ALDOHALOKETENES AND THE STEREOCHEMISTRY OF

ALDOHALOKETENE CYCLOADDITIONS

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ALDOHALOKETENES AND THE STEREOCHEMISTRY OF ALDOHALOKETENE CYCLOADDITIONS

DISSERTATION

Presented to the Graduate Council of the
North Texas State University in Partial
Fulfillment of the Requirements

For the Degree of

DOCTOR OF PHILOSOPHY

By

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Denton, Texas

May, 1970

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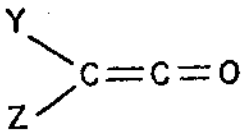
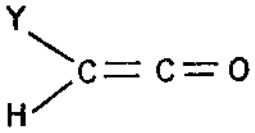
CHAPTER I

INTRODUCTION

Ketenes are a group of organic compounds which have been known for nearly sixty-five years. Excluding the first member of this family, there are two general types of ketenes, keto-ketenes which are disubstituted and aldoketenes which are mono-substituted.



a ketoketene



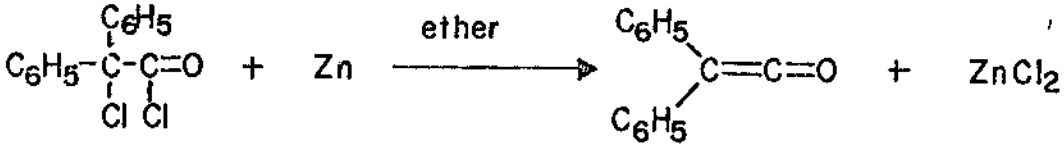
an aldoketene

All aldoketenes are obviously unsymmetrical, while ketoketenes may be symmetrical or unsymmetrical, depending on whether Y and Z are alike or different. A majority of the vast amount of work reported in the literature on ketoketenes, is concerned with symmetrical ketenes such as diphenylketene and dimethyl-ketene.

All ketenes are susceptible to dimerization and poly-merization, the difference in the stabilities of ketenes is usually a matter of the degree to which these processes occur. Ketoketenes are much more stable than aldoketenes, and many can be isolated by distillation; e.g., diphenylketene, dimethyl-ketene, butylethylketene, ditertiarybutylketene, etc. However, some ketoketenes such as the halogenated ketoketenes, are

apparently so unstable that isolation is most difficult. There are very few reports in the literature concerning the chemistry of aldoketenes, because of the instability of these compounds. Aldoketenes as a class are much more susceptible to dimerization and polymerization than ketoketenes; therefore aldoketenes are not usually isolated but rather are trapped by <u>in situ</u> reactions. In instances where aldoketenes have been isolated, very low temperatures (-78°C. to -196°C.) were employed.

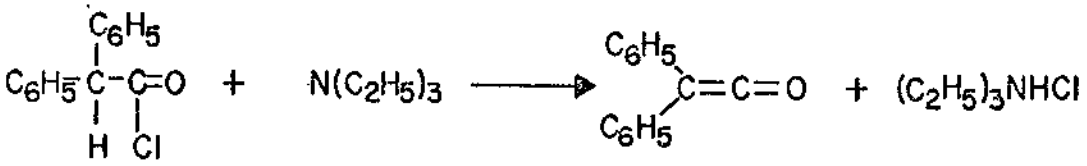
There are some general methods for the preparation of ketenes. Although some ketenes can be made by several methods, certain methods are better than others for the preparation of specific ketenes. Staudinger reported in 1905, the preparation of the first ketene, diphenylketene, by the dechlorination of chlorodiphenylacetyl chloride, employing activated zinc suspended in ether as the dehalogenating agent (33).



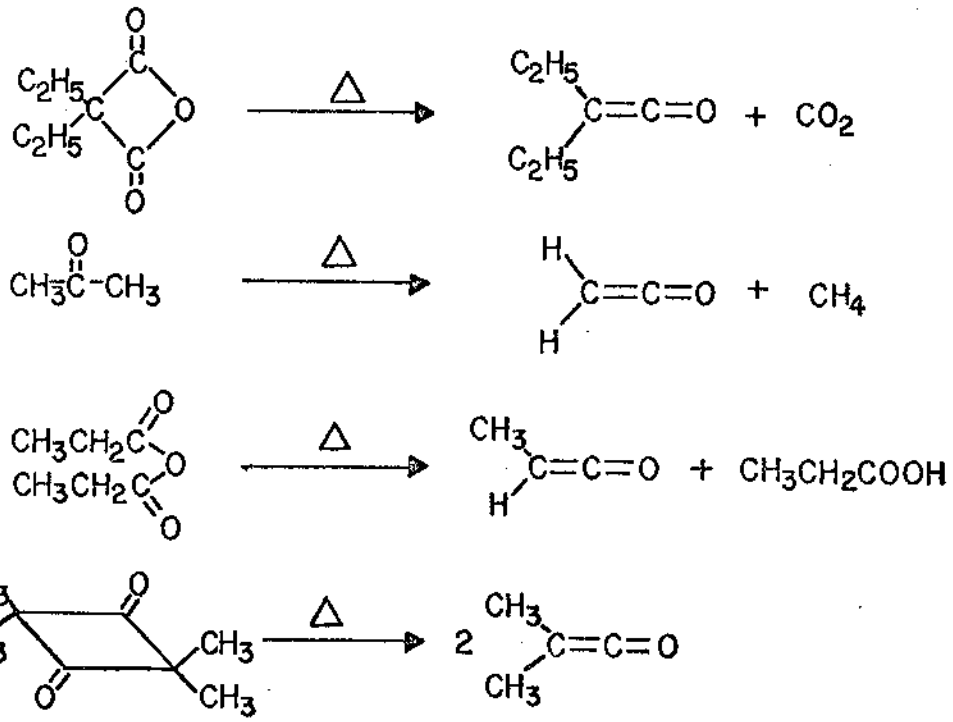
This method has been widely used since that time for the preparation of a variety of ketenes.

The most widely used method for ketene preparation is the dehydrohalogenation of an acid halide with a tertiary amine (34). This reaction is usually conducted in a hydrocarbon solvent employing triethylamine as the tertiary amine. The triethylammonium halide salt precipitates from the reaction mixture

thus providing a hydrocarbon solution of the ketene.



Pyrolysis of different types of compounds permits generation of a variety of ketenes (24, 25, 35, 38).

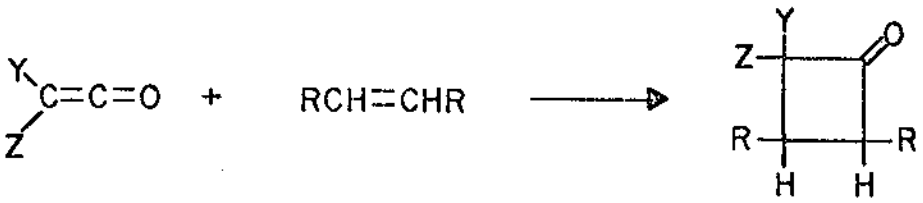


Only ketenes of relatively low molecular weight are produced by pyrolysis.

There are certainly other methods by which ketenes are generated (13, 14, 27), but the three methods indicated are

the most widely used.

Ketenes have been known, for many years, to undergo 1,2-cycloaddition reactions with olefinic compounds to produce substituted cyclobutanones (34). It is important to note that ketenes undergo this 1,2-cycloaddition even with conjugated dienes; that is, no 1,4-cycloaddition occurs, even when the cisoid conformation is dominant.

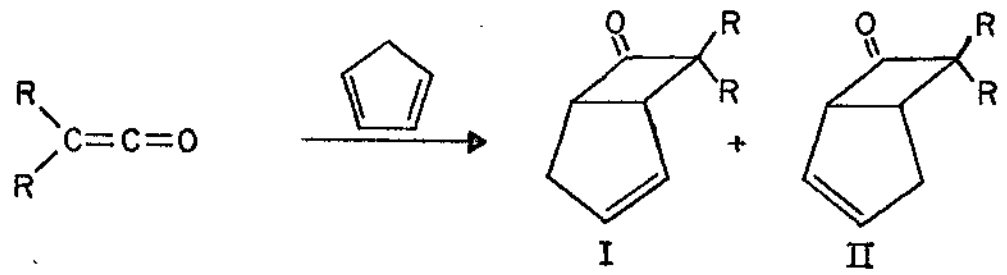


This cycloaddition reaction is characteristic of ketenes and is accepted as proof of the existence of the material in reaction systems where the ketenes cannot be isolated.

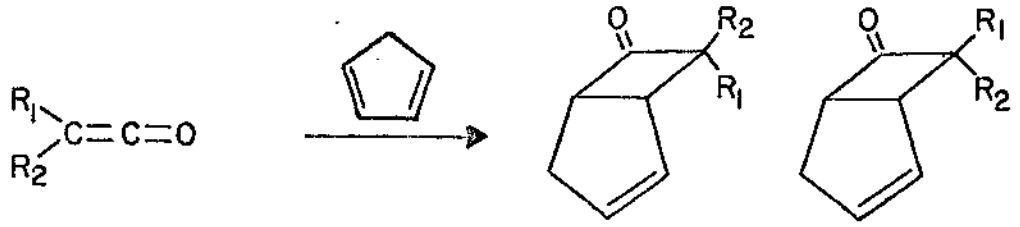
Ketenes which have only transient existence and those which react sluggishly, are most easily trapped by nucleophilic unsaturated compounds such as conjugated dienes, enamines and vinyl ethers (36). Cyclopentadiene is a particularly good cycloaddition partner because it is nucleophilic and because steric hinderance is minimized, since the ends of the olefin chain are bent back out of the way in forming the ring (36); that is, the olefin is locked in a cisoid conformation.

It would appear that the cycloaddition of cyclopentadiene with a symmetrical ketene would produce two isomers as illustrated on the following page. However, numerous reports indi-

that ketenes and cyclopentadiene form only bicyclo [3.2.0] - hept-2-ene-6-ones (2, 11, 14, 26, 32), as shown by structure I.

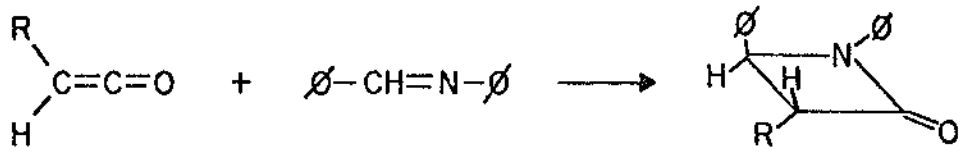


Thus, an unsymmetrical ketene may undergo 1,2-cycloaddition with cyclopentadiene to form only two isomers.

