I. THE SYNTHESIS, ABSOLUTE CONFIGURATION, AND STEREOCHEMISTRY OF THERMAL DECOMPOSITION OF (+)-3R,5R- AND (+)-3R,5S-3-ETHYL-5-METHYL-1-PYRAZOLINE

II. MECHANISTIC INVESTIGATIONS OF THE THERMAL DECOMPOSITIONS OF 2H-AZIRINES

Thesis by

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In Partial Fulfillment of the Requirements

for the Degree

Doctor of Philosophy

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To my parents

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It is my pleasure to thank the faculty and graduate students of Caltech for contributing to a learning atmosphere characterized by its openness and informality. In particular, the stimulating interaction with the members of the Bergman research group has proven itself invaluable over the past four years.

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ABSTRACT

I. (+)-3R,5R- and (+)-3R,5S-3-ethyl-5-methyl-1-pyrazolines (34T and 34C, respectively) have been prepared in optically active form. Their stereochemistries have been determined by correlation with (-)-R-3-hexanol and (-)-R-2-bromohexane. Pyrolysis of these pyrazolines in the gas phase at 292° allows a complete study of the stereochemistry of the 1-pyrazoline decomposition. 34T yields cis-1-ethyl-2-methylcyclopropane (48C) in nearly racemic form and trans-1-ethyl-2-methylcyclopropane (48T) 22.5% optically active with predominant inversion of the alkyl groups. 34C yields cis-1-ethyl-2-methylcyclopropane (48C) 36.5% optically active with predominant retention of stereochemistry and trans-1-ethyl-2-methycyclopropane (48T) 14.2% optically active with predominant single inversion of the ethyl group.

II. A series of phenyl-substituted 2H-azirines: 3,3-dimethyl-2-phenyl-2H-azirine (33c), 3-methyl-2-phenyl-2H-azirine (33a), 3-ethyl-2-phenyl-2H-azirine (33b), and 2,3-dimethyl-3-phenyl-2H-azirine (33d), were synthesized and their thermal decompositions were investigated. 2-aza-1,3-butadienes were formed as primary pyrolysis products from 33a-c, which indicates that the thermal reaction proceeds via carbon-carbon bond cleavage leading to imino-carbene intermediates. 33d yields 2,3-dimethylindole as its only pyrolysis product, which indicates initial carbon-nitrogen bond

cleavage leading to vinyl nitrene intermediates. Further thermal reactions of the azabutadienes to yield olefins and nitriles, and dihydroisoquinolines were also studied.

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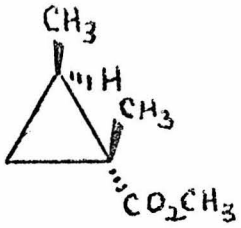
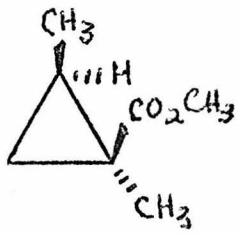
THE SYNTHEIS, ABSOLUTE CONFIGURATION, AND STEREOCHEMISTRY OF THERMAL DECOMPOSITION OF (+)-3R,5R- AND (+)-3R,5S-3-ETHYL-5-METHYL-1-PYRAZOLINE

I. History of Stereospecific 4-Electron Thermal Extrusions

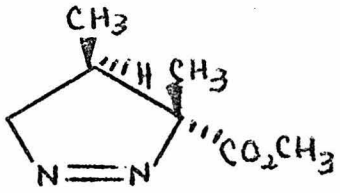
The thermal decomposition of 1-pyrazolines to yield cyclopropanes and nitrogen was first recorded by Buchner in 1888 (2). Until the work of Van Auken and Rinehart in 1962, it was generally accepted that, in the gas phase, substituted 1-pyrazolines stereospecifically decomposed to cyclopropanes which predominantly retained the stereochemistry of the starting pyrazolines. Van Auken and Rinehart demonstrated that (1C) and (1T) exhibit only a slight preference for retaining initial stereochemistry in the cyclopropane products (2C) and (2T) (3).



2C



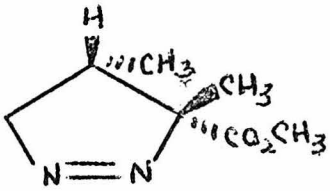
2T



55.5%

44.5%

1C

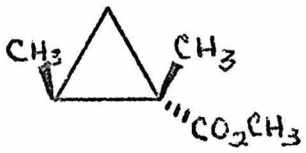


43.5%

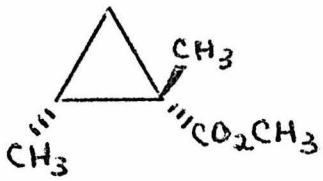
56.5%

1T

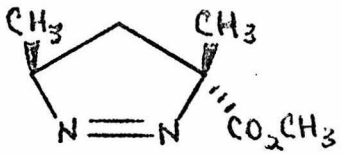
In 1964, McGreer and coworkers demonstrated that pyrazolines (3C) and (3T) show a significant tendency for inverting the stereochemistry of the pyrazolines in the cyclopropane products, (4C) and (4T) (4).



4C



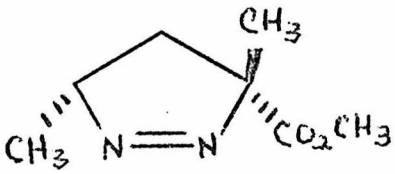
4T



3C

23%

65%



3T

76%

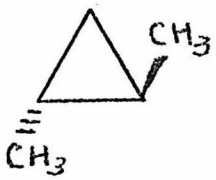
15%

This "inversion" of stereochemistry formally corresponds to inverting the stereochemistry of the substituted carbon atoms an odd number of times in forming the major cyclopropane isomer (net single inversion). Similarly, zero or an even number of inversions must be performed in arriving at the minor product (net retention).

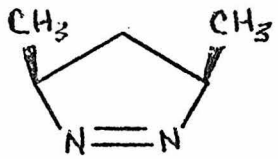
As demonstrated by the work of Van Auken and Rinehart, and McGreer (3, 4), the nature of the substituents can have a pronounced effect upon the stereochemical course of this reaction. Since 1965, much effort has been directed toward study of substituted pyrazolines in an effort to elucidate steric effects and evaluate the inherent mechanistic preferences involved in the thermal decompositions of 1-pyrazolines (5a-5i).

When the two carbon atoms which are involved in the inversion processes are made equivalent, the tendency for an odd number of inversions remains. This is demonstrated by pyrazolines (5C) and (5T) (Scheme Ia) (5b, c).

6C



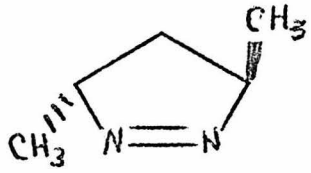
6T



33.2%

66.1%

5C



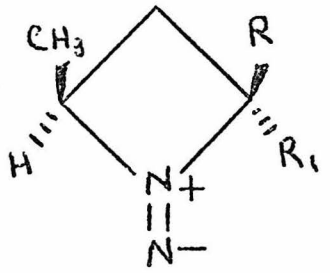
72.6%

25.4%

5T

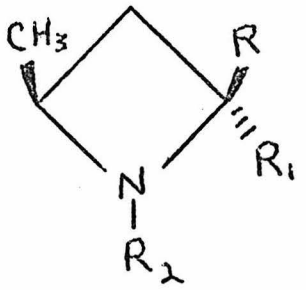
Scheme Ia

The net single inversion involved in formation of the major cyclopropane product is not restricted to the thermal decomposition of 1-pyrazolines, but also appears to be present in several other 4-electron fragmentation processes. The interesting work of Freeman and coworkers involving the thermal decomposition of a series of diazenes shows a stereospecificity closely resembling that of the 1-pyrazolines (6). Freeman investigated the thermal decomposition of the diazenes (7C) and (7T) generated from three different types of precursors: 8C, 9C, 9T, 10C, and 10T.



7C: R = CH_3 ; R_1 = H

7T: R = H ; R_1 = CH_3



8C: R = CH_3; R_1 = H; R_2 = H

9C: R = CH_3; R_1 = H; R_2 = NO

9T: R = H; R_1 = CH_3; R_2 = NO

10C: R = CH_3; R_1 = H; R_2 = NH_2

10T: R = H; R_1 = CH_3; R_2 = NH_2

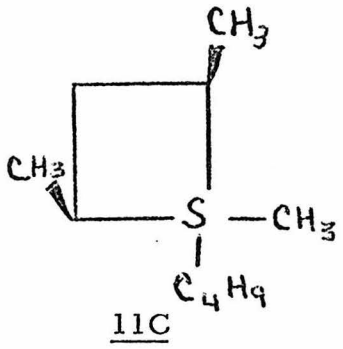
The cyclopropanes formed from the 7C decomposition show this process to be more stereospecific than the decomposition of either the analogous 1-pyrazolines (5C) or (5T). The 7T decomposition shows a specificity similar to that of 5C (Table 1). Freeman rules out the possibility of diazene rearranging to pyrazoline prior to decomposition by attempted detection of pyrazolines, 1-pyrazolines being stable under the reaction conditions.

Trost and coworkers enunciate the similarity of the decomposition of 1-pyrazolines and the (presumably) tetraalkyl sulfur compounds 11C and 11T at -78°C (Scheme Ib) (7).

Table 1

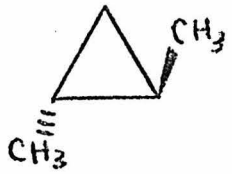
Products of Azetidine Deaminations

Reaction	Solvent	Temp., °C	% Yield Hydrocarbons	% Relative Yields		
						Olefins
8C + HNF_2	neat	0	65	16.8	83.2	< 0.3
9C + $Na_2S_2O_4$	25% aqueous EtOH	40	67	15.6	84.4	< 0.3
9T + $Na_2S_2O_4$	25% aqueous EtOH	40	67	68.5	31.5	< 0.3
10C + HgO	EtOH	40	71	15.5	84.5	< 0.3
10C + HgO	1-pentanol	140	not determined	18.7	81.3	< 0.3
10T + HgO	EtOH	40	71	67.7	32.3	< 0.3

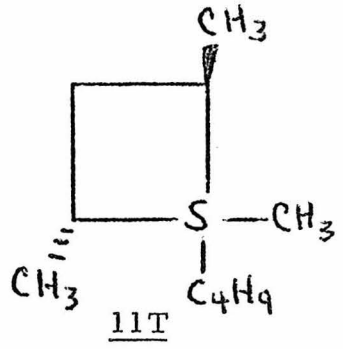


11C

8.5%



91.5%



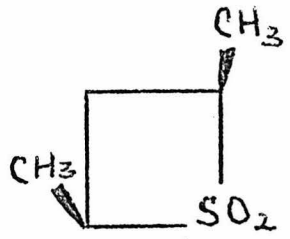
11T

88.6%

11.4%

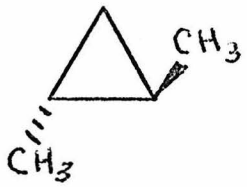
Scheme Ib

Cyclopropanes are obtained in approximately 25% yield. Sulfones (12C) and (12T) give approximately 60% yields of hydrocarbons, but the stereospecificity of the reaction is greatly reduced relative to the other 4-electron fragmentation processes mentioned (7).

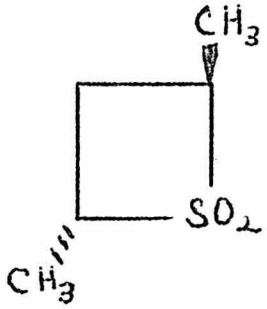


12C

33.8%



40.1%

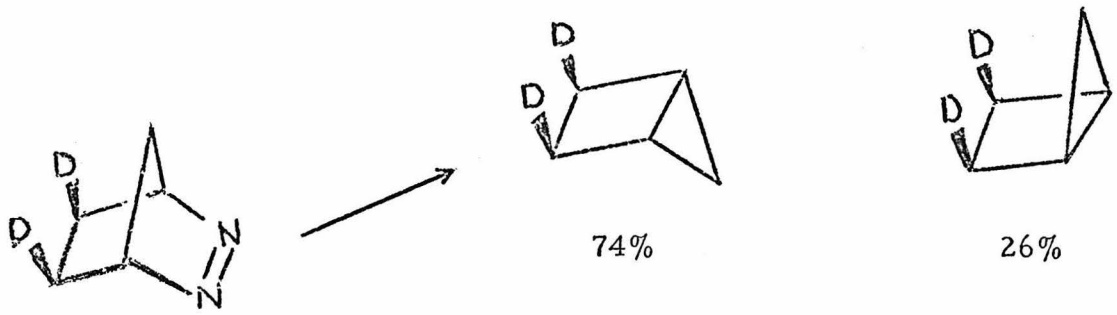


12T

39.2%

32.9%

Another class of compounds, containing a saturated three-carbon chain attached at each end of an azo unit, is the family of substituted 2,3-diazo-bicyclo[2.2.1]heptyl compounds. 13 exhibits thermal decomposition products representative of this type of azo compound (see Scheme I).

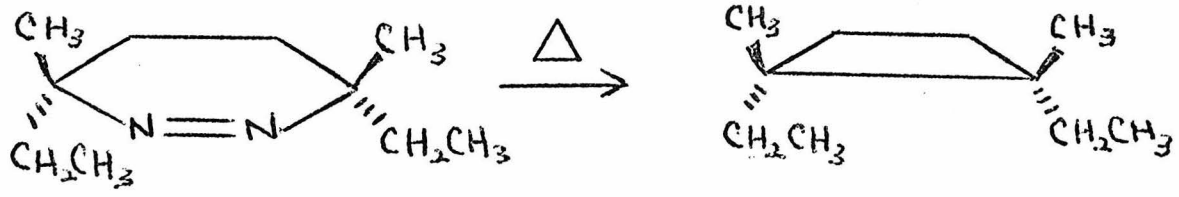


13

Scheme I

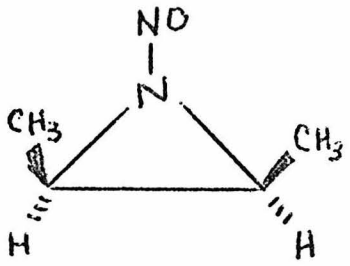
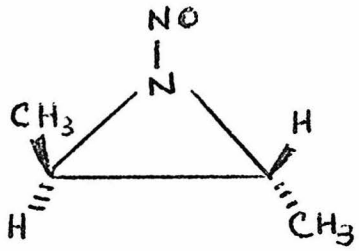
Both cyclopropanes formed from 13 involve zero or an even number of inversions. The geometry of this molecule imposes special constraints on the inversion modes available to the carbon atoms; the relevance of this system to the 4-electron fragmentation of 1-pyrazolines will be discussed in another section.

Azo compounds containing four or more saturated carbon atoms in a chain do not show thermal decomposition stereochemical behavior analogous to the pyrazolines. Azo compound (14) shows almost complete retention of stereochemistry in its cyclobutane products (9).



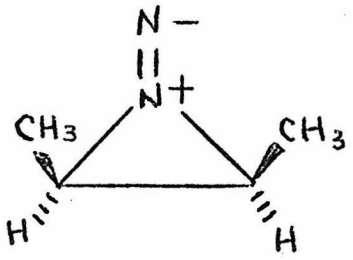
14

There are few reports of stereospecific 4-electron fragmentation processes involving only a two carbon-atom bridging chain. However, several cases have been reported where there is strong evidence for stereospecific formations of olefins from three-membered rings. The N-nitroaziridines (15C) and (15T) were generated from the corresponding aziridines and nitrosyl chloride at low temperatures and were decomposed by warming to room temperature (10).

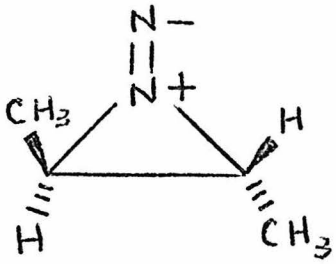
	cis-2-butene	trans-2-butene
	99.1%	0.9%
15C		
	0.3%	99.7%
15T		

Freeman and Graham generated diazenes (16C) and (16T) from the appropriate aziridine and difluoroamine. Each diazene

rendered the 2-butene of retained stereochemistry (better than 96% retention) (11).



16C

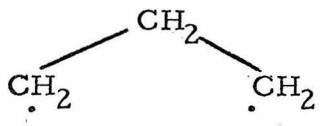


16T

II. Mechanistic Considerations

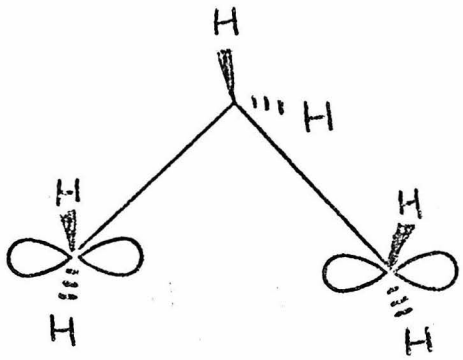
A. The 0, 0-Trimethylene Diradical

In 1968, Hoffman performed an extended Hückel Theory (EHT) calculation on the trimethylene diradical, (17) (12).



(17)

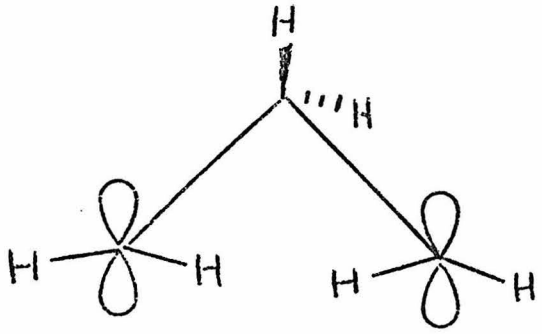
He fixed the two terminal methylene groups as trigonal (sp^2) and calculated the total energy as a function of the central C-C-C angle and rotations of the terminal methylene groups. Hoffman's calculations predicted the lowest energy species (for central bond angles less than 80°) to be the anticipated 90, 90 structure, where the plane of both sets of terminal methylene hydrogens forms a 90° angle with the plane defined by the three carbon atoms.



90, 90

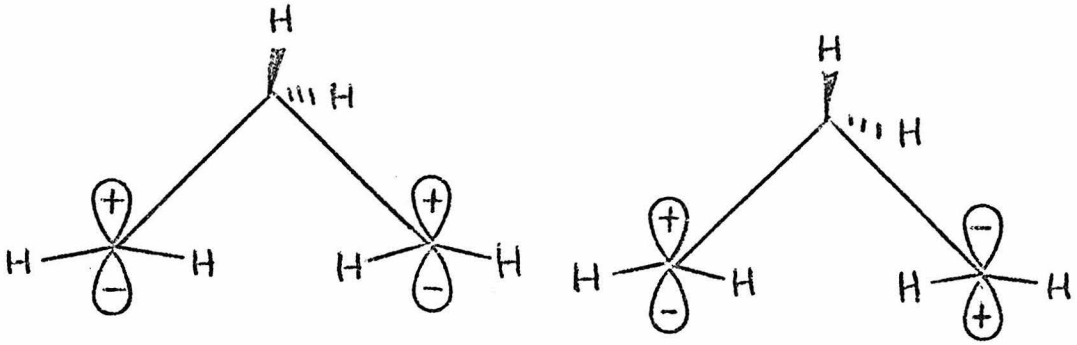
A surprising result of these calculations was that a minimum at a central bond angle of 125° was also calculated. The geometry of

this species had the plane of each set of terminal methylene hydrogens lying in the same plane as the one defined by the three carbon atoms (0, 0 structure).



0, 0

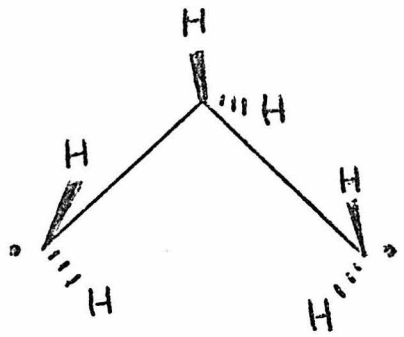
Hoffman's calculations predicted the lowest energy reaction path between the 0, 0 structure and cyclopropane to be via conrotation of the terminal methylenes over a barrier of about 1 kcal. This preference for conrotation is based on the assignment of the antisymmetric π-type molecular orbital for trimethylene as the HOMO of the system.



symmetric (S) antisymmetric (A)

This is rationalized by postulating that the central methylene C-H σ orbitals strongly mix with the S π-type molecular orbital and destabilize the S configuration while leaving the A configuration unaffected. Orbital symmetry (13) considerations require conrotation of the two-electron A system to cyclopropane.

It should be recognized that Hoffman's calculations neglected configuration interaction, but were nevertheless in qualitative agreement with later ab initio SCF-MO calculations, including configuration interaction, by Salem (14) and ab initio GVB calculations by Goddard (15). However, the last two calculations did predict that if the terminal methylene groups are allowed to be pyramidal, the lowest energy structure at central bond angles greater than 110° is the canted diradical (18) or so-called "crab" structure.

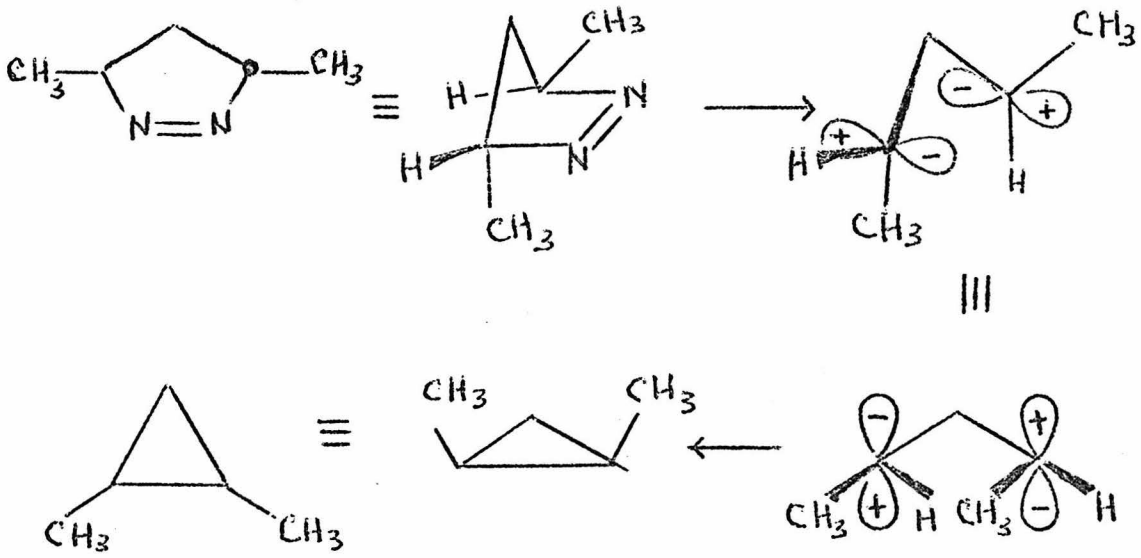


18 - 90C, 90C

Structure (18) is predicted to experience no barriers for conversion to cyclopropane.

Crawford has invoked the 0, 0 diradical as an intermediate in a mechanism capable of explaining the net single inversion observed in the thermal decomposition of 1-pyrazolines (5a, h). The two

major tenets of this mechanism are 1) concerted or fast sequential extrusion of N_2 from an envelope conformation of pyrazoline, with concomitant formation of the 0, 0 diradical; 2) conrotatory ring closure of the 0, 0 radical to cyclopropane. This mechanism is represented for trans-3, 5-dimethyl 1-pyrazoline in Scheme II.

