at bp 65° at 0.05 mm; n.m.r., δ, 0.96 (t) and 1.02 (s) total of 12 H, 2.28 (q, 2 H), 2.50 (2 s, 2 H) and 3.78 (s, 3 H).

Analysis: Calculated for $C_{11}H_{19}ClO_3$: C, 55.70; H, 8.24; Cl, 15.15. Found: C, 55.92; H, 8.24; Cl, 15.03.

Methyl 2-t-Butyl-4-chloro-5,5-dimethyl-
3-ketohexanoate (XXII)

This methyl ketoester was derived from the 2-oxetanones from $\underline{t}$-butylchloroketene and $\underline{t}$-butylketene was obtained at bp 58-60° at 0.05 mm; n.m.r., δ, 1.10 (s, 18 H), 3.64 (s, 1 H), 3.70 (s, 3 H) and 4.0 (s, 1 H).

Analysis: Calculated for $C_{13}H_{23}ClO_3$: Cl, 13.52. Found: Cl, 13.35.

Methyl 4-Bromo-2-t-butyl-5,5-dimethyl-3-ketohexanoate (XXIII)

This ester was derived from the 2-oxetanone from t-butyl-bromoketene and t-butylketene and was obtained at bp 60-65° at 0.025 mm; n.m.r., δ, 1.08 (s, 9 H), 1.12 (s, 9 H), 3.68 (s) and 3.70 (s) total of 4 H, and 4.04 (s, 1 H); mol. wt. 274 by mass spect., theory 274.

Methyl 4-Chloro-3-keto-2,2,5,5-tetramethylhexanoate (XXVI)

This β-ketoester was obtained from the 2-oxetanone from t-butylchloroketene and dimethylketene and distilled at bp 90-92° at 0.1 mm; n.m.r., δ, 1.12 (s, 9 H), 1.40 (s, 3 H), 1.52 (s, 3 H), 3.74 (s, 3 H) and 4.42 (s, 1 H).

Analysis: Calculated for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.10; Cl, 15.14. Found: C, 56.53; H, 8.40; Cl, 15.20.

Methyl 4-Chloro-3-keto-2,2,5-trimethylhexanoate (XXVII)

This ester was obtained from the 2-oxetanone from iso-propylchloroketene and dimethylketene and distilled at 57-59° at 0.5 mm; n.m.r., δ, 1.00 (2 d, 6 H), 1.44 (s, 3 H), 1.52 (s, 3 H), 2.40 (m, 1 H), 3.83 (s, 3 H) and 4.40 (d, 1 H).

Analysis: Calculated for $C_{10}H_{17}ClO_3$: C, 54.42; H, 7.71; Cl, 16.09. Found: C, 54.65; H, 7.80; Cl, 15.52.

Methyl 4-Chloro-2,2-diethyl-3-ketohexanoate (XXVIII)

The methanolysis of the 2-oxetanone from diethylketene and ethylchloroketene distilled at bp 52-54° at 0.05 mm; n.m.r.,

δ, 0.90 (m, 9 H), 2.00 (m, 6 H), 3.76 (s, 3 H), and 4.40 (t, 1 H).

Analysis: Calculated for $C_{11}H_{19}ClO_3$: C, 56.29; H, 8.10; Cl, 15.14. Found: C, 56.64; H, 8.21; Cl, 14.72.

General Procedure for the Dehydrochlorination of β-Keto Acid Chlorides

To 0.06 mol of triethylamine in 20 ml benzene was added 0.03 mol of β-keto acid chloride (4-chloro-2,2-dimethyl-3-ketopentanoyl chloride or 4,4-dichloro-2,2-dimethyl-3-keto-butanoyl chloride) in 5 ml benzene. After the addition, the reaction mixture was refluxed for about 5 hr. The amine salt was removed by filtration and washed with benzene. The solvent was removed by evaporation and the residue vacuum distilled.

3,3-Dimethyl-4-(1-chloroethylidene)- 2-oxetanone (XXIX)

This compound appeared to undergo some decomposition during the distillation. The crude product was characterized by ir, 1887, 1818 cm^{-1} (C=O) and 1754 cm^{-1} (C=C), n.m.r., δ, 1.48 (s, 6 H) and 2.02 (s, 3 H), and M^+, 160 (m/e).

3,3-Dimethyl-4-(dichloromethylidene)- 2-oxetanone (XXX)

This oxetanone was distilled at 37-39° at 0.24 mm; ir, 1890, 1818 cm^{-1} (C=O) and 1695 cm^{-1} (C=C); n.m.r., δ, 1.52 (s), M^+; 180 (m/e).

Analysis: Calculated for $C_6H_6Cl_2O_2$: C, 39.77; H, 3.31; Cl, 39.22. Found: C, 39.85; H, 3.42; Cl, 38.95.

Attempted Isomerizations of a 1,3-Cyclobutane-dione and a 2-Oxetanone

A 1.0 g sample of the 2-oxetanones, XVI and XVIII were separately refluxed with a catalytic amount of aluminum chloride in heptane for 24 hr. No isomerization was observed by an infrared analysis.

A 1.0 gram portion of a mixture of the dione (VIII) and the 2-oxetanone obtained from the preparation of (VIII) was refluxed in hexane for 24 hr. No change in the isomer distribution was observed. The addition of triethylamine and triethylammonium chloride and continued reflux for about 24 hr also caused no change in the isomer distribution.

General Procedure for the Preparation of Pentamethylene-ketene by the Dehydrohalogenation Method

A solution of 0.1 mol of cyclohexanecarboxyl chloride in 50 ml of dry benzene was added dropwise to a refluxing solution of 0.15 mol of triethylamine and 0.2-0.3 mol of an unsaturated compound in 150 ml of dry benzene. After completion of the addition, refluxing was continued for about 20 hr. The amine salt was removed by filtration and washed with benzene. Concentration of the filtrate afforded the crude cycloadduct. Vacuum distillation or recrystallization resulted in purification of the pentamethyleneketene adduct.

Pentamethyleneketene Cyclopentadiene Cycloadduct (XXXII)

This adduct was obtained in 65% yield at 67-69° (0.1 mm); ir, 1767 cm^{-1} (C=O), and 1601 cm^{-1} (C=C); n.m.r., δ, 1.50

(m, 10 H), 2.42 (m, 2 H), 3.15 (m, 1 H), 3.75 (two t or three d, 1 H), and 5.7 (m, 2 H).

After distillations, this adduct contained a small amount of the ketene dimer as an impurity. Consequently, the cycloadduct was hydrogenated in ethanol under 50 psi of hydrogen employing platinum oxide as a catalyst. An 80% yield of the saturated spiroketone (XXXIII) resulted at 57-58° (0.08 mm); n.m.r., δ, 1.70 (m, 16 H), 2.52 (two t or three d, 1 H), and 3.65 (two t or three d, 1 H).

Analysis: Calculated for $C_{12}H_{18}O$: C, 80.89; H, 10.11. Found: C, 80.63; H, 9.75.

Pentamethylketene Dihydropyran Cycloadduct (XXXIV)

This cycloadduct was produced in 67% yield at 90-92° (0.2 mm); ir, 1767 cm^{-1} (C=O); n.m.r., δ, 1.60 (m, 14 H), 3.30 (two t or three d, 2 H), 3.80 (two t or three d, 1 H) and 4.10 (d, 1 H).

This compound was also contaminated with the ketene dimer and was reduced with sodium borohydride in ethanol. The corresponding alcohol (XXXV) was recrystallized from ether: mp 53-55°; ir, 3450 cm^{-1} (OH); n.m.r., δ, 1.42 (m, 14 H), 2.1-2.6 (s, H of OH), 2.43 (m, 1 H), 3.30 (m, 1 H) and 3.80 (m, 3 H).

Analysis: Calculated for $C_{12}H_{20}O_2$: C, 73.46; H, 10.21. Found: C, 73.28; H, 9.99.

Pentamethyleneketene Tetramethylallene Cycloadduct (XXXVI)

A 60% yield of crystalline solid which was recrystallized from ethanol was obtained: mp 47-48°; ir, 1725 cm^{-1} (C=O) and 1639 cm^{-1} (C=C); n.m.r., δ, 1.28 (s, 6 H), 1.84 (s, 3 H), 2.08 (s, 3 H) and 1.25-2.0 (m, 10 H). The three singlets are out of the multiplet at δ 1.25-2.0. The chemical shift values for the unequivalent methyl protons attached to the vinyl linkage and the equivalent methyl protons on the β-carbon are in excellent agreement with other tetramethylallene ketene cycloadducts.[15]

Analysis: Calculated for $C_{14}H_{22}O$: C, 81.43; H, 11.05. Found: C, 81.55; H, 10.68.

Pentamethyleneketene Diisopropylcarbodiimide Cycloadduct (XXXVII)

This adduct was prepared in 51% yield and was recrystallized from ether; mp 83-85°; ir, 1818 cm^{-1} (C=O) and 1686 cm^{-1} (C=N); n.m.r., δ, 1.20 (d, 6 H), 1.48 (d, 6 H), 1.94 (m, 10 H), and 3.80 (m, 2 H).

Analysis: Calculated for $C_{14}H_{24}N_2O$: C, 71.19; H, 10.18; N, 11.68. Found: C, 71.31; H, 10.56; N, 11.36.

Pentamethyleneketene N-t-Butylbenzylimine Cycloadduct (XXXVIII)

The cycloadduct was obtained in 48% yield and was recrystallized from ether: mp 105-106°; ir, 1748 cm^{-1} (C=O); n.m.r. (CDCl$_3$) δ, 1.30 (s) and 1.60 (m) (accounts for 19 H), 4.35 (s, 1 H) and 7.30 (s, 5 H).

Analysis: Calculated for $C_{18}H_{25}NO$: C, 79.70; H, 9.22; N, 5.16. Found: C, 80.00; H, 9.03; N, 5.08.

Pentamethyleneketene Chloral Cycloadduct (XXXIX)

To a mixture of 0.3 mol of activated zinc and 0.2 mol of freshly distilled chloral in 100 ml of dry ether containing a trace amount of $AlCl_3$ with vigorous stirring was added drop-wise a solution of 0.1 mol of α-bromocyclohexanecarboxyl chloride in 15 ml of ether. After the addition was complete, the reaction mixture was refluxed for 24 hr. The unreacted zinc was removed by filtration and the filtrate was concentrated on a rotatory evaporator. The residue was extracted with three 50-ml portions of CCl_4 to remove the cycloadduct from the zinc halide etherate. The combined extracts were concentrated and distilled under vacuum. The condensate solidified and was recrystallized from ethanol: mp 77-78°; ir, 1837 cm^{-1} (C=O); n.m.r., δ, 1.80 (m, 10 H) and 4.57 (s, 1 H).