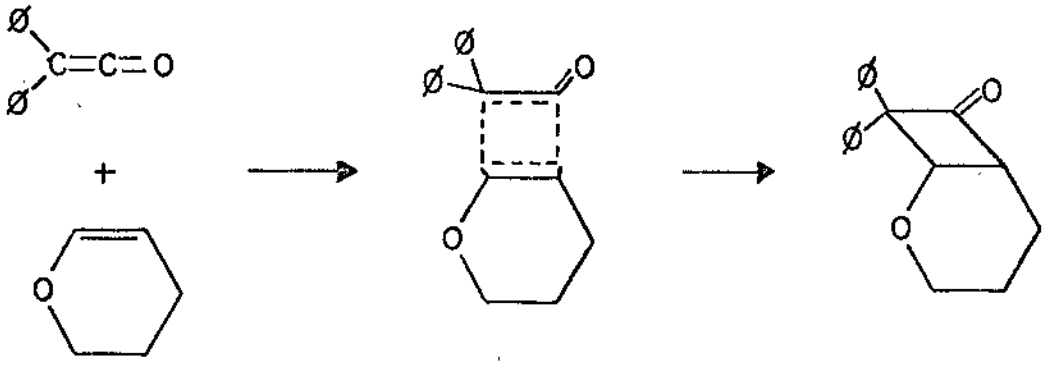


There are only a few scattered reports in the literature on this type of cycloaddition. Hasek and Martin have reported the preparation of the cycloadduct of butylethylketene with cyclopentadiene (29). Jaz and Denis have reported the preparation of cyclopentadiene adducts with methylketene, ethylketene, n-propylketene, isopropylketene and n-butylketene (22). However, no mention was made in either report about isomers of the cycloadduct. The only report in which the stereochemistry of aldoalkylketene cycloadducts is established, appeared after the study was initiated. However, the unsaturated compound in this system was not an olefin, but an imine, benzalaniline. Therefore, the cycloadduct was a β-lactam rather than a cyclobutanone. Nevertheless, the reaction was

stereospecific with only the trans isomer of the cyclo-adduct being produced.

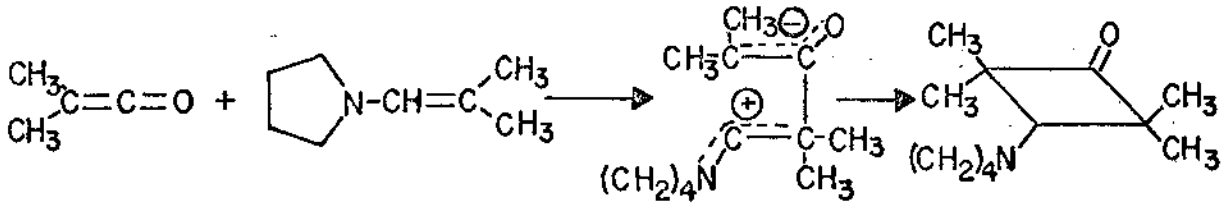


The mechanism of the 1,2-cycloaddition of ketenes and olefins has received a lot of attention in recent years. Solvent effects (8), activation parameters (8), stereochemistry (20, 28), isotopic labeling experiments (1, 23), and trapping experiments (8), indicate that the cycloaddition of a ketene to an olefin is a "near concerted" or "quasi concerted" process (8).

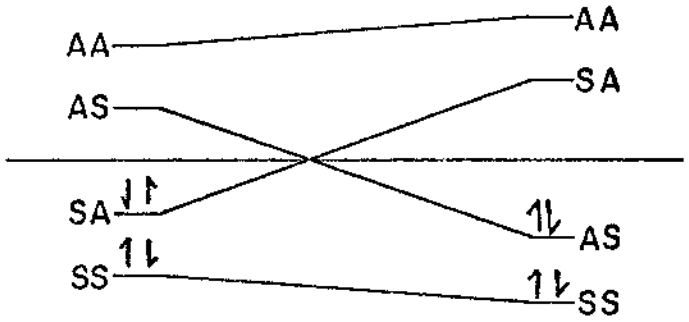


However, it has been shown very recently by Huisgen and also by Ghosez that a very nucleophilic olefin, such as an enamine, may undergo 1,2-cycloaddition with a ketene, by a two step process involving a dipolar intermediate (15, 31).

Huisgen has more recently demonstrated that dimethylketene and isobutenyldialkylamines undergo cycloaddition by a dual mechanism (concerted and dipolar) (21).



The fact that ketenes and most olefins undergo thermal concerted [2 + 2] cycloadditions has been a point of interest for some time. This reaction is forbidden, according to the original Woodward-Hoffmann selection rules (19), because the transition from the ground state of the reacting molecules to the ground state of the products, involves a crossing over of states in the correlation diagram for the cycloaddition.

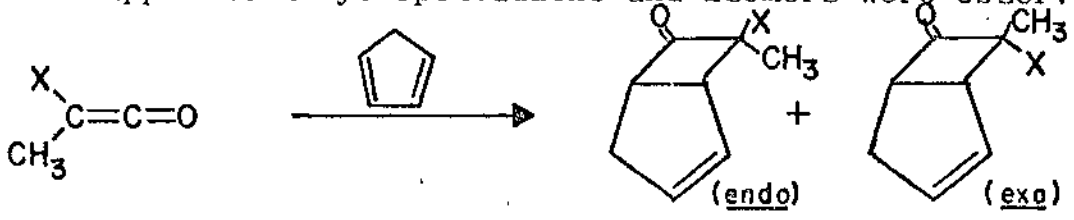


This crossing over results in orbitals which are bonding in the reactants becoming antibonding orbitals in the product. This is not energetically desirable and is therefore the basis for disallowing the cycloaddition. A recent extension of the

Woodward-Hoffmann rules offers a convincing explanation for why concerted thermal [2 + 2] cycloadditions are allowed with ketenes (39).

In recent years there has been considerable interest in the halogenated ketenes where at least one halogen is attached to the ketene functionality. Several ketenes of this type have recently been prepared; e.g., difluoroketene, dichloroketene, and dibromoketene as well as fluoromethylketene. These new reactive intermediates for organic syntheses have been found to be so reactive that isolation was not possible; however, the ketenes were trapped very effectively by cyclopentadiene by <u>in situ</u> preparations (4, 12, 17, 37). The interest in haloketenes has been extended to the preparation of substituted tropolones (37), β-lactams (3, 16), β-imino-β-lactams (5), β-lactones (3), cycloadducts with other olefins (10), and perhaps other compounds.

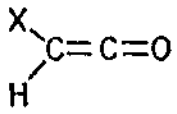
Recently methylchloroketene (6) and methylbromoketene (7) were trapped with cyclopentadiene and isomers were observed.



The ratio of the isomers was determined by vapor phase chromatography, but establishing the identity of the isomers could not be done <u>a priori</u>. However, the isomers were separated by distillation and the p.m.r. data which was subsequently obtained revealed a difference in the chemical

shifts of the methyl singlets in the two isomers. Upon addition of molecular bromine to saturate the residual carbon-carbon double bonds of the isomers, only one of the methyl resonances shifted. It was reasoned that the endo-methyl was the one that shifted since its environment had been changed. In this manner the identity of the isomers was established. The ethylchloro and ethylbromoketene cyclopentadiene adducts have also been reported and both isomers are found in each case, and the assignments of the isomer structures have been recently verified by p.m.r. studies (9).

There has been only one brief mention of an aldohaloketene in the literature.



an aldohaloketene

In a report on ketene-enamine cycloadditions, Opitz indicated that chloroketene had apparently been trapped by an enamine, since the corresponding enamine adduct was isolated in thirty per cent yield. However, no information was given regarding isomer distribution (30).

The recent intensified interest in halogenated ketenes, the virtual nonexistence of information regarding aldohaloketenes (22), and the fact that essentially no work had been done on the stereochemistry of cyclopentadiene adducts with unsymmetrical ketenes, made it obvious that there was a need

for further investigations in this area. Thus it was decided that an attempt would be made to synthesize several aldohaloketenes, study the stereochemistry of the cycloadditions, and perhaps elucidate the mechanism of the cycloaddition. Hence, the objective of this research problem was to synthesize aldohaloketenes and investigate the chemistry of this new class of ketenes.

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CHAPTER II

EXPERIMENTAL

Infrared spectral data was obtained with a Perkin-Elmer Model 237 Grating Infrared Spectrophotometer. Samples were run neat between sodium chloride discs or as solutions in fixed thickness sodium chloride cells (0.5 mm. thickness). Proton magnetic resonance (p.m.r.) spectra were obtained with a Varian A-60 Nuclear Magnetic Resonance Spectrometer, employing tetramethylsilane as the internal standard. Vapor phase chromatography (v.p.c.) separations were accomplished with an Aerograph AP-49 or a Varian Model 1525-B instrument, using thermal conductivity detectors. Separations were achieved using a 10-ft.-x-$\frac{1}{4}$-in. column packed with 15 per cent Ucon 50 HB 2000 Polar and 2 per cent Oronite NIW on Chromosorb W (DMCS) 60/80 mesh, or a 10-ft.-x-$\frac{1}{4}$-in. column packed with 10 per cent QF-1 on Chromosorb W (acid washed) 60/80 mesh. Elemental analyses were performed by analysts in the Chemistry Department of North Texas State University, Denton, Texas, and C. F. Geiger, Ontario, California.

Preparation of Reagents

Solvents were dried and purified by distillation from calcium hydride or lithiumaluminum hydride and were subsequently stored over calcium hydride or Molecular Sieves,

Type 4A. Commercially available triethylamine was dried in a similar manner.

Cyclopentadiene was obtained by thermally cracking commercially available dicyclopentadiene at about 140°C. The monomer was stored at -10°C. for no more than five days. Cyclopentadiene treated in this manner was more than 95 per cent monomeric. Other olefins were used as received from the distributor or were dried over Molecular Sieves, Type 4A, distilled through a 24-inch Vigreaux column, and stored over Molecular Sieves.

Chloroacetyl bromide was prepared from commercially available chloroacetic acid and phosphorous tribromide. A 94 g. portion (1.0 mole) of the acid was placed in a 500 ml. one-necked flask equipped with a reflux condenser and a dropping funnel. A 271 g. portion (1.0 mole) of phosphorous tribromide was added dropwise through the condenser. The mixture was refluxed for three hours and distilled through a 24-inch Vigreaux column. The product distilled at 123-125°C. at atmospheric pressure. There was obtained 126 g., corresponding to a yield of 80 per cent. The boiling point reported in the literature is 124-126°C. (12).

Bromoacetyl bromide was made from commercially available bromoacetic acid in the same manner as chloroacetyl bromide. A 139 g. portion of the acid yielded 169 g. of acid bromide, nearly a 70 per cent yield. The bromoacetyl bromide was distilled at 147-150°C. at atmospheric pressure. The boiling point reported in the literature is 148-150°C. (4).