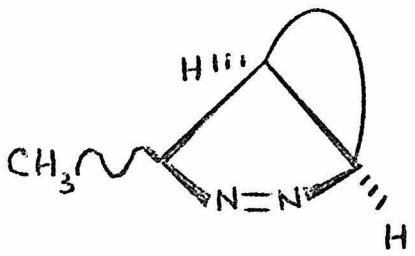


Scheme II

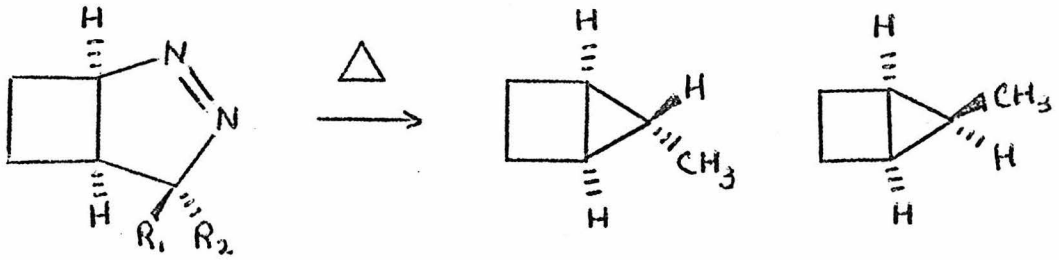
The normal central C-C-C bond angle of the pyrazoline in the envelope conformation is 109°, implying that no significant change in geometry is necessary for conversion to the 0, 0 diradical. The minor product of the pyrazoline decompositions cannot be

rationalized by this mechanism. Consequently, invocation of a competing reaction pathway, such as disrotatory closure from the 0, 0 diradical or a freely rotating diradical, becomes necessary.

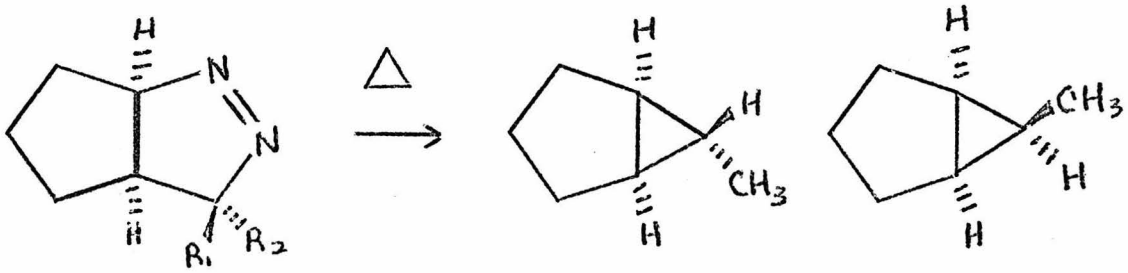
While the 0, 0 diradical conveniently explains the predominant single inversion, there are two experiments which raise questions as to its applicability (16, 17). Both experiments are based on the idea of creating enough strain in the purported 0, 0 diradical to distort it from its favored geometry. This was accomplished by connecting the 3- and 4-carbons of a pyrazoline with a short, carbon-atom bridge and placing a methyl group label on the 5-carbon of the pyrazoline.



The 0, 0 diradical from such a pyrazoline should be greatly distorted from its preferred geometry, and decreased product selectivity would be anticipated. Independent work of Bergman (16) and Crawford (5i) on pyrazolines (20N&X) and (21N&X), respectively, do not show any significant decreased stereospecificity in the cyclopropanes formed.



20N:	$R_1 = CH_3$; $R_2 = H$	54.5%	31.7%
20X:	$R_1 = H$; $R_2 = CH_3$	8.2%	31.3%

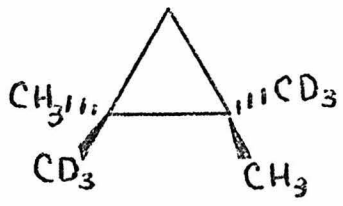


21N:	$R_1 = CH_3$; $R_2 = H$	67.2%	21.2%
21X:	$R_1 = H$; $R_2 = CH_3$	8.1%	72.8%

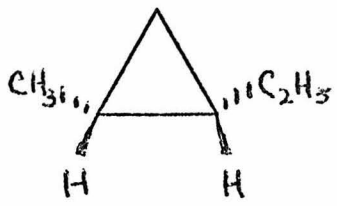
B. The "Other" Trimethylene Diradical

A trimethylene diradical has been suggested as the intermediate involved in formation of olefins and stereomutation observed upon pyrolysis of cyclopropanes (17). Is this diradical identical with the 0, 0 diradical, a postulated intermediate in the thermal decomposition of 1-pyrazolines?

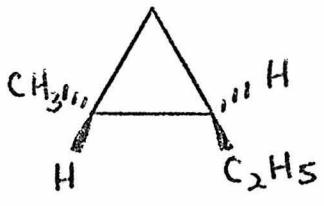
If the intermediate obtained from cyclopropane ring opening favored conrotatory ring closure, one would predict that racemization of an optically active cyclopropane should proceed much more rapidly than geometrical isomerization. Both Berson (18) and Bergman (19) have shown independently using optically active substituted cyclopropanes 18C, 19C and 19T that in these systems racemization is competitive with geometrical isomerization. Berson and Bergman pyrolyzed cyclopropanes (18), and (19C) and (19T), respectively.



18



19C

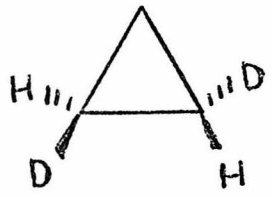


19T

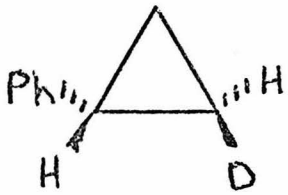
In a related experiment, Wilcott has shown that stereomutation of vinyl cyclopropane is consistent with a randomly rotating intermediate (20). These results imply that the intermediate generated

by cyclopropane ring opening is probably not identical with the intermediate formed upon 1-pyrazoline decomposition (29).

It has been pointed out by Berson that the substituents on the cyclopropanes studied may alter the true stereoelectronic preferences of the parent trimethylene diradical (18). Berson and Pedersen have recently investigated this possibility in an elegant study (21). A detailed kinetics analysis of the stereomutation of optically active trans-cyclopropane-1, 2-d_2-(19a) yields relative rate constants for racemization and geometric isomerization most consistent with a coupled rotation of methylene groups. In an accompanying publication, Berson and coworkers (22) have reported compelling evidence for at least 78-82% synchronous double rotation in the stereomutation of 1-phenylcyclopropane-2-d (19b). However, these experiments cannot differentiate between conrotatory and disrotatory synchronous rotations.



19a

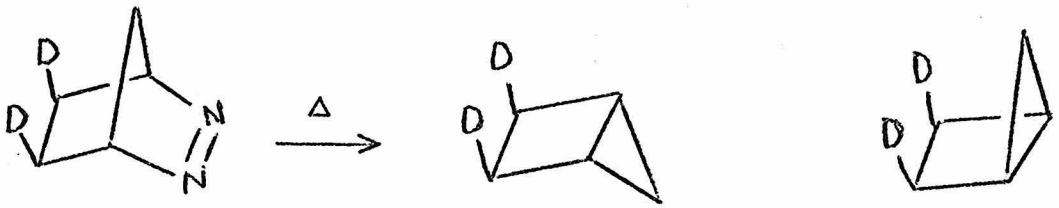


19b

The work of Berson would seem to suggest that either substituents can have a very subtle and pronounced effect on the behavior of the trimethylene intermediate, or that more than one bond is breaking in disubstituted cyclopropane pyrolysis.

C. The Sequential Cleavage Mechanism

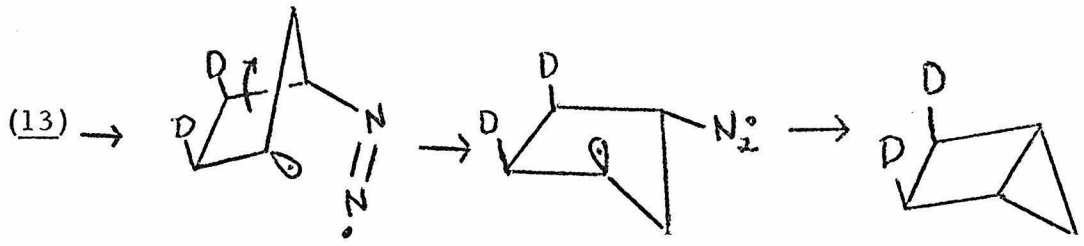
The mechanism which to date seems the most logical alternative to a trimethylene intermediate was introduced by Roth and Martin (8) and is commonly referred to as the "sequential cleavage mechanism." In 1967, Roth and Martin observed predominant double inversion upon pyrolysis of 13 (Scheme III).



13 75% 25%

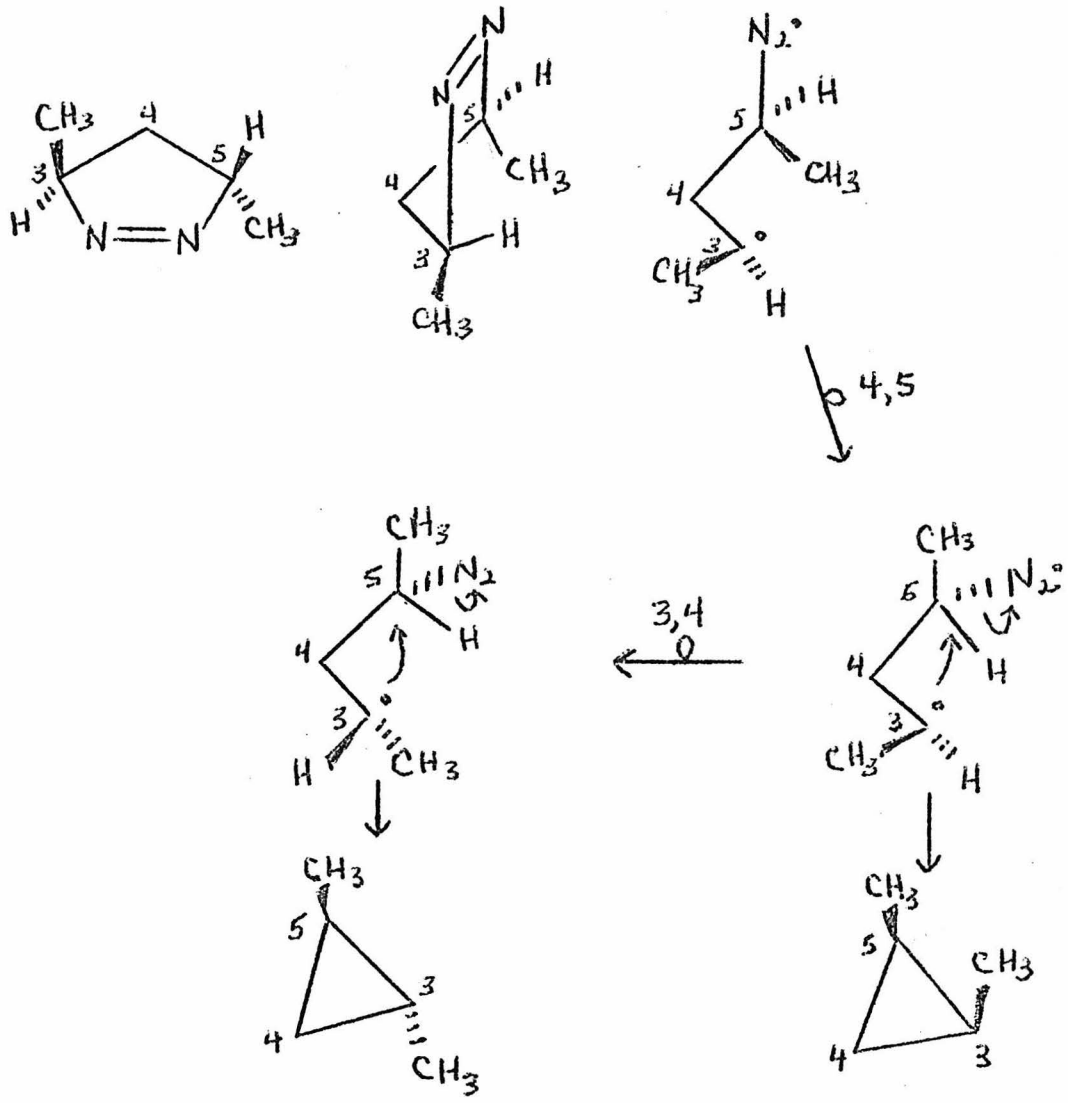
Scheme III

They assumed initial cleavage of only one C-N bond, rehybridization of the carbon radical orbital, and backside displacement of the diazo fragments (Scheme IV) (8).



Scheme IV

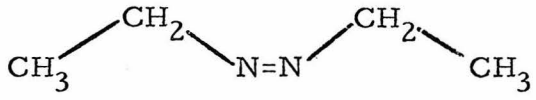
These workers explained the minor product as occurring from a nitrogen-free diradical. An adaptation of this mechanism to the 3, 5-dimethyl pyrazoline decomposition is outlined in Scheme V.



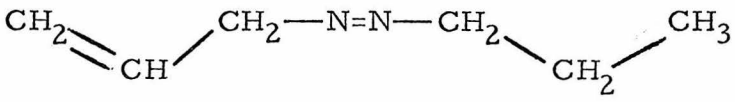
Scheme V

As demonstrated, the sequential cleavage mechanism can also explain the minor product from pyrazoline decompositions. Apparent sequential cleavage has been observed for the fragmentation

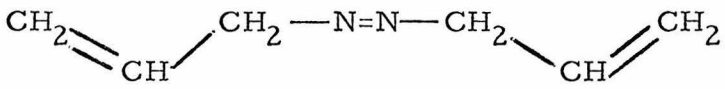
of certain acyclic azo compounds. Compound (23) decomposes with an activation energy of 48.5 kcal/mole, while both compounds (24) and (25) decompose with activation energies of 36 kcal/mole (23, 24).



(23)



(24)

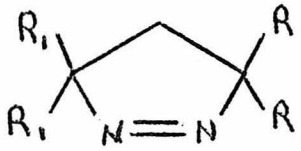


(25)

One would expect 24 to have an approximately 12 kcal/mole lower activation energy than 23 with either sequential or simultaneous rupture of the C—N bonds. However, if both C—N bonds are breaking in the rate determining step, 25 should have a transition state stabilized by an additional 12 kcal/mole over 24.

Crawford has looked at a series of 1-pyrazolines and relied on utilization of a secondary deuterium kinetic isotope effect to assess the likelihood of sequential C—N bond cleavage (5g). The rate constants for decomposition of compounds (26), (30), and (31)

are consistent with a simultaneous bond cleavage mechanism and a k_H/k_D = 1.1 per D.



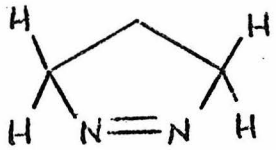
<u>26</u>: R = R_1 = H

<u>30</u>: R = H; R_1 = D

<u>31</u>: R = R_1 = D

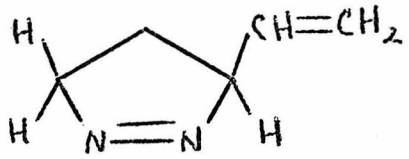
Unfortunately this conclusion is ambiguous, since utilizing a k_H/k_D = 1.2 per D, the decomposition rate constants are consistent with a sequential bond cleavage process. Work by Seltzer (25) indicates that values of k_H/k_D between 1.1 and 1.2 per D are very typical for secondary deuterium kinetic isotope effects.

Crawford and coworkers performed another study with 1-pyrazolines (<u>26a</u>), (<u>27</u>), (<u>28C & T</u>), and (<u>29</u>) (26).



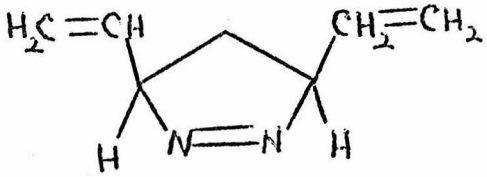
<u>26a</u>

E_a = 42.4 kcal/mole



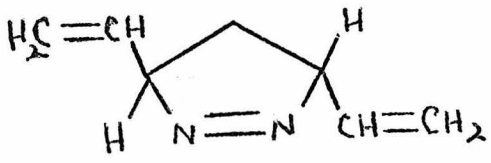
<u>27</u>

E_a = 32.3 kcal/mole



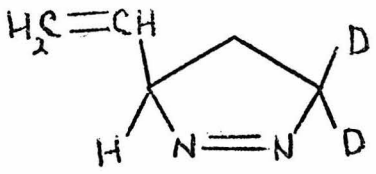
<u>28C</u>

E_a = 22.2 kcal/mole



<u>28T</u>

E_a = 25.1 kcal/mole

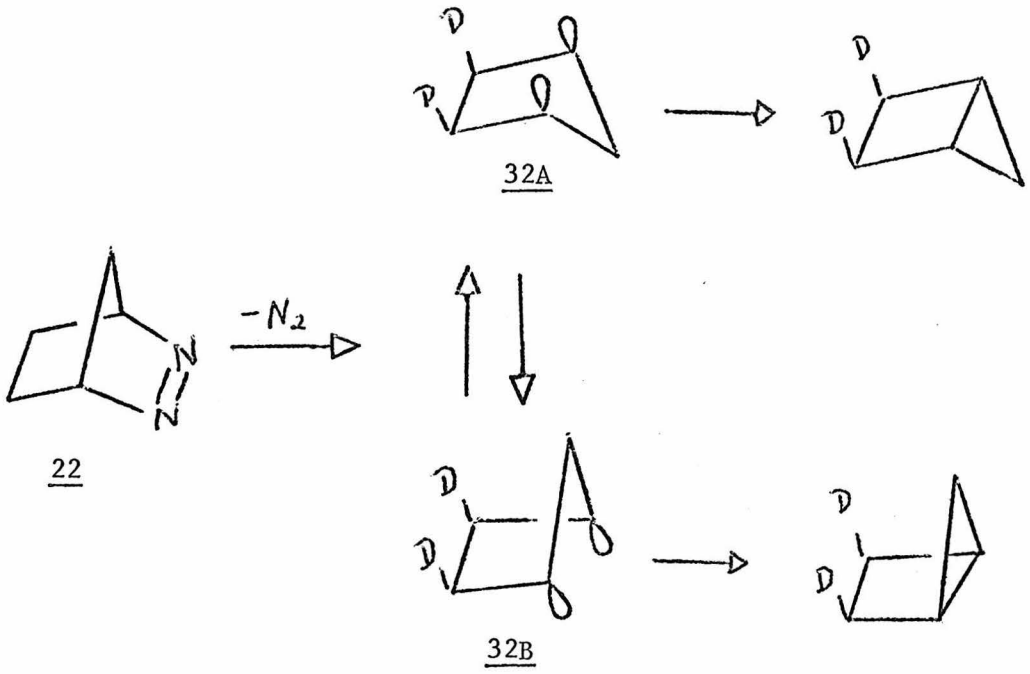


29

27 shows an approximately 10 kcal/mole stabilization of its transition state over 26a, but in this series the divinyl compounds 28C & T show an additional 10 kcal/mole decrease in activation energy relative to 27. Compound (29) decomposed with an activation energy indicative of a secondary deuterium kinetic isotope effect of 1.1 per D relative to 27. This study indicates that sequential C—N bond cleavage is not occurring for this particular series of 1-pyrazoline decompositions.

D. The Recoil Mechanism

Allred and coworkers have investigated several 2,3-diazabicyclo[2.2.1]heptyl systems (27) and have reported stereochemical observations similar to the results of Roth and Martin (8) for 13. However, an entirely different mechanistic interpretation was postulated by these workers. Allred suggested linear extrusion of nitrogen results in a "recoil" of the carbon atoms, followed by ring closure (Scheme VI).

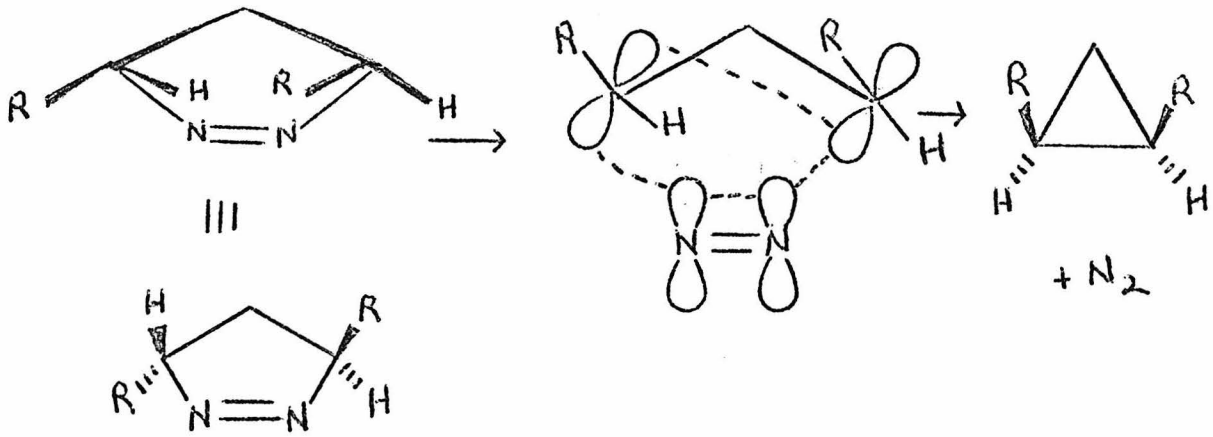


Scheme VI

The minor product from this decomposition is explained by some interconversion of diradicals (32A) and (32B).

E. Concerted Formation of Cyclopropane

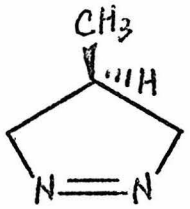
The feasibility of concerted 2s + 2a formation (13) of cyclopropane and nitrogen has been discounted mainly as a result of geometrical strain arguments (1a). For an orbital symmetry preferred 2s + 2a process, the reaction must proceed via a twisted transition state. One possibility is shown in Scheme VII (17).



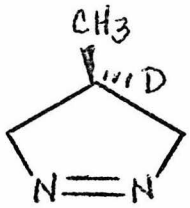
Scheme VII

In systems like trimethylene, where very subtle stereoelectronic interactions are in play, it is dangerous to make judgments about what constitutes a "reasonable" transition state.

In a study designed to assess the likelihood of an intermediate being involved in 1-pyrazoline decompositions, Crawford and coworkers pyrolyzed 35 and 35-D (5c);



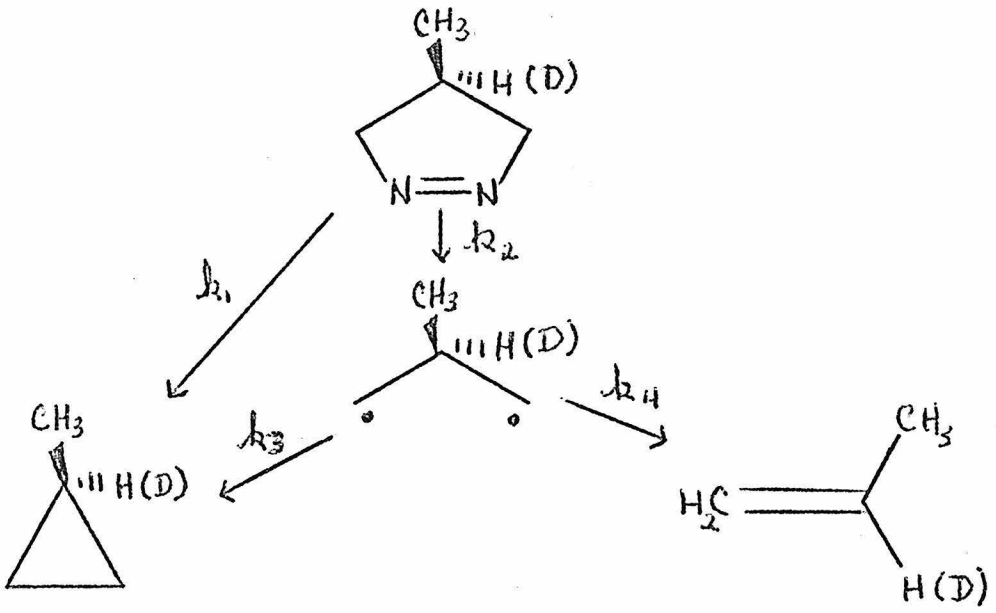
35



35-D

the product mixture of these pyrazolines is composed of over 30%

olefin (2-methylpropene). Crawford observed a large increase in the cyclopropane to propene ratio for (35-D) relative to (35). Since the decomposition rate of pyrazoline remained constant for both 35 and 35-D, the authors concluded that 2-methylpropene and cyclopropane must be formed from the same intermediate. However, they did not consider the possibility of concerted formation (k_1) of cyclopropane occurring simultaneously with formation of an intermediate (k_2) which decomposes to cyclopropane and olefin (Scheme VIII).