Analysis: Calculated for $C_9H_{11}Cl_3O_2$: C, 41.94; H, 4.27. Found: C, 41.78; H, 3.93.

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CHAPTER III

RESULTS AND DISCUSSION

Most ketenes are very susceptible to dimerization when
heated or when allowed to stand at room temperature for a
sufficient length of time.[1] The dimerization of ketoketenes
usually produces a 1,3-cyclobutanedione and aldoketenes
usually form β-lactones (2-oxetanones). No reports have
appeared on the dimerization of halogenated ketenes although
numerous papers on cycloaddition reactions of these ketenes
are found.[2] This investigation has developed the codimeri-
zations of halogenated ketenes with ketoketenes and with
aldoketenes.

A chloroform solution of t-butylchloroketene was pre-
pared by the dehydrochlorination of 2-chloro-3,3-dimethyl-
butanoyl chloride as evidenced by the ketene band at 2110 cm^{-1}.
An ether solution of dimethylketene was added and a 40% yield
of the mixed dimer, I, was obtained in about three hours.
The 1,3-cyclobutanedione was characterized by elemental
analysis, infrared and n.m.r. spectroscopy. This reaction

I

41
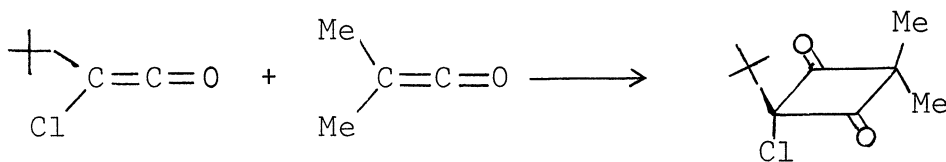
was accompanied by some polymer from the halogenated ketene and less than 10% of the homodimer of dimethylketene. All halogenated ketene reactions are accompanied by some polymerization of the ketene to yield a dark, nonvolatile, sticky polymeric substance.

Mixed dimerizations involving other alkylhaloketenes were accomplished by generating the alkylhaloketene in the presence of dimethylketene, i.e., an in situ cycloaddition reaction. The alkylchloroketenes were prepared by the triethylamine dehydrochlorination of α-chloro acid chlorides in the presence of dimethylketene in ether solution. The 1,3-cyclobutanedione mixed dimers were produced in 1-2 hr in yields up to 55%. Some halogenated ketene polymer and a small

I, R = t-Bu
II, R = Et
III, R = Me
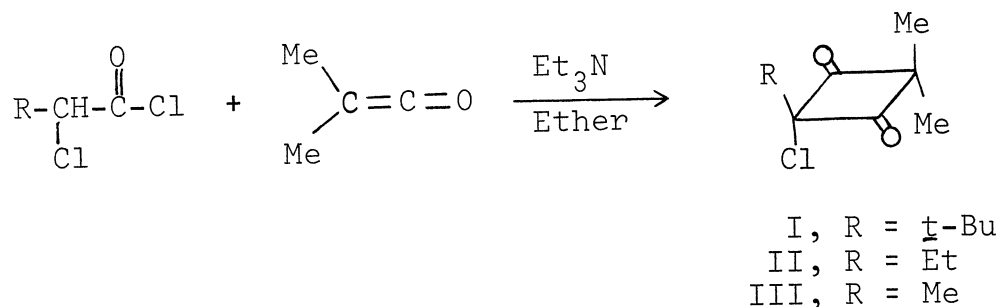
amount of homodimer of dimethylketene was also produced. The attempted mixed dimerizations of diphenylketene with methylchloro- or ethylchloroketenes in a similar manner were not successful. Only a trace amount of the mixed 1,3-cyclobutanedione dimer was produced as evidenced by n.m.r. and infrared spectroscopy.

The most successful method for preparation of the mixed
dimers involves a simultaneous generation of the halogenated
ketene and the dialkylketene from the respective acid halides.
This general method is illustrated below. The unsymmetrical

$$\underset{X}{R'CH}-\overset{O}{\underset{}{C}}-Cl \;+\; \underset{R}{R-CH}-\overset{O}{\underset{}{C}}-Cl \;\xrightarrow[C_6H_6]{NEt_3}\;$$
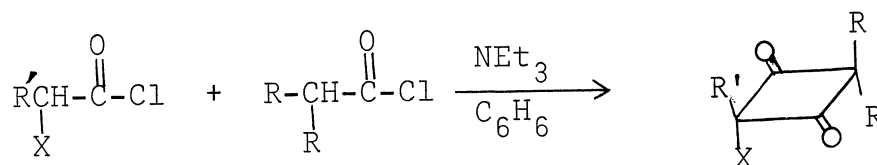
halo-1,3-cyclobutanediones prepared by this method are illus-
trated in Tables I and II.

The cyclobutanediones were all characterized by a band
in the infrared spectra at 1750-1760 cm^{-1} and n.m.r. and ele-
mental analysis. These reactions were all accompanied by some
polymeric material of the halogenated ketenes and some homo-
dimers of the dialkylketenes (<10%). The reaction time is
very dependent upon the particular dialkylketene selected.
Pentamethylene-, diethyl-, n-propylmethyl- and isopropylmethyl-
ketenes are formed very slowly from the respective acid halides
and thus the reaction time is usually several days to obtain
the optimum yield of the mixed dimer. Conversely, dimethyl-
ketene is formed very rapidly and the reaction time for the
mixed dimerization with this ketene is about 1-3 hr.

It is well known that certain α-haloacid halides react
with triethylamine to yield α-halovinyl esters.[3] Vinyl esters
were found in some of the reactions described above. The

TABLE I

UNSYMMETRICAL HALO-1,3-CYCLOBUTANEDIONES
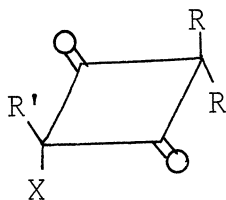
	R	R'	X	Yield (%)
III	Me	Me	Cl	34
VI	Et	Me	Cl	62
IV	$-(CH_2)_5-$	Me	Cl	63
VII	Et	Et	Cl	51
V	$-(CH_2)_5-$	Et	Cl	35
II	Me	Et	Cl	41
VIII	Me	i-Pr	Cl	40
I	Me	t-Bu	Cl	56
IX	Et	t-Bu	Cl	43
X	$-(CH_2)_5-$	t-Bu	Br	36

TABLE II

UNSYMMETRICAL HALO-1,3-CYCLOBUTANEDIONES
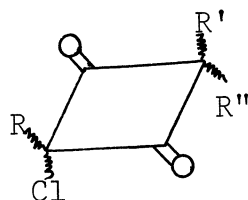
	R	R'	R"	Yield (%)	Isomer Ratio
XI	Me	Me	n-Pr	57	1
XII	Me	Me	i-Pr	42	1
XIII	t-Bu	Me	n-Pr	48	1

α-halovinyl esters will react with triethylamine to regenerate the halogenated ketenes. An α-halovinyl ester could be used in place of the α-haloacid chloride as a source of the halogenated ketene with those dialkylketenes which formed slowly.

$$
\begin{array}{c}
\text{O} \qquad\quad \text{R'} \\
\| \qquad\quad / \\
\text{R'}-\text{CH}-\text{C}-\text{O}-\text{C}=\text{C} \\
| \qquad\quad | \quad \backslash \\
\text{Cl} \qquad \text{Cl} \quad \text{Cl}
\end{array}
\quad + \quad
\begin{array}{c}
\text{O} \\
\| \\
\text{R}_2\text{CH}-\text{C}-\text{Cl}
\end{array}
\xrightarrow{\text{NEt}_3}
$$
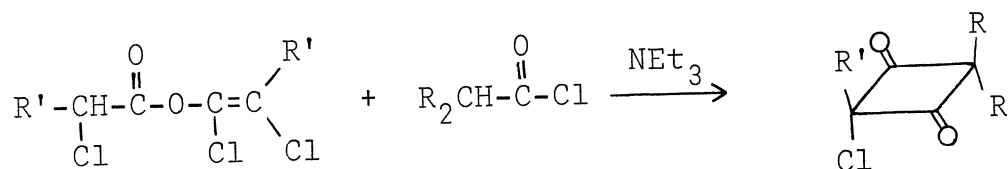
IV, R' = Me, R = $-(CH_2)_5-$

V, R' = Et, R = $-(CH_2)_5-$

The mixed dimerizations of halogenated ketenes and dialkylketenes are very dependent upon the rates of formation of the two ketenes. Since halogenated ketenes are generated faster than dialkylketenes, the α-halovinyl esters are formed because of the instability of the haloketenes and no other reaction path is available other than the undesirable polymerization.[*] The α-halovinyl esters regenerate the haloketenes slowly in the presence of triethylamine to dimerize with the dialkylketenes. This is demonstrated in Scheme I.[4] However, the bulky haloketenes such as t-butylbromo- and t-butylchloroketenes do not form vinyl esters but are generated slowly from the acid halides and dimerize readily with the dialkyl ketenes.[5]

---

[*]When haloketenes are generated in the presence of reactive cycloaddition partners, cycloadducts are formed in good yield rather than vinyl esters.