Fluoroacetyl chloride was prepared in 75 per cent yield from sodium fluoroacetate and phosphorous pentachloride (11). Rodenticide grade sodium fluoroacetate was obtained from Roberts Chemicals Incorporated, Nitro, West Virginia. This material was dried for 48 hours in a beaker over phosphorous pentoxide prior to conversion to the acid halide. A 99 g. portion (1 mole) of the salt was placed in a 500 ml. 3-necked flask equipped with a mechanical stirrer and a distillation head, and 250 g. (1.2 moles) of phosphorous pentachloride were quickly added to the system. The two solids were slowly mixed with evolution of enough heat to distill some of the product. After thorough mixing was achieved, fluoroacetyl chloride was distilled at 70-73°C. at atmospheric pressure.

Dichloroacetyl bromide was prepared from commercially available dichloroacetic acid and phosphorous tribromide, in the same manner as chloroacetyl bromide. A 128 g. portion (1 mole) of the acid produced 143 g. (0.75 mole) of dichloroacetyl bromide, distilling at 126-129°C. This corresponds to a 75 per cent yield. The boiling point reported in the literature is 125-219°C. (7).

Propionyl chloride, butryl chloride, and phenylacetyl chloride were used as received from Aldrich Chemical Company, of Milwaukee, Wisconsin.

Isovaleryl chloride was prepared from isovaleric acid and phosphorous trichloride. A 102 g. portion (1.0 mole) of the acid was placed in a 1-necked flask equipped with reflux condenser and dropping funnel;139 g. (1.0 mole) of phosphorous trichloride were added dropwise through the condenser.

The reaction mixture was refluxed three hours and the product was distilled at 105-107°C. There was obtained 88 g. of the acid halide which corresponds to a 72 per cent yield. The boiling point reported in the literature is 105-108°C. (8).

Tri-n-butyltin hydride was prepared from commercially available tri-n-butyltin chloride and lithium aluminum hydride in the following manner (6). A 6.0 portion (0.15 mole) of lithium aluminum hydride was suspended in 250 ml. of anhydrous ether, in a one liter three-necked flask, provided with a sealed stirrer, reflux condenser with drying tube, and a dropping funnel with gas inlet tube. After purging the system with nitrogen, 48.8 g. (0.15 mole) of tri-n-butyltin chloride dissolved in 100 ml. of ether were added gradually with stirring. The mixture was refluxed 2 $\frac{1}{2}$ hours and then cooled to room temperature, before adding 500 mg. of hydroquinone. Upon stirring, 12 ml. of water was added followed by 300 ml. of a 20 per cent aqueous solution of sodium potassium tartrate to dissolve the precipitated alumina. Etheral extracts of this solution were dried with anhydrous sodium sulfate. The ether was removed by distillation and the product collected by vacuum distillation at 76-81°C. at 0.7-0.9 mm. in 74 per cent yield.

Chloroketene-Cyclopentadiene Cycloadduct

A solution containing 11.6 g. (0.115 mole) of triethylamine, and 84.4 g. (1.3 moles) of cyclopentadiene in 250 ml. of hexane was placed in a 500 ml. three-necked flask,

equipped with a sealed stirrer, a dropping funnel, and a drying tube. A 17 g. portion (0.108 mole) of chloroacetyl bromide was placed in the dropping funnel and the reaction flask was cooled with a dry ice-acetone bath. The acid halide was added dropwise to the cold, well-stirred solution, over a period of about thirty minutes. After the addition was complete, the cold bath was removed and the reaction mixture was allowed to stir overnight at room temperature. A white salt precipitated immediately upon addition of the acid halide and its color gradually changed to light yellow over a period of several hours. The reaction mixture was filtered, using a Buchner funnel and the salt was washed twice with 100 ml. portions of hexane. The filtrate was concentrated by rotoevaporation at room temperature, at about 10 cm. The concentrate was vacuum distilled at 64°C. at 0.6 mm. to yield 9 g. of 7-chlorobicyclo [3.2.0] hept-2-ene-6-one, which was equivalent to a 59 per cent yield. The i.r. spectrum showed carbonyl absorption at 1795 $cm.^{-1}$ and carbon-carbon double bond absorption at 1605 $cm.^{-1}$; p.m.r. spectrum of the adduct in CCl_4 solution revealed resonances at: 2.6 p.p.m. (multiplet, 2H) for the bridgehead protons, 5.08 p.p.m. (multiplet, 1H) for the proton geminal to chlorine, 5.81 p.p.m. (multiplet, 2H) for the vinyl protons.

Analysis: Calculated for C_7H_7ClO: C, 58.8; H, 4.91. Found: C, 58.55; H, 4.93.

Bromoketene-Cyclopentadiene Cycloadduct

The apparatus and conditions for this preparation were the same as those described for the chloroketene-cyclopentadiene system. A 60 ml. portion of ether, 50 g. (0.5 mole) of triethylamine, and 80 g. (1.41 moles) of cyclopentadiene were stirred at -78°C. while 50.5 g. (0.25 mole) of bromoacetyl bromide were added dropwise to the solution. A dark brown precipitate was formed as each drop of acid halide was added. After the addition was completed, the brown reaction mixture was allowed to warm to room temperature and stir overnight. The work-up was the same as that described for the chloroketene-cyclopentadiene system. After removal of the solvent by rotoevaporation, such a small amount of liquid remained, that distillation was not attempted. Purification was accomplished by v.p.c., on a Ucon-Oronite column at 150°C. with a flow rate of about 50 ml./min. Estimations from the chromotagraphic work indicate that the yield was approximately 5 per cent of the 7-bromobicyclo [3.2.0] hept-2-ene-6-one. The i.r. spectrum revealed carbonyl absorption at 1795 $cm.^{-1}$. The p.m.r. spectrum of the adduct in CCl_4 solution showed resonances at: 2.6 p.p.m. (multiplet, 2H) for bridgehead protons, 5.15 p.p.m. (multiplet; 1H) for the proton geminal to bromine, 5.8 p.p.m. (multiplet, 2H) for vinyl protons.

Analysis: Calculated for C_7H_7BrO: C, 44.8; H, 3.74. Found: C, 45.1; H, 3.96.

Fluoroketene-Cyclopentadiene Cycloadduct

Apparatus and conditions for this system were the same as for the chloroketene-cyclopentadiene system. A solution containing 125 ml. of anhydrous ether, 40 g. (0.395 mole) of triethylamine, and 120 g. (1.87 moles) of cyclopentadiene was placed in the reaction vessel. This solution was cooled to a -78°C. and 34.5 g. (0.35 mole) of fluoroacetyl chloride were added dropwise with stirring. A white salt was immediately formed as the acid halide was added, but turned brown as stirring continued overnight. The reaction mixture was worked up in the same way as the chloroketene-cyclopentadiene system and 16.1 g. of 7-fluorobicyclo [3.2.0] hept-2-ene-6-one were obtained by distillation at 73.5°C. at 4.5 mm. This was equivalent to a 36 per cent yield. The i.r. spectrum of this compound showed absorptions at 1800 $cm.^{-1}$, for the carbonyl function, and at 1605 $cm.^{-1}$, for the carbon-carbon double bond. The p.m.r. spectrum showed resonances at: 2.6 p.p.m. (multiplet, 2H) for methylene protons, 3.45 p.p.m. (multiplet, 1H) and 3.85 p.p.m. (multiplet, 1H) for the bridgehead protons, a pair of multiplets separated by 55 cycles, centered at 5.52 p.p.m. (1H) for the proton geminal to fluorine, (the downfield half of the resonance was obscured by vinyl resonance) for the vinyl protons. (See figure 1.)

Analysis: Calculated for C_7H_7FO: C, 66.65; H, 5.59. Found: C, 66.50; H, 5.55.

Bromination of 7-Fluorobicyclo [3.2.0] hept-2-ene-6-one

A 0.16 g. portion (0.0013 mole) of the chloroketene-cyclopentadiene adduct was placed in an p.m.r. tube with 0.25 ml. of carbon tetrachloride. A solution of 0.204 g. (0.00127 mole) of bromine in 0.25 ml. of carbon tetrachloride was added to the p.m.r. tube with intermittent agitation. The p.m.r. spectrum of this reaction mixture indicated saturation of the carbon-carbon double bond because the vinyl resonance disappeared and upfield resonances were more complicated. Elimination of the vinyl resonance revealed the other half of the resonance for the proton geminal to fluorine. (See figure 2.) The brominated product could not be distilled or chromatographed without decomposition.

Hydrogenation of 7-Fluorobicyclo [3.2.0] hept-2-ene-6-one

Hydrogenations were conducted near atmospheric pressure in the apparatus illustrated in figure 1. Approximately 0.1 g. of palladium black catalyst (obtained from Fisher Scientific Company) was placed in the reaction flask, along with 50 ml. of absolute ethanol. The system was sealed with Teflon tape. With the stopcock to the graduated vessel closed, the system was evacuated and then purged with hydrogen. This flushing procedure was repeated four times before filling the entire system (including the graduated vessel) with hydrogen. The system was allowed to stir for an hour to allow the catalyst to absorb hydrogen and attain equilibrium. After the

equilibrium time had elapsed, 1.4 g. (0.011 mole) of fluoroketene-cyclopentadiene adduct was injected through the septum into the system. Hydrogen was absorbed fairly rapidly for about 1.5 hours; the system was allowed to stand for a total of 3 hours before it was opened. During this 3-hour period, 252 ml. (0.011 mole) of hydrogen were absorbed. Most of the alcohol was removed by distillation and the hydrogenated product was purified by v.p.c., at 150°C. on a 10-ft.-x-$\frac{1}{4}$-in. XF-1150 column. The i.r. spectrum revealed absorption at 1795 cm^{-1}, for the carbonyl function, and no absorption at 1605 cm^{-1}, indicating the absence of the carbon-carbon double bond. The p.m.r. spectrum showed resonances at 1.86 p.p.m. (multiplet, 6H) for methylene protons, 3.38 p.p.m. (multiplet, 2H), and a pair of multiplets separated by 55 cycles, centered at 5.52 p.p.m. (1H) for the proton geminal to fluorine.

Fluoroketene-Diisopropylcarbodiimide Cycloadduct

The apparatus used for this cycloaddition was the same as that used in the chloroketene-cyclopentadiene system except that a reflux condenser with a drying tube was placed in the system. A 150 ml. portion of hexane, 24 g. (0.24 mole) of triethylamine, and 15.1 g. (0.12 mole) of diisopropylcarbodiimide were placed in the reaction flask. The mixture was brought to a gentle reflux and 11.4 g. (0.12 mole) of fluoroacetyl chloride were added dropwise over a period of about 30 minutes. The reaction mixture was stirred and refluxed an

additional two hours and then allowed to cool to room temperature. The mixture was filtered, the salt was washed with hexane, and the filtrate was concentrated on a rotoevaporator. Distillation at 50-51°C. at 0.7 mm. yielded 7.5 g. of 3-fluoro-1-isopropyl-4-isopropyliminoazetidin-2-one. This was equivalent to a yield of 33 per cent. The i.r. spectrum revealed absorptions at 1832 $cm.^{-1}$ for the carbonyl function and 1710 $cm.^{-1}$ for the carbon-nitrogen double bond. The p.m.r. spectrum showed resonances at: 1.32 p.p.m. (multiplet, 12H) for the methyl protons, 3.85 p.p.m (multiplet, 2H) for the tertiary protons, 5.94 p.p.m. (doublet, 1H; J_{HF} = 55 cycles) for the proton geminal to fluorine.