Scheme VIII

As much as 40% concerted reaction could be occurring if one presumes a primary isotope effect of 3.0 for the rate of intermediate rearranging to propylene; an isotope effect of 1.8 is consistent with 100% of the products arising through an intermediate (5c).

Crawford's experiment does indicate the necessity of formation of an intermediate after nitrogen extrusion from (35) and (35-D); however, the intermediate need not be the precursor to all the pyrolysis products. The importance of the intermediate for other 1-pyrazoline systems where olefins typically comprise less than 4% of the product distribution has not been evaluated.

F. Reaction Dynamics Mechanisms

In 1972, Freeman (6) suggested a mechanistic approach to the trimethylene intermediate problem which could "simultaneously accommodate the results of the nitrogen elimination reactions and cyclopropane isomerizations." It was suggested that product distributions arising from the trimethylene intermediate were dictated by the intermediate's precursor. In other words, reaction dynamics could control the course of different reactions proceeding, in part, on a common energy surface.

A mechanistic postulation along similar lines was postulated in 1974 by Doering (28) for cyclopropane stereomutation. Doering introduced the concept of the continuous diradical, a transition state capable of stereochemical preference as a result of dynamic aspects involved in bond rupture.

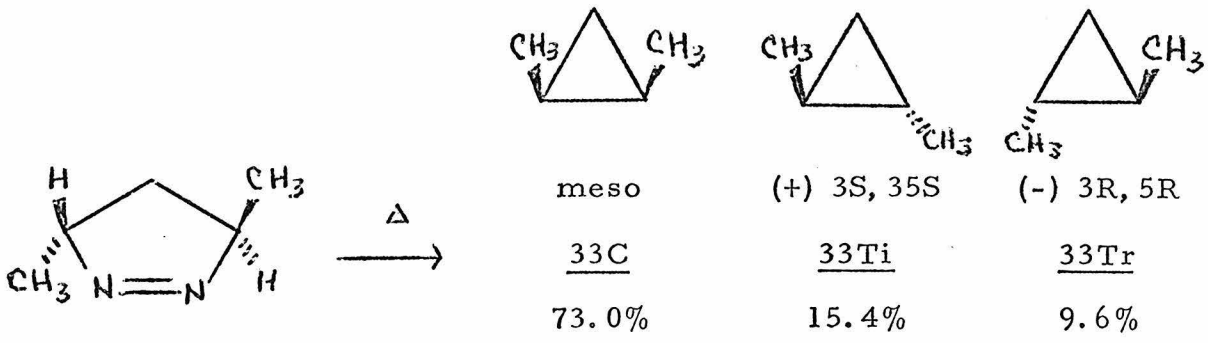
The reaction dynamics (6, 28) approach solves the trimethylene ambiguity by stating that a given structure on an energy surface may display behavior dependent upon its momentum. To the extent that trimethylene's momentum is determined by how it is

generated, the diradical formed from pyrazoline decomposition may exhibit reaction preferences different from those of the diradical formed from cyclopropane bond cleavage.

III. Results and Discussions

A. Nature and Purposes of This Study

Crawford has observed that at least 6% of the cyclopropane products from pyrolysis of optically active 3, 5-dimethyl-1-pyrazoline (33) must be formed via a chiral reaction path (Scheme IX) (5h). However, 73% of the product mixture from 33 was the meso cis-1, 2-dimethylcyclopropane (33C).



(+) 3R, 5R

33

meso

33C

73.0%

(+) 3S, 35S

33Ti

15.4%

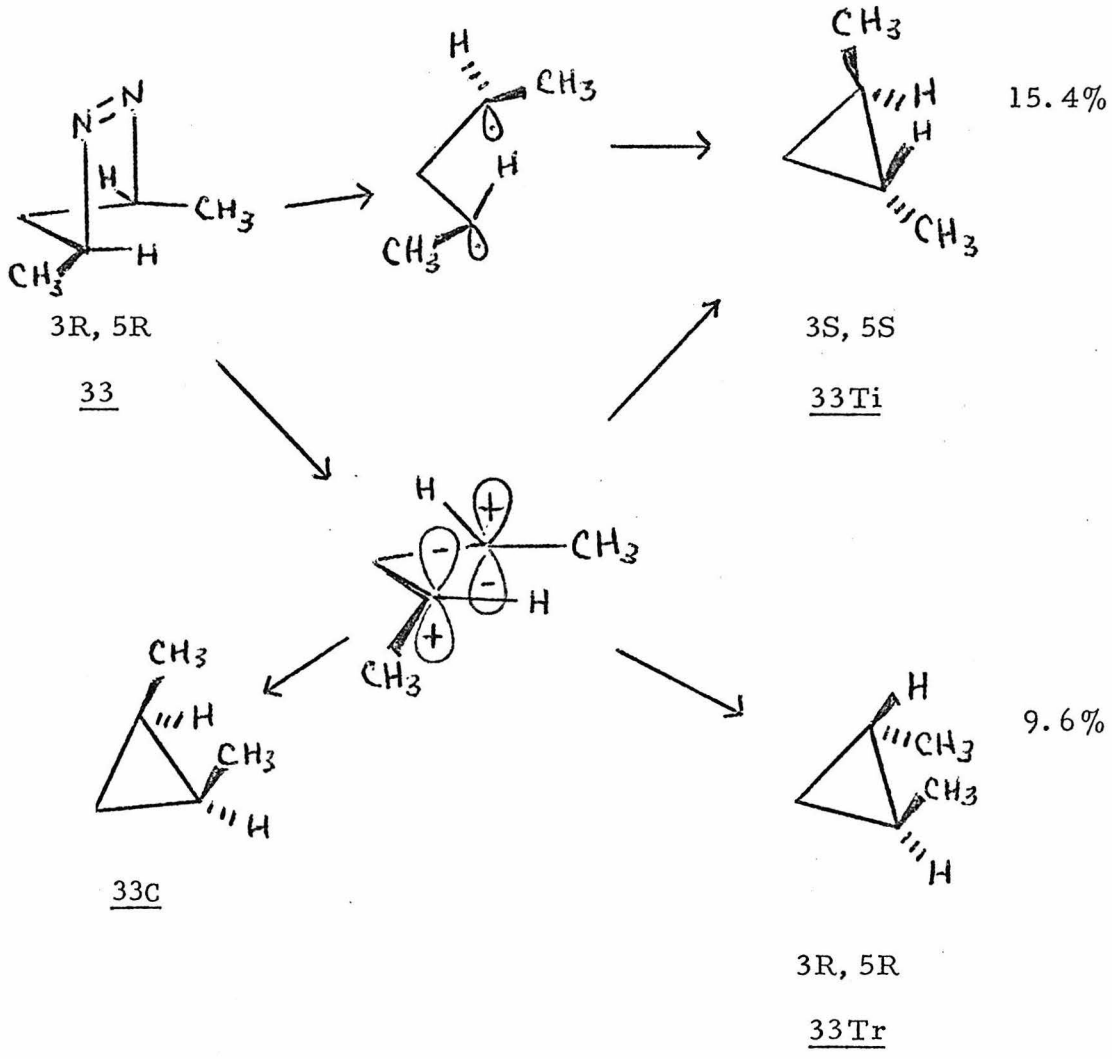
(-) 3R, 5R

33Tr

9.6%

Scheme IX

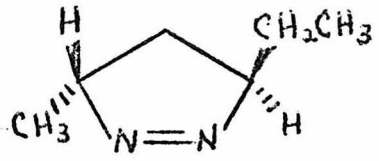
The authors invoked the recoil mechanism to account for the preferred double inversion in the minor trans products (see Scheme X).



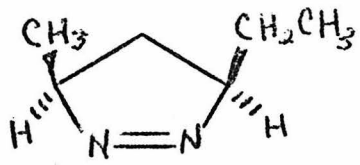
Scheme X

Crawford also has pointed out that the 6% of optically active trans-cyclopropane could also be arising from the sequential cleavage mechanism of Roth and Martin (see Scheme IV). The major cyclopropane product from 33 is meso; consequently, one cannot distinguish between the processes of double retention or double inversion for 33C.

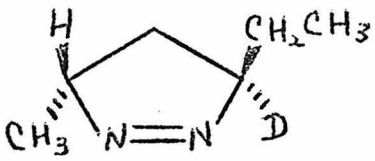
Stimulated by the possibility of a large proportion of chiral products being involved in pyrazoline decompositions, we chose to investigate a system where 100% of the stereochemical course of reaction could be evaluated. For this study the series of optically active 1-pyrazolines (34C & T), (36C & T) was synthesized.



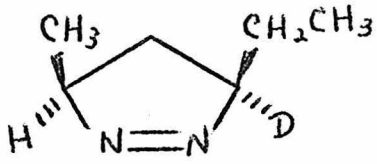
34T, (+) 3R, 5R



34C, (+) 3R, 5S



36T, (+) 3R, 5R



36C, (+) 3R, 5S

Our study of the thermal decomposition of these pyrazolines was designed to answer the following questions.

1) What is the minimum percentage of cyclopropanes being formed via chiral routes? All the cis- and trans-cyclopropane product mixtures formed from 34C & T and 36C & T are potentially optically active. Consequently, the stereochemistry for 100% of the reaction products can be studied, and a minimum estimate of the importance of chiral pathways can be made.

In evaluating the intervention of a 0, 0 diradical intermediate, a knowledge of the optical purity of the major cyclopropanes formed is imperative (see Section III-E). The 0, 0 diradical is achiral and any cyclopropanes formed from such an intermediate must be racemic. However, racemic cyclopropanes do not necessitate the existence of an achiral intermediate.

2) Do cis- and trans-3, 5-dialkyl-1-pyrazolines decompose by similar reaction pathways? While net single inversion is observed for the decomposition of both cis and trans pyrazolines, the complete stereochemistry of decomposition has never been followed. In a system where the balance of steric and electronic effects appears to be so delicate (6, 18-22, 28), and where reaction routes could be governed by dynamic effects, this is an important question.

Racemic major product from both 34C & T would not necessitate similar decomposition paths, or even achiral paths. However, if, for example, 34C gave racemic products while 34T gave chiral products, one is obligated to either propose fundamentally different mechanisms (and an explanation why this is reasonable) or suggest a mechanism which accommodates all the results via chiral routes.

Our study will probably not unambiguously answer this question, but considerably more insight into the nature of cis-trans-pyrazoline decomposition modes will be gained.

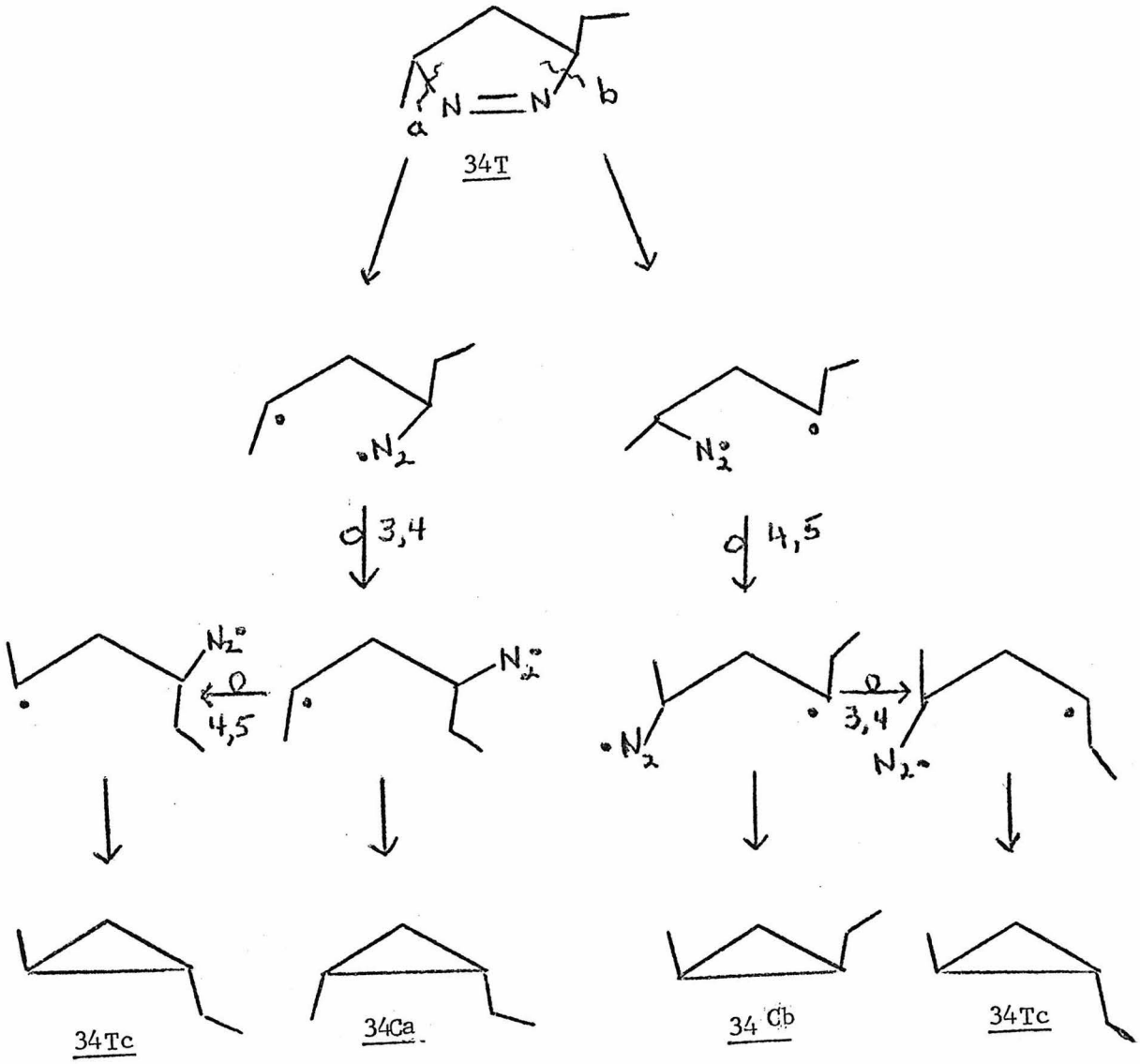
3) Can the sequential cleavage mechanism account for a significant portion of the cyclopropanes formed? If the sequential cleavage mechanism is operative in 1-pyrazoline decompositions,

one would expect products to be formed by the sequence depicted in Scheme XI (1a).

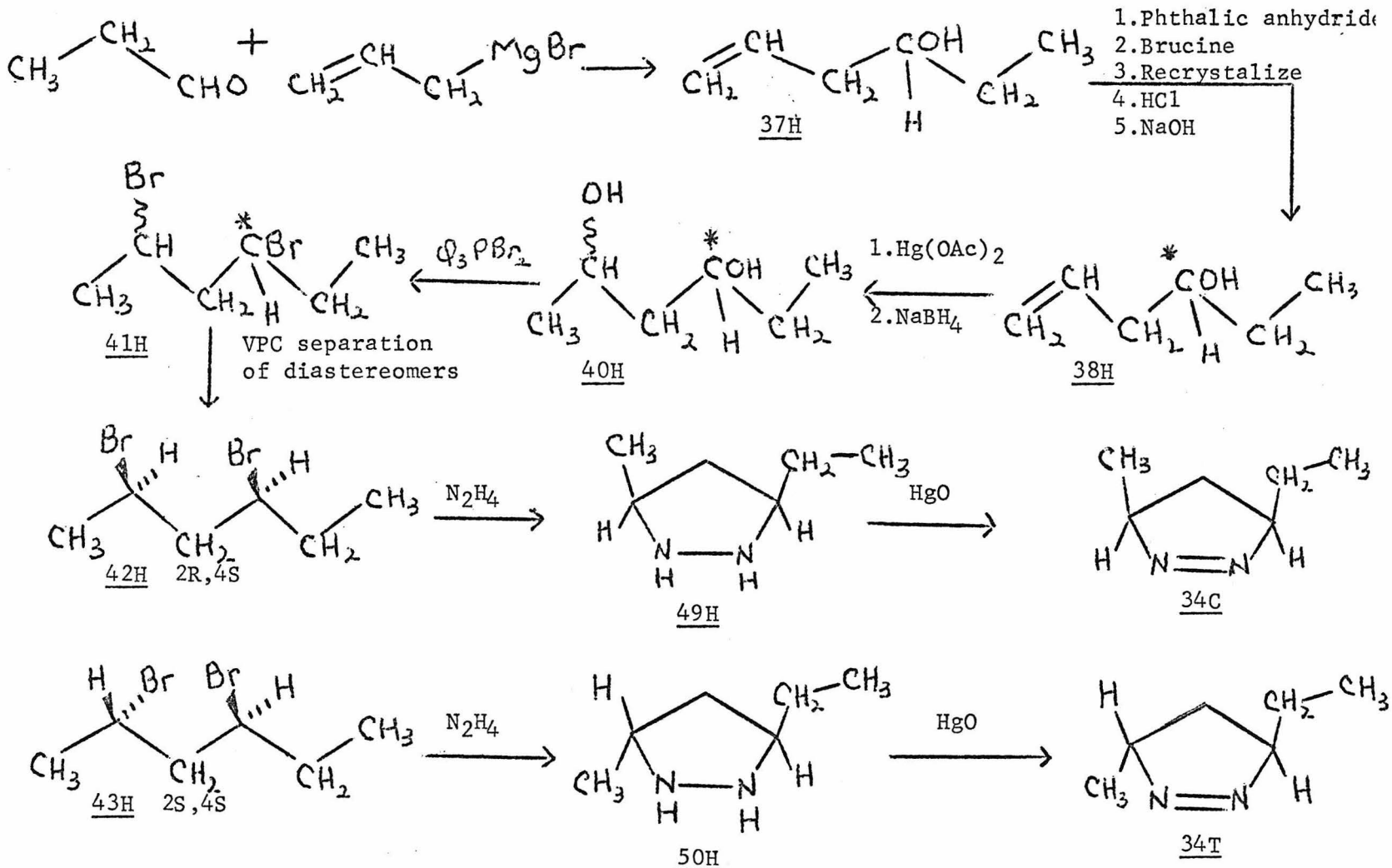
Since bonds a and b probably break with equal facility in 34T (similar stabilities of the radicals formed), 34Ca and 34Cb would be formed in equal quantities. It is interesting that if the minor product also arises entirely via this mechanism, its stereochemistry should be doubly inverted from that of the starting pyrazoline as is observed for 33Ti, Scheme IX. By substituting a deuterium at either the 3- or 5-carbon, the rate of bond breaking at either b or a, respectively, should be retarded by approximately 10% (k_H/k_D = 1.1) (25). For 36T, we would predict enhancement of the deuterated analogue of 34Ca relative to the analogue of 34Cb. This prediction is based on the assumption that no deuterium secondary kinetic isotope effects occur after the decomposition step. Identical product distributions for 34C and 36C, and 34T and 36T would provide confirmation of this assumption.

B. Synthesis

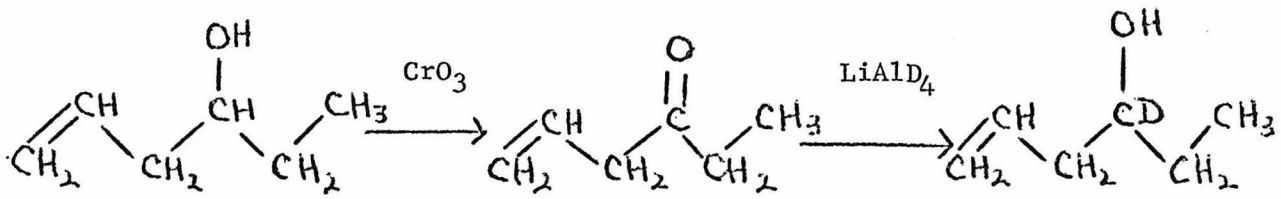
The synthesis of 34C, 36C and 36T is essentially identical to the procedure developed by Clarke for 34T (1a). The synthetic route utilized is depicted in Scheme XII and is based on Crawford's generalized synthesis of 1-pyrazolines (30). The deuterated pyrazolines (36C) and (36T) were synthesized by the same route as depicted in Scheme XII. Deuterium was incorporated by the sequence depicted in Scheme XIII.



Scheme XI


1.Phthalic anhydrid
2.Brucine
3.Recrystalize
4.HCl
5.NaOH
37H
38H
1.Hg(OAc)2
2.NaBH4
40H
Ph3PBr2
41H
VPC separation
of diastereomers
42H 2R,4S
N2H4
49H
HgO
34C
43H 2S,4S
N2H4
50H
HgO
34T

Scheme XII



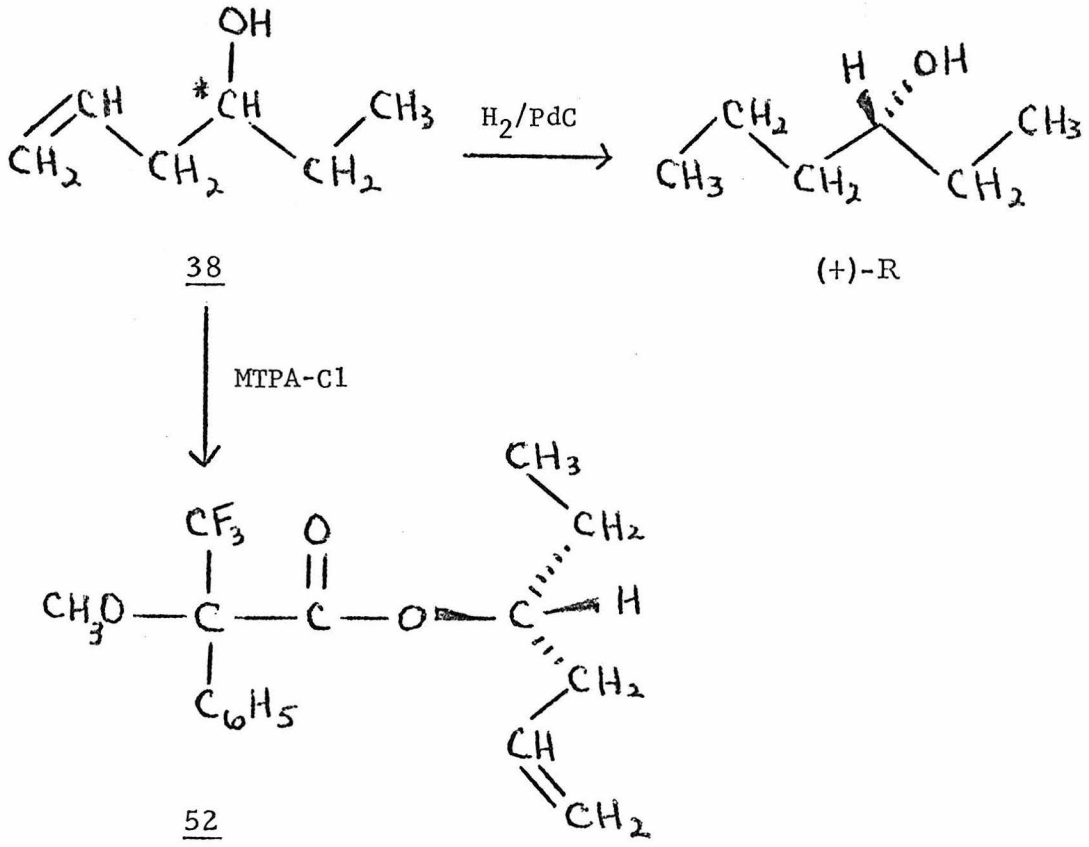
37H 39 37D

Scheme XIII

Formation of 1-hexen-4-ol (37H) was readily accomplished by the Grignard condensation of allyl magnesium bromide and propionaldehyde (31). At this point, in the deuterated series, the alcohol is subjected to a careful Jones oxidation and workup under gentle conditions, followed by reduction with $LiAlD_4$ for incorporation of deuterium at the 4-position. 87.3% d_1 was determined by mass spectral analysis of 37D.