<u>Scheme I</u>

$$R'-CH-\overset{\overset{O}{\|}}{C}-X \quad + \quad NEt_3$$
$$\qquad \underset{X}{|}$$

[chemical scheme showing reaction pathways]
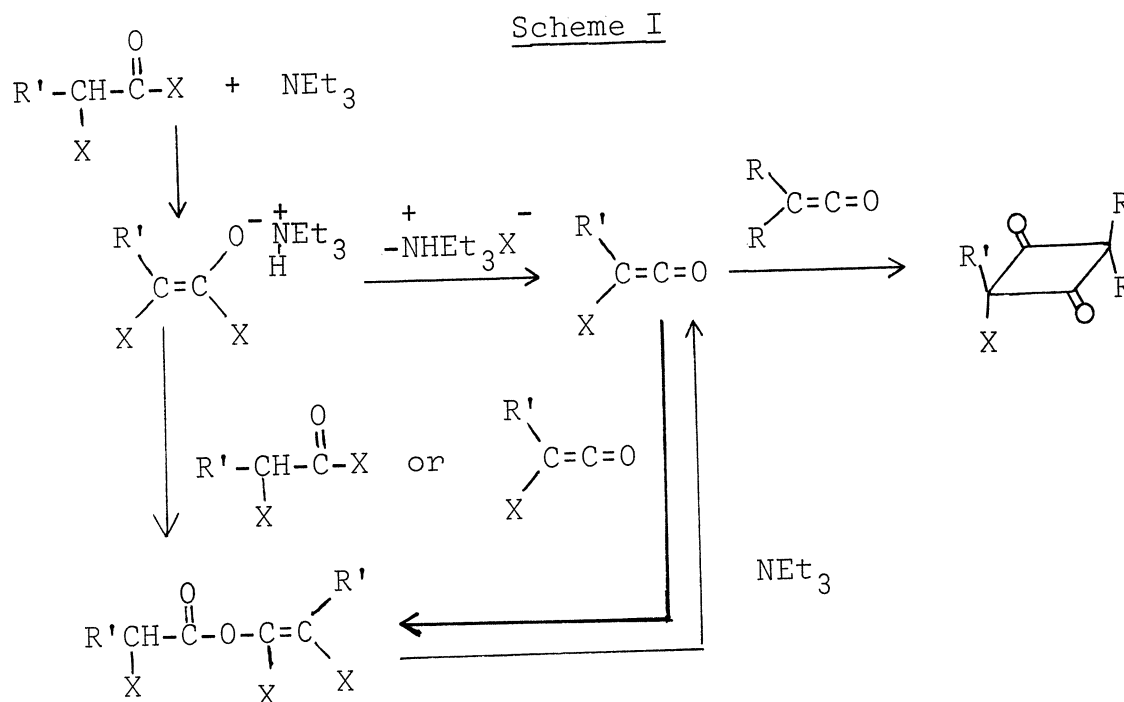
t-Butylketene was generated by triethylamine dehydro-
chlorination in hexane from 3,3-dimethylbutanoyl chloride.
This ketene was unusually stable in the reaction mixture at
room temperature, lasting for two or three days as evidenced
by the infrared absorption at 2119 cm^{-1}.[*] Attempts to isolate
the ketene were unsuccessful due to the equilibrium between
the ketene and the acid halide and the polymerization of the
ketene. Refluxing the reaction mixture for three days
resulted in a 30% yield of the β-lactone homodimer. The <u>in
situ</u> cycloaddition of this previously unprepared ketene with

[*]Aldoketenes are normally quite unstable and dimerize or
polymerize readily in the reaction mixture. The large bulky
t-butyl group would be expected to retard these reactions and
undoubtedly is responsible for the stability of this ketene.

cyclopentadiene and diisopropylcarbodiimide resulted in 32

and 42% yields of cycloadducts, respectively.

XV (endo-t-Bu:exo-t-Bu= 3)   XIV
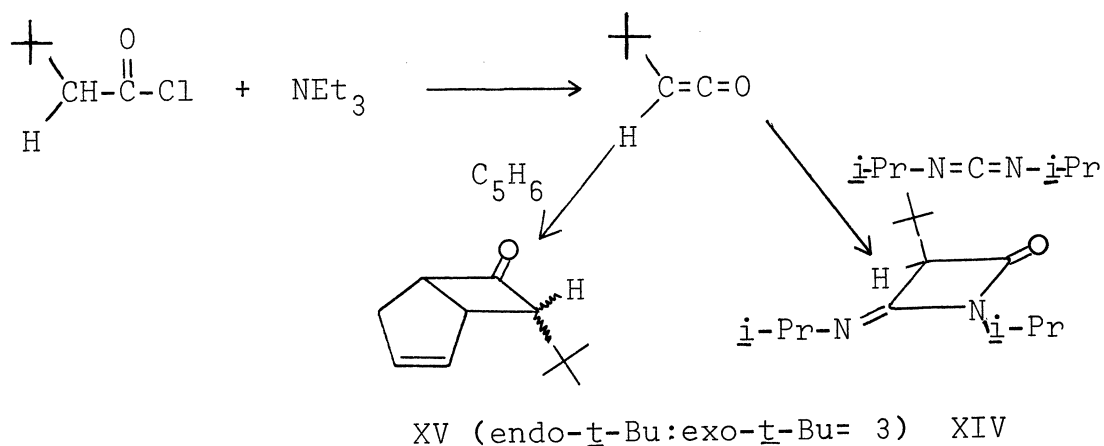
t-Butylketene was codimerized with halogenated ketenes

in situ to produce only β-lactone dimers in poor to moderate

yields. Two such β-lactones are possible depending upon
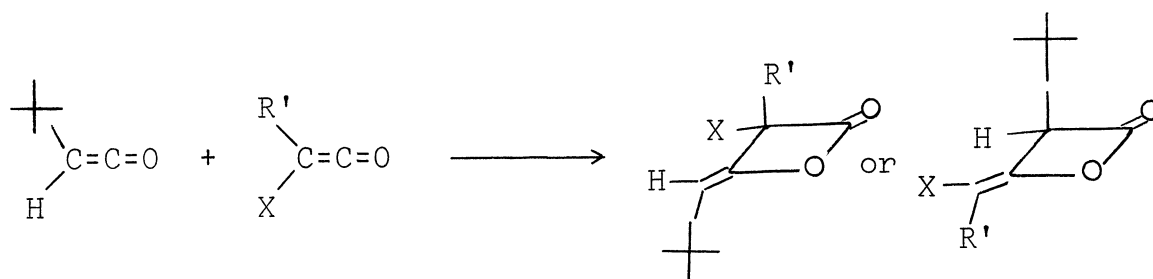
XVI. R' = Me, X = Cl; XVIII. R' = t-Bu, X = Cl
XVII. R' = Et, X = Cl; XIX.   R' = t-Bu, X = Br

whether cycloaddition occurs across the carbon-oxygen double

bond of the halogenated ketene or the t-butylketene as illus-

trated above. Only one β-lactone was produced in each system

but the structure of the dimer was dependent upon the particu-

lar alkylhaloketene. The β-lactone exhibited bands in the

infrared at 1887-1900, 1828-1835 cm^{-1} (C=O) and 1710-1742 cm^{-1}

(C=C). The assignment of structure of the β-lactone could
be made on the basis of the α-proton and the vinyl proton
in the n.m.r. The α-protons appeared in the range δ 3.80-3.86
and the vinyl protons in the range δ 4.80-4.85, a comparison
of these values with the α-proton and vinyl proton of the homo-
dimers of ethyl- and t-butylketenes allowed assignment to be
made (Table III). Methanolysis of the β-lactone was used to
confirm the n.m.r. assignments. The distinction was made on
the basis of the γ-hydrogen in the n.m.r. Methyl 2-t-butyl-
5,5-dimethyl-3-ketohexanoate was synthesized from the β-lactone
dimer of t-butylketene with methanol for comparison purposes
and it was found that the γ-hydrogen was revealed in the n.m.r.
at δ 2.30. Since the β-ketoesters produced had values of 2.5
and 4.0, it was apparent that those with a chemical shift of
δ 2.5 were derived from a β-lactone which resulted from cyclo-
addition across the carbon-carbon double bond of the halogenated
ketenes. Those β-ketoesters with a chemical shift of δ 4.0

XX. R' = Me, X = Cl
XXI. R' = Et, X = Cl

XXII. R' = t-Bu, X = Cl
XXIII. R' = t-Bu, X = Br
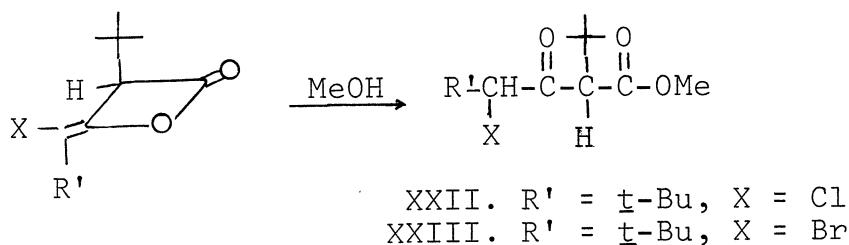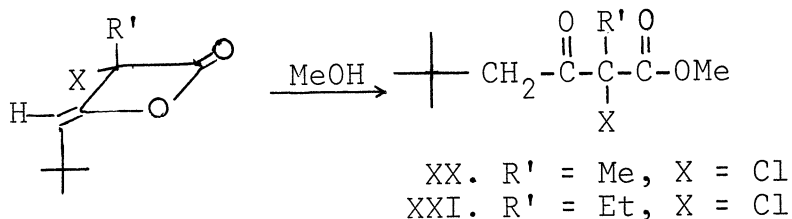
TABLE III

METHYL AND PROTON CHEMICAL SHIFTS (δ) OF THE β-LACTONES
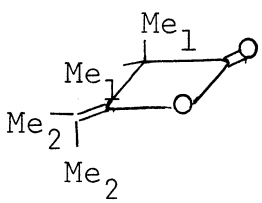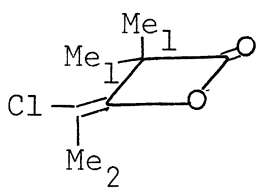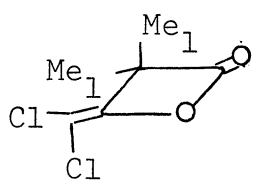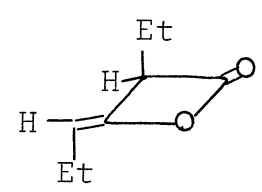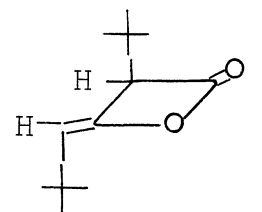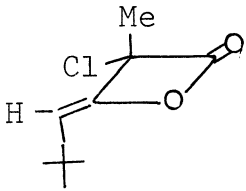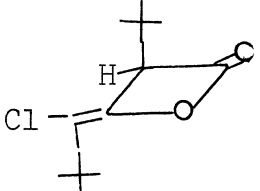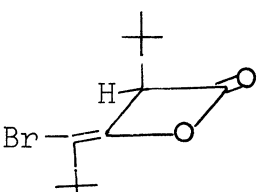
Compound	Me_1	Me_2	H (α-)	H (vinyl)
(structure: Me$_1$, Me$_1$, Me$_2$, Me$_2$ β-lactone)	1.4	1.58, 1.60		
(structure: Me$_1$, Me$_1$, Cl, Me$_2$ β-lactone)	1.48	2.02		
(structure: Me$_1$, Me$_1$, Cl, Cl β-lactone)	1.52			
(structure: Et, H, H, Et β-lactone)			3.88	4.64
(structure: H, H β-lactone)			3.74	4.64

TABLE III (Continued)

Compound	Me$_1$	Me$_2$	H (α-)	H (vinyl)
	1.86			4.85
			3.86	
			3.80	

were derived from the β-lactone which resulted from cyclo-
addition across the carbon-carbon double bond of the t-butyl-
ketene. It was found that for mixed dimerizations of t-butyl-
ketene with methylchloro- or ethylchloroketenes cycloaddition
occurred only across the carbon-carbon double bond of the
haloketenes. However, for t-butylbromo- and t-butylchloro-
ketenes cycloaddition occurred only across the carbon-carbon
double bond of t-butylketenes.