Analysis: Calculated for $C_9H_{15}FN_2O$: C, 58.1; H, 8.07; N, 15.5. Found: C, 58.37; H, 8.26; N, 15.21.

Dichloroketene-Cyclopentadiene Cycloadduct

The reaction apparatus and conditions were the same for this system as for those of the chloroketene-cyclopentadiene system. A 200 ml. portion of hexane, 66 g. (1 mole) of cyclopentadiene, and 28 g. (0.275 mole) of triethylamine were placed in the reaction vessel, and 48 g. (0.25 mole) of dichloroacetyl bromide were added dropwise to the mixture after it was cooled to -78°C. The reaction mixture was allowed to stir overnight at room temperature before it was worked up as described in the chloroketene-cyclopentadiene system. A 50 per cent yield (22 g.) of 7, 7-dichlorobicyclo [3.2.0] hept-2-ene-6-one was obtained by distillation at 38°C.

at 0.25 mm. Analytical data was the same as that reported in the literature (10).

Reduction of 7,7-Dichlorobicyclo [3.2.0] hept-2-ene-6-one

A solution of 16.26 g. (0.056 mole) of tri-n-butyltin hydride in 5 ml. of toluene was slowly added to 8.85 g. (0.056 mole) of 7,7-dichlorobicyclo [3.2.0] hept-2-ene-6-one in 15 ml. of toluene. The addition was accomplished at room temperature and the reaction mixture was allowed to stand an hour prior to isolation of the products. Distillation of the mixture at a pressure of 0.2 to 0.3 mm. yielded 6.0 g. of a product boiling at 40-45°C.; this was equivalent to a yield of 84 per cent. The p.m.r. spectrum of the reaction mixture gave no evidence of more than one isomer of the reduced ketone. The i.r. and p.m.r. spectra of the distilled product were identical to those of the chloroketene-cyclopentadiene cycloadduct.

Methylketene-Cyclopentadiene Cycloadduct

Apparatus and conditions for this cycloaddition were the same as for the fluoroketene-diisopropylcarbodiimide system. A 100 ml. portion of hexane, 50 g. (0.5 mole) of triethylamine, and 165 g. (2.5 moles) of cyclopentadiene were placed in the reaction flask and brought to a gentle reflux; 46 g. (0.5 mole) of propionyl chloride were added dropwise to the reaction mixture over a period of about 15 minutes, and refluxing was continued for a total of 90 minutes. The reaction mixture

was allowed to stand overnight prior to the work-up as described in the chloroketene-cyclopentadiene system. Distillation at 60-65°C. at 4.7 mm. yielded 57 g. of a mixture of liquids. Separation of the liquids by v.p.c. showed that approximately 20.4 g. of 7-methylbicyclo [3.2.0] hept-2-ene-6-one was present in the mixture; this was equivalent to a yield of 33 per cent. The i.r. and p.m.r. data was in agreement with that in the literature (5).

Methylketene Prepared by Pyrolysis

A 200 ml. boiling flask was equipped with an eight inch Pyrex tube containing about eight feet of Nichrome Wire which was coiled such that the coil was about six inches long. A twelve inch reflux condenser was attached to the Pyrex tube; the condenser was also connected to a series of three "U" tubes. A 60 ml. portion of propionic anhydride was placed in the boiling flask and the "U" tubes were attached to a vacuum pump in order to maintain a pressure of 5 cm. on the system during pyrolysis. The wire was connected to a variable transformer and the voltage was increased until the coil glowed with a bright orange color. The propionic anhydride was then slowly refluxed over the coil, yielding propionic acid and methyl ketene which were condensed in the liquid nitrogen cooled "U" tube. The methylketene was purified by two bulb-to-bulb distillations.

Almost 3 g. of the pure ketene and 20 g. of cyclopentadiene in 50 ml. of acetonitrile were placed in a bomb

which was then sealed. The bomb was heated at 120°C., for 16 hours; then the reaction mixture was vacuum distilled, yielding a liquid which was mostly dicyclopentadiene. Analysis of this liquid by v.p.c. indicated a very small amount of 7-methylbicyclo [3.2.0] hept-2-ene-6-one.

Hydrogenation of 7-Methylbicyclo [3.2.0] hept-2-ene-6-one

The apparatus and conditions for this experiment were the same as for the hydrogenation of the fluoroketene-cyclopentadiene adduct, except that hydrogen was continually added to the system for about four hours at a very slow rate. Approximately 1.6 g. (0.013 mole) of 7-methylbicyclo [3.2.0] hept-2-ene-6-one were injected into the hydrogenation vessel, but no attempt was made to determine the volume of hydrogen absorbed, because the sample being hydrogenated was quite large and impure. The hydrogenation solution was concentrated by distillation of the alcohol; the hydrogenated cycloadduct was purified by v.p.c. at 125°C., using the Ucon-Oronite column. The i.r. spectrum of this compound revealed carbonyl absorption at 1744 $cm.^{-1}$ and no carbon-carbon double bond. The p.m.r. spectrum showed resonances at 0.95 p.p.m. (doublet, 3H) for the methyl protons. 1.72 p.p.m. (multiplet, 6H) for methylene protons, 2.95 p.p.m. (multiplet, 2H) for bridgehead protons, and 3.5 p.p.m. (multiplet, 1H) for the proton geminal to the methyl group.

Bromination of 7-Methylbicyclo [3.2.0] hept-2-ene-6-one

Bromine was added slowly, cautiously and dropwise from a small syringe to a 30 per cent solution of 7-methylbicyclo [3.2.0] hept-2-ene-6-one in carbon tetrachloride. This addition was done intermittently and was continued until p.m.r. spectra showed no resonance for vinyl protons. The p.m.r. spectrum of the brominated product also revealed that the proton geminal to the methyl group had been displaced by bromine; this was obvious because the methyl doublet (0.99 p.p.m.) disappeared and a singlet appeared downfield, at 1.9 p.p.m. (1). Attempts to purify the brominated product resulted in its decomposition; thus, other analytical data was not obtained.

Ethylketene-Cyclopentadiene Cycloadduct

The apparatus and conditions for this experiment were the same as for the dluoroketene-diisopropylcarbodiimide system. A 100 ml. portion of chloroform, 34 g. (0.336 mole) of triethylamine, and 66 g. (1 mole) of cyclopentadiene were placed in a reaction flask and refluxed gently. A 32 g. portion (0.30 mole) of butyryl chloride was added dropwise over a period of about 15 minutes. Refluxing was continued for an additional 75 minutes, and then the mixture was allowed to stand overnight at room temperature prior to working it up as described in the chloroketene-cyclopentadiene system. Vacuum distillation of the reaction products yielded 13.8 g. (34 per cent yield) of 7-ethylbicyclo [3.2.0] hept-2-ene-6-one,

distilling at 70-71.5°C. at 4.7 mm. The i.r. spectrum of this compound possessed a carbonyl absorption at 1773 cm.$^{-1}$ and a carbon-carbon double bond absorption at 1613 cm.$^{-1}$. The p.m.r. spectrum possessed resonances at 1.02 p.p.m. (multiplet, 3H) for the methyl protons, a multiplet centered at 1.90 p.p.m. (2H) for the methylene protons adjacent to a methyl group, 2.45 p.p.m. (multiplet, 2H) for the methylene protons on the five-membered ring, a multiplet from 3.2 to 4.1 p.p.m. (3H) for the two bridgehead protons and the proton geminal to the ethyl group, and 5.8 p.p.m. (multiplet, 2H) for the vinyl protons.

Partial bromination of the cycloadduct with a 10 per cent solution of bromine in carbon tetrachloride, resulted in replacement of the proton geminal to the ethyl group by bromine. This was evident from the p.m.r. spectrum, because part of the multiplet at 3.2 to 4.1 p.p.m. was eliminated, and a pattern appeared at 4.3 p.p.m. which was easily recognized as part of the cis isomer of the ethylbromoketene-cyclopentadiene cycloadduct (2, 3).

The 2, 4-dinitrophenylhydrazone derivative was prepared by a standard procedure.

Analysis: Calculated for $C_{15}H_{16}N_4O_4$: C, 56.96; H, 5.06; N, 17.72. Found: C, 57.22; H, 5.14; N, 17.96.

Isopropylketene-Cyclopentadiene Cycloadduct

Apparatus and conditions for this cycloaddition were the

same as the fluoroketene-diisorpopylcarbodiimide system. A 120 ml. portion of chloroform, 66 g. (1 mole) of cyclopentadiene, and 25 g. (0.25 mole) of triethylamine were placed in the reaction flask and brought to a gentle reflux. A 24.1 g. portion (0.2 mole) of isovaleryl chloride was added dropwise over a period of about 15 minutes, and refluxing was continued an additional 75 minutes. The reaction mixture was allowed to stand overnight prior to work-up as described in the chloroketene-cyclopentadiene system. Distillation of the concentrate at 79-80°C. at 4.7 mm. afforded the cycloadduct, 7-isopropylbicyclo [3.2.0] hept-2-ene-6-one, in 36 per cent yield. The i.r. spectrum revealed absorptions at 1770 $cm.^{-1}$, for carbonyl and 1607 $cm.^{-1}$, for carbon-carbon double bond. The p.m.r. spectrum showed resonances at: 0.94 p.p.m. (multiplet, 6H) for methyl protons, 1.6 p.p.m. (multiplet, 1H) for tertiary proton of isopropyl group, 2.4 p.p.m. (multiplet, 2H) for methylene protons 3.0-3.9 p.p.m. (multiplet, 3H) for proton geminal to isopropyl group, and for bridgehead protons, and 5.8 p.p.m. (multiplet, 2H) for vinyl protons.

Analysis: Calculated for $C_{10}H_{13}O$: C, 80.0; H, 9.33. Found: C, 80.3, H, 9.59.

Partial bromination of the cycloadduct with a 10 per cent solution of bromine in carbon tetrachloride, resulted in replacement of the proton geminal to the isopropyl group by a bromine atom. This was apparent from the p.m.r.

spectrum because part of the resonance at 3.0-3.9 p.p.m. was eliminated, and part of it was displaced downfield to 4.25 p.p.m. as a pattern which was recognized as part of the cis isomer of the isopropylbromoketene-cyclopentadiene cycloadduct (3, 9).