Resolution of both series was accomplished by conversion of 37 to the phthalate half ester (51) (32), followed by formation of the brucine salt and tedious fractional recrystallization from ethyl acetate. It was never possible to obtain the phthalate half ester in crystalline form. After cutback of the brucine salt and saponification of the half ester, optically active 1-hexen-4-ol 38 was obtained with 38.4% optical purity in the protio series and 39.5% optical purity in the deuterio series. Since a precise knowledge of the optical purity of 38 is imperative, its purity was determined by two independent methods. 38 was hydrogenated in order to correlate it with 3-heptanol, whose absolute configuration and maximum rotations

have been established (1a). We checked the correlation results by utilizing Mosher's (39) method of converting the alcohol to its ester (52) with α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA-Cl), followed by integration of the diastereomeric CF_3 peaks in the ^{19}F nmr spectrum of the ester (see Scheme XIV) (34). The optical purity for both series of 38 was confirmed by agreement of the polarimetric determination with the nmr integration to within 0.5%, which is within the 1% accuracy of the nmr technique.

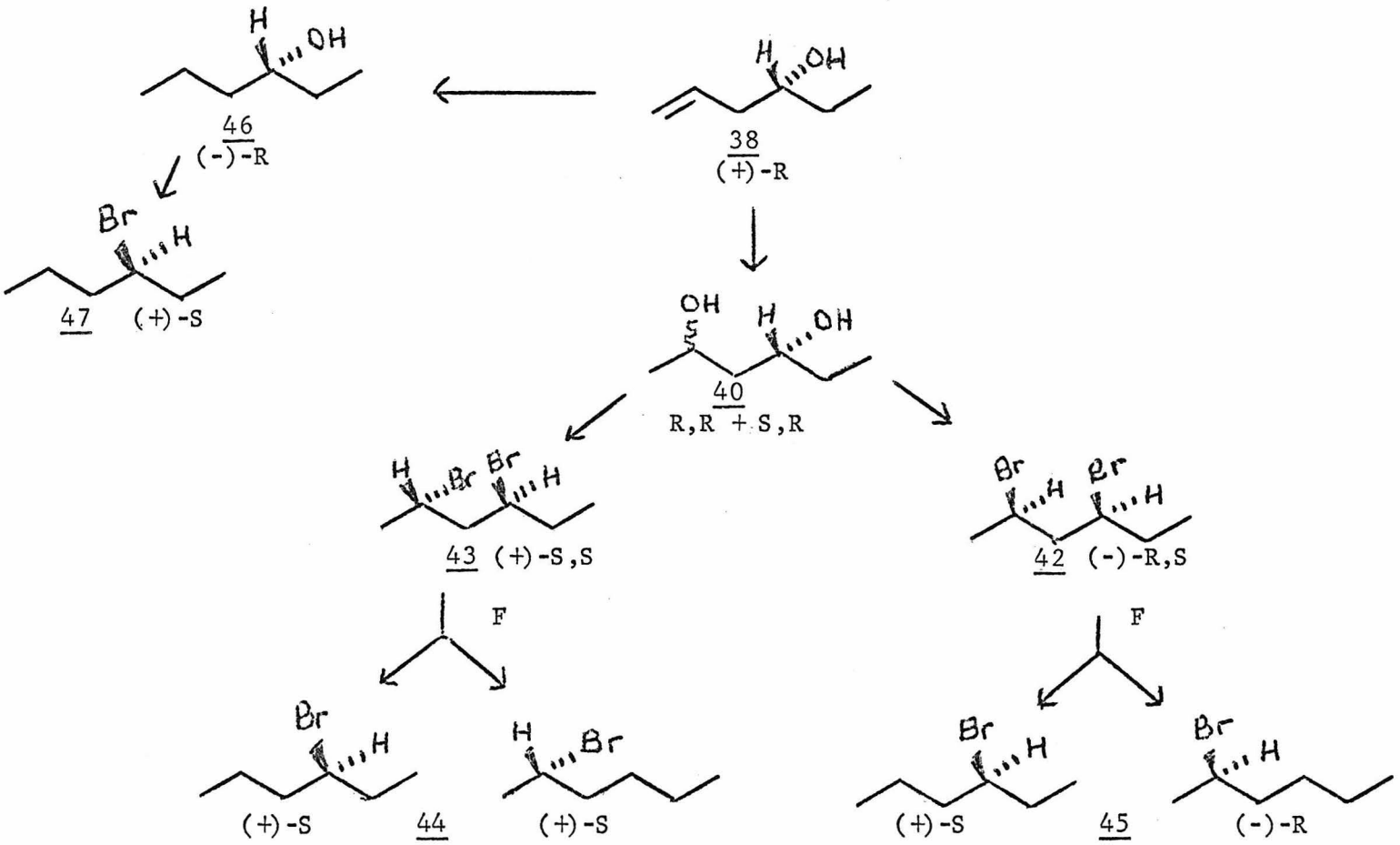


Scheme XIV

Comparison of the optical purities by these two methods also shows that 38H and 38D have virtually identical α_{max}'s (35). (38) was converted to the diastereomeric diols (40) by the convenient oxymercuration-hydroboration technique of Brown (36).

(40) was reacted with triphenyl phosphine dibromide to form the diastereomeric mixture of dibromides (41). Since we were never able to develop methods for the physical separation of either the cis- and trans-pyrazolidines or pyrazolines, the dibromide diastereomers (42) and (43) were separated by laborious vapor phase chromatography at this point.

There are no rigorous proofs in the literature that the diol (40) to dibromide (41) conversion is completely stereospecific with inversion at both centers (37). Crawford does present strong suggestive evidence for the stereospecificity of this reaction (5h). We have confirmed Crawford's results by means of the double correlation outlined in Scheme XV. After separation, diastereomers (-)-2R, 4S (42) and (+)-2S, 4S (43) were subjected to partial reduction with tri-n-butyl tin hydride (F, Scheme XV). (42) yielded a mixture of 58% (+)-S-3-bromohexane and 42% (-)-R-2-bromohexane (45). 43 yielded a mixture of 58% (+)-S-3-bromohexane and 42% (+)-S-2-bromohexane (44). The observed rotations of both these mixtures were recorded, and two simultaneous linear equations, with the specific rotations of the 2- and 3-bromohexanes as unknowns, were derived and solved. The $[\alpha]_{589}$ for (+)-S-2-bromohexane when compared with $[\alpha]_{589\,max}$ for this compound, as determined by Reutov (38), confirms at least 98%


H
OH
46
(-)-R
Br
H
47 (+)-S
38
(+)-R
OH
H
OH
40
R,R + S,R
H
Br
Br
H
43 (+)-S,S
Br
H
42 (-)-R,S
F
F
Br
H
(+)-S
44
H
Br
(+)-S
Br
H
(+)-S
45
Br
H
(-)-R

Scheme XV

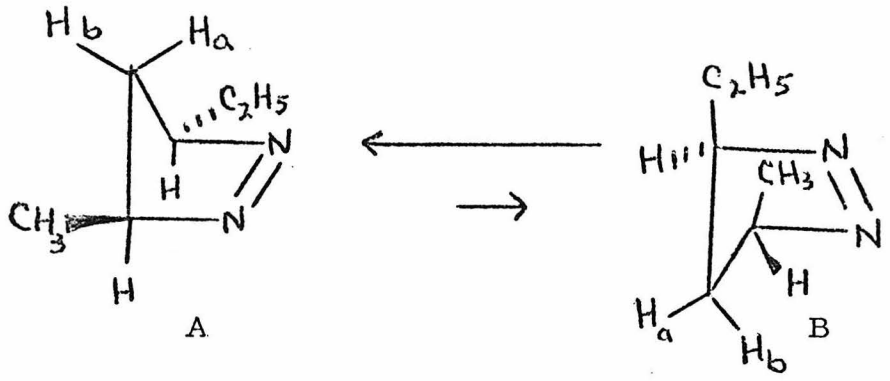
stereospecificity. The $[\alpha]_{365}^{max}$ for 3-bromohexane (47) was obtained by stereospecific synthesis from 8.2% optically active 3-hexanol (46). The synthesis was accomplished from 46 via the formation of the tosylate followed by reaction of lithium bromide in acetone for one hour at room temperature. Comparison of $[\alpha]_{365}$ of the (+)-3-bromohexane from partial reduction with $[\alpha]_{365\,max}$ confirms that no racemization has occurred at the 3-position.

Conversion of (42) and (43) to their respective pyrazolidines (49) and (50) is accomplished by reaction with 97% hydrazine. We found that more strenuous conditions were required for this conversion than those described by Crawford (30) (see Experimental).

Oxidation of the pyrazolidine to the 1-pyrazoline was performed using HgO. Purification of the 1-pyrazoline was accomplished by preparative vapor phase chromatography on glass columns.

The purity of the cis- or trans-pyrazoline is assumed to be identical with the purity of the dibromide precursor. This assumption, also made by Crawford (30), is reasonable since there is no obvious way the dibromide diastereomers can interconvert under the conditions of pyrazolidine or pyrazoline formation. The nmr spectra of the cis- and trans-pyrazolines offer a limited confirmation of our assumption. The nmr spectra of the trans-3-ethyl-5-methyl pyrazolines, (34T) and (36T), show the C_4 protons to be nearly equivalent and to absorb at δ 1.3-1.4. This is presumably because of facile ring flipping which interconverts the two envelope conformations. The cis-pyrazolines, (34C) and (36C), heavily favor

the envelope conformation which places both alkyl groups in pseudo-equatorial positions (A, Scheme XVI).



Scheme XVI

Thus, H_a is shielded relative to H_b and absorbs at δ 0.62, while H_b absorbs near δ 2 (overlaps with methylene protons of ethyl group). Since 34T and 36T have no absorbances above δ 1.2, one could easily detect 5% cis-pyrazoline by any absorbances at δ 0.62.

The methine proton absorbances provide a means of evaluating the minimum purity of the cis-pyrazolines and an additional check on the purity of the trans-pyrazolines. For 34C and 36C, the methine proton(s) absorb at δ 4.12; for (34T) and (36T) the methine proton(s) absorb at δ 4.52. Therefore, a cis or trans pyrazoline contaminant of 5% could have been detected.

C. Pyrolysis

Injection Port

The purposes of the injection port pyrolyses were: 1) an exact determination of product distributions for i) comparison with other 1-pyrazoline systems, ii) use in calculating exact amounts of the various enantiomers obtained from the large scale pyrolyses, iii) investigating the possibility of deuterium secondary kinetic isotope effects occurring after the decomposition step; and 2) observation of any temperature dependence on the product distribution.

The pyrolyses of 34C & T and 36C & T were carried out in the glass lined injection port of a Hewlett-Packard 5750 Research Chromatograph, and the product distribution was analyzed by a Spectra Physics, System I Computing Integrator.

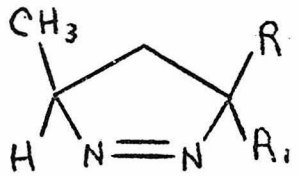
Clarke had previously determined the vapor phase chromatography retention times of all pyrolysis products by comparison with authentic samples. Control experiments demonstrated that no product interconversion was occurring on the vpc column, and that the pyrazoline was decomposing only in the injection port. It should be noted that we were unable to separate cis-3-hexene from the cis-cyclopropanes, but by analogy with the 3, 5-dimethyl-1-pyrazoline system (30), we assume that the olefin will account for less than 1% of the pyrolysate. All product distributions were measured at least three times at any given temperature and are reproducible to within ±1%.

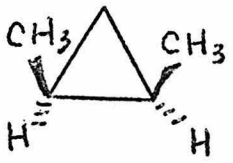
The results of the injection port pyrolysis are displayed in Tables 2-6. The results show that the product distributions for 34C & T compare closely to those observed by Crawford on the 3, 5-dimethyl system (Scheme XVII). Comparison of the product distributions of 34C with 36C, and 34T with 36T shows a slight decrease in the cis/trans ratio for the deuterated cases. The slight temperature dependence (decreasing product stereospecificity with increasing temperature) was anticipated by analogy with other pyrazoline systems (5).

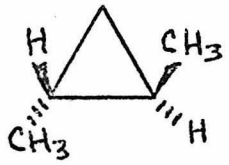
Large Scale Pyrolysis

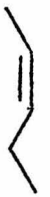
The large scale flow pyrolyses of 34C & T and 36C & T were carried out at 292° at atmospheric pressure with a helium carrier gas flow of 60 ml/min. The cis/trans-cyclopropane ratios for 34C, 34T, 36C, and 36T were .49, 2.66, .51, and 2.70. This constitutes reasonable agreement with the injection port pyrolyses for the same temperature (see Tables 2-6).

The cyclopropanes were separated and purified by preparative vapor phase chromatography. Vpc analysis on a glass column showed no unreacted pyrazoline. Enantiomer distributions displayed in Tables 7 and 8 are based on the maximum rotations and absolute configurations for the 1-ethyl-2-methyl-cyclopropanes determined by Bergman (19). In addition to vapor phase chromatography, the cyclopropanes were identified by comparison of their nmr spectra with published spectra (19).









(5C): R = CH_3; R_1 = H	33.2%	66.1%	0.68%	0.0%
5T : R = H; R_1 = CH_3	72.6%	25.9%	1.08%	0.92%

Scheme XVII

Table 2

Percent Product Distributions in the Pyrolysis of

Racemic trans-3-Ethyl-5-methyl-1-pyrazoline (1a)

Temp., °C					C/T
150	–	–	–	–	–
261	25.4	74.5	0.1	trace	2.9
306	26.8	71.3	1.2	0.8	2.7
352	27.9	69.2	1.6	1.1	2.5

Table 3

Percent Product Distribution in the Pyrolysis of

Optically Active trans-3-D-3-ethyl-5-methyl-1-pyrazoline (36T)

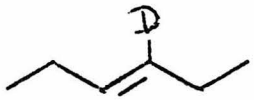
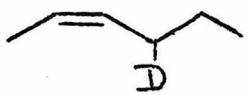
Temp., °C					C/T
150	—	—	—	—	—
260	26.2	71.2	1.2	1.4	2.7
292	27.9	69.5	1.2	1.4	2.5
314	28.6	68.6	1.5	1.3	2.4
350	29.4	67.2	1.8	1.7	2.3

Table 4

Percent Product Distribution in the Pyrolysis of Racemic cis-3-Ethyl-5-methyl-1-pyrazoline (1a)

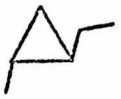
Temp., °C					C/T
150	—	—	—	—	—
261	70.6	29.4	trace	trace	.42
300	67.0	32.2	0.9	trace	.48
350	65.2	33.3	1.4	0.1	.51

Table 5

Percent Product Distribution in the Pyrolysis of

Optically Active cis-3-Ethyl-5-methyl-1-pyrazoline (34C)

Temp., °C					C/T
150	–	–	–	–	–
260	67.6	31.1	.8	.4	.46
314	65.7	32.1	1.2	.6	.49
350	64.7	33.2	1.4	.5	.51

Table 6

Percent Product Distribution in the Pyrolysis of

Optically Active cis-3-D-3-ethyl-5-methyl-1-pyrazoline (36C)

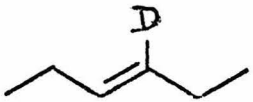
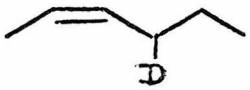
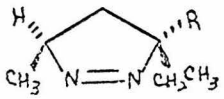
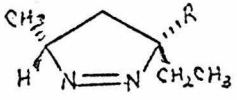
Temp., °C					C/T
150	—	—	—	—	—
260	67.7	31.2	0.8	0.5	.46
300	67.6	31.1	1.0	0.3	.46
350	65.7	32.1	1.7	0.7	.49

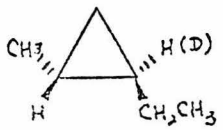
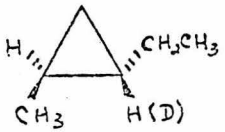
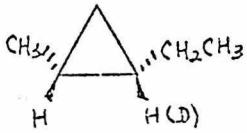
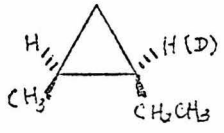
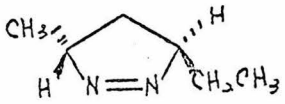
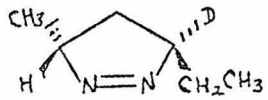
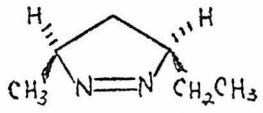
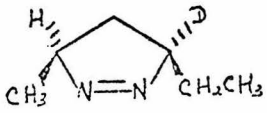
Table 7

Percent Yields and Absolute Stereochemistry of Cyclopropane Products Formed in the Thermal Decomposition of (+)-3R, 5R- and (+)-3R, 5S-3-Ethyl-5-methyl-pyrazolines at 292°, gas phase, He flow system (atmospheric pressure).

Starting Material		Products[a] 48T: Percent yield	Predom. stereochem.	% preserv'n. of opt. purity	48C: Percent yield	Predom. stereochem.	% preserv'n. of opt. purity	Olefin, % yield
 34C 36C	R=H	65.7	Ethyl Rotation	14.2 ± .4	32.1	Double Retention	36.5 ± 2.9	1.8
	R=D	67.6		16.9 ± .6	31.1		29.9 ± 1.5	1.3
 34T 36T	R=H	27.1	Double Inversion	22.5 ± .5	70.6	Methyl Rotation	0.85 ± .02	1.9
	R=D	28.6		23.8 ± 1.2	68.8		0.87 ± .03	2.6

[a] Product percentages determined by vapor phase chromatography (Hewlett Packard 5750) using digital integration (Autolabs System I). Optical rotations were taken in solution at five wavelengths between 589 and 365 nm using a Perkin-Elmer 141 digital polarimeter.

Table 8

Starting Material	Products, %			
	 (-)-48T	 (+)-48T	 (-)-48C	 (+)-48C
 (+)-34T	10.5 ± 0.2	16.6 ± 0.3	35.0 ± 0.1	35.6 ± 0.6
 (+)-36T	10.9 ± 0.3	17.7 ± 0.4	34.0 ± 0.6	34.6 ± 0.6
 (+)-34C	28.2 ± 0.4	37.5 ± 0.5	10.2 ± 0.4	21.9 ± 0.8
 (+)-36C	28.1 ± 0.5	39.5 ± .6	10.9 ± 0.3	20.2 ± 0.4

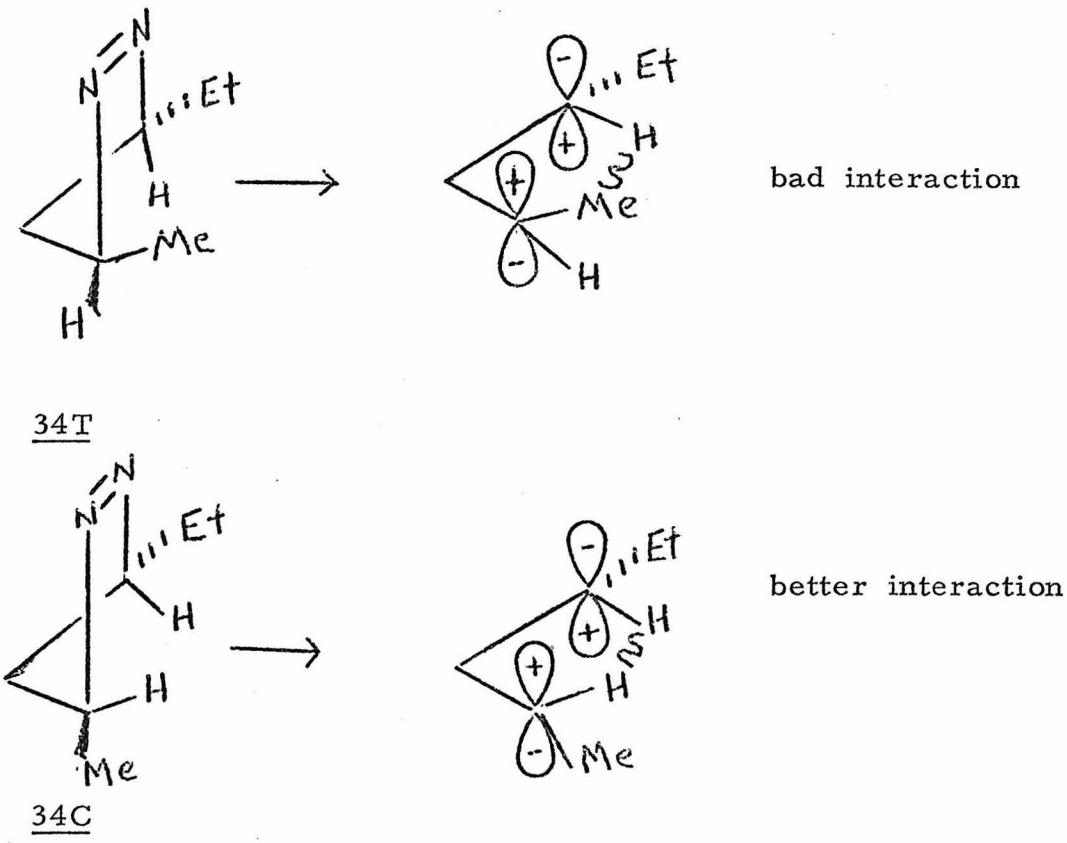
D. Discussion

The cis/trans ratio of cyclopropane products (48C) and (48T) (Table 7) very closely resemble the ratios obtained by Crawford (5h) for the cis- and trans-3, 5-dimethyl systems, (5C) and (5T). An even closer evaluation is possible by comparing (34T) with the optically active trans-3, 5-dimethyl-1-pyrazoline (33) (Scheme IX). In this comparison, the amounts of each comparable trans cyclopropane enantiomer formed from (34T) and (33) are very similar. Consequently, we are confident that the general decomposition mode for 3, 5-dimethyl-1-pyrazolines is not altered in our unsymmetrical ethyl-methyl system.

The most striking result of this study is portrayed in Table 7. 34T yields the major cis product (48C) as nearly racemic and the minor trans product (48T) with 22.5% retention of optical purity and is predominantly doubly inverted. However, 34C gives the major product (48T) with 14.2% optical purity (predominant single inversion at the 3-carbon) and minor cis product (48C) with 36.5% retention of configuration! Compounds 36C and 36T mirror the behavior of their protio analogues and also display a deuterium secondary kinetic isotope effect.

The data in Table 7 make it necessary to postulate that at least 6% of the products from 34T, and that 20% of the products from 34C, are produced via chiral routes. An isotope effect on the optical purities of the cis- and trans-cyclopropane enantiomers confirms this, since there is no way deuterium can influence the optical purity of species derived from an achiral intermediate.

It is possible to construct a mechanism utilizing the achiral 0, 0 diradical as a precursor to the racemic part of the products and a different, chiral path for the remainder of the products. However, it is difficult to understand why the cis pyrazoline should not give the larger proportion of racemic products. This is because presumably the 0, 0 diradical is most easily formed by nitrogen extrusion from the envelope conformation of the pyrazoline. The preferred envelope conformation for the cis pyrazoline has both alkyl groups in sterically favorable pseudo-equatorial positions (see Scheme XVIII). The trans-pyrazoline must always have one alkyl group in an axial position; upon conversion to the 0, 0 diradical, the axial alkyl group must occupy a sterically crowded position.



Scheme XVIII

Consequently, it is concluded that the cis-pyrazoline should decompose more readily to the 0, 0 diradical and give a larger percentage of achiral products. The opposite of this prediction is observed!

In light of the preceding discussion, and in an effort to adhere to the principles of generality and simplicity in design of reaction mechanisms, we prefer to suggest one mechanism which is capable of rationalizing all the decomposition products. Any mechanism must explain the following phenomena: 1) a large fraction of chiral products (most reasonably suggesting predominantly chiral reaction pathways); 2) single inversion (5) of major products from both cis and trans pyrazolines; 3) predominant inversion of the

ethyl group in the conversion 34C → 48T and predominant inversion of the methyl group in the conversion 34T → 48C; 4) predominant double inversion in the conversion 34T → 48T and 5T → 6T (5h), and double retention in the 34C → 48C conversion; and 5) probable simultaneous C—N bond rupture in the rate determining step of the reaction.

After considering many possibilities, the only satisfactory mechanism (that we can develop) which adequately accounts for the pyrazoline decomposition results is depicted in Scheme XIX.