The attempted mixed dimerizations of methylchloro- or
t-butylchloroketenes with methyl-, ethyl- or isopropylketenes
by the generation of these ketenes from the respective acid
chlorides resulted in only the β-lactone homodimers of the
aldoketenes.

Several of the mixed dimerizations of halogenated ketenes
and dialkylketenes described above yielded in addition to the
unsymmetrical cyclobutanediones a β-lactone mixed dimer.
Methanolysis was used to determine which of the two possible
β-lactones (XXIV & XXV) was produced. The β-ketoester pro-
duced revealed only an α-proton in the n.m.r. at δ 4.4.
Methyl 3-keto-2,2,4-trimethylpentanoate was synthesized
from tetramethylcyclobutanedione and the α-hydrogen was
revealed in the n.m.r. at 2.8.[6] Since the β-ketoester pro-
duced had a δ value of 4.4, it is concluded that the β-lactone,
XXIV, was produced whereby cycloaddition occurred only across
the carbon oxygen linkage of the halogenated ketene. This

is consistent with what England and Krespan found for bis-
(trifluoromethyl)ketene.[7] The mixed dimerizations of

R-CH-C-C-C-OMe (structure XXIV → product)
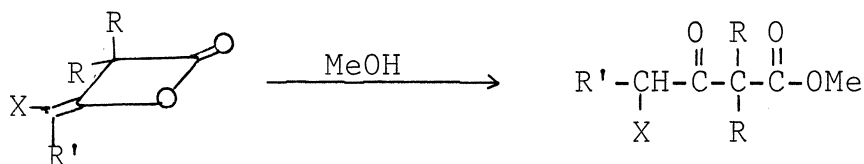
XXIV

XXVI, R = Me, R' = t-Bu
XXVII, R = Me, R' = i-Pr
XXVIII, R = Et, R' = Et

R-CH-C-C-C-OMe (structure XXV → product)
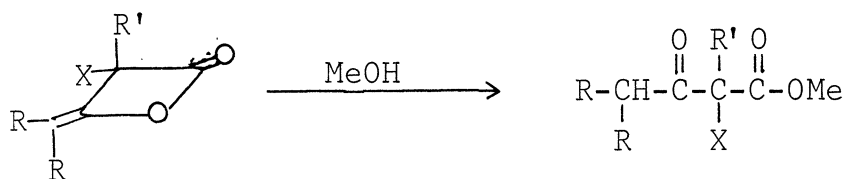
XXV

halogenated ketenes with pentamethylene-, n-propylmethyl- or
isopropylmethylketenes did not form any β-lactones. In some
of the other cases the β-lactones were produced but in yields
of less than 10%.

The codimerizations of certain unsymmetrical dialkyl-
ketenes with haloketenes yielded isomeric diones in equal
amounts (Table II and IV). Apparently the small difference
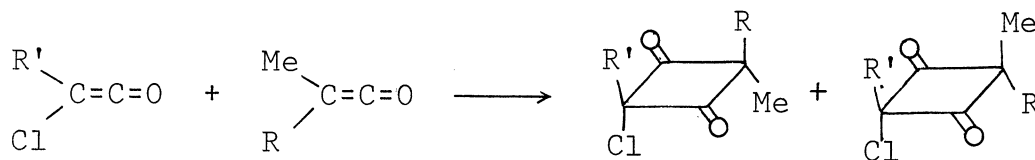
XI.   R' = Me, R = n-Pr
XII. R' = Me, R = i-Pr
XIII. R' = t-Bu, R = n-Pr

TABLE IV
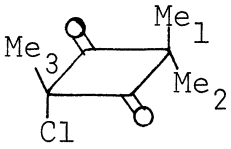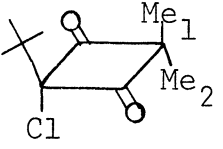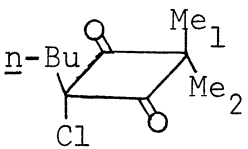
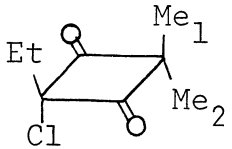METHYL CHEMICAL SHIFTS (δ) OF CYCLOBUTANEDIONES
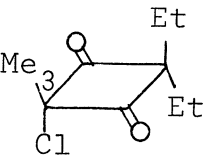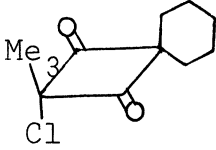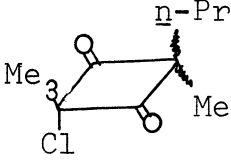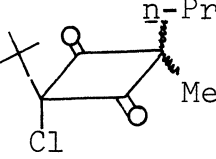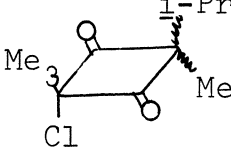
Compound	Me$_1$ (trans to Cl)	Me$_2$ (cis to Cl)	Me$_3$ (gem. to Cl)
	1.36	1.52	1.70
	1.28	1.60	
	1.34	1.52	
	1.34	1.54	
			1.72

TABLE IV (Continued)

Compound	Me$_1$ (trans to Cl)	Me$_2$ (cis to Cl)	Me$_3$ (gem. to Cl)
			1.72
	1.36	1.52	1.64,1.72
	1.28	1.56	
	1.32	1.48	1.60,1.68

in size of the substituents on either one of the ketenes is responsible for this equal distribution, i.e., a large difference in size of the two substituents on both ketenes is necessary for a preferred isomer by the $_\pi2_s+_\pi2_a$ process.

The attempted mixed dimerizations of isopropylmethylketene with isopropylchloro- or t-butylchloroketenes were unsuccessful as no evidence of dione or β-lactone was detected. It was anticipated that the stereochemistry of the cycloadducts would reveal some insight into the mechanism of formation of the mixed dimers. Apparently, the larger substituents retarded the dimerization and the polymerization predominated.

There are two reasonable mechanistic retionales for the formation of the mixed dimers from the respective acid halides. One is a concerted $_\pi2_s+_\pi2_a$ cycloaddition as previously described. Secondly, the mixed dimers could be formed from an intermediate, β-ketoacid halide. 4,4-Dichloro-2,2-dimethyl-3-ketobutanoyl
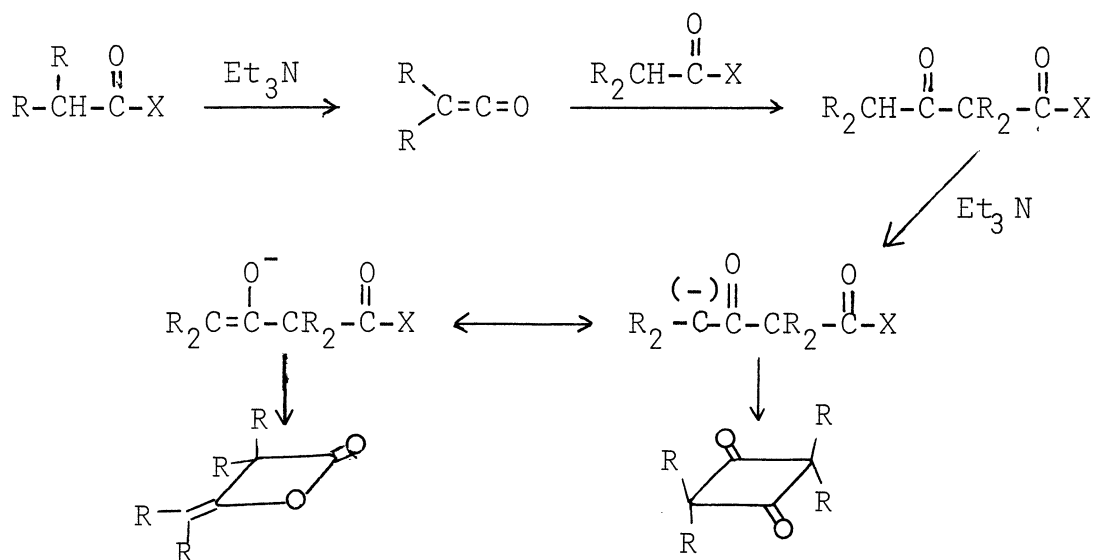
chloride and 4-chloro-2,2-dimethyl-3-ketopentanoyl chloride
were synthesized by the addition of dimethylketene to 2-
chloropropanoyl chloride and dichloroacetyl chloride, respec-
tively. These β-ketoacid chlorides were treated separately
with triethylamine in benzene under the same conditions as
the mixed dimerizations. The β-lactones were produced in
both cases with no evidence of the dione dimer. The two
β-lactones were characterized by infrared, n.m.r. (see Table
III), mass spectroscopy and elemental analysis. Apparently,
triethylamine abstracts the α-hydrogen to form an enolate
anion, which can then undergo an intramolecular nucleophilic
displacement to form the β-lactone.
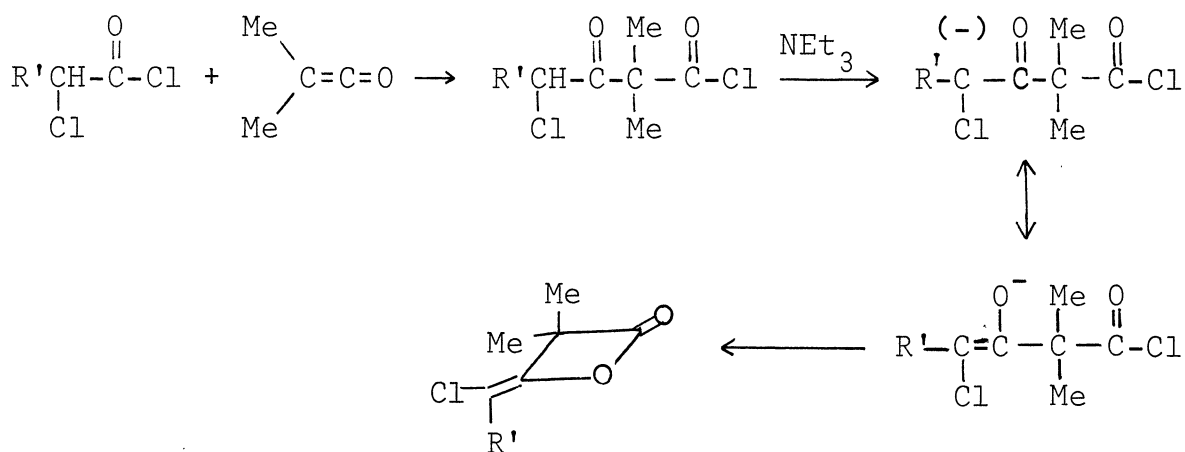
XXIX. R' = Me
XXX. R' = Cl

Several attempts to synthesize the β-ketoacid halide from
dimethylketene and 2-chloro-3,3-dimethylbutanoyl chloride were
unsuccessful. Also, attempts to isolate the β-ketoacid chloride
from the reaction mixture of equal molar amounts of

2-chloropropanoyl chloride, isobutanoyl chloride and tri-
ethylamine in benzene resulted in producing only the α-chloro-
vinyl ester and the mixed dimer. No evidence of the β-ketoacid
chloride could be found. Furthermore, the addition of 2-
chloropropanoyl chloride to a solution of n-propylmethylketene
and triethylamine in benzene resulted in only the formation
of the α-chlorovinyl ester and the mixed dimer. No evidence
of any β-ketoacid chloride could be found.