Relative Reactivity of Methylketene and Chloroketene at 30°C.

Apparatus and procedure were the same for this experiment as for the chloroketene-cyclopentadiene system, except that a water bath rather than a dry ice-acetone bath was used for cooling the reaction mixture. A 200 ml. portion of hexane, 51 g. (0.5 mole) of triethylamine, and 16.5 g. (0.25 mole) of cyclopentadiene were placed in a reaction flask and stirred. A mixture of 28 g. (0.25 mole) of chloroacetyl chloride and 23 g. (0.25 mole) of propionyl chloride was added dropwise over a period of about 30 minutes. The reaction flask was cooled with a water bath which rose in temperature to 30°C. The reaction mixture was allowed to stand overnight prior to analysis. A 10 microliter sample of the reaction mixture was chromatographed, showing peaks with retention times identical to the retention times of known samples of 7-chlorobidyclo [3.2.0] hept-2-ene-6-one and 7-methylbicyclo [3.2.0] hept-2-ene-6-one. The ratio of the areas of the two cycloadduct peaks was approximately nine to one, in favor of the methylketene adduct.

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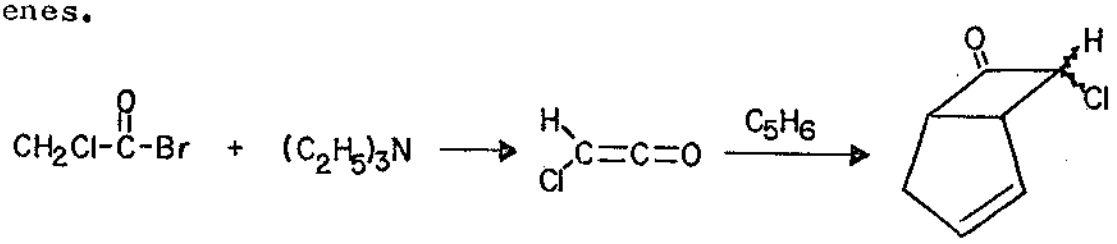
CHAPTER III

RESULTS AND DISCUSSION

The reports of earlier investigators indicate that aldoketenes and haloketenes are very unstable and difficult if not impossible to isolate (3, 5, 8, 12). Therefore, no attempts were made initially, to isolate aldohaloketenes or solutions of these compounds. The success of other investigators (3, 4, 8, 21) in trapping halogenated ketenes with cyclopentadiene, prompted the use of this olefin as a cycloaddition partner for aldohaloketene systems.

The dehydrobromination of chloroacetyl bromide with triethylamine in the presence of cyclopentadiene to produce 7-chlorobicyclo [3.2.0] hept-2-ene-6-one, was the first approach utilized in the attempted synthesis and trapping of aldohaloketenes.

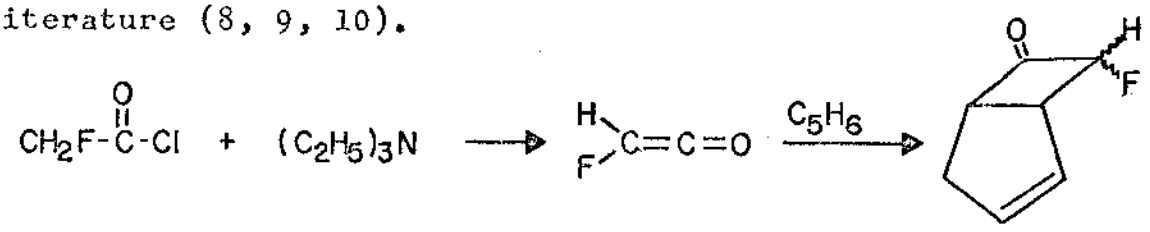


This method was selected over others because of the availability of the starting materials and the ease with which such an experiment could be executed. The results were successful and so interesting that other methods were not

investigated.

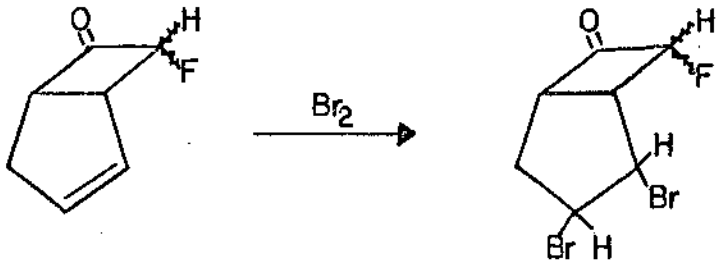
The addition of acid halide to the reaction mixture at -78°C. was observed to result in the immediate formation of an insoluble salt, but v.p.c. of the cold reaction mixture did not reveal the formation of any cycloadduct, not even after the reaction mixture was kept (in the cold) for 48 hours. The cold reaction mixture was allowed to warm to room temperature where v.p.c. revealed that cycloadduct was rapidly formed in good yield in two hours. However, the extremely exothermic nature of the dehydrohalogenation and decreased yields of cycloadduct at higher temperatures were detrimental to effecting the dehydrohalogenation at room temperature. Variation of the reaction temperature, stoichiometry of the reactants, order of addition of reagents, and reaction time, resulted in the selection of reaction conditions as stated in the experimental section. Yields of 60 per cent were observed repeatedly under these conditions.

The success experienced with the chloroketene system prompted investigation of the analogous fluoroketene system, under the same conditions. This resulted in a 40 per cent yield of 7-fluorobicyclo [3.2.0] hept-2-ene-6-one, which was among the first fluorinated ketenes to be reported in the literature (8, 9, 10).

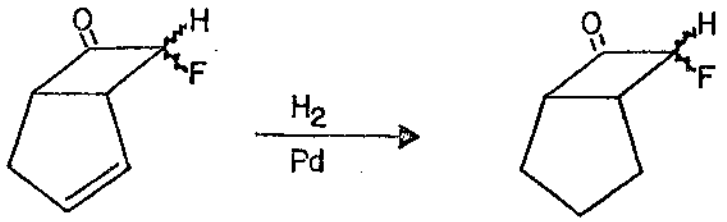


Variation of the reaction conditions did not result in an improved yield.

Integration of the p.m.r. spectrum of this compound revealed that the area for the vinyl resonance was too large and the area for the proton geminal to fluorine was too small. It was proposed that the large coupling constant (approxmately 55 c.p.s.) of fluorine geminal to hydrogen caused half of the resonance for this proton to occur downfield where it was obscured by the vinyl resonance. This was verified by bromination of the carbon-carbon double bond which eliminated the vinyl resonance and revealed a multiplet of equal area, 55 cycles downfield from the resonance assigned to the proton geminal to fluorine (see figure 2). The brominated product could not be distilled or chromatographed, thus further characterization was not achieved.

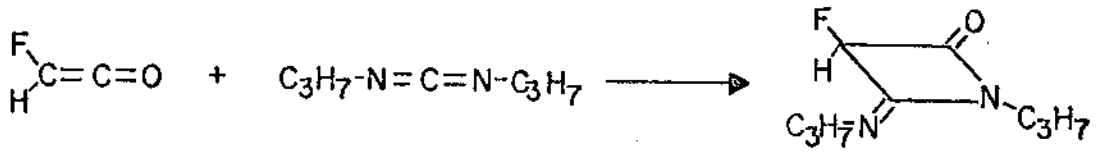


A more convincing proof of structure resulted from hydrogenation of the carbon-carbon double bond and complete characterization of the hydrogenated product.



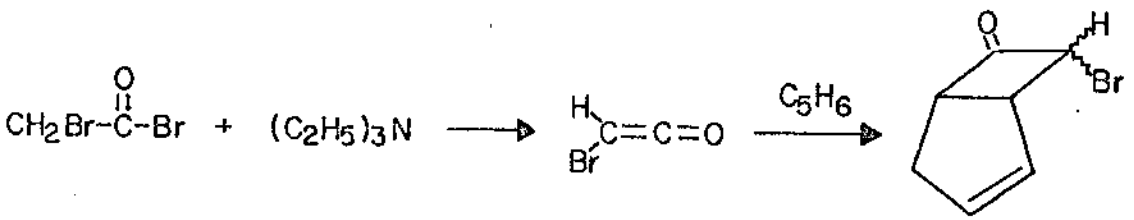
The p.m.r. spectrum of the hydrogenated product also revealed a multiplet (area equivalent to $\frac{1}{2}$ proton) which was 55 cycles downfield from the resonance assigned to the proton geminal to fluorine (area $\frac{1}{2}$ proton).

The existence of fluoroketene was further established by trapping this elusive compound with diisopropylcarbodiimide to form the 1,2-cycloadduct, 3-fluoro-1-isopropyl-4-isopropyl-iminoazetidin-2-one. The dehydrohalogenation was accomplished in the presence of the carbodiimide.



This cycloaddition did not occur at -78°C., and only to a very slight extent at room temperature. However, a reasonably good yield (33 per cent) could be obtained at the temperature of refluxing hexane.

Difficulty was encountered in the attempted dehydrobromination of bromoacetyl bromide to produce bromoketene with subsequent <u>in situ</u> trapping with cyclopentadiene.

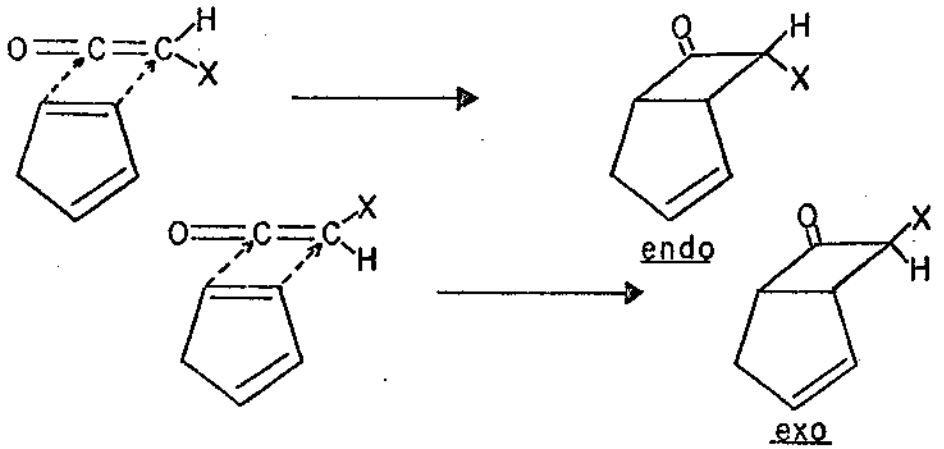


Regardless of the reaction conditions, the cycloadduct was

difficult to obtain. Approximately a five per cent yield was produced, a portion of which was collected by v.p.c. and characterized by p.m.r.

All of the aldohaloketene preparations and cycloadditions were accompanied by the formation of some insoluble tarry material. This is believed to be the result of polymerization of the ketene. Apparently, bromoketene is more susceptible to this undesirable polymerization or less reactive toward cycloaddition.