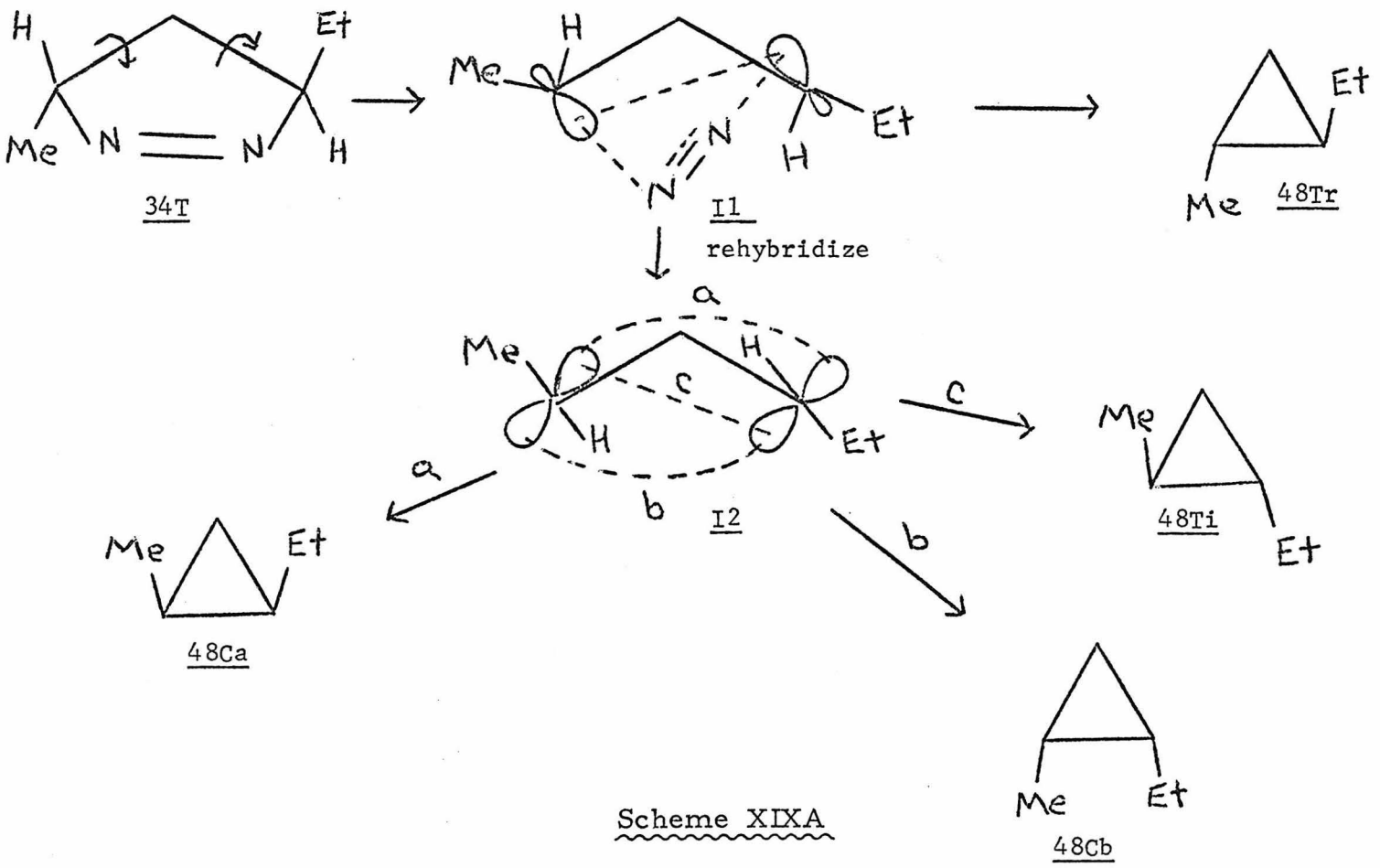
The underlying premise of this mechanism is based on a non-linear (13) extrusion of N_2 from the 1-pyrazoline. This causes a conrotatory motion of the terminal methylene groups in whichever direction is sterically most accessible. We will now discuss in detail the mechanism outlined in Schemes XIXA & B.

"Trans" Mechanism

For the trans-pyrazoline (34T), conrotation is in the sterically accessible clockwise direction, pushing the alkyl groups away from sterically-crowded positions and rotating the terminal hydrogens toward one another (I1). It is at this point that (48Tr) with retained stereochemistry is formed.

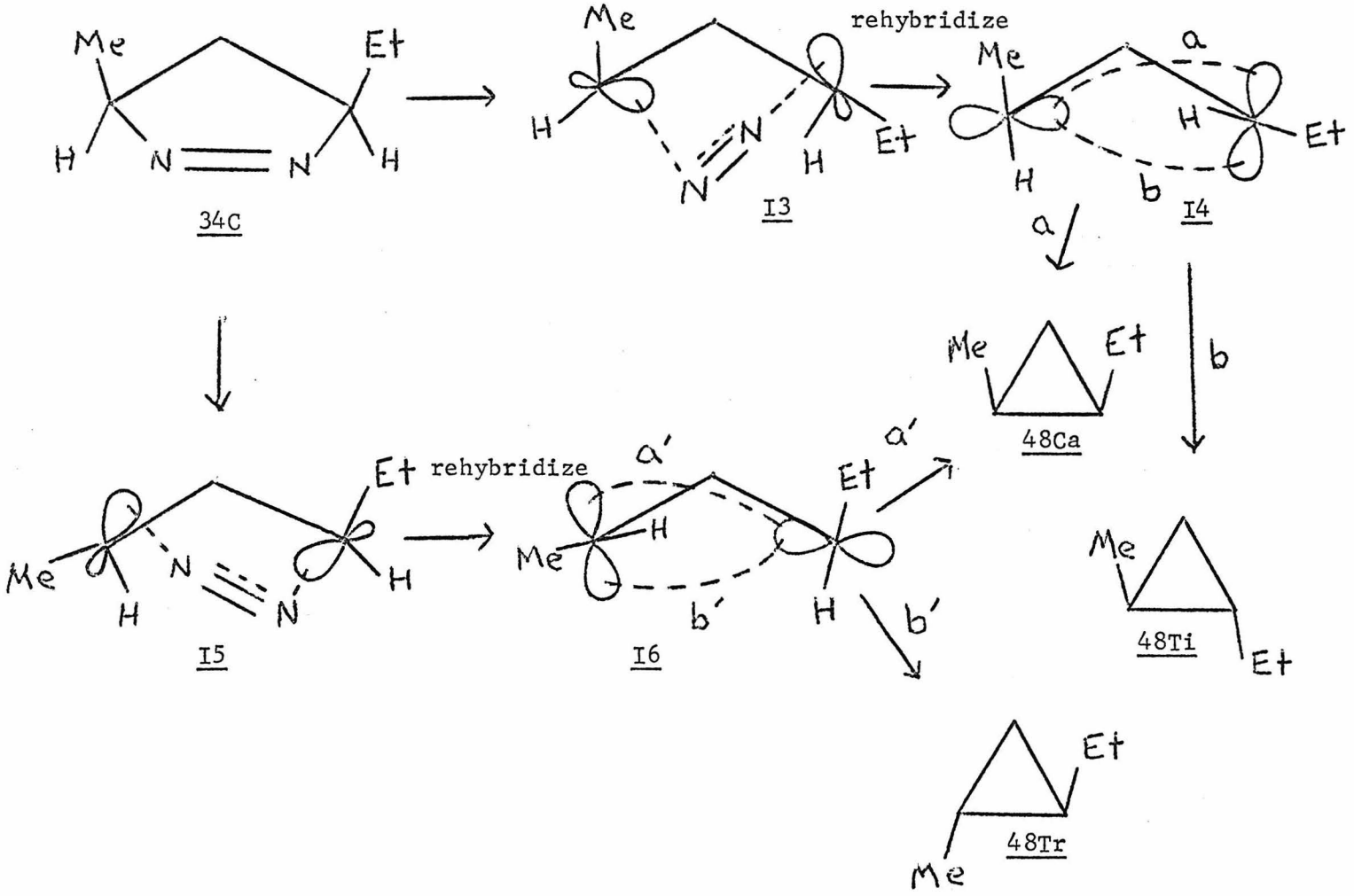
Rehybridization from I1 to I2 occurs by movement of the relatively light hydrogens through the plane defined by the ring carbons and into the plane perpendicular to the now-p orbitals. The exact process of rehybridization is obviously purely speculative. Species I1 may be a pyramidal diradical of finite lifetime

Trans Mechanism



Scheme XIXA

Cis Mechanism



Scheme XIXB

from which the terminal hydrogens "pop" through the ring plane simultaneously or consecutively, or rehybridization and product formation may be part of a continuous process initiated by extrusion.

From I2 there are three reasonable bonding interactions (indicated by dotted lines labeled a, b, and c). Interactions a and b are equivalent, explaining the nearly equal amounts of 48Ca and 48Cb formed (see Tables 7 and 8). Interaction c results in formation of the double inverted trans-cyclopropane (48Ti).

"Cis" Mechanism

For the cis-pyrazoline (34C), one preferred conrotation is not obvious, since rotation in either direction forces an alkyl group into a sterically poor position. Nevertheless, the electronic preference still dictates the nitrogen extrusion and the result is rotation in each direction a fraction of the time (34C → I3; 34C → I5). However, the rotations of the methyl-bearing carbon in I3 and the ethyl-bearing carbon in I5 are greatly impeded by steric interaction. Consequently, rehybridization at these carbon atoms proceeds by movement of the hydrogen through a plane almost perpendicular to the plane of the ring carbons. Rehybridization at the ethyl-bearing carbon for I3 and the methyl-bearing carbon for I5 proceeds by movement of the hydrogen through the plane of the ring atoms (rotation at these carbons has not been impeded).

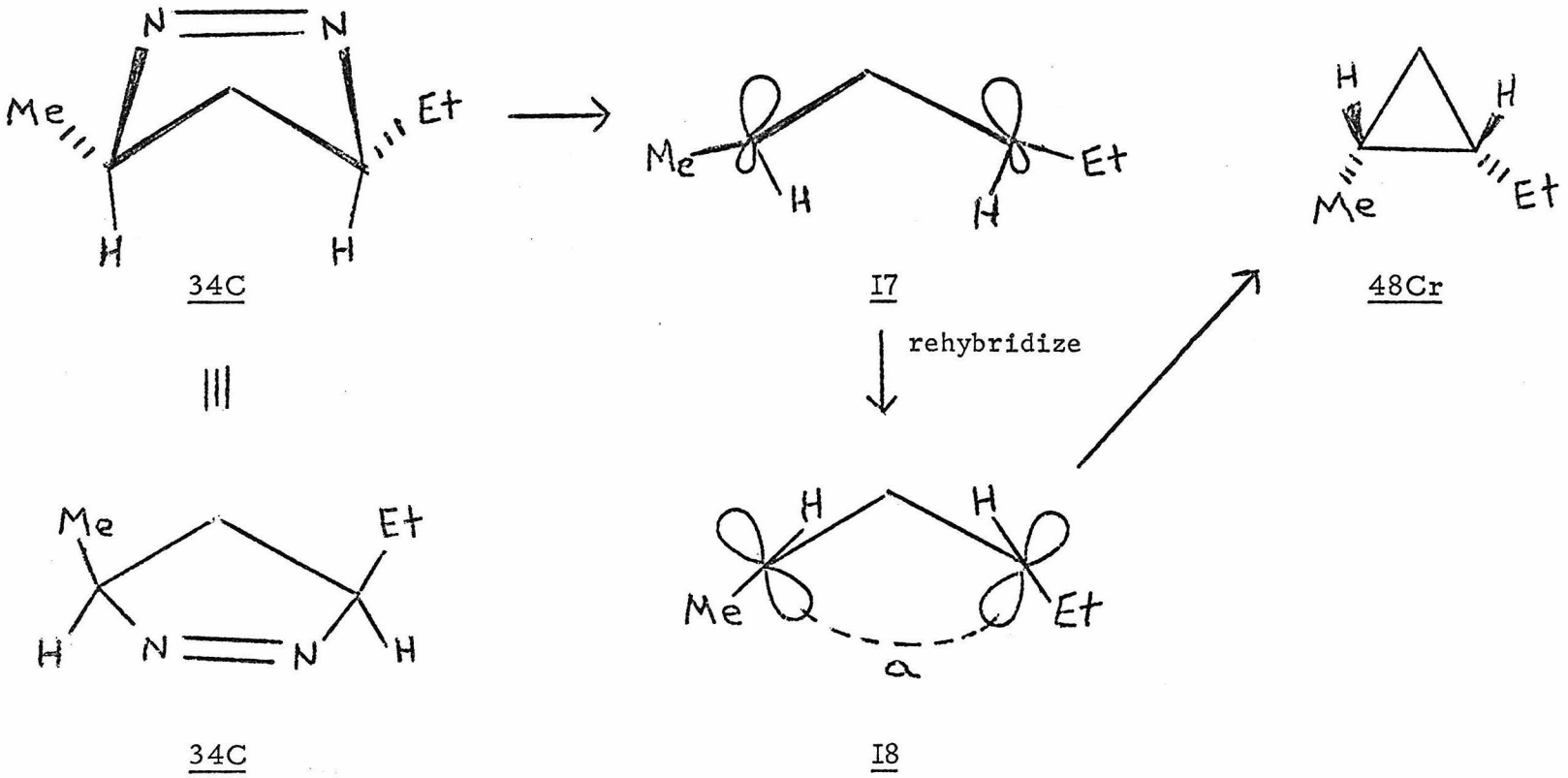
From I4, bonding interaction "a" leads to 48Ca and interaction "b" leads to 48Ti. From I6, bonding interaction "a'" leads to 48Ca and

interaction "b" leads to 48Tr.

The easiest way to account for the 10% doubly inverted cis cyclopropane from 34C (see Table 8) is to postulate a small amount of disrotation (Scheme XX). Linear extrusion of nitrogen (13) is most consistent with formation of I7 from 34C. Rehybridization to form I8 is accomplished by moving the hydrogens through the ring plane, and interaction "a" results in formation of 48Cr.

The product distributions displayed in Tables 2-6 indicate that a deuterium isotope effect(s) is occurring after the product decomposition step (cis/trans ratios are altered). Consequently, we are unable to evaluate the likelihood of sequential bond cleavage, as discussed in Question 3 of Section III.

Considering the subtle balance of electronic, steric and dynamic effects (and the present lack of our knowledge of these effects), it is very difficult to predict how this balance will be tipped in other azo or even 1-pyrazoline decompositions. For example, it is impossible to guess what will be the behavior of the parent trimethylene generated from 1-pyrazoline. Is rehybridization to sp^2 by movement of only one hydrogen reasonable? For a 3, 4-dialkyl substituted 1-pyrazoline, the complication of different steric interactions, as well as an unsubstituted terminal methylene on the substituted-trimethylene diradical, is present. While our suggested mechanism is consistent with all results from other 3, 5-dialkyl 1-pyrazoline decompositions, only the optically active 3, 5-dimethyl system (5h) offers the stereochemical detail sufficient for confirmation.


N
N
Me
Et
H
H
34C
III
Me
Et
H
N
N
H
34C
Me
H
H
Et
a
I8
rehybridize
I7
H
H
Me
Et
48Cr

Scheme XX

We suggest that non-linear nitrogen extrusion for 1-pyrazoline decompositions (and perhaps for other 4-electron extrusion reactions) may be the fundamental electronic preference. Substituent effects can alter electronic preferences and greatly contribute to the stereochemical course of the reaction. It presently appears that reaction dynamics may be playing a very significant role in pyrazoline decompositions and perhaps will be the clue to an ultimate understanding of the trimethylene intermediate problem (17).

IV. Experimental

A. General

Proton nmr spectra were obtained on either an A-60-A or T-60 Varian Associates Analytical nmr spectrometer. ^{19}F nmr spectra were obtained on an XL-100 Varian Associates Analytical nmr spectrometer. Carbon tetrachloride or deuterochloroform were used as solvents with tetramethylsilane as an internal standard for all proton spectra. Spectra are reported as: chemical shift (in order of increasing δ); multiplicity, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet splitting; relative number of H's; assignment. All ^{19}F nmr spectra were run using deuterochloroform as solvent with trifluoroacetic acid as an external standard.

Infrared spectra were obtained on a Perkin-Elmer 257 Grating Infrared Spectrophotometer using carbon tetrachloride or chloroform as solvent. Optical rotations were obtained on a Perkin-Elmer 141 digital readout Polarimeter, using a 1 ml microcell with a 10 cm pathlength. Concentrations are reported in g/ml.

All analytical vapor phase chromatography was performed on a Hewlett-Packard 5750 Research Chromatograph equipped with an Autolabs System I Computing Integrator. The chromatograph was equipped with a flame ionization detector; maximum sensitivity was maintained at the following gas pressures (lb/in^2): He, 40; H_2, 14; air, 30. One-eighth inch stainless steel columns were utilized for all analytical work.

Preparative vapor phase chromatography was performed on a Varian Aerograph 90-P3 chromatograph equipped with a thermal conductivity detector. All preparative columns were constructed of either 1/4" or 3/8" o.d. glass.

VPC Columns

Column A: 10' × 1/4", 30% SE-30 on 60/80 Chromosorb W-AW DMCS, glass;

Column B: 10' × 3/8", 10% DEGS on 60/80 Chromosorb P-NAW, glass;

Column C: 12' × 3/8", 10% UCW-98 on 60/80 Chromosorb W-AW, glass;

Column D: 10' × 1/4", 20% Carbowax 20CM on 60/80 Chromosorb P-NAW, glass;

Column E: 20' × 1/8", 25% STAP on 100/120 Chromosorb W-AW DMCS, stainless steel;

Column F: 25' × 1/8", 25% ββ-ODNP on 100/120 Chromosorb W-AW DMCS, stainless steel.

Mass spectral analyses were performed on a DuPont 21-492B high resolution mass spectrometer. All elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Michigan. All boiling points are uncorrected.

B. Synthesis

1-Hexene-4-ol (37) was prepared exactly as described by Clarke (1a, 31). 150.0 g of 37 (80.4% yield) was isolated. The spectra for 37 agree exactly with those reported by Clarke. Ir: 3570, 3400 (broad), 3075, 3400 (broad), 3075, 2960, 2920, 2880, 1640, 1440, 1000, 995, 920 cm^{-1}. Nmr (CCl_4): δ 0.93 (t, 3H; J = 6.5 Hz, $-CH_2\underline{CH_3}$); 1.38 (q, 3H, $-CHOH-\underline{CH_2}-CH_3$); 1.73 (s, 1H, -O<u>H</u>); 2.0-2.3 (m, 2H, $-2H-\underline{CH_2}-$); 3.48 (quintuplet, 1H, -<u>CH</u>OH); 4.8-5.2 (m, 2H, vinyl CH_2); 5.4-6.2 (m, 1H, vinyl CH).

1-Hexene-4-one (39). Jones reagent was prepared by mixing 150 g CrO_3 with 200 ml water at 0°C in a 500 ml Erlenmeyer flask. Then 131 ml concentrated H_2SO_4 was slowly added, followed by addition of 400 ml water; this solution was maintained at 5°C. Into a 2-liter, three-necked flask equipped with magnetic stirrer, thermometer, 500-ml addition funnel, and 0°C cooling bath was placed 120 g (1.20 mol) (37) in 600 ml acetone. The precooled Jones reagent was added dropwise at such a rate as to maintain the reaction temperature at less than 20°C. The reaction was stirred for 4 hours at 5°C after addition was complete.

After warming to room temperature, the reaction mixture was decanted from the chromium salts and diluted with 1 liter of saturated aqueous NaCl solution. The aqueous phase was separated and washed four times with a total of 850 ml of pentane, which was combined with the organic phase. The organic phase was washed with cold, saturated aqueous $NaHCO_3$, which in turn was extracted

with pentane. The combined organics were washed quickly with a saturated NaCl solution and dried over Na_2SO_4.

Most of the pentane was distilled off through a Vigreaux column with the pot maintained at 45°C. The product was distilled at 48-50°C at 30 mm to yield 48 g (39) (40.0% yield). Ir: 3090, 2990, 2920, 2890, 1720, 1640, 1475, 1430, 1415, 1385, 1355, 1145, 1110, 1050, 1030, 995 and 925 cm^{-1}. Nmr (CCl_4): δ 1.01 (t, 3H, J = 7.5 Hz, $-CH_2\underline{CH_3}$); 2.36 (q, J = 7.5 Hz, 2H, $-\underline{CH_2}CH_3$); 3.06 (d, J = 7.0, 2H, $CH_2=CH-\underline{CH_2}-$); 4.8-5.25 (m, 2H, $\underline{CH_2}=C-$); 5.6-6.25 (m, 1H, $CH_2=\underline{CH}-$).

4-d-1-Hexen-4-ol (37D). Into a 1-liter, three-necked flask fitted with a mechanical stirrer, 500-ml addition funnel, water condenser, and N_2 inlet were placed 5.0 g (.119 mol) lithium aluminum tetradeuteride (Stohler Isotope Chemicals 99%D) and 250 ml anhydrous ethyl ether. The flask was cooled to -20°C and 37 g (.37 mol) of 39 in 300 ml anhydrous diethyl ether was added dropwise with stirring. After the addition was complete, the reaction was stirred at -20°C for one hour and then warmed to 0°C. An additional 100 ml of diethyl ether was added, followed by the cautious, dropwise addition of 5 ml water over the course of one hour. Then 5 ml of a 15% NaOH/water solution was added dropwise, followed by the dropwise addition of 15 ml water.

The fine, white aluminum salts were filtered off, washed with ethyl ether and the combined organic phase was dried over $MgSO_4$. The ether was slowly distilled off through a 12" Vigreaux column. The product was fractionated through a 6 cm Vigreaux yielding

32 g of 37D (85.0% yield, bp 62° at 50 mm). Ir: 3570, 3400 (broad), 2960, 2920, 2880, 2100, 1665, 1640, 1460, 1440, 1000, 920 cm^{-1}. Nmr ($CDCl_3$): δ 0.93 (t, J = 6.5, 3H, $-CH_2\underline{CH_3}$), 1.43 (t, $\underline{CH_2}CH_3$), 1.90 (s, 1H, -OH).

Resolution and Recovery of 4-d-1-Hexen-4-ol (38D). The procedure described by Clarke (1a, 32) was used for resolution and recovery of 38D.

a) 1-Hexen-4-yl phthalate half ester (51). 32 g (.32 mol) racemic 37D and 46.7 g (.32 mol) phthalic anhydride were reacted to yield 59 g (.24 mol) of 51. Despite various attempts, the oily 51 could not be induced to crystallize.

The nmr spectrum agrees with what one would anticipate by comparison with the 38H spectrum (Clarke) (1a). Nmr ($CDCl_3$): δ 0.97 (t, J = 6.5 Hz, 3H); 1.72 (q, J = 6.5 Hz, 2H); 2.45 (d, J = 6.0 Hz, 2H); 4.90-5.40 (m, 2H); 5.40-6.40 (m, 1H); 7.30-8.05 (m, 4H); 11.70 (s, 1H).

b) Brucine Salt Formation and Recrystallization. 93.5 g (.24 mol) of brucine was reacted with 59 g (.24 mol) of 51. Eleven recrystallizations of the resulting salt from ethyl acetate accomplished the desired resolution.

c) Brucine Salt Decomposition was performed on 64 g of the brucine salt by reaction with concentrated hydrogen chloride. 25.0 g (.10 mol) of the half ester (51) was recovered.

d) Saponofication of (51) was accomplished with aqueous sodium hydroxide. After steam distillation and drying, 7.5 g

(.075 mol) of 38D was isolated. The following observed rotations were obtained on the neat alcohol: α_{589} = -.166, α_{578} = -.157, α_{546} = -.213, α_{436} = -.728, α_{365} = -1.840. Comparing these values with those obtained on the nondeuterated alcohol by Clarke (correlated with 3-hexanol), (38D) is 39.5% optically pure. The polarimetric determination was checked by making the ester of 38D with α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA-Cl) and integration of the nmr absorbances of the diasteromeric CF_3 groups. This technique suggests 38D to be 40%± 1% optically pure. Comparison of the ^{19}F nmr results with polarimetry confirms that α_{max} for 38H and 38D are virtually identical.