Consequently, this study suggests that β-ketoacid halides
are probably produced in certain systems and β-lactones result
from these intermediates. However, since the formation of
β-keto acid halides is not a general ketene reaction, the
possibility of a [2+2] cycloaddition reaction to yield the β-
lactone dimer can not be excluded. The diones are more likely
the result of $_\pi 2_s +_\pi 2_a$ cycloadditions.

The dimerization of t-butylketene with methylchloro- or
ethylchloroketene resulted in the formation of a β-lactone
mixed dimer (XVI and XVII, respectively) which is the result
of cycloaddition across the carbon-carbon double bond of the
halogenated ketene. The formation of these β-lactones from
the corresponding β-ketoacid halide is very unlikely because
it would require haloketene adding to 3,3-dimethylbutanoyl
chloride.[8] This is quite unlikely for steric reasons but
more importantly because acid halides require activation to
add to ketenes. Conversely, this aldoketene with t-butylbromo-
or t-butylchloroketenes formed the β-lactone (XVIII and XIX,

respectively) whereby the addition occurred across the carbon-carbon double bond of t-butylketene. An examination of the orthogonal [2+2] process with molecular models reveals a prohibitive steric interaction between the large t-butyl groups in going from the orthogonal state to the β-lactone. However, the formation of the necessary β-ketoacid halides seems quite likely. Consequently, the most likely route to the β-lactone mixed dimer is through the β-ketoacid halide intermediate.

Since it is known that 1,3-cyclobutanedione dimers of ketenes can isomerize to the β-lactone dimers, and vice versa, it seemed necessary to demonstrate whether isomerization of any kind was occurring in the reaction mixtures.[9] It was found that a mixture of the 1,3-cyclobutanedione and the β-lactone mixed dimers of dimethylketene and isopropylchloroketene, when refluxed in hexane containing triethylamine and triethylammonium chloride for 24 hr, underwent no change. The β-lactone dimers of t-butylketene with t-butylchloro- or methylchloroketenes in heptane or hexane containing a catalytic amount of sodium methoxide, upon refluxing for 24 hr, underwent no change. Consequently, it is concluded that no isomerization occurred under the reaction conditions and the ratio of cyclobutanedione to β-lactone does in fact represent the actual cycloaddition results.

During the course of this investigation pentamethylene-ketene was prepared and subjected to mixed dimerizations with halogenated ketenes. Good yields of spiro[5.3]diones were

obtained. Cycloaddition reactions of this ketene have not

received much attention in the literature. Wasserman and co-

workers have recently described the cycloaddition of penta-

methyleneketene and ethoxyacetylene to yield a thermally

unstable cycloadduct.[10] The cycloaddition of this ketene with

sulfur dioxide has also been recently reported.[11] Consequently,

in an effort to develop a general synthesis of a wide variety

of spiro[5.3]nonanes, the cycloadditions of this ketene with

various unsaturated compounds were studied.

Pentamethyleneketene (XXXI) is quite susceptible to

dimerization; e.g., the reaction of cyclohexanecarboxyl

chloride with triethylamine produces a good yield of the dimer,

dispiro[5.1.5.1]tetradecane-7,14-dione. Therefore, it seemed

desirable to effect in situ cycloadditions with reactive

unsaturated compounds.

The dehydrochlorination of cyclohexanecarboxyl chloride

with triethylamine in the presence of cyclopentadiene resulted

in a 65% yield of the spiro[5.3]nonane (XXXII) accompanied by

some ketene dimer. The optimum conditions appear to be the

dropwise addition of the acid halide to a refluxing solution

of triethylamine and cyclopentadiene in benzene and continued

refluxing for 20 hr. A reaction time of this length is neces-

sary because the ketene is slowly formed from the acid halide

and amine under these conditions. Complete separation of

this cycloadduct from the dimer was not achieved. Conse-

quently, hydrogenation to the corresponding saturated

ketone (XXXIII), resulted in a compound which could be purified.

XXXI   XXXII   XXXIII
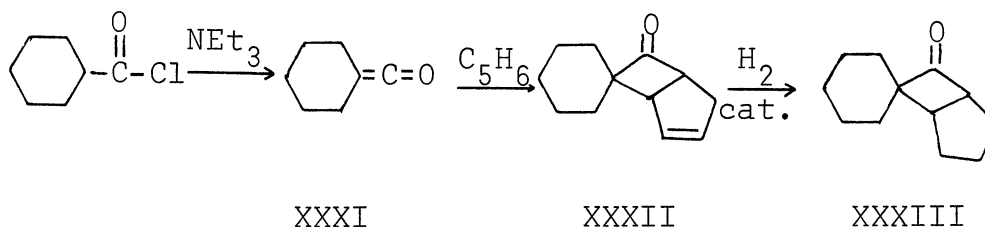
The cycloaddition of pentamethyleneketene and dihydro-pyran occurred readily and the cycloadduct was isolated in 67% yield (XXXIV). This adduct was also difficult to separate from the ketene dimer and was reduced with sodium borohydride to the corresponding alcohol, (XXXV), which was easily separated from the ketene dimer and thus completely characterized. Although two regioisomers of this cycloadduct are possible, only one was detected. The presence of the bridgehead protons in the nmr at δ 4.1 and 3.8 dictates that the isomer indicated is the one produced.[12] This is quite consistent with numerous other ketene cycloadditions where some charge separation in the transition state is indicated.

XXXI +   XXXIV   XXXV
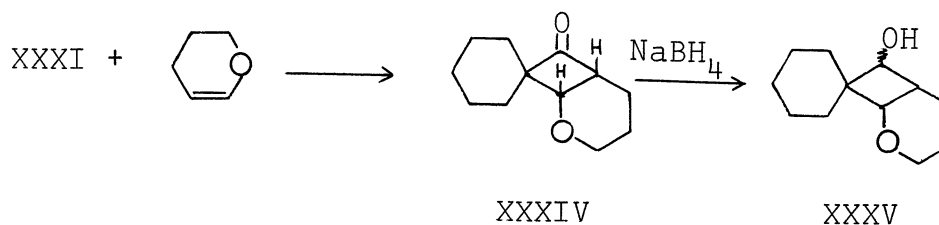
Tetramethylallene was cycloadded to pentamethyleneketene to yield an α,β-unsaturated spiro[5.3]nonane (XXXVI) in 60% yield which was easily purified by recrystallization. Only one regioisomer was detected and this was the expected α,β-unsaturated adduct, which is the only regioisomer that has been detected in these cycloadditions.[6,13]
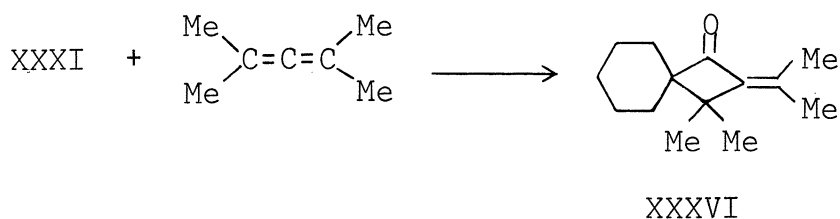
XXXVI

The *in situ* cycloaddition of pentamethyleneketene with diisopropylcarbodiimide and N-t-butylbenzylimine was also effected. These reactive imino compounds yielded the expected spiroimino-β-lactam in 51% yield (XXXVII) and the spiro-β-lactam in 48% yield (XXXVIII).

XXXVII

XXXVIII
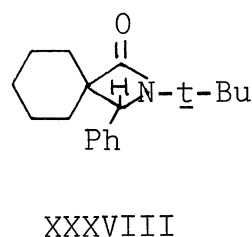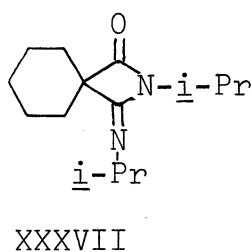
The dehydrochlorination of cyclohexanecarboxyl chloride in the presence of chloral did not produce the expected spiro-2-oxetanone. Triethylamine readily reacts with chloral, which complicates this *in situ* cycloaddition, and numerous attempts

with simultaneous and various orders of additions were
unsuccessful. However, the zinc dehalogenation of α-bromo-
cyclohexanecarboxyl chloride in the presence of chloral
produced a 45% yield of the spiro-2-oxetanone (XXXIX). This
method of generating pentamethyleneketene offers the advan-
tage of not having a reactant which reacts with chloral, and
also the by-product in this reaction, zinc halide etherate,
activates the carbonyl compound for cycloaddition. The ketene
dimer is also produced by this method.

XXXIX
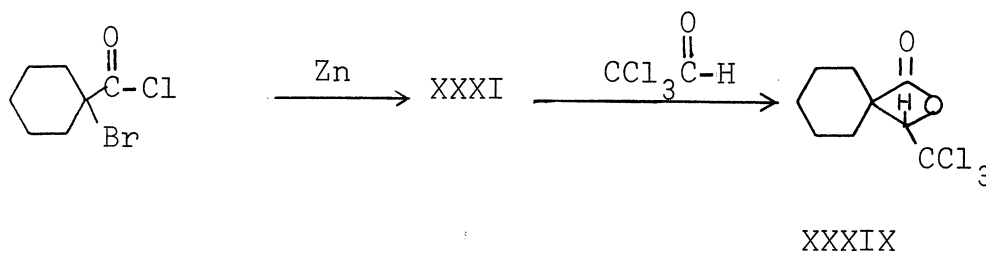
The attempted cycloaddition of cyclohexene with penta-
methyleneketene by both the dehydrochlorination and dehalo-
genation methods were unsuccessful. It should be emphasized
that all the successful cycloadditions described above involve
activated unsaturated compounds. Essentially all the penta-
methyleneketene cycloadditions described are accompanied by
some dimer of the ketenes. Consequently, if unactivated
olefins such as cyclohexene are employed, dimerization occurs
completely at the expense of cycloaddition with other olefins.
Other unsaturated compounds which were investigated with
little or no success included phenylacetylene,

5-methylene-2-norbornene, ethyl thioisocyanate, quinone,
p-cylorobenzaldehyde and N-phenyl benzalaliline.[14]

In summary, alkylhaloketenes and ketoketenes undergo a
codimerization to yield primarily the unsymmetrical halo-1,3-
cyclobutanediones. These mixed dimers have been prepared by
several different methods. In certain systems, a β-lactone
mixed dimer is formed, which probably results from a β-keto-
acid chloride intermediate. The mixed dimerizations of
t-butylketene appear to be quite sensitive to steric effects
but the [2+2] process seems more sensitive than the β-keto
acid halide pathway. Pentamethyleneketene readily cycloadds
to reactive unsaturated compounds to yield spiro[5.3]nonanes.