At the time this work was done, the cycloaddition of ketenes to olefinic compounds was believed to occur by a parallel approach of the reactants. This would be expected to result in the formation of two isomers, perhaps with a predominance of the sterically favored, <u>exo</u> isomer.



However, distillation of the reaction products from each of the aldohaloketene-cyclopentadiene systems yielded only one fraction which contained cycloadduct (as indicated by i.r.). Analysis of each fraction by v.p.c. suggested only

one isomer was present. Since two isomers were expected in all of the aldohaloketene cyclopentadiene cycloadditions, an extensive effort was made separate the expected isomers by v.p.c. This resulted in the utilization of many different chromatographic columns under varying conditions. However, the desired separation could not be accomplished. Hence, it was concluded only one isomer was present.

To show that the other isomer was not unstable and destroyed during distillation or some how underwent isomerization to form the observed isomer, a v.p.c. analysis of the undistilled reaction mixture was made. The result was the detection of only one isomer. Thus, it was concluded that aldohaloketenes undergo stereospecific cycloaddition with cyclopentadiene. It was of course not known which isomer was produced, but the exo isomer was expected.

In order to establish with certainty the stereochemistry of the aldohaloketene cycloadducts, the endo-chloro adduct was synthesized by an independent method. The cycloadduct of dichloroketene and cyclopentadiene was stereoselectively reduced with tri-n-butyltin hydride to produce the endo isomer of 7-chlorobicyclo [3.2.0] hept-2-ene-6-one (14, 16, 19, 20).*

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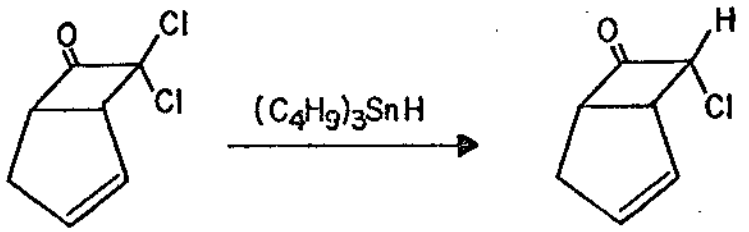
*Organotin hydrides reduce alkyl halides by a free radical mechanism and the exo halogen is selectively removed because of steric hinderance (16). The radical thus formed apparently does not undergo interconversion to give the exo isomer, because of torsional strain (14, 19, 20).



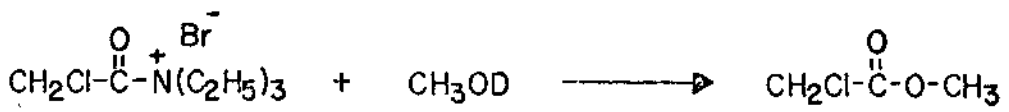
The p.m.r. spectrum of the endo isomer was compared to the p.m.r. spectrum of the chloroketene-cyclopentadiene cycloadduct. The two spectra were identical. Also, this same endo-chloro isomer was prepared by Professor Andre Dreiding of the University of Zurich in Zurich, Switzerland. This preparation involved the zinc-acetic acid stereoselective reduction of the dichloroketene cyclopentadiene adduct. As the result of communications with Professor Dreiding, a p.m.r. spectrum of this endo-chloro isomer was obtained. This spectrum was identical to the two mentioned above. Consequently, chloroketene undergoes cycloaddition with cyclopentadiene stereospecifically to produce only the endo isomer.

The p.m.r. spectra of the fluoroketene and bromoketene cycloadducts with cyclopentadiene were found to be consistent with assignment as the endo isomers. Thus, all of the aldohaloketenes investigated were found to undergo stereospecific cycloaddition to cyclopentadiene to form the sterically disfavored endo isomers of the 7-halobicyclo [3.2.0] hept-2-ene-6-ones.

The reaction of certain acid halides with tertiary amines has been reported to result in the formation of acyl quaternary ammonium salts, a number of which have been isolated (1, 18, 22). The tertiary amine portion of these salts

is indeed a bulky substituent, and perhaps the participation of bulky intermediates in the reaction under investigation, could result in a reversal of the expected stereochemistry. This would be even more likely if the acyl quaternary ammonium salt were involved in the transition state of the cycloaddition, instead of the ketene, as had previously been considered. This appeared to be a reasonable consideration since repeated efforts to observe the spectra of ketenes had not been fruitful. Also, the conditions employed for the cycloaddition reactions were at low temperature and acyl quaternary ammonium salts are apparently stable at low temperatures.

A trapping experiment was devised to prove the existence of the salt under the conditions of the cycloaddition reaction. The dehydrobromination of chloroacetyl bromide at low temperature should result in the formation of an acyl quaternary ammonium salt; addition of deuterated methanol to this salt at low temperature should result in the formation of an ester without any deuterium on the α-carbon. When this experiment

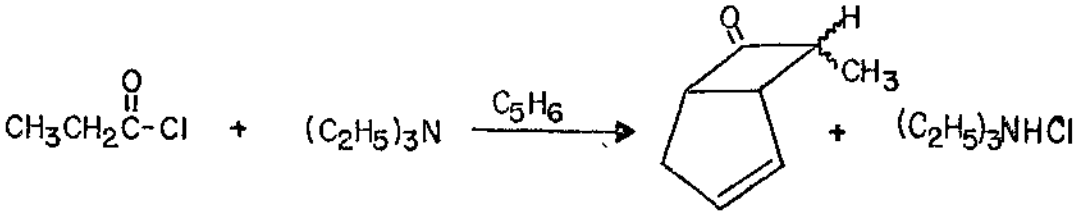


was actually performed, deuterium was found on the α-carbon. Control experiments revealed that exchange had not occurred. Consequently, deuterium incorporation was additional proof of the existence of ketene in the system and indicated the absence of an acyl quaternary ammonium ion intermediate.

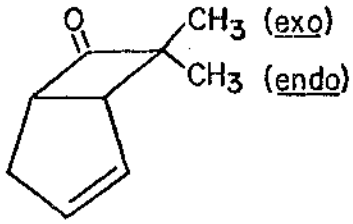
Perhaps a more obvious explanation for the stereospecificity of the aldohaloketenes previously described is some type of interaction between the orbitals on the halogen atoms and the π-system of the residual carbon-carbon double bond in the adduct. Molecular models reveal that the endo halogen atom is right over the π-system. Hence, in an effort to determine if the halogen was causing the endo specificity, the investigation of some aldoalkylketene systems was undertaken.

Aldoalklylketene cycloadducts with cyclopentadiene have been reported, but no information is available in the literature about the stereochemistry of these cycloadducts (12). Thus, it was in order to determine the stereochemistry of aldoaklylketene cycloadducts to determine if a mixture of isomers was formed or if these ketenes also underwent stereospecific cycloaddition.

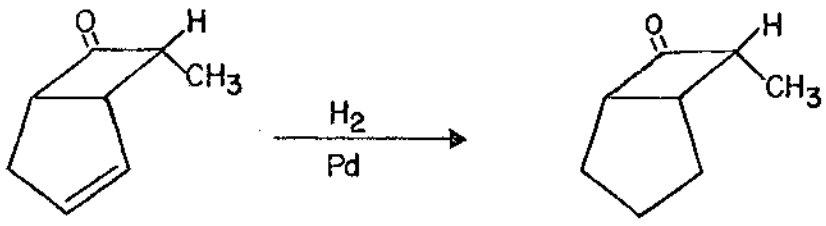
The methylketene cycloadduct with cyclopentadiene was synthesized utilizing the procedure and conditions which were so successful for the chloroketene system. This resulted in a very low yield (about 10 per cent), but the reaction conditions and solvents were varied to increase the yield to about 35 per cent. Table 1 shows the relative yield with variation of solvents and temperature.



The methylketene-cyclopentadiene cycloadduct was distilled, and v.p.c. analysis indicated only one isomer; the p.m.r. spectrum of this compound showed a methyl doublet at 0.99 p.p.m. The p.m.r. data was not adequate to establish the identity of the isomer, but comparison of the data to that reported in the literature for the dimethylketene cycloadduct with cyclopentadiene, was revealing (17). The dimethylketene adduct had two methyl resonances, separated by about 0.3 p.p.m. The exo methyl resonance occurred at 1.28

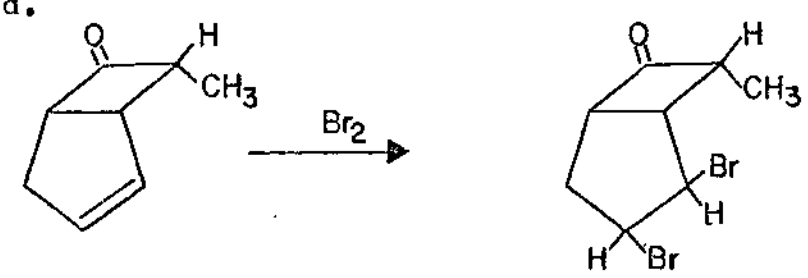


p.p.m. and the endo methyl resonance occurred at 0.93 p.p.m., and since the methylketene cycloadduct showed a resonance at 0.99 p.p.m., it appeared likely that this adduct was the endo isomer. Further proof of structure was desired, and the residual carbon-carbon double bond was hydrogenated. Hydrogenation of the vinyl system would remove the π-orbitals and should eliminate any shielding affect these orbitals might have on the endo methyl group. The p.m.r. spectrum of the hydrogenated

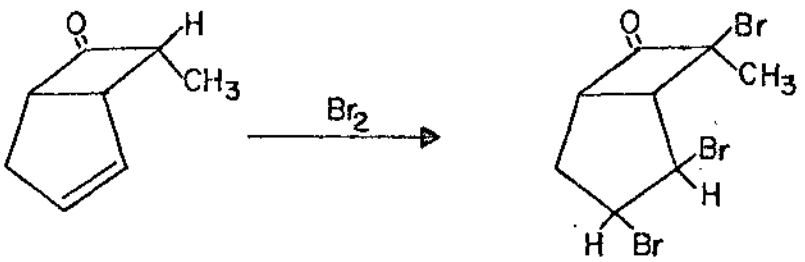


cycloadduct did reveal the elimination of vinyl protons and the formation of more methylene protons, but the methyl protons were shifted only about two c.p.s.

The experiment which offered conclusive proof of structure involved bromination of 7-methylbicyclo [3.2.0] hept-2-ene-6-one. Bromination of the residual carbon-carbon double bond would drastically affect the electrical environment of an <u>endo</u> methyl substituent, but should have little affect on an <u>exo</u> methyl substituent because of the distance involved.