MTPA Ester Formation. The procedure of Mosher (39) was followed. Four drops 38D, six drops MPTA-Cl, ten drops CCl_4 and ten drops pyridine were stirred for twelve hours in a 5-ml, single-necked flask equipped with a drying tube. 1 ml of water was added to the reaction mixture and the solution was extracted with diethyl ether, washed with aqueous 1N HCl, 1N NaOH, and saturated Na_2CO_3 solutions and dried over Na_2SO_4. The solvent was removed by rotary evaporation and the ester was dissolved in $CDCl_3$ for the nmr spectra. ^1H Nmr: δ 0.65-1.15 (m, 3H, $-CH_2-\underline{CH_3}$); 1.40-1.90 (m, 2H, $-\underline{CH_2}-CH_3$); 2.25-2.55 (m, 2H, $CH_2=CH-\underline{CH_2}$); 3.55 (m, 3H, $O-CH_3$); 4.80-6.00 (m, 3H, $\underline{CH_2}=\underline{CH}-$); 7.52 (s, 5H, phenyl). ^{19}F Nmr: 456 Hz downfield from external TFA (relative area 30); 481 Hz

downfield from external TFA (relative area 70); decoupled diastereomeric CF_3 absorbances.

α-Methoxy-α-trifluoromethylphenyl acetic acid (MTPA) was prepared by the method of Mosher.

a) Trifluoromethylphenylketone was synthesized by the method of Levine (40) from the Grignard reaction of phenyl magnesium bromide and trifluoro acetic acid in 57% yield. Ir: 1720 (strong), 1120-1220 (strong) cm^{-1}. Nmr (CCl_4): distorted ab pattern δ 7.30-8.30 (3H:2H).

b) α-Methoxy-α-trifluoromethylphenylacetonitrile was prepared by reacting sodium cyanide with trifluoromethylphenylketone, followed by alkylation with dimethyl sulfate. The desired nitrile was isolated in 66% yield. Nmr (CCl_4): δ 3.40 (s, 3H, OMe), 6.80-8.00 (m, 5H, phenyl).

c) MTPA. The acid hydrolysis of the nitrile to the acid, as described by Mosher, was unsuccessful in our hands. Consequently, the following basic hydrolysis was developed. To 50 g (.23 mol) of the nitrile and 100 ml ethylene glycol in a 1-liter, three-necked flask equipped with thermometer, reflux condenser, and addition funnel was added a solution of 50 g (1.2 mol) NaOH in 150 ml water. The reaction was refluxed at 106°C for thirty minutes, 50 ml water was added, and the reaction was stirred at 95°C for twelve hours. 100 ml water was added and the reaction was allowed to cool to room temperature.

The reaction mixture was washed with ether; the aqueous layer was acidified with HCl and then extracted with ether. The layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. Vacuum distillation through a short path condenser yields 32 g MTPA (61% yield; bp ~ 120°C at 2 mm). Nmr (CCl_4): δ 3.56 [m(d?), 3H, -OMe]; 7.10-8.00 (m, 5H, phenyl); 9.60 (s, 1H, $CO_2\underline{H}$). The spectrum correlates exactly with a commercial sample (Aldrich Chemicals).

d) Resolution of MTPA. To 51 g (.22 mol) racemic MTPA in 175 ml absolute ethanol was added 26.1 g (.22 mol) (+)-α-phenylethylamine. The white salt which immediately formed was dissolved by heating on a steam bath. The flask was placed in a dewar for sixty hours. The salt was filtered, washed with cold ethanol, and recrystallized once again. The salt was decomposed with a slight excess of dilute aqueous HCl, and the regenerated acid was extracted into ether. The extracts were dried over $MgSO_4$, and the solvent was removed by rotary evaporation. The acid was distilled to yield 10.0 g resolved MTPA (bp 114°C at 1.2 mm; $[\alpha]_{589}^{25}$ = +76.6°, c = .0130 g in 1 ml methanol). A commercial MTPA sample has $[\alpha]_{589}$ = +73.2°, c = .0165 g/1 ml methanol.

The more soluble salt fractions were decomposed also with dilute, aqueous HCl. The isolated acid was treated with (-)-α-phenylethylamine and recrystallized one time from absolute ethanol. After cutting back from the salt, and distillation, 8.2 g of (-) MTPA was isolated ($[\alpha]_{589}^{25}$ = -74.3°, c = .0205 g in 1 ml methanol).

2,4-Hexanediol (40D) was synthesized from 38D by the method of Brown and Geoghegan (36). Into a 1-liter, three-necked flask equipped with a mechanical stirrer and two addition funnels were placed 24.9 g (.08 mol) mercuric acetate in 80 ml water. 80 ml tetrahydrofuran was added to give a bright yellow suspension. 7.5 g (.075 mol) of 38 was added over a ten minute period, during which time the yellow suspension became a colorless solution. The solution was stirred an additional twenty-five minutes. 80 ml of an aqueous 3N NaOH solution was added dropwise over ten minutes and the solution again turned yellow. Finally, a solution of 1.42 g $NaBH_4$ in 75 ml of an aqueous 3N NaOH solution was added dropwise over twenty-five minutes; the reaction was stirred for an additional thirty minutes.

The reaction mixture was saturated with NaCl and extracted four times with a total of 200 ml tetrahydrofuran; the extracts were dried over K_2CO_3.

The solvent was removed by distillation through a Vigreaux column and the residue was distilled to yield 6.84 g of a colorless viscous liquid (40) (77.0% yield; bp 73-74°C at 1.2 mm). The spectra are what one would anticipate by comparison with 40H prepared by Clarke (1a). Ir: 3650-3040 (very broad), 2980, 2960, 2890, 2120, 1465, 1380, 1330, 1150, 1130, 1075, 1060, 975, 960, 930, 870, 850 cm^{-1}. Nmr ($CDCl_3$): δ 0.75-2.70, overlapping multiplets, 10H containing 0.94 (t, J = 6.5 Hz, 3H, $-CH_2\underline{CH_3}$); 1.15 and 1.20 pair of doublets (J = 6.0 Hz, 3H, $CHOH-\underline{CH_3}$, diastereomeric); 2.95 (broad, 2H, -OH); 3.80-4.50 (m, 2H, -CH-OH-).

2, 4-Dibromohexane (41D). Into a 250 ml, three-necked flask equipped with a reflux condenser, addition funnel, N_2 inlet and magnetic stirrer was placed 31.04 g (.118 mol) triphenyl phosphine (recrystallized from benzene) and 51.5 ml spectroquality acetonitrile (distilled). The reaction flask was cooled to 0°C and 18.37 g (.115 mol) Br_2 was added dropwise with stirring. The flask was allowed to warm to room temperature and 6.84 g (.028 mol) of (40) in 7.2 ml acetonitrile was added dropwise at such a rate as to keep the reaction just under reflux; as the addition proceeded, an oil bath at 60°C was applied for ten minutes, then the reaction was allowed to return to room temperature over a forty-five minute period with stirring.

Most of the acetonitrile was distilled off at aspirator pressure. The dibromide was quickly distilled from the reaction flask at .05 mm; the temperature of the pot was raised to 160°C during the course of the distillation. The distillate was dissolved in 20 ml of diethyl ether and washed with 9 ml of a saturated, aqueous $NaHCO_3$ solution, which in turn was extracted with 10 ml of diethyl ether. The organic layer was dried over $MgSO_4$.

Most of the ether was distilled off through a 9 cm Vigreaux column; the dibromide was distilled quickly at .05 mm, bp ~ 32-35°C.

The two diastereomeric dibromides (42D) and (43D) were found to separate cleanly on vpc column B (120°, 100 ml/min). 43 and 42 were formed approximately in a ratio of 2.8 : 1.0. The dibromides were separated by preparative vpc. For 42D, Ir:

3010, 2970, 2400, 1520, 1425, 1380, 1220, 1045, 925, 875, 848 cm^{-1}. Nmr ($CDCl_3$): δ 1.08 (t, J = 7.0 Hz, 3H, $-CH_2-\underline{CH_3}$); 1.70 (d, J = 6.5 Hz, 3H, $CHBr-\underline{CH_3}$); 1.60-2.80 (m, 4, $-\underline{CH_2}-CBrD-\underline{CH_2}-$); 4.30 (sextet, J = 6.5 Hz, 1H, $-BrC-\underline{H}$). For 43D, Ir: 3010, 2970, 2920, 2400, 1520, 1380, 1295, 1257, 1220, 1186, 1135, 1005, 927, 900, 850 cm^{-1}. Nmr ($CDCl_3$): δ 1.05 (t, J = 7.0, 3H, $-CH_2-\underline{CH_3}$); 1.74 (d, J = 6.5 Hz, 3H, $-CBr-\underline{CH_3}$); 1.60-2.30 (m, 4H, $-\underline{CH_2}-CBrD-\underline{CH_2}-$); 4.55 (sextet, J = 6.5 Hz, 1H, $-BrC-\underline{H}$).

(+)-(3R, 5R)-trans-3-d-3-Ethyl-5-methyl-1-pyrazoline (36T)

a) Pyrazolidine (50D) (1a,30). Into a 25 ml, single-necked flask equipped with a magnetic stirrer and rubber septa were placed 5.25 ml 98% ethanol and 1.60 ml (.051 mol) 95% hydrazine. The flask was cooled to 0°C, and 3.15 g (.013 mol) of >99.99% vpc pure (+) (2S, 4S) 43T was added dropwise with a syringe over five minutes. The flask was gradually warmed to 60°C and was stirred for eleven days and twenty-two hours. The reaction was monitored by vpc on column A (100°, 110 ml/min). (Note that pyrazolidines are metal sensitive.)

The reaction was cooled to 0°C at which time $N_2H_4 \cdot HBr$ solidified. The reaction flask was stored overnight in a -50°C freezer. The flask was allowed to warm to room temperature and the ethanol layer was decanted from the $N_2H_4 \cdot HBr$ salt. The salt was washed with ethanol and the organic fractions were combined and stored over 2.2 g crushed KOH for three hours in the refrigerator.

Most of the ethanol was distilled off at 80 mm through a 9" Vigreaux column. The remaining solution was vacuum transferred, leaving behind a white residue. This pyrazolidine (50D)/ethanol solution was used directly in the oxidation to 1-pyrazoline.

b) Pyrazoline (36T). Into a 100 ml, single-necked flask, equipped with magnetic stirrer and addition funnel with drying tube, was placed 5.97 g (.028 mol) red mercuric oxide, 3.9 g (.028 mol) anhydrous sodium sulfate powder, and 27 ml of olefin-free, P_2O_5-distilled pentane. The flask was cooled to 0°C and the pyrazolidine solution was added dropwise over the course of five minutes. The solution immediately turned black (elemental mercury is formed). The reaction was stirred for one additional hour at 0°C.

After warming to room temperature, the pentane was decanted off and the residue was thoroughly washed with pentane. The pentane solutions were combined and most of the solvent was distilled off through a 20 cm Vigreaux column, keeping the pot temperature at less than 45°C.

180 mg of the pure pyrazoline was isolated by preparative vpc, column C (100°C, 75 ml/min). Ir: 2970, 2940, 2870, 1710, 1545, 1460, 1375, 1285, 1250, 1210, 1150, 1130, 1055, 1000, 970, 895 cm^{-1}. Nmr (CCl_4): δ 0.85-2.20 (m, 4H); 1.01 (t, J = 7.0, 3H, $-CH_2-\underline{CH_3}$); 1.34 (d, J = 7.0, 3H, $-\underline{CH_3}$); 4.52 (six line pattern, 1H, $-\underline{\overset{|}{C}H}-$). Optical rotations (c = .0125 g in n-heptane): $[\alpha]_D^{25}$ + 145°, $[\alpha]_{578}^{25}$ + 151°, $[\alpha]_{546}^{25}$ + 175°, $[\alpha]_{436}^{25}$ + 340, $[\alpha]_{365}^{25}$ + 787°. High resolution mass spectrum calculated: 85.100173. High resolution mass spectrum observed: 85.1004.

A low intensity parent peak was observed at m/e 113, but the much larger P-28 (N_2) mass was measured at high resolution.

(+)-(3R, 5S)-cis-3-d-3-Ethyl-5-methyl-1-pyrazoline (36C). The synthetic and work-up procedures used were the same as for 36T. However, only 1.67 g (6.8 mmol) of (-) (2R, 4S) (42D), 99.15% vpc pure, was available. The dibromide diastereomer (42D) was contaminated with 0.85% of the dibromide diastereomer (43). Here the reaction was allowed to proceed for eight days and twenty-one hours.

After oxidation, 125 mg of 1-pyrazoline (99.15% cis, .15% trans) was isolated by preparative vpc, column C (100°C, 75 ml/min). Ir: 2965, 2915, 2870, 1558, 1458, 1372, 1326, 1247, 1200, 1100, 1055, 1000, 970, 898 cm^{-1}. Nmr (CCl_4): δ 0.37-0.87 (broadened d of d, J = 12.5, J = 9.0, 1H, one C_4-H); 1.08 (t, J = 7.0, 3H, $-CH_2\underline{CH_3}$); 1.53 (d, J = 7.0, 3H, $-CH_3$); 1.62-2.30 (m, 3H, $-\underline{CH_2}-CH_3$ and C_4-H); 4.12 (six line pattern, 1H, -CH-). Optical rotations: (c = .0060 g in 1 ml n-heptane); $[\alpha]^{25}_{589}$ + 3.6°, $[\alpha]^{25}_{578}$ + 4.5°, $[\alpha]^{25}_{546}$ + 5.6°, $[\alpha]^{25}_{436}$ + 25°, $[\alpha]^{25}_{365}$ + 108°. High resolution calculated: 85.100173. High resolution observed: 85.1005. Low intensity peak observed at m/e 113, but the much larger P-28 mass was measured at high resolution.

(+)-(3R, 5S)-cis-3-Ethyl-5-methyl-1-pyrazoline (34C). The synthetic and work-up procedures used were the same as for 36T. However, 1.83 g (7.5 mmol) of the dibromide diastereomer (42), 97.9% vpc pure, was available. 42 was contaminated with 2.1% of the dibromide diastereomer (43). In this case the reaction was

allowed to proceed for eight days and 13 hours.

After oxidation, 120 mg of the pyrazoline (97.9% cis, 2.1% trans) was isolated by preparative vpc, column C (100°C, 75 ml/min). Spectra correlate with spectra obtained by Clarke for racemic 34C. Ir: 3010, 2970, 2920, 1520, 1470, 1375, 1285, 1210, 1150, 1043, 960, 923 cm^{-1}. Nmr (CCl_4): δ 0.30-0.85 (d of t, J = 12.5, J = 9.0, 1H, one C_4H); 1.07 (t, J = 7.0, 3H, $-CH_2\underline{CH_3}$); 1.53 (d, J = 7.0, 3H, $-\underline{CH_3}$); 1.65-2.30 (m, 3H, $-\underline{CH_2}-CH_3$, one C_4H); 4.12 (seven line pattern, 2H, $-\underline{\dot{C}H}-$). Optical rotations: (c = .0098 g in 1 ml n-heptane); $[\alpha]^{25}_{589}$ + 3.4°, $[\alpha]^{25}_{578}$ + 4.4°, $[\alpha]^{25}_{546}$ + 5.3°, $[\alpha]^{25}_{436}$ + 22°, $[\alpha]^{25}_{365}$ + 106°. Anal. calculated for $C_6H_{12}N_2$: C, 64.29; H, 10.71; N, 25.00. Found; C, 64.09; H, 10.84; N, 24.51.

(+)-S-3-Bromohexane (47). To 200 mg (2 mmol) of 8.2% optically pure (-)-R-3-hexanol (46) and 5 ml pyridine in a 10 ml Erlenmeyer flask was added 420 mg (2.2 mmol) tosyl chloride (recrystallized from diethyl ether) at 0°C. The flask was placed in a refrigerator; after two days needle-like white crystals of pyridine hydrochloride had come out of solution, and the reaction mixture developed a slight yellow tinge.

The solution was poured into 30 ml of an ice-water mixture and was stirred for 15 minutes. A white oil settled out of solution and was taken up in 100 ml diethyl ether. The ether layer was washed with aqueous HCl, followed by water, and was dried over Na_2SO_4. The ether was removed by rotary evaporation and 100 mg of

the white oil tosylate was recovered.

The tosylate (.4 mmol) was taken up in 100 mg spectro-quality acetone in a screw-cap vial. 42 mg (.5 mmol) LiBr in 300 mg acetone was added. After thirty minutes lithium tosylate precipitated from solution. After one hour total reaction time, 18.6 mg of 3-bromo-hexane was prepped directly from the reaction mixture; column A (90°, from 80 ml/min). Nmr: δ 0.85-1.25 (overlapping triplets, 6H, $-CH_2\underline{CH_3}$), 1.30-2.20 (m, 6H, $\underline{CH_2}-$); 3.90 (pentet, J = 6.5 Hz, 1H, $Br\overset{1}{C}\underline{H}-$). Optical rotations: (c = .0186 g in $CHCl_3$): $[\alpha]^{25}_{589}$ + 1.1°, $[\alpha]^{25}_{436}$ + 1.5°, $[\alpha]^{25}_{365}$ + 2.4°.

Partial Reduction of (+)-(2S, 4S)-2, 4-Dibromohexanes (43H). To 100 mg (.41 mmol) 43H, vpc pure, and 1 ml 2, 6, 20, 14-tetramethyl pentadecane, in a 5 ml, single-necked flask at 0°C, was added dropwise 500 mg (2.8 mmol) tri-n-butyl tin hydride. The addition was monitored by vpc and terminated when the monobromide attained a maximum value relative to unreduced (43) and completely reduced hexane.

The bromide mixture was vacuum transferred at .02 mm and purified by preparative vpc, column A (100°, 75 ml/min). The composition of the mono bromohexane mixture (44) was determined (as 58% 3-bromohexane, 42% 2-bromohexane) by analytical vpc, column E (65°, 30 ml/min). Relative FID sensitivities of 2-bromo-hexane/3-bromohexane = 1.44/1.00 were determined by integration of authentic samples using the same vpc conditions. Observed

optical rotations: (.0123 g in 1 ml $CHCl_3$); $[\alpha]_{589}^{25}$ + .110°, $[\alpha]_{578}^{25}$ + .113°, $[\alpha]_{546}^{25}$ + .133°, $[\alpha]_{436}^{25}$ + .226°, $[\alpha]_{365}^{25}$ + .354°.

Partial Reduction of (-)-(2R, 4S)-2, 4-Dibromohexane (42H).

(-)-(2R, 4S)-2, 4-dibromohexane (42H) was partially reduced by the same procedure as for (+)-(2S, 4S) diastereomer (43H). The monobromohexane mixture (45) was purified and determined to have a 58% 3-bromohexane, 42% 2-bromohexane composition in the same manner as for the (+)-(2S, 4S) diastereomer. Optical rotations: (.0149 g in 1 ml $CHCl_3$); $[\alpha]_{589}^{25}$ - .060°, $[\alpha]_{578}^{25}$ - .069°, $[\alpha]_{546}^{25}$ - .081°, $[\alpha]_{436}^{25}$ - .131°, $[\alpha]_{365}^{25}$ - .215°.

Pyrolyses

Injection Port Pyrolyses. The pyrolyses of 34C, 34T, 36C and 36T were carried out on the injection port of a Hewlett-Packard 5750 Research Vapor Phase Chromatograph equipped with a flame ionization detector and a Spectra Physics, Autolabs System I Computing Integrator. The injection block was packed with glass wool to maintain temperature stability. Product analyses were performed on column F (25°, 10 ml/min). Satisfactory peak separation was attained with the exception of the separation of cis-3-hexene from the cis-cyclopropane. However, since the hexene accounts for less than 1% of the products, little error will be introduced by this problem.

Injection of authentic samples of the reaction products (prepared by Clarke) (1a), demonstrated that no product interconversion occurred on the column or injection port. The pyrazolines were

injected as 10% solutions in n-octane. Injection of the pyrazoline at an injection port temperature of 100°C shows that no pyrazoline decomposition to reaction products is occurring by some sort of catalytic process on the vpc column. Pyrolyses were performed at least three times at a given temperature with reproducibility within 1% (see Tables 2-5).

Flow Pyrolyses. Flow pyrolyses were carried out utilizing a quartz tube flow system contained in a Hoskins tube furnace. Auxiliary heating wires, wrapped with asbestos tape, prevented sample condensation in the flow system at both the inlet and outlet sides. The pyrolysis products were collected in a double U-tube trap filled with Pyrex helices. The first trap was maintained at -78°C and the second trap was maintained at -196°C. Drying towers attached to the traps prevented any condensation of moisture in the traps. The temperature of the quartz tube was monitored by an iron-constantan thermocouple. The neat pyrazoline was introduced into the pyrolysis zone by a flow of helium (60 ml/min).

In a typical pyrolysis, ~ 100 mg of vpc purified pyrazoline was carried through the reaction zone over the course of three hours. The pyrolysis products were vacuum transferred from the collection traps. Vpc analysis on column C (100°, 75 ml/min) showed no unreacted pyrazoline. The cis- and trans-methyl, ethyl-cyclopropanes were separated and purified by preparative vpc using column D (60°C, 65 ml/min).

Table 9

Specific Rotations of 1-Ethyl-2-methyl-cyclopropane Pyrolysis Products

Precursor	λ nm	trans Δ (g/ml, n-hexane)	$[\alpha]_\lambda^{25}$	cis Δ (g/ml, n-heptane)	$[\alpha]_\lambda^{25}$
(34C)	589	.0136	+2.0° ± .2°	.0056	+2.9° ± .4°
	578		+2.2° ± .2°		+2.1° ± .4°
	546		+2.4° ± .2°		+2.2° ± .4°
	436		+3.9° ± .2°		+4.6° ± .5°
	365		+5.7° ± .2°		+7.9° ± .4°
(36C)	578	.0159	+2.6° ± .1°	.0133	+2.3° ± .1°
	546		+2.9° ± .1°		+2.6° ± .2°
	436		4.7° ± .2°		+4.4° ± .1°
	365		7.1° ± .2°		+6.6° ± .2°
(36T)	589	.0035	+2.8° ± .6°	.0155	+0.2° ± .1°
	578		+4.2° ± .6°		+0.3° ± .2°
	546		+5.4° ± .7°		+0.2° ± .1°
	436		+7.9° ± .7°		+0.1° ± .1°
	365		+10.0° ± .7°		+0.2° ± .1°

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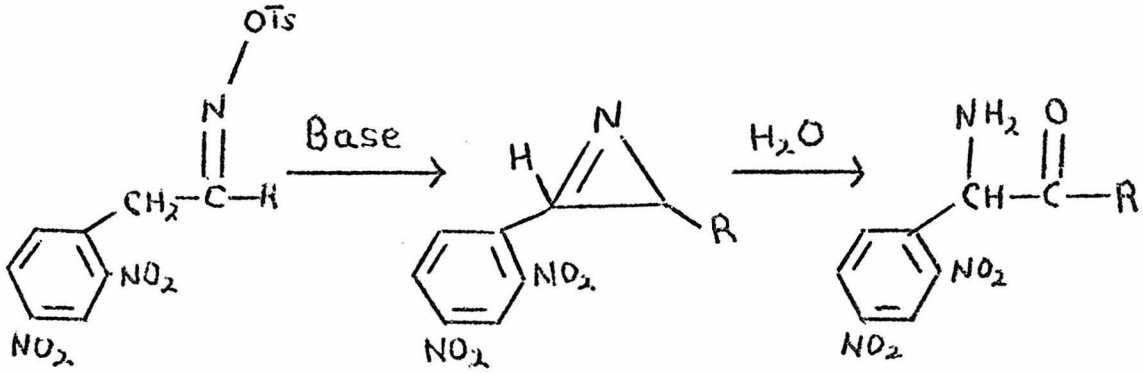
MECHANISTIC INVESTIGATIONS OF THE THERMAL DECOMPOSITIONS OF 2H-AZIRINES

I. Introduction

A. History

The first 2H-azirine (1) was isolated by Neber in 1932 as an intermediate in the reaction of an oxime tosylate with base to produce an α-amino ketone (2). The postulation of (1) as a stable molecule was

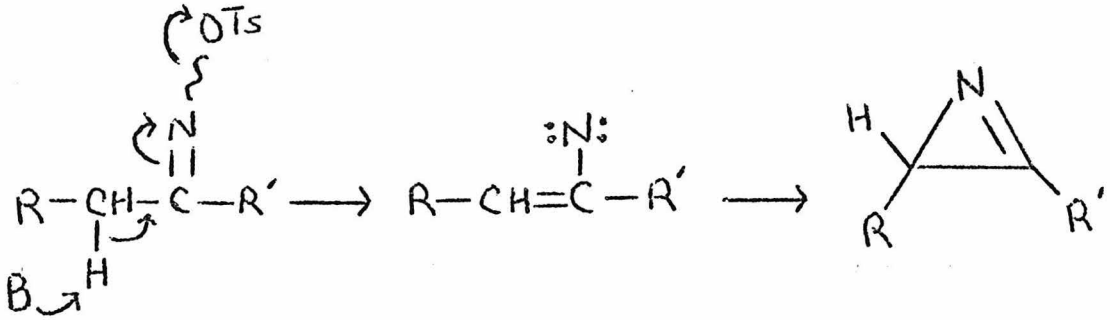


1

criticized in Neber's time, and it was not until 1953 that Cram and Hatch rigorously established the structure of 1 (3).