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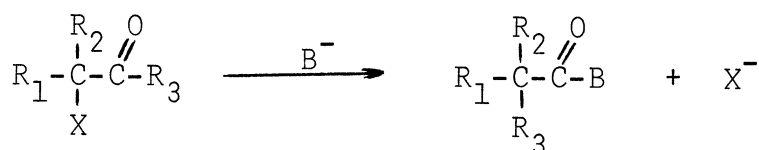   Brady, W. T. and Ting, P. L., Tetrahedron Lett., 2619,
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PART II

REARRANGEMENTS OF 8-CHLORO-8-METHYL

BICYCLO[4.2.0]OCT-2-EN-7-ONES

CHAPTER I

INTRODUCTION

In the presence of nucleophiles such as hydroxides,
alkoxides or amines, α-haloketones undergo skeletal
rearrangement to carboxylic acid salts, esters or amides,
respectively.

$$R_1-\overset{\overset{\displaystyle R_2}{|}}{\underset{\underset{\displaystyle X}{|}}{C}}-\overset{\overset{\displaystyle O}{\parallel}}{C}-R_3 \quad \xrightarrow{\quad B^-\quad} \quad R_1-\overset{\overset{\displaystyle R_2}{|}}{\underset{\underset{\displaystyle R_3}{|}}{C}}-\overset{\overset{\displaystyle O}{\parallel}}{C}-B \quad + \quad X^-$$

This reaction was discovered by Favorskii in 1894 and is
general for α-halocycloalkanones containing six to ten carbon
atoms in the ring.[1] The fact that α-halocyclopentanones fail
to undergo this reaction is perhaps responsible for the lack
of study of small ring systems; α-halocyclobutanones. How-
ever, α-bromocyclobutanone was recently reported to rearrange
with high yield and stereospecificity.[2]

X = Cl, Br

I   II   III

67
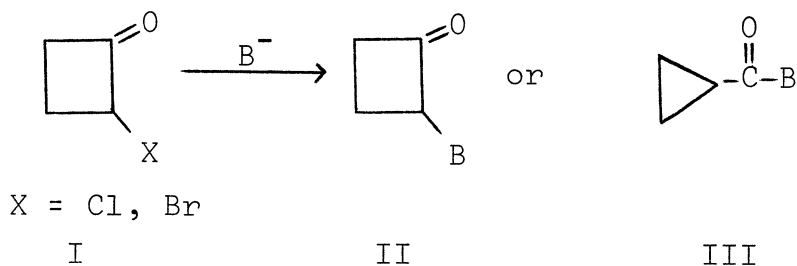
Thus, the reaction of a base with α-halocyclobutanone (I) can lead to substitution product (II) and/or rearranged acid derivatives (III). The choice of base and solvent can profoundly affect the yield of rearranged products. Correlations have been established between the nature of the base and the product of the reaction.[3]

The facility and specificity of this rearrangement provide a synthesis for three-membered rings from four-membered ring systems which is just as useful as the interconversion of related cyclobutyl, cyclopropylcarbinyl and allylcarbinyl derivatives via carbonium ion reactions.[4,5]

The cycloaddition of halogenated ketenes to olefinic compounds provides an excellent source of α-halocyclobutanone derivatives. Recent reports on the treatment of such α-halo-cyclobutanone derivatives with different bases under various conditions,[6] describe products of ring expansion, ring contraction and substitution.

Fletcher and Hassner have reported that the dichloro-ketene adducts of cholestene (IV) and cyclohexene (V) undergo a quantitative ring contraction to bifunctional cyclopropanes (VI) and (VII), respectively under the influence of sodium methoxide in methanol.[7]

IV   VI (exo:endo, 1:2)

V → VII (exo:endo,20:1)
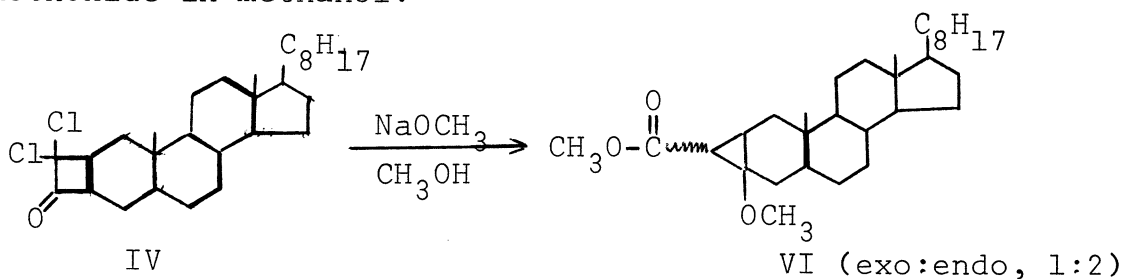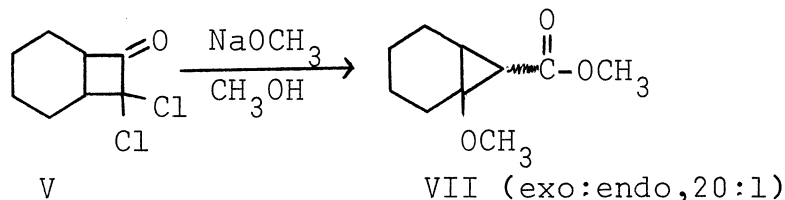
A proposed mechanism involves enolization, followed by methoxy substitution on C-6 and subsequent loss of the second chlorine atom and rearrangement to the bicyclo[4.1.0]heptane derivatives. When the cycloadduct of methylchloroketene and cyclohexene (VIII) was treated with sodium methoxide in methanol, a substitution product (IX) was obtained.[8] This compound corresponds to Hassner's intermediate, except that in this case a second leaving group is not available for further rearrangement. Similarly, when the adduct of methylbromoketene

VIII   IX
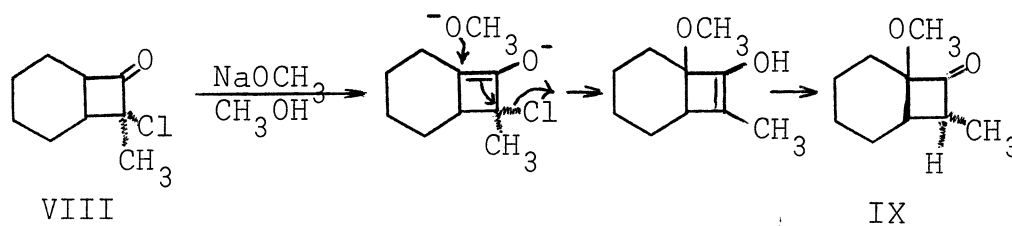
and cis-2-butene (X) was treated with sodium methoxide in methanol, the substitution product (XI) was obtained.

X   XI
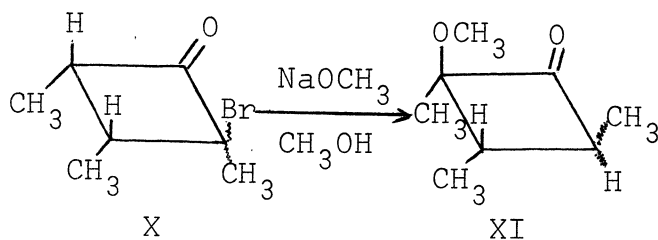
However, when the methylchloro- and methylbromoketene
adducts of cyclopentadiene (XII) were treated with sodium
methoxide in methanol, rearrangement occurred rather than
substitution. The tendency for cyclopentadiene adducts to
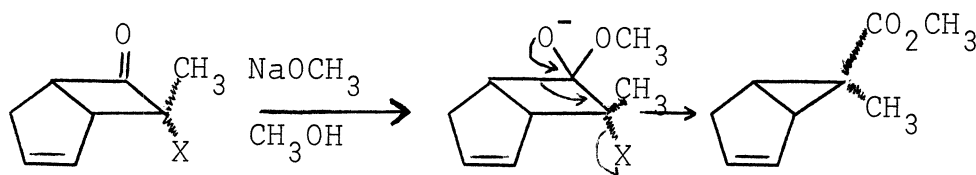
X = Br, Cl

XII

undergo rearrangement, to the exclusion of substitution on
C-5, can be explained by considering the stability of the
enol formed by the loss of the bridgehead hydrogen adjacent
to the carbonyl. This enol must be formed to account for sub-
stitution at this carbon. It is obvious that this enol would
be more stable in the cis-2-butene and cyclohexene adducts
than in the adducts of cyclopentadiene, due to the increased
amount of strain in the latter system. Therefore, the treat-
ment of the halogenated ketene-olefin cycloadducts with sodium
methoxide results in substitution, except when enolization is
retarded, and then a Favorskii type rearrangement occurs.