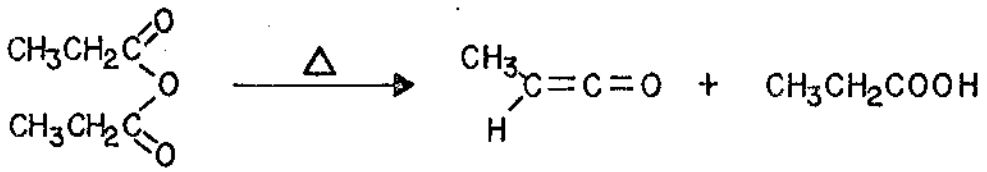


Unfortunately, bromination of the cycloadduct did not stop with saturation of the carbon-carbon double bond. The proton geminal to the methyl group was displaced; this was evident from the p.m.r. spectrum, since the methyl resonance became a singlet and was shifted downfield. It appeared that this p.m.r. data was of little value, because of the deshielding



effect of bromine which was geminal to the methyl group. However, the endo-methyl isomer of 7-bromo-7-methylbicyclo [3.2.0] hept-2-ene-6-one was available and the p.m.r. spectrum of the brominated product was identical to the p.m.r. spectrum of the methylketene-cyclopentadiene cycloadduct, after bromination (6). This was taken as evidence that methylketene had added stereospecifically to cyclopentadiene to form the sterically disfavored product, as had the aldohaloketenes.

All of the aldoketenes prepared in this investigation had, up to this time, been prepared by dehydrohalogenation. Perhaps the stereochemistry of the cycloadducts which had been produced was influenced by the method of ketene preparation. To test this possibility, two procedures other than dehydrohalogenation were utilized in attempts to generate methylketene. Dechlorination of α-chloropropionyl chloride with activated zinc was completely unsuccessful, in that the dehalogenation could not be initiated. However, methylketene was successfully prepared by the pyrolysis of propionic anhydride. Methylketene, a gas at room temperature



and atmospheric pressure, was passed into a cold solution of cyclopentadiene in each of three different solvents. In no

instance was cycloadduct isolated by this procedure. The same technique was tried again, except that the cyclopentadiene solution was refluxed as the system was purged with methylketene, and again, no cycloadduct was formed.

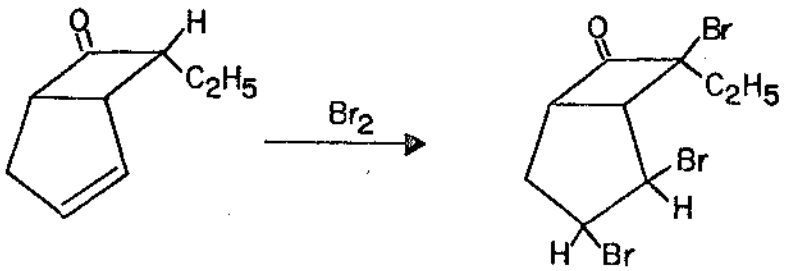
A reference was found, in which ketene was observed to undergo cycloaddition with cyclopentadiene, as the result of forcing conditions (7). A solution of ketene was placed in a stainless steel bomb with cyclopentadiene and heated; this resulted in a modest yield of the expected cycloadduct. Extension of this procedure to the methylketene system resulted in the formation of a low yield of the endo-isomer of 7-methylbicyclo [3.2.0] hept-2-ene-6-one. Thus, methylketene undergoes stereospecific cycloaddition with cyclopentadiene to form the sterically disfavored isomer, even when the ketene is prepared by a method other than dehydrohalogenation.

Equal molar quantities of chloroketene and methylketene were generated simultaneously at room temperature, in the presence of a deficiency of cyclopentadiene. The ratio of chloroketene adduct to methylketene adduct was less than 1:2. However, at low temperature, the chloroketene cycloadduct is produced in sixty per cent yield and methylketene cycloadduct is produced in about six per cent yield. Thus, using yields as an indication of reactivities, chloroketene appears to be more reactive than methylketene, in cycloaddition reactions at low temperatures. By the same rea-

soning, methylketene appears to be more reactive than chloroketene in cycloaddition reactions at room temperature.

All of the data presented regarding aldoketene cycloadditions has been consistent, in that the only cycloadducts observed are endo isomers. Perhaps a more bulky ketene substituent would result in the formation of at least some of the exo isomer. Due to the availability of butyryl chloride, ethylketene was selected to test this proposal.

Cycloaddition of ethylketene to cyclopentadiene resulted in the isolation of only one isomer of 7-ethylbicyclo [3.2.0] hept-2-ene-6-one, as was evident from v.p.c. data. Consideration of p.m.r. data for the compound gave no insight as to which isomer was formed. Bromination did not cause a shift in the methyl region of the p.m.r. spectrum, and the methylene region was too complicated to observe a shift in the resonances which could be explained by a shielding or deshielding argument. However, the p.m.r. data revealed the proton geminal to the ethyl group had been replaced by bromine.



Both endo and exo isomers have been reported for a number of alkylhaloketene-cyclopentadiene cycloadducts; p.m.r. spectra of these compounds have been thoroughly investigated and a pattern observed for endo and exo isomers (6). The

resonance for the hydrogen on carbon number five was observed to occur at 4.26 p.p.m. when the ethyl group was endo on the ethylbromoketene cycloadduct; when the ethyl group was exo, resonance occurred at 3.90 p.p.m. Bromination of the ethylketene adduct yielded a spectrum like that of the ethylbromoketene cycloadduct, with a resonance at 4.3 p.p.m. and no resonance at 3.90 p.p.m.; thus, ethylketene underwent stereospecific cycloaddition with cyclopentadiene to form the endo isomer of 7-ethylbicyclo [3.2.0] hept-2-ene-6-one.

This investigation was extended to another, even more bulky aldoaklylketene system. Isopropylketene was generated by the dehydrochlorination of isovaleryl chloride in the presence of cyclopentadiene, and gain, only one isomer was isolated. Examination of the p.m.r. spectrum did not aid in establishing the identity of the isomer, but bromination of the adduct indicated that the cycloadduct was the endo isomer of 7-isopropylbicyclo [3.2.0] hept-2-ene-6-one. This conclusion was formed by consideration of the resonance of the hydrogen on carbon number five, as discussed in the following paragraph.

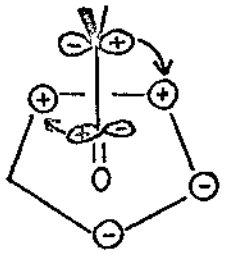
The p.m.r. spectrum of the endo-alkyl isomer of the isopropylbromoketene-cyclopentadiene adduct had a resonance at 4.27 p.p.m. for the hydrogen on carbon number five (6). The exo-alkyl isomer showed a resonance at 3.97 p.p.m. for the same hydrogen. Bromination of the isopropylketene-cyclopentadiene adduct resulted in the appearance of a characteristic resonance at 4.25 p.p.m. and no resonance at 3.97 p.p.m.

Thus, isopropylketene also underwent stereospecific cycloaddition with cyclopentadiene to form the endo isomer.

In summary, all of the aldoketenes investigated in this work, were observed to undergo stereospecific cycloaddition with cyclopentadiene to form the sterically disfavored adduct. Even bulky ketene substituents did not alter the stereochemistry of the cycloaddition. Thus the previously considered parallel approach of the cycloaddition partners is probably not accurate. However, this is not too surprising, because it is the highest occupied π-molecular orbitals of one of the reactants (in this case, the cyclopentadiene) which overlap with the lowest unoccupied π-orbitals of lowest energy of the other reactant (in this case, the ketene), in a symmetry allowed concerted cycloaddition (11). The signs of the π orbitals which participate in bond formation, must be alike in order for a concerted cycloaddition to be an allowed process. In the thermal concerted $[2 + 2]$ cyloaddition of a ketene to an olefin, these symmetry requirements cannot be met by a parallel approach of the cycloaddition partners. This is the basis upon which it has been stated that $[2 + 2]$-cycloadditions are symmetry forbidden as thermal, concerted processes (11). It is a characteristic of ketenes to undergo these "forbidden" cycloadditions. Thus it is apparent that the unexpected stereochemical results of these reactions must be related to the mechanism of the cycloaddition.

A very timely extension of the Woodward-Hoffmann rules

states that in order for a [2 + 2]-cycloaddition to be symmetry allowed as a thermal, concerted process, the reacting molecules must approach one another in an orthogonal manner (23). In the following drawing, the circles signify the upper portion of the bonding orbitals of cyclopentadiene, and the "figure eights" represent the antibonding orbitals of the reacting ketene. It is obvious that symmetry conditions



are correct for overlap which may result from a slight rotation of the ketene, as is indicated by the arrows.

There are actually four different orthogonal approaches of an unsymmetrical ketene to cyclopentadiene, which may give rise to symmetry-allowed orbital overlap (I-IV on the next page). Approaches III and IV are not sterically allowed because the substituents on the ketene interact sterically with the cyclopentadiene ring. Approach I is sterically preferred to II because in II the larger substituent is down toward the ring.*

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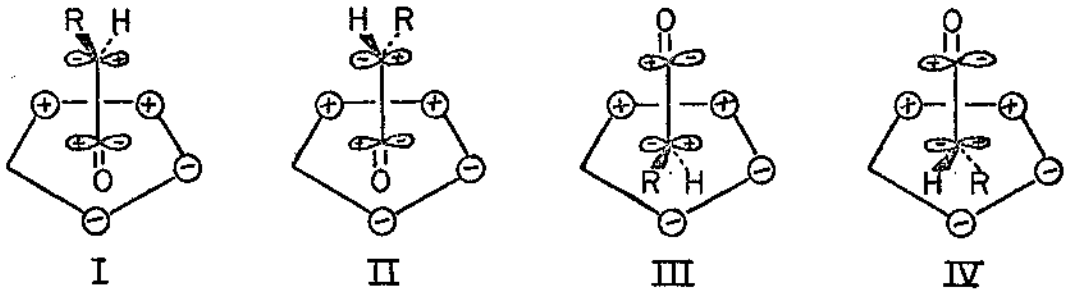
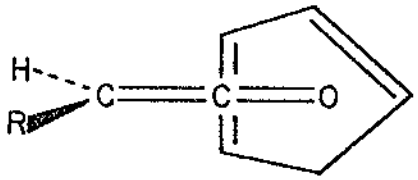
*In a private communication, Professor Roald Hoffmann, Cornell University, suggested that the orientation of an aldoketene and cyclopentadiene would be that depicted in I, and that orientation would lead to the formation of the endo isomer.