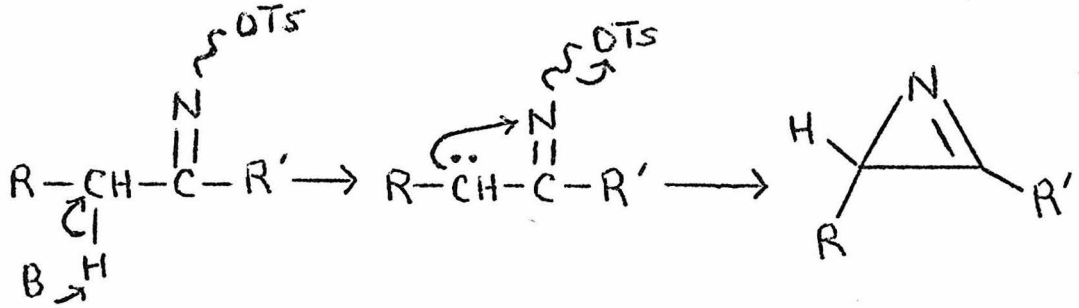
The mechanism of the Neber rearrangement has not yet been unambiguously determined (4). The mechanism favored by Cram and Hatch (3) involved base-induced γ-elimination and subsequent vinyl nitrene formation (Scheme I).

This mechanism is in accord with azirine formation via purported vinyl nitrenes from pyrolysis and photolysis of vinyl azides (see later discussion in this section). However, there is no definitive evidence for the existence of vinyl nitrenes, and the possibility of



Scheme I

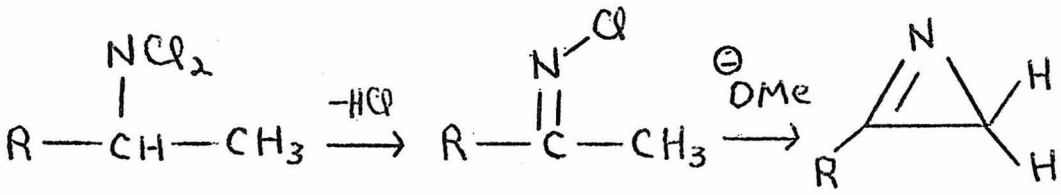
tosylate displacement by the initially-formed carbanion is also a tenable alternative mechanistic possibility (Scheme II) (4).



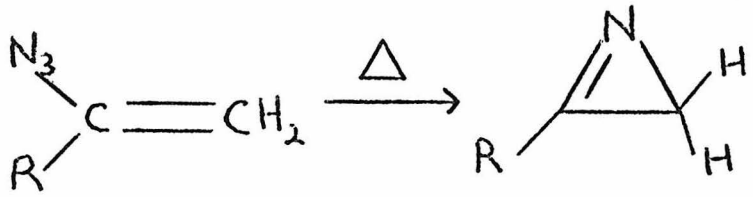
Scheme II

Several other azirine syntheses (5,6) similar to the Neber rearrangement have been reported, but the generality of this approach has not been exploited. Parcell has utilized dimethylhydrazone methiodide as an azirine precursor. Baumgarten and Bower (6) have reported the

formation of azirines in reasonable yields from the treatment of N,N-dichloro-sec-alkyl amines with sodium methoxide.



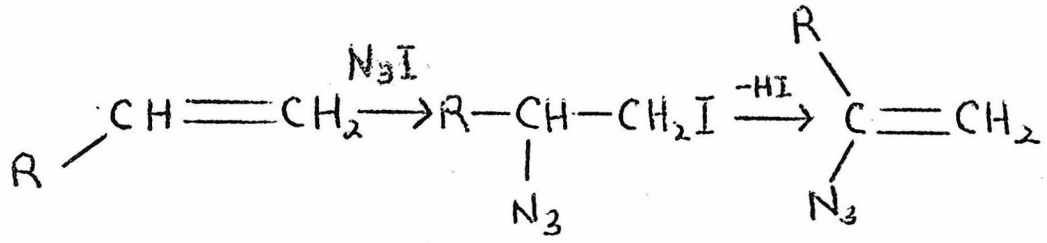
In 1961 Smolinsky (7) reported the thermal conversion of vinyl azides to 2H-azirines. The generality of this approach appeared to be



R = C_6H_5, ortho-$CH_3C_6H_5$, n-butyl

limited only by the availability of appropriately substituted vinyl azides; in 1961, this was indeed a severe limitation.

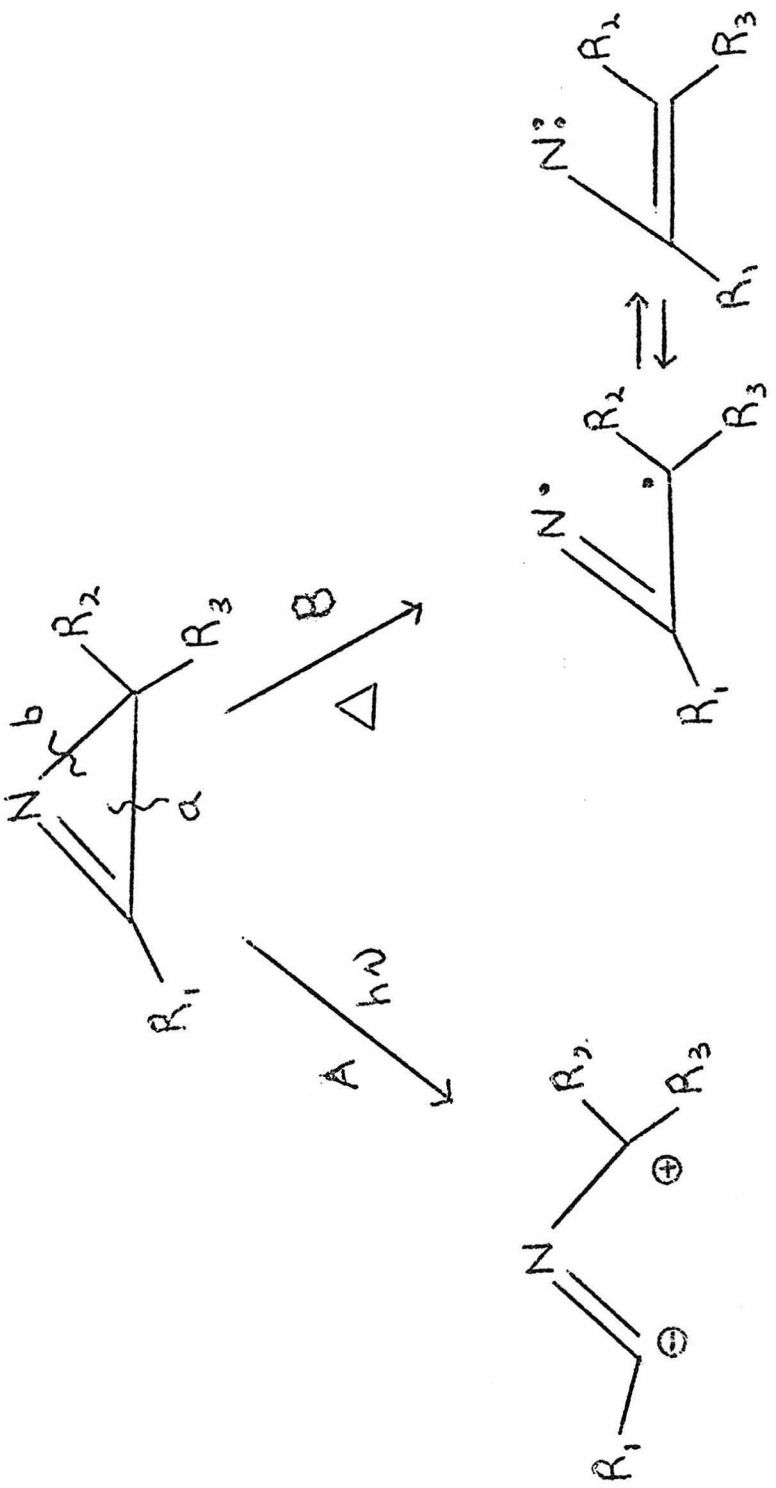
In 1965, Hassner and co-workers (8) developed a general synthesis of vinyl azides, and established the vinyl azide route as the preferred method of synthesizing 2H-azirines. Hassner's convenient synthesis is based on Markownikoff addition of iodine azide (IN_3) to an olefin, followed by base-induced, stereoselective dehydrohalogenation.



Conversion to the azirine via photolysis of the azide proceeds in excellent yield.

B. Reactions

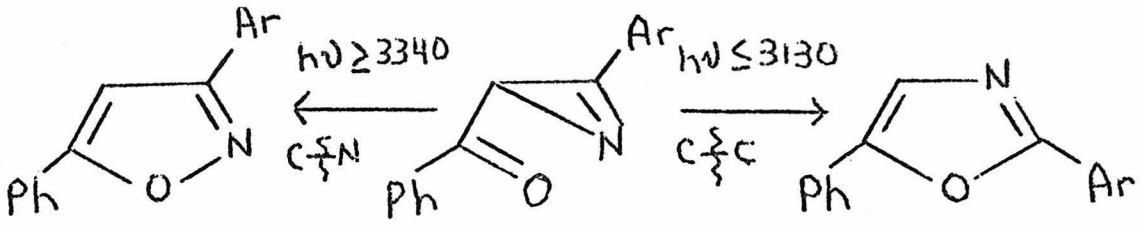
With the advent of a generalized azirine synthesis, a significant effort has been aimed at characterizing the thermal and photochemical structural isomerizations of 2H-azirines. The photochemical and thermal bond cleavage preferences are quite distinct; photochemical isomerizations appear to always involve carbon-carbon bond cleavage (path A, Scheme III), while thermal isomerizations usually appear to involve initial carbon-nitrogen bond cleavage (path B, Scheme III).



Scheme III

Photochemical Isomerizations

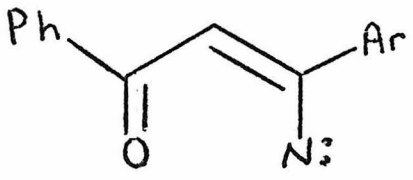
In 1967 Singh and Ullman (9) reported that the photochemical rearrangement of 3,5-diarylisoxazoles (2) to 2,5-diaryloxazoles (3) proceeds via 3-aroyl-2-aryl-2H-azirines (4). These authors also showed that photolysis of the isolated azirine intermediate with light of 3130-A or shorter wavelength resulted in quantitative isomerization to oxazoles, whereas 3340-A or longer wavelength light produced only rearrangement to isoxazoles (Scheme IV). Sensitization studies



2 4 3

Scheme IV

suggested a triplet excited state of the azirines was involved in isoxazole formation, and a singlet excited state of the azirine lead to the oxazole. The authors proposed a mechanism wherein the singlet and triplet excited azirines collapse to ground state species (5) (by C-N cleavage) and (6) (by C-C cleavage) respectively, which then close to the appropriate products. It was suggested that the excited



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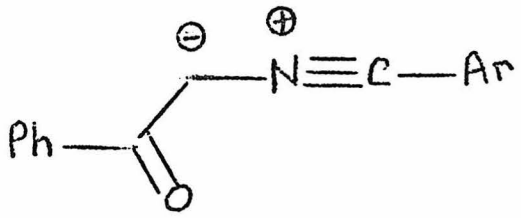

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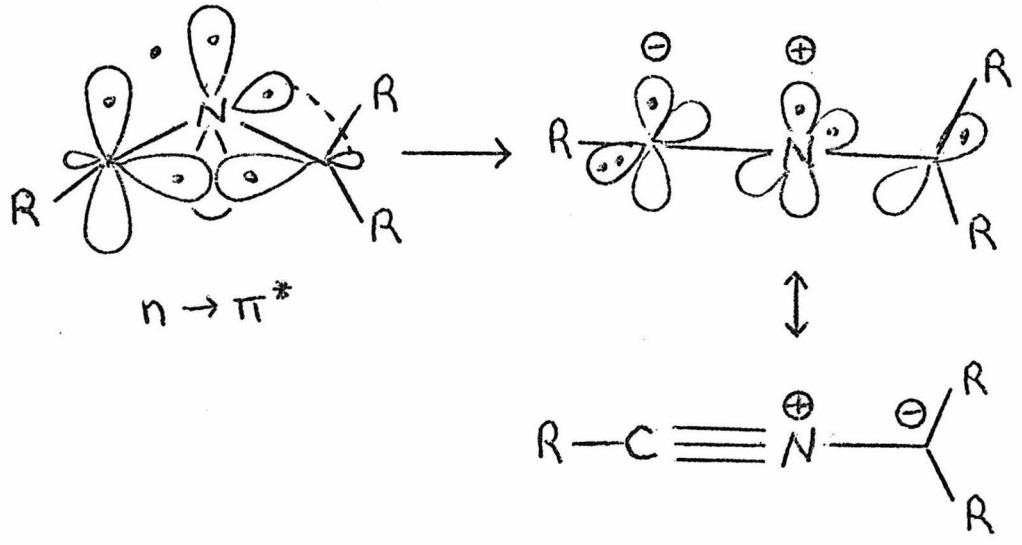
state precursor of (6) was produced by the n $\rightarrow \pi^*$ transition of the ketimine chromophore. It is reasonable that the lone pair orbital of the electrophilic nitrogen, in the excited singlet azirine, overlaps with the back lobe of the carbon-carbon sigma bond at the saturated carbon (Scheme V). This causes cleavage of the C-C bond and generation of the ylide after electronic demotion (10a). Intermediate (5) prob-



Scheme V

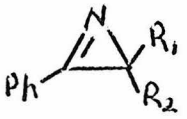
ably results from a carbonyl transition and consequently is not a fundamental photochemical process of azirines (9).

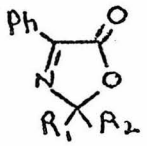
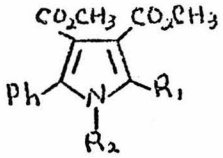
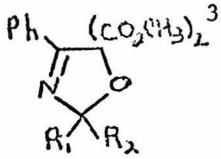
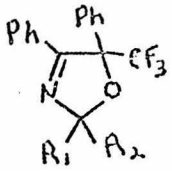
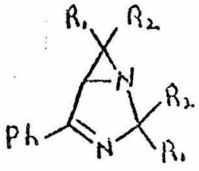
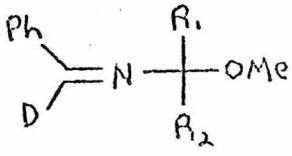
Beginning in 1971, Padwa (10) and Schmid (11) have shown in independent studies that upon photolysis, 3-phenyl-2H-azirines undergo cycloadditions with a variety of 1,3-dipolarophiles (Table 1). These reactions apparently all proceed by C-C cleavage, leading to dipolar species similar to (6).

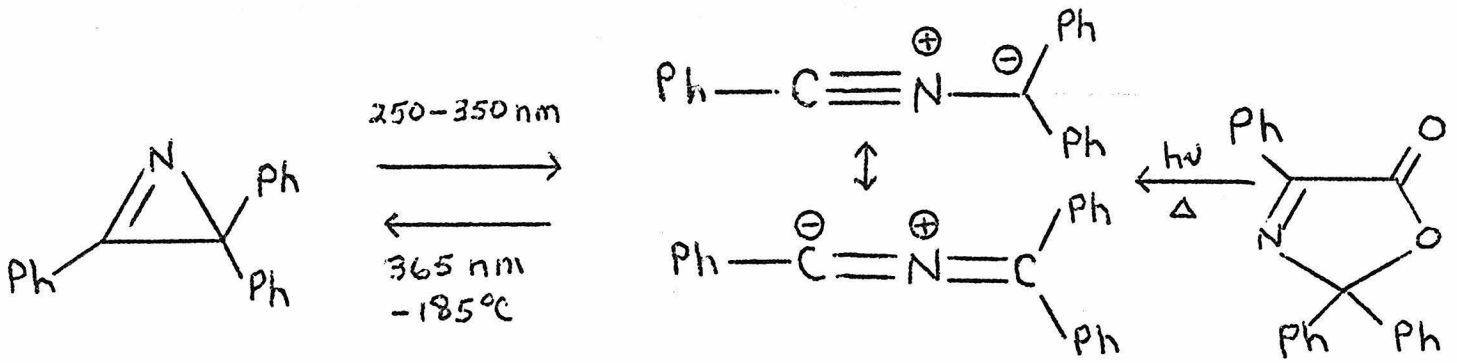
Schmid (13) has also photolyzed triphenyl-2H-azirine (7) in a 2,2-dimethylbutane/pentane matrix at -185°C and observed a new UV maximum at ca. 350 nm, $\epsilon \sim 10^4$. The authors assigned this band to nitrile ylide species (8, Scheme VI). They further showed that the ylide rearranged to starting azirine only photochemically. Upon irradiation of the oxazolinone (9), the ca. 350 nm absorbance was also produced. Low temperature trapping experiments of the ylide with methyl trifluroacetate yielded 5-methoxy-5-trifluoromethyl-2,2,4-triphenyl-3-oxazoline (10) (Scheme VI).

Recent ab initio MO calculations by Salem (14), utilizing a configuration interaction treatment, indicate that upon cleaving a C-C azirine bond, the ground state nitrile ylide energy surface is best reached by internal conversion from a singlet n,π^* state at a C-N-C bond angle of 100°. Salem's calculations also predict a large barrier for thermal conversion of the ylide to azirine, but suggest a facile photochemical conversion.

Table 1: Trapping Products Formed Upon Irradiation of 2H-Azirines.



R	Dipolarophile	Product	Yield	Reference
R_1 = H; Ph R_2 = H	CO_2		60%	11a
R_1 = Ph; R_2 = H	Dimethyl acetylene dicarboxylate		40%	11a
R_1 = R_2 = CH_3 R_1 = H; R_2 = CH_3 R_1 = H; R_2 = Ph	$(CH_3O_2C)_2CO$		35-60%	11b
R_1 = R_2 = CH_3 R_1 = H; R_2 = Ph			80-90%	11b
R_1 = H, CH_3; R_2 = H			10%	11c,d
R_1 = R_2 = H R_1 = Q; R_2 = H R_1 = R_2 = CH_3	MeOD		98%	12



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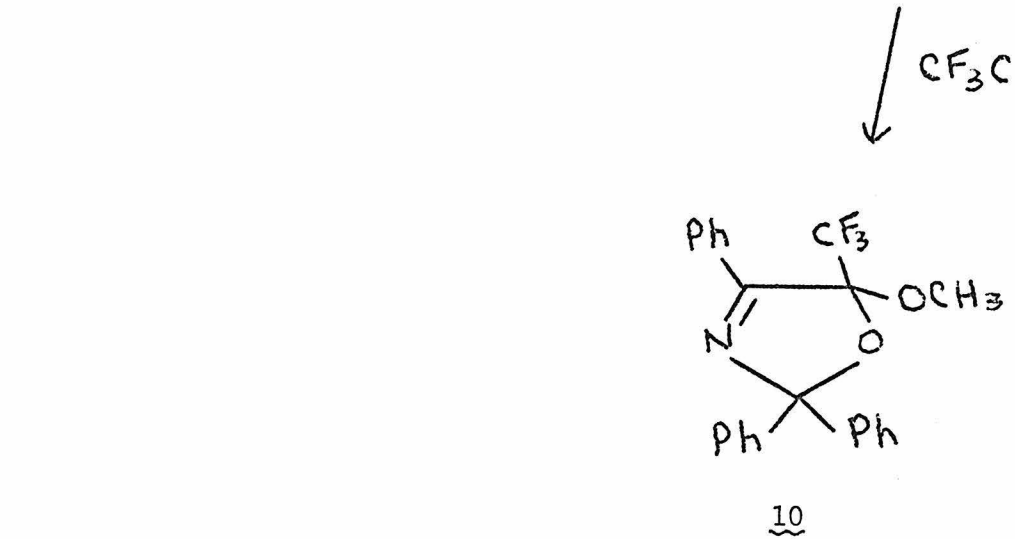

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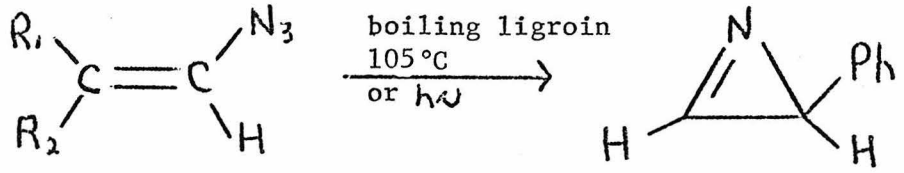
Scheme VI

Thermal Isomerizations

Relative to the well-defined photochemistry of 2H-azirines, their thermal behavior is not as well understood. Thermal reactions of 2H-azirines appear to be very substituent dependent, and due to the scarcity of systems investigated to date, the inherent mechanistic preferences are largely unknown.