The endo-alkyl isomers of 7-alkyl-7-halobicyclo[3.2.0]-
hept-2-en-6-ones (XIIIa) rearrange in base to 2-alkylcyclo-
hept-2,4,6-trienones (2-alkyltropones) (XIV) accompanied by
some stereospecific rearrangement products and exo-alkyl
isomers (XIIIb) undergo a stereospecific ring contraction.
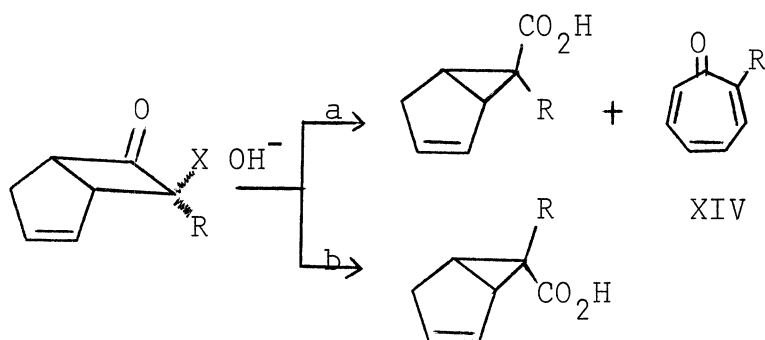
a = endo-alkyl
b = exo-alkyl

Garin and Cammack have reported that the stereospecific substitution and rearrangement of 7-chloro-7-methylbicyclo-[3.2.0]hept-2-en-6-ones are dependent upon the base strength and stereochemistry at C-7 of the starting material. Brook and Harrison have reported that conformational effects in the cyclobutanone ring of 7-exo-chloro-7-endo-isopropylbicyclo-[3.2.0]hept-2-en-6-one causes abnormal rearrangement to yield hydroxycyclohexenecarboxylic acids (XV).[6]

XV
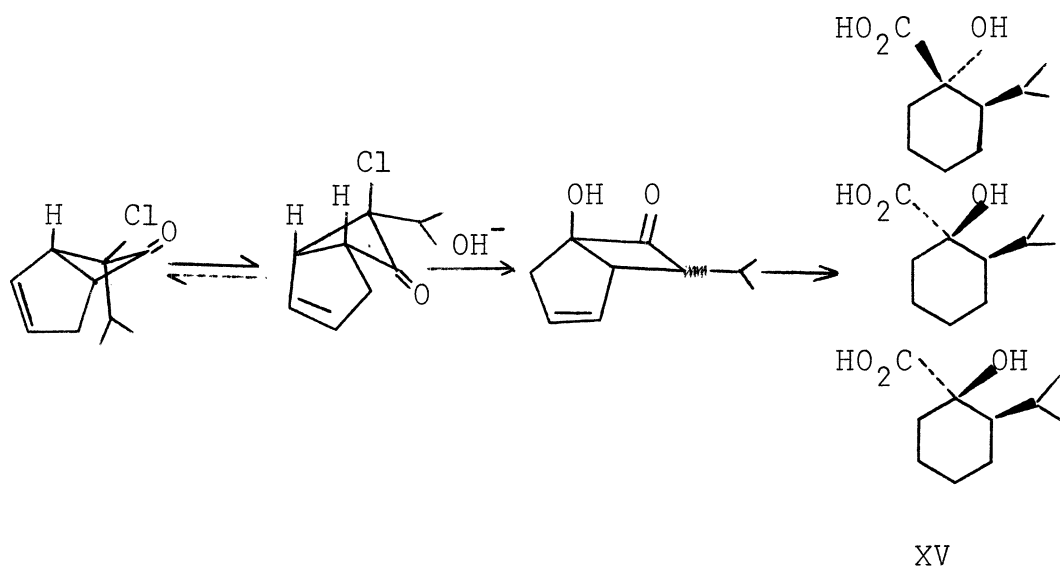
Hence, the objective of this research problem was to examine the details of rearrangements of 8-chloro-8-methyl-bicyclo[4.2.0]oct-2-en-7-ones.[9] The _endo_-methyl and _exo_-methyl systems were synthesized, separated and examined separately by bases of various strengths. This system was selected because it is not as stereochemically rigid as the bicyclo[3.2.0]heptenone system; e.g., enolization is not as restricted due to the strain of the five-membered ring.

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CHAPTER II

EXPERIMENTAL

Proton nuclear magnetic resonance (n.m.r.) spectra were recorded on a Jeolco PS-100 spectrometer employing tetra-methylsilane as an internal standard and carbon tetrachloride as the solvent. Gas chromatography was performed on an F. & W. Scientific model 700 instrument with a 10 ft. x 1/4 in. column packed with 10% SE-30 on acid washed Chromosorb W (60/80).

The infrared spectra were obtained using a Perkin-Elmer Model 237 Grating Infrared Spectrometer. The cell used for sample handling was 0.1 mm fixed thickness sodium chloride cell.

Mass spectra of samples were obtained on a Hitachi Perkin-Elmer RMU-6E Mass Spectrometer.

Elemental analyses were performed by Midwest Microlab. Ltd., 6000 East 46th Street, Indianapolis, Indiana 46226.

Preparation of Reagents

Hexane and acetonitrile were commercially available. Hexane was dried over metallic sodium and distilled prior to use. Acetonitrile was dried over Linde 4 $\overset{\circ}{A}$ molecular sieves.

Triethylamine was commercially available, and was dried over sodium metal and distilled prior to use.

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1,3-Cyclohexadiene was commercially available but was also prepared by the following method.

t-Butyl Hypochlorite

To a 500 ml cold commercial household bleach solution (containing 5-6% NaOCl) was added 0.39 mol t-butyl alcohol and 0.43 mol glacial acetic acid. The flask was kept below 10°C and dark. Stirring was continued for about three min.

The entire solution was poured into a 1-1. separatory funnel. The lower aqueous layer was discarded, and the oily yellow organic layer was washed first with a 50 ml portion of 10% aqueous sodium carbonate and then with 50 ml of water. The product was dried over calcium chloride and filtered.[1]

3-Chlorocyclohexene

To a refluxing solution of 500 grams of cyclohexene containing 2 grams benzoyl peroxide was added dropwise 82 grams of t-butyl hypochlorite. The solution was refluxed for half an hour, cyclohexene removed by distillation through an 80 mm column and the product collected at 76-78°C in 77% yield.

1,3-Cyclohexadiene

In a 1-1. three-neck flask, equipped with an addition funnel, a mechanical stirrer and a 12 mm column, 117 grams of 3-chlorocyclohexene with 360 grams of N,N-dimethylaniline were heated in an oil bath at 180°C. The distillate was dried over calcium chloride and redistilled at 79-81°C.[2]

2-Chloropropanoyl chloride was prepared from 2-chloro-propanoic acid with thionyl chloride. The solution was refluxed for four hours and distilled at 110-112°C (lit. 110-112°C).

Preparation of Methylchloroketene-1,3-Cyclohexadiene Cycloadducts

8-Chloro-8-methylbicyclo[4.2.0]oct-2-en-7-one (I) and (II)

To a refluxing solution of 1,3-cyclohexadiene(0.4 mol) and triethylamine(0.3 mol) in hexane or acetonitrile (200 ml) was added 2-chloropropanoyl chloride(0.25 mol) in hexane or acetonitrile (25 ml). After the addition was completed, reflux was maintained for four hours. The amine salt was removed by filtration and washed with the solvent. The filtrate was concentrated on a rotatory evaporator and the residue vacuum distilled to yield the adduct. A distribution of 4.9 endo:exo-methyl isomers was produced in hexane (50% yield) and 0.13 in acetonitrile (45% yield). The isomers were separated by fractional distillation at reduced pressure employing a 12 in. Vigreux column. This distillation provided material of isomeric purity 90-95%; endo-methyl isomer b.p. 45°C at 0.05 mmHg and exo-methyl isomer b.p. 48-50°C at 0.05 mm.[3]

Rearrangements of Methylchloroketene-1,3-
Cyclohexadiene Cycloadducts

6-Methoxy-8-methylbicyclo[4.2.0]oct-2-en-7-one (III)

A mixture of methanol (150 ml) and sodium (4 grams) was
vigorously refluxed while a solution of the exo-chloroketone
(I) (5 grams) in methanol (10 ml) was added. There was an im-
mediate precipitation of sodium chloride. Refluxing was
continued for 1 hr and then the mixture was added to water
(100 ml) and extracted with chloroform. The combined extracts
were dried, the solvent was removed on a rotatory evaporator,
and the residue was distilled in vacuum to yield the isomeric
ketones (III) (both ketones epimeric at C-8), b.p. 41-42°C at
0.05 mm (80% yield), m.p. 57-59°C (both isomers, recrystal-
lized from ethanol. ν_{max} 1780 cm^{-1} (C=O); δ 1.1 (endo-methyl)
and 1.2 (exo-methyl) (3H, d), 2.0 (5H, m), 2.6 (1H, quintet),
3.3 (3H, s) and 5.9 (2H, m) (the isomer distribution was
determined on the crude product and found to be ca. 10:1 in
favor of the exo-methyl isomer). Treatment of (II) (5 grams)
under the same conditions yielded an identical mixture of
methoxy-substituted products.

Analysis: Calculated for $C_{10}H_{14}O_2$: C, 72.3; H, 8.45;
Found: C, 71.75; H, 8.4.

7-Methylbicyclo[4.1.0]hept-2-en-7-carboxylic Acid (IV)

The exo-chloro-ketone (I) (5 grams) was refluxed with
aqueous 10% sodium hydroxide solution (150 ml) for 4-6 hr.

The mixture was cooled, acidified, and extracted with chloroform, and the combined extracts were dried, and concentrated on a rotatory evaporator. Distillation in vacuum afforded the <u>endo</u>-methyl acid (65% yield), b.p. 96-97°C at 0.05 mm; m.p. 81-83°C. The <u>exo</u>-methyl isomer (II) produced the <u>exo</u>-methyl acid (21% yield) b.p. 86-90°C at 0.01 mm; m.p. 86-88°C. No other volatile products could be obtained from the reaction mixture. ν_{max} 1690 cm^{-1} (C=O); δ 1.18 (<u>endo</u>-methyl) and 1.38 (<u>exo</u>-methyl) (3H, s), 2.0 (6H, m), 5.85 (2H, m) and 10-11 (OH, s).

Analysis: Calculated for $C_9H_{12}O_2$: C, 71.05; H, 7.9; Found: C, 70.7; H, 8.0.

6-Hydroxy-8-methylbicyclo[4.2.0]oct-2-en-7-one (V)

The <u>exo</u>-chloro-ketone (I) (5 grams) in aqueous 20% sodium carbonate solution was refluxed for 10 hr. Upon cooling, the mixture was extracted with chloroform, and the combined extracts were dried, and concentrated on a rotatory evaporator. Vacuum distillation afforded the isomeric hydroxy-ketones (V) (60% yield), b.p. 77-79°C at 0.5 mm (both isomers); m.p. 67-70°C. ν_{max} 1765 cm^{-1} (C=O) and 1635 cm^{-1} (C=C); δ 1.02 (<u>endo</u>-methyl) and 1.09 (<u>exo</u>-methyl) (3H, d), 1.8 (5H, m), 3.3 and 2.7 (1H, quintet), 4-5 (OH, s) and 5.9 (2H, m).

Analysis: Calculated for $C_9H_{12}O_2$: C, 71.05; H, 7.9; Found: C, 70.95; H, 7.8.

The exo-methyl isomer (II) produced the same mixture of isomers (65% yield). The ratio of isomers in both cases was ca. 8:1 in favor of the exo-methyl isomer. Also, with both (I) and (II), a small amount (< 5%) of the stereo-specific ring contracted product (IV) was produced.