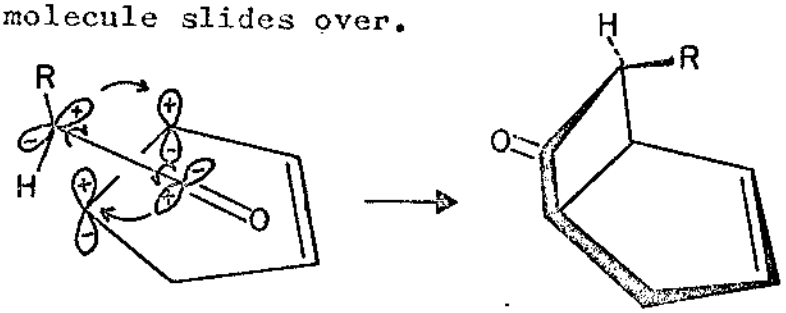


I II III IV

The sequence of events by which an aldoketene and cyclopentadiene undergo cycloaddition, is probably as follows. The initial interaction between the reactants is probably due to the nucleophilic character of the olefin and the electrophilic character of the carbonyl carbon of the ketene. This results in placement of the carbonyl carbon of the ketene directly over one of the carbon-carbon double bonds of the cyclopentadiene.



The two molecules come closer together and the electrostatic interaction gives away to an orbital interaction, as the ketene molecule slides over.



Orbital overlap is initiated as the ketene rotates in the

direction indicated by the large arrows. As overlap is maximized, that is, as σ-bond formation in the cycloadduct proceeds, there is a twisting about the ketene carbon-carbon bond, in the directions indicated by the small arrows. This results in placing the larger ketene substituent over the residual carbon-carbon double bond, that is, in formation of the endo isomer.

In conclusion, aldohaloketenes and aldoalkylketenes have been prepared and trapped in situ by cyclopentadiene, forming only the sterically disfavored endo isomers of 7-substitutedbicyclo [3.2.0] hept-2-ene-6-ones. The method of preparation does not offer an explanation for the observed results. Increasing the size of the ketene substituent does not result in the formation of any detectable amount of the exo isomer. A very recent extension of the Woodward-Hoffman Selection Rules for Concerted Cycloaddition Reactions predicts the observed stereochemistry. Thus this work is apparently the first or among the first which offers a direct conformation of the extended Woodward-Hoffmann Rules.

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APPENDIX

TABLE I

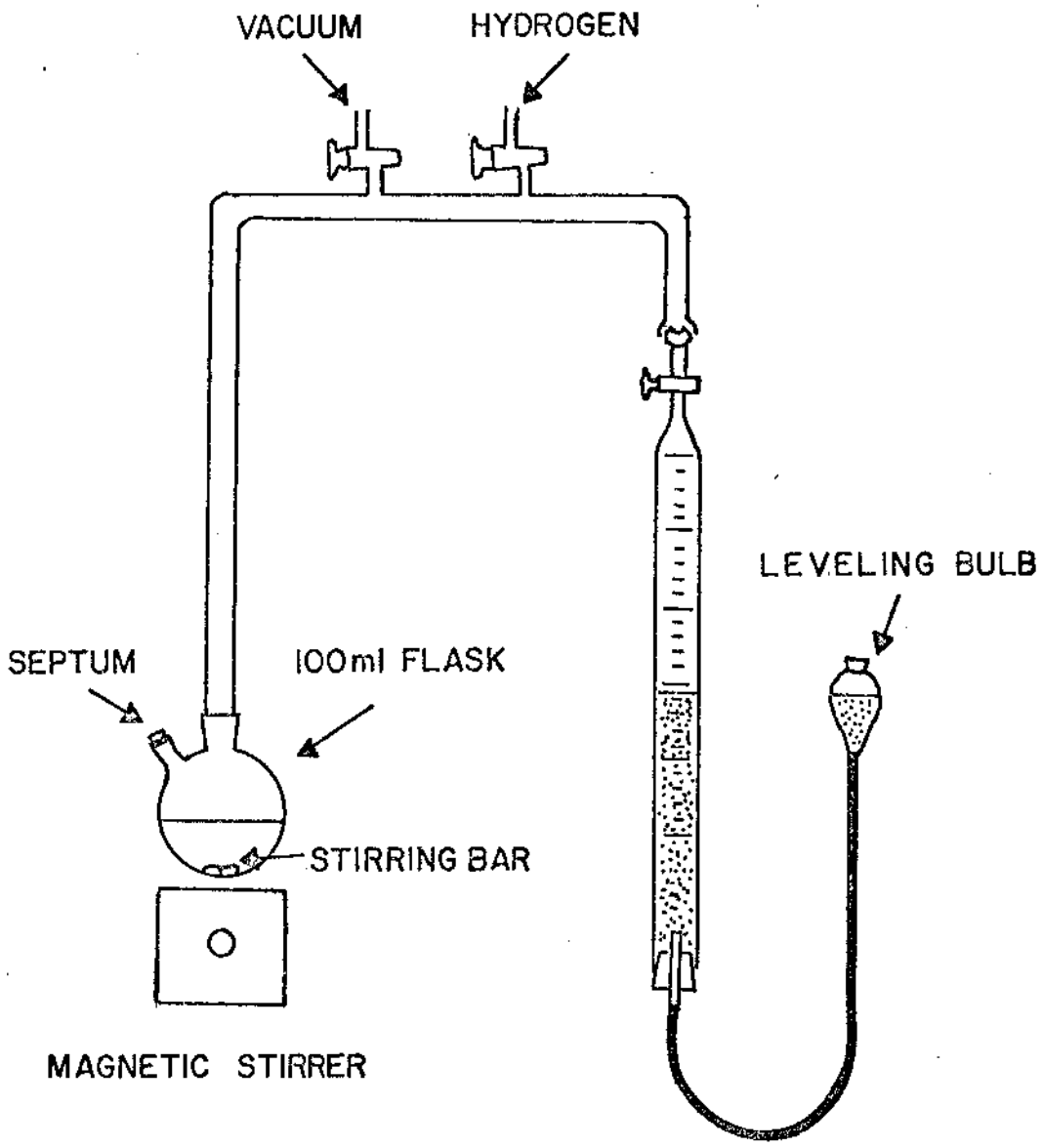
RELATIVE YIELD OF 7-METHYLBICYCLO [3.2.0] HEPT-2-ENE-6-ONE WITH VARIATION OF REACTION CONDITIONS AND SOLVENTS

Solvent	Temperature (°C.)	Reaction Time (hours)	Relative Yield (per cent)
chloroform	61[a]	1½	37
chloroform	27[b]	16	15
chloroform	-78[c]	16	0
hexane	68[a]	1½	35
hexane	27[b]	16	13
hexane	-78[c]	16	6
acteonitrile	80[a]	1½	20
acetonitrile	27[b]	16	3
acetonitrile	-78[c]	16	0

[a]The reaction mixture was refluxed and then worked up.

[b]The reaction mixture was allowed to stand overnight.

[c]The reaction occurred at -78°C. and the mixture was allowed to stand at room temperature over night.


VACUUM
HYDROGEN
LEVELING BULB
SEPTUM
100ml FLASK
STIRRING BAR
MAGNETIC STIRRER

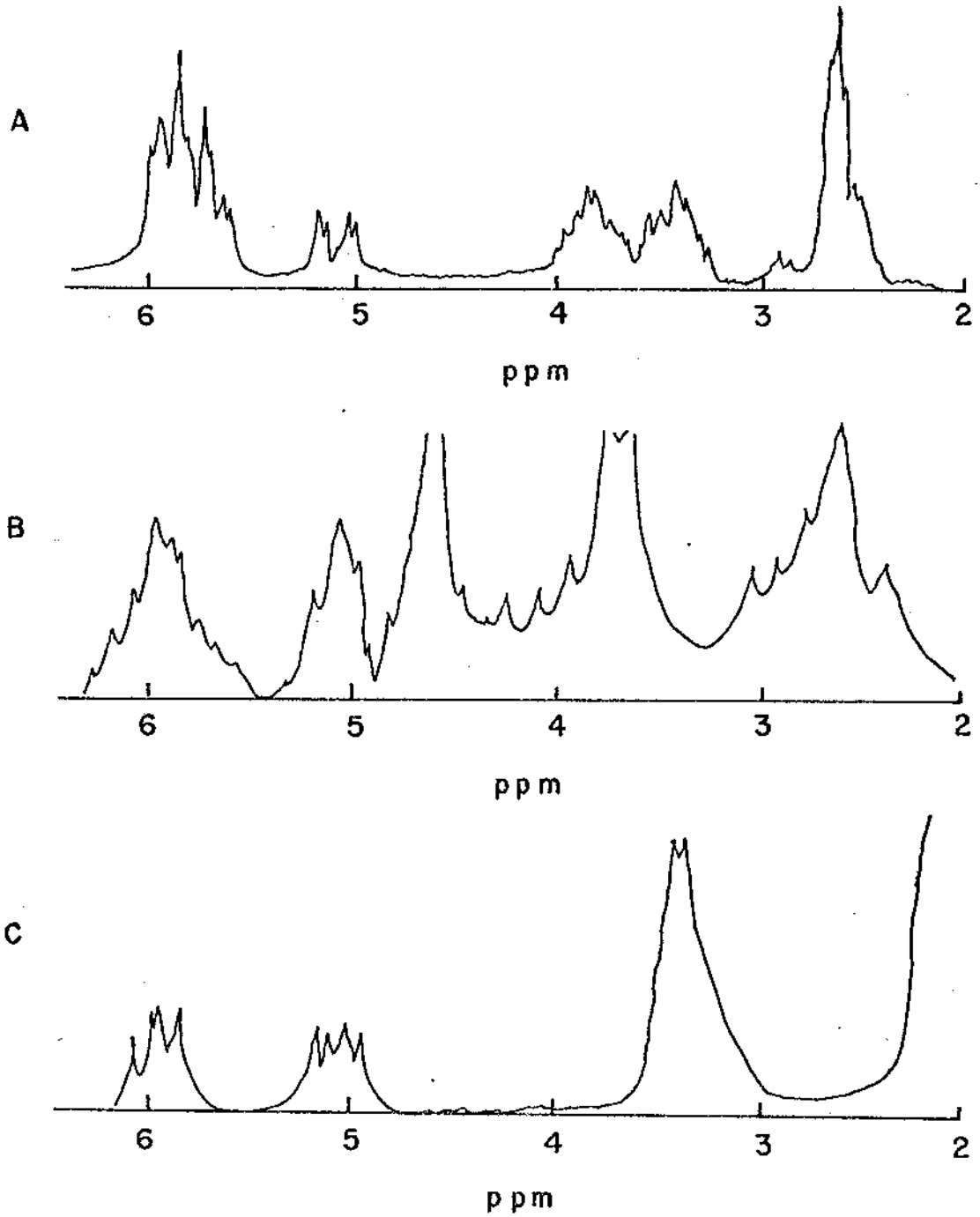


Fig. 2-- P. m. r. spectra of fluoroketene cycloadduct.

A. 7-fluorobicyclo [3.2.0] hept-2-ene-6-one
B. 7-fluorobicyclo [3.2.0] hept-2-ene-6-one + bromine
C. 7-fluorobicyclo [3.2.0] hept-2-ene-6-one + hydrogen

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