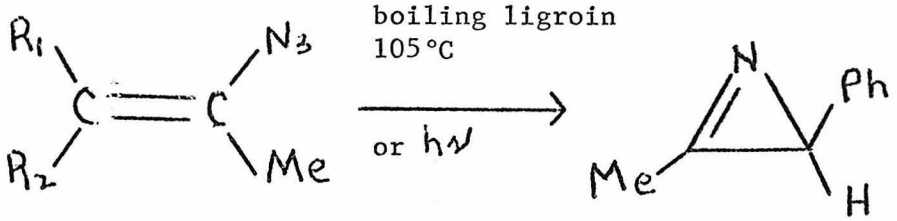
The first report of a 2H-azirine pyrolysis was made by Isomura and co-workers in 1968 (15). Azirines (10a) and (11) were prepared by photolytic or thermal decomposition of the vinyl azides (12C and T), and (13C and T) respectively (Scheme VII). Thermal decomposition of



12C: R_1 = Ph; R_2 = H

12T: R_1 = H; R_2 = Ph

10a



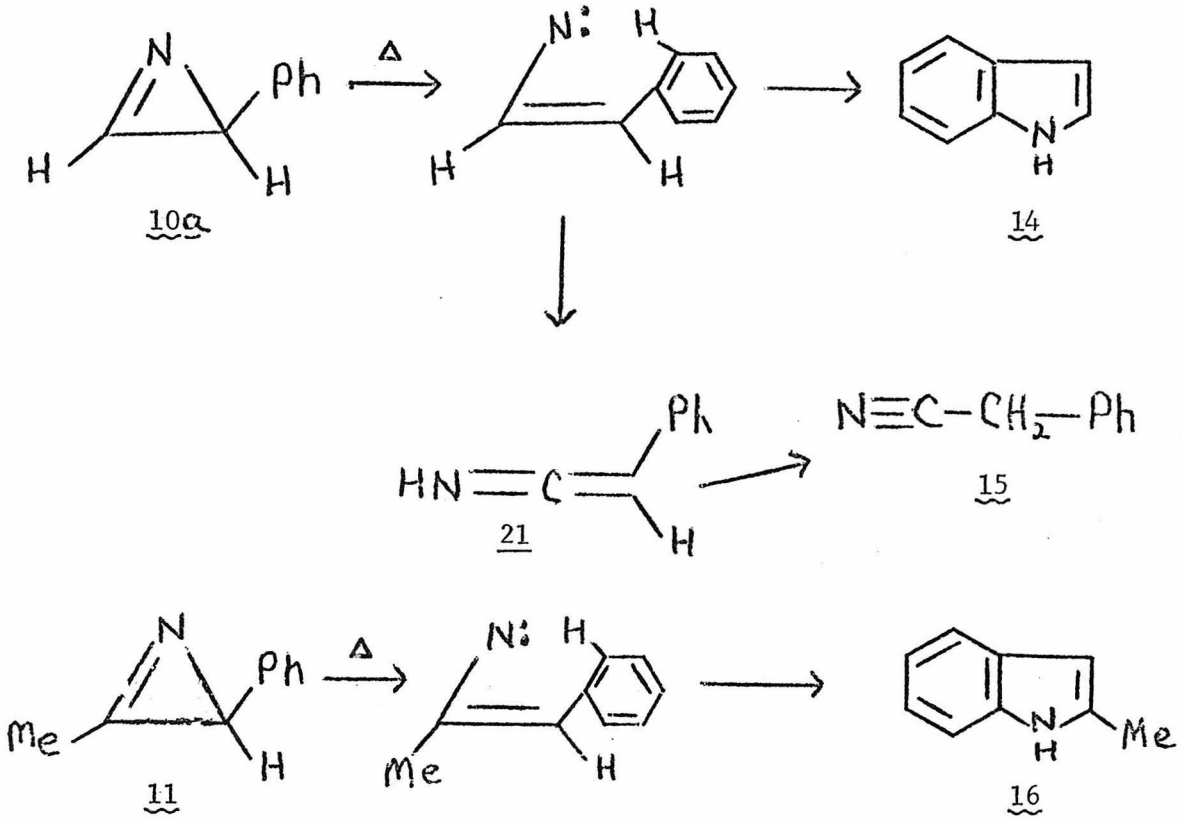
13C: R_1 = H; R_2 = Ph

13T: R_1 = Ph; R_2 = H

11

Scheme VII

10a in boiling hexadecane yielded a 1:1 mixture of indole (14) and phenylacetonitrile (15) in 86% isolated yield. Similar treatment of 11 gave only 2-methyl indole (16). The most obvious mechanistic explanation for formation of 14, 15, and 16 is via a vinyl nitrene generated by rupture of the carbon-nitrogen bond, followed by insertion into the phenyl group or α-carbon-hydrogen bond (see Scheme VIIa). It is very interesting that the decomposition of the corre-

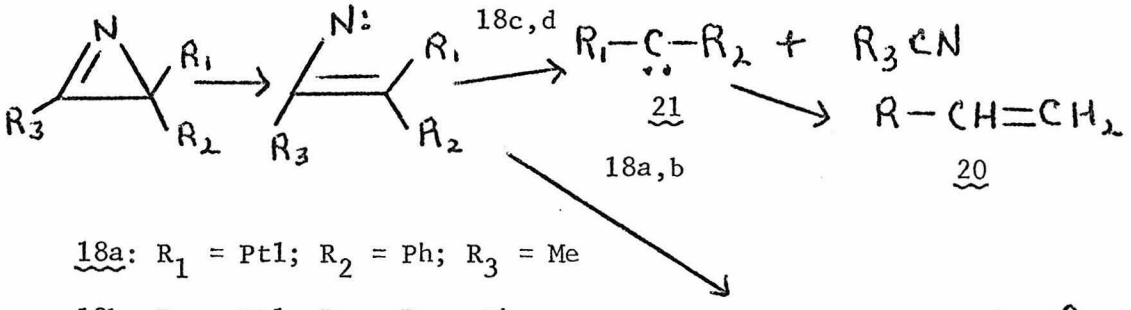


Scheme VIIa

sponding vinyl azides, which presumably also proceeds via a vinyl nitrene, produces none of the azirine decomposition products (actually a "trace" of 15 is formed upon thermal decomposition of 10a). This will be discussed after several more examples are presented.

In 1972, the Isomura research group published a study of the thermal rearrangements in dilute solution of a series of 3-vinyl-2H-azirines (16). The results of this study, which can again be explained by C-N cleavage leading to a vinyl nitrene, are displayed in Scheme VIII.

Rees and co-workers have flash-vacuum pyrolyzed the series of 2H-azirines (18a-d) at 400-500°C (17). Their results may also be accounted for by initial carbon-nitrogen bond cleavage (Scheme IX). Rees



18a: R_1 = Ptl; R_2 = Ph; R_3 = Me

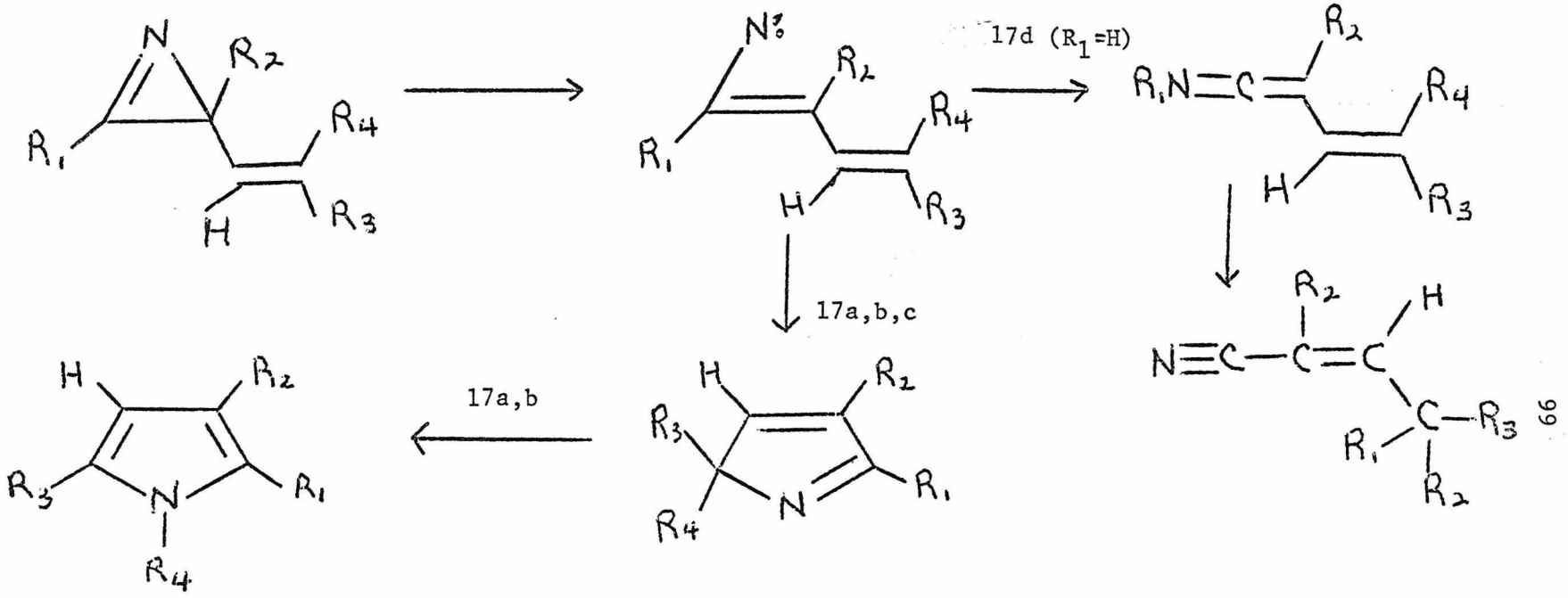
18b: R_1 = Ptl; R_2 = R_3 = Ph

18c: R_1 = Ptl; R_2 = R_3 = Me

18d: R_1 = Ptl; R_2 = Me; R_3Ph

(Ptl = phthalimido)

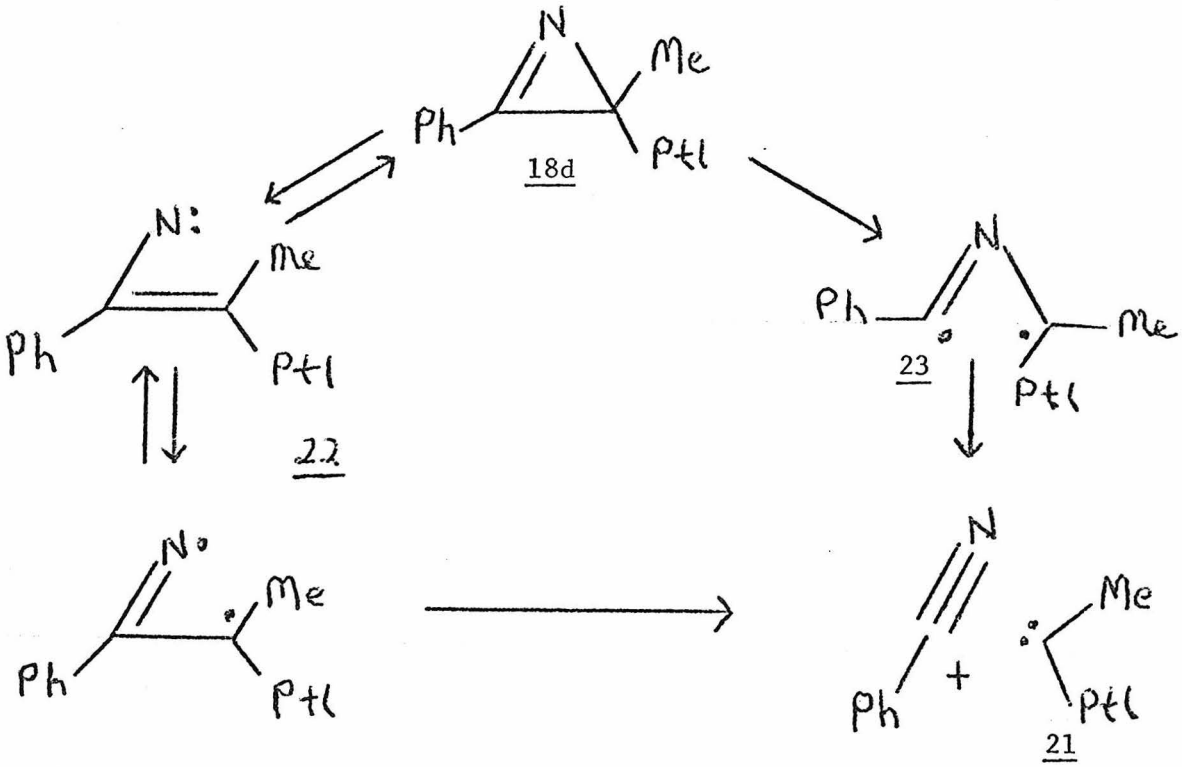
Scheme IX



	R_1	R_2	R_3	R_4
17a	H	H	Ph	H
17b	CH_3	Ph	Ph	H
17c	CH_3	Ph	Ph	Ph
17d	H	Ph	Ph	Ph

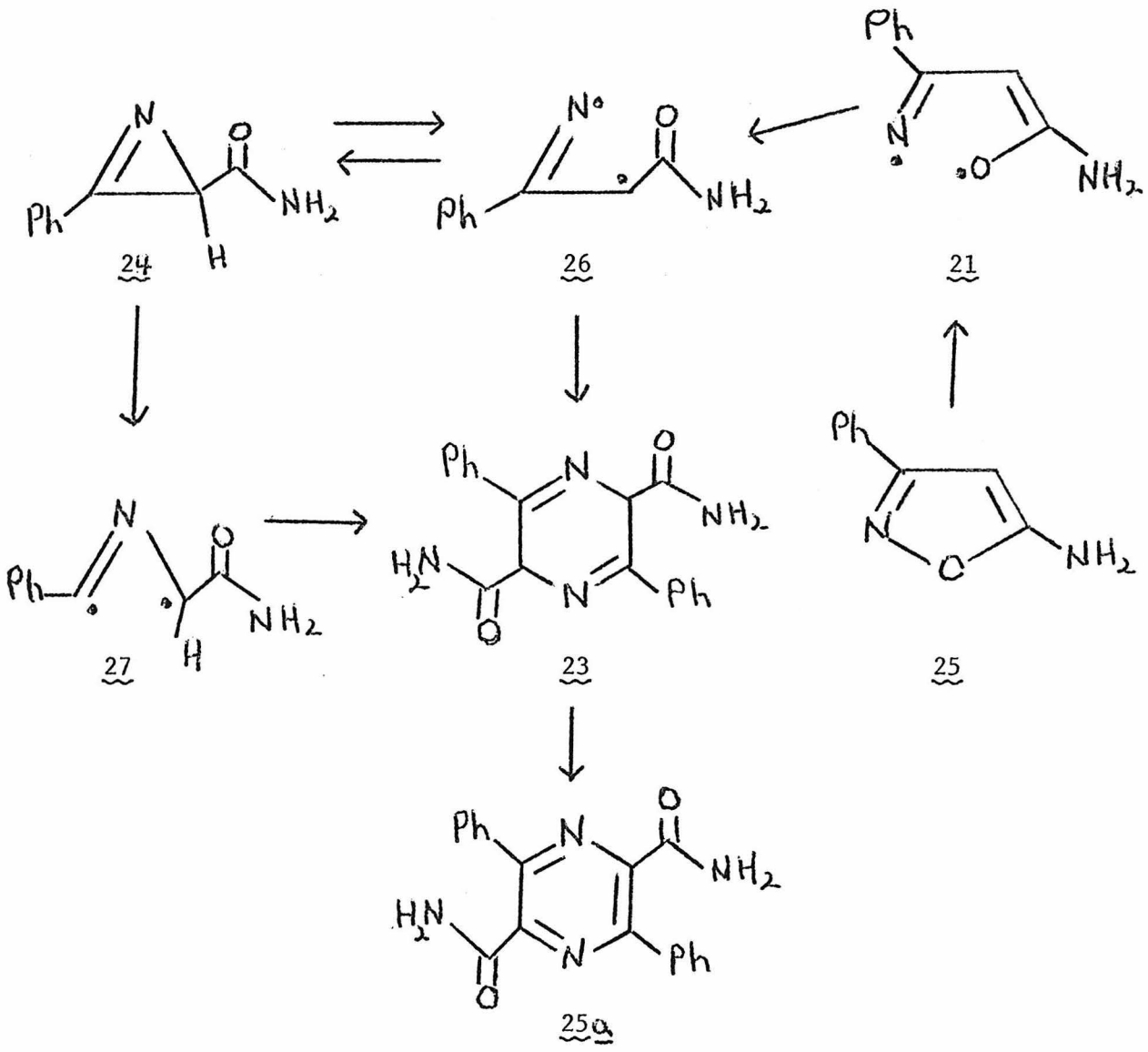
Scheme VIII

suggests that when R_1 and R_2 are not phenyl groups and R_3 is not hydrogen, "fragmentation" of the azirine results in formation of carbene (21) (17). The carbene then rearranges to the olefin (20). When R_1 or R_2 are phenyl, nitrene insertion into a phenyl C-H bond forms indole (19). When R_3 is hydrogen (and R_1 or R_2 is not phenyl) presumed ketenimine formation via the vinyl nitrene is the preferred reaction (Scheme VII). While the authors do not comment on the carbene extrusion process, two possible immediate precursors (22) and (23) to the carbene (21) can be postulated (Scheme X). This mechanistic possibility will be discussed in detail in another section.



Scheme X

Nishiwaki and co-workers (18) have reported results describing the neat pyrolysis of 2H-azirine-2-carboxamides (24) and 5-aminoisoxazoles (25). The authors suggest that intermediate (26) has diradical



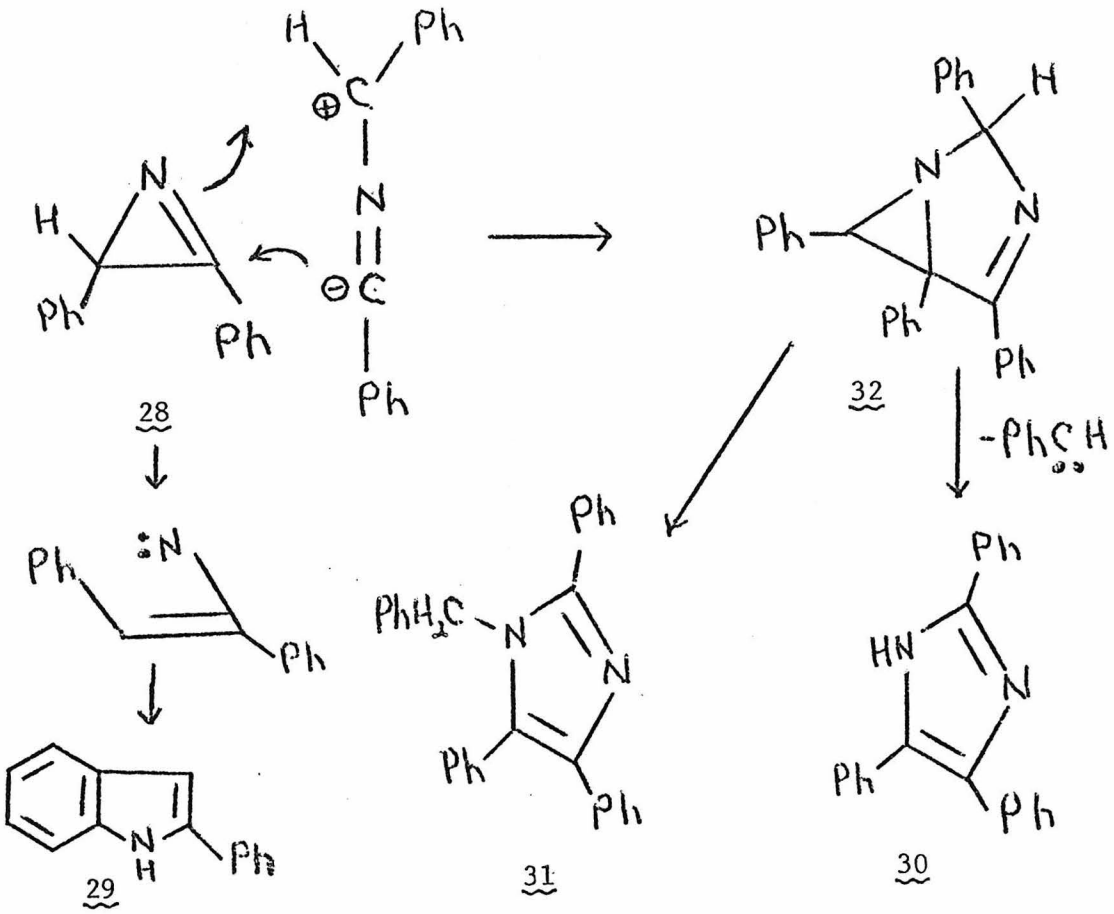
Scheme XI

character, but a vinyl nitrene would also be consistent with the reaction products. Nishiwaki points out that cleavage of the azirine C-C bond to form intermediate (27) is also a mechanistic possibility.

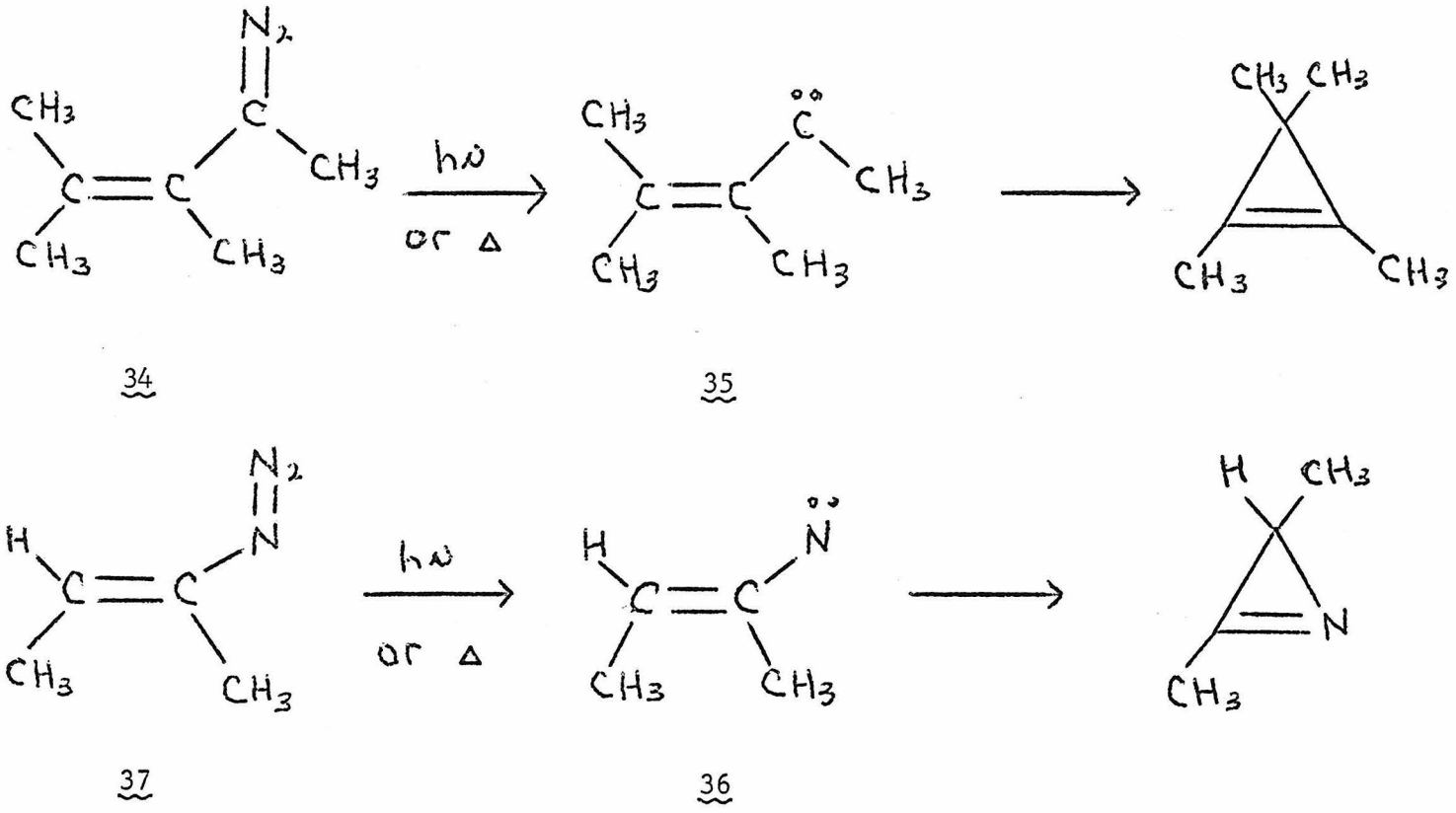
Another report which implies that carbon-carbon azirine bond rupture may be accessible thermally was made by Bowie and co-workers (19). Major products from the 250°C, sealed-tube pyrolysis of 2,3-diphenyl-2H-azirine (28) included 2-phenylindole (29), 2,4,5-triphenylimidazole (30) and 1-benzyl-2,4,5-triphenylimidazole (31); 89% conversion to product was attained (Scheme XII). The indole (29) can be easily rationalized as resulting from intramolecular C-H insertion of a vinyl nitrene. The authors suggest that (30) and (31) may be formed from the cycloaddition product (32) of a 1,3-dipole and azirine as demonstrated in Scheme XII. An analogous compound to (32) was isolated upon photolysis of 3-methyl-2-phenyl-2H-azirine (11c,d).

The work of Isomura (16) (Schemes VIIa and VIII) raises two questions concerning vinyl nitrenes: 1) Is a vinyl nitrene generated upon thermal decomposition of vinyl azides? 2) Is this vinyl nitrene the same species as is generated by 2H-azirine pyrolysis?

The intermediate generated upon thermal or photolytic decomposition of vinyl azides (37) mirrors the behavior of the purported vinyl carbene generated by thermal or photolytic decomposition of diazo-alkenes (34) (20) (Scheme XIII). While, the vinyl carbene (35) and nitrene (36) are attractive intermediates for conversion of diazo-alkenes and vinyl azides to their corresponding three-membered


H
Ph
⊕C
N
⊖C
Ph
N
H
Ph
Ph
28
Ph
:N
Ph
N
H
Ph
29
Ph
H
N
Ph
N
Ph
Ph
32
-PhCH
Ph
PhH2C
N
N
Ph
Ph
31
Ph
HN
N
Ph
Ph
30

Scheme XII