Methyl 7-methylbicyclo[4.1.0]hept-2-en-7-exo-carboxylate (VI)

Upon the addition of the exo-chloro-ketone (I) (10 grams) to a refluxing solution of silver nitrate (15 grams) in methanol (150 ml), a white precipitate was formed immediately and the reaction was continuously refluxed for 24 hr. The salt was removed by filtration and the filtrate concentrated on a rotatory evaporator. The residue was diluted with water and extracted with chloroform, and the combined extracts were concentrated and distilled affording the bicyclic ester (VI) (60% yield), b.p. 52-54°C at 0.05 mm; v_{max} 1720 cm^{-1} (C=O); δ 1.10 (3H, s), 1.80 (6H, m), 3.55 (3H, s), and 5.62 (2H, m).

Analysis: Calculated for $C_{16}H_{14}O_2$: C, 72.3; H, 8.45; Found: C, 72.45; H, 8.45.

Methyl 7-methylbicyclo[4.1.0]hept-2-en-7-endo-carboxylate (VI)

The endo-chloro-ketone (II) was treated with silver nitrate in methanol as described above for 8 days to give the ester (26% yield), b.p. 39-40°C at 0.1 mm. v_{max} 1720

cm^{-1} (C=O); δ 1.30 (3H, s), 1.85 (6H, m), 3.50 (3H, s), and 5.50 (2H, m).

Analysis: Calculated for $C_{16}H_{14}O_2$: C, 72.28; H, 8.43; Found: C, 71.95; H, 8.7.

Thermal Rearrangement of Methylchloroketene-1,3-Cyclohexadiene Cycloadducts

The chloro-ketone (I)/(II) (5 grams) was heated neat for 2.5 days on an oil bath (165-170°). Vacuum distillation afforded propiophenone (2 grams, 60% yield), b.p. 52-56°C at 0.05 mm.[4] Comparison with an authentic sample revealed identical retention times on g.l.c. and identical n.m.r. spectra.

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CHAPTER III

RESULTS AND DISCUSSION

Due to the labile nature of halogenated ketenes, the cycloadditions were run *in situ* by dehydrochlorination of 2-chloropropanoyl chloride with triethylamine in the presence of 1,3-cyclohexadiene to provide the α-chlorocyclobutanones for this study.[1] The cycloaddition in hexane afforded a 50% yield and an isomer distribution of 4.9, endo:exo-methyl, (I):(II). The cycloaddition in acetonitrile produced a 45% yield with an isomer distribution of 0.13, endo:exo-methyl. The isomer distributions were determined by n.m.r. The methyl resonance appeared as a singlet and the chemical shift of the endo-methyl (δ 1.18) was considerably more upfield than the exo-methyl (δ 1.38) resonance.[1] The isomers were separated and purified to the extent of 90-95% by fractional distillation. The dependence of the isomer distribution on the polarity of the solvent is apparently due to increased solvation of the halogen substituent in the more polar solvent thus increasing the size of that substituent and producing more endo-halo-isomer. This is consistent with the sterically favored ortho-gonal approach of unsymmetrical ketenes and cyclopentadiene. The magnitude of the change of isomer distribution in this system is consistent with that in the bicyclo[3.2.0]heptenone system.[2]
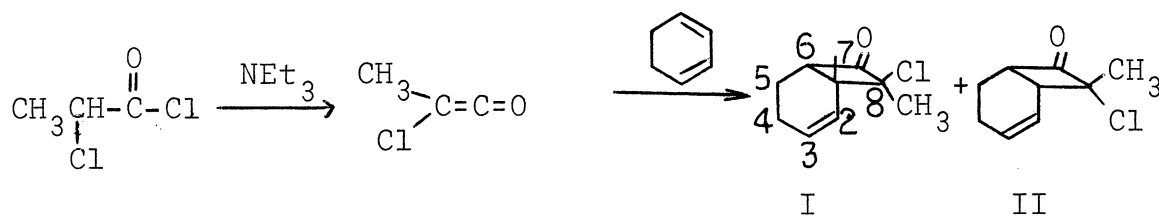
Treatment of (I) with sodium methoxide in methanol at reflux yielded an immediate precipitate of sodium chloride and an 80% yield of the 6-methoxy-substitution products epimeric at C-8, (III). The exo-methyl isomer (II) underwent the same substitution reaction yielding, as expected, an identical isomer distribution of (III) (ca. 10:1 in favor of the thermodynamically more stable exo-methyl isomer). This substitution must occur through the 6-enol form of the cyclobutanone.


III
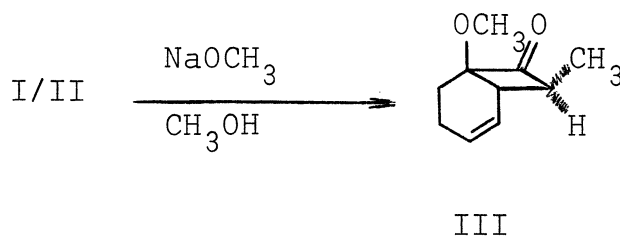
Reaction of (I) with 10% aqueous sodium hydroxide at reflux produced a stereospecific ring contraction endo-methyl product (IV), in 65% yield. Treatment of (II) under identical conditions produced the exo-methyl ring-contracted acid in 21% yield. The reaction mixture from (II) was viscous and polymeric, and no further volatile products could be isolated.

The isomeric ring-contracted acids are easily distinguished by the chemical shift of the methyl group in the n.m.r. spectra.

$$I/II \xrightarrow[\text{(aq.)}]{10\% \text{ NaOH}}$$

IV
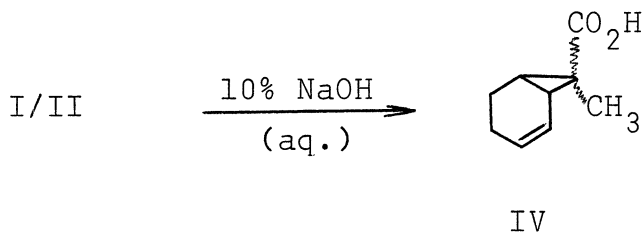
These ring contractions are quite similar to those observed when the corresponding bicycloheptenones are refluxed with aqueous base except that with the endo-alkyl-bicycloheptenone isomers a competing ring expansion occurs to yield 2-alkylcyclohepta-2,4,6-trienones (2-alkyltropone). No such ring expansion is observed in the bicyclooctenones, presumably because the attainment of an aromatic system is not as easily accessible as in the bicycloheptenone system.

Ring contraction and substitution both occurred when (I) and (II) were separately refluxed in 20% aqueous sodium carbonate. The substitution product (V) was produced in 60 and 65% yield respectively and only $\leq$ 5% of the stereospecific ring-contracted product (IV) was produced in each case. The exo-methyl isomer of (V) predominated to the extent of ca. 8:1.

$$I/II \xrightarrow[\text{(aq.)}]{20\% \text{ Na}_2\text{CO}_3} \quad + \quad IV$$

V
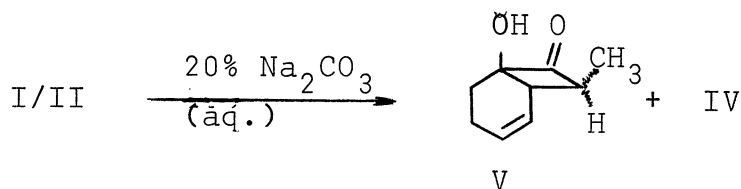
Treatment of (I) with silver nitrate in methanol at reflux afforded a 60% yield of a ring-contracted endo-methyl ester (VI). However, (II) reacted much slower under these conditions (24 hr vs. 8 days) and the exo-methyl ester was formed in only a 26% yield along with an unidentified product. This result is consistent with a recent report by Harding and Trotter.[3]

I/II $\xrightarrow[\text{CH}_3\text{OH}]{\text{AgNO}_3}$

VI
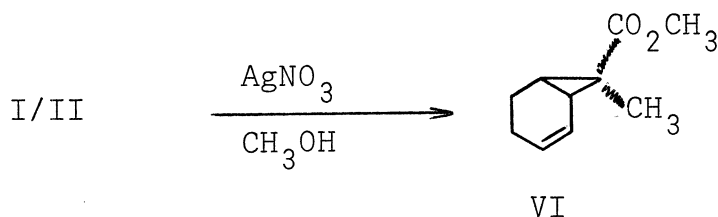
Refluxing (I) and (II) with triethylamine in hexane overnight resulted in no substitution or ring-contraction as the starting ketones were recovered.

The bicyclic ketones (I) and (II) were treated with sodium borohydride and also with aluminum isopropoxide, in an attempt to prepare the corresponding α-halocarbinols for investigation, but rearrangements occurred during the reduction; mixtures of the products were produced and the alcohols were not isolated.

The bicyclic ketones (I) and (II) underwent an interesting rearrangement upon heating neat at 165-170°C for 2-1/2 days; propiophenone was produced in 60% yield. This reaction is similar to the thermal decomposition of 2-chlorocyclobutanone as recently reported by Metcalfe and Lee.[5] If dehydrochlorination and isomerization occurred, the conjugated diene (VII)

I/II $\xrightarrow[-HCl]{\Delta}$ [structure VII] $\longrightarrow$ [structure: C_6H_5-$\overset{O}{\overset{\|}{C}}$-$CH_2CH_3$]

VII
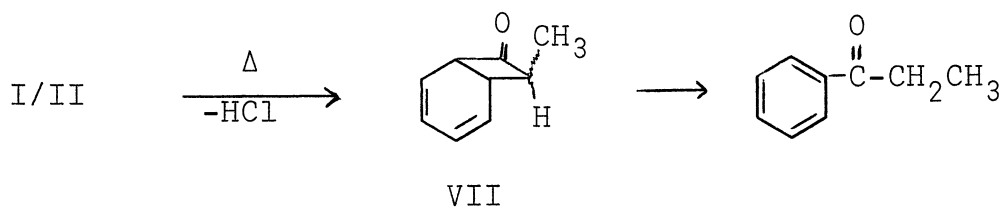
might be produced. An aliquot of the reaction mixture after a short period of heating revealed two extra doublets in the n.m.r. spectrum at δ 1.2 and δ 1.3 which could correspond to the endo- and exo-isomers of the isomerized dehydrochlorinated product. Also, these two extra doublets were observed whenever (I) was vacuum distilled and the oil bath temperature exceeded 120°C. Further isomerization and ring opening of the isomerized dehydrochlorination product would be expected to lead to the aromatic ketone. The ketone (I) and (II) upon refluxing in dilute or concentrated sulfuric acid also produced propiophenone.

In summary, formation of the substitution vs. rearrangement product is dependent upon the nature of base employed[5] and the fact that enolization occurs in the bicyclic ketone.[6] The chemistry of the 8-chloro-8-methylbicyclo[4.2.0]oct-2-en-7-one was not dependent upon the stereoisomers as observed in the 7-halo-7-alkylbicyclo[3.2.0]hept-2-en-6-one. This is apparently due to the fact that enolization occurs in the former system.

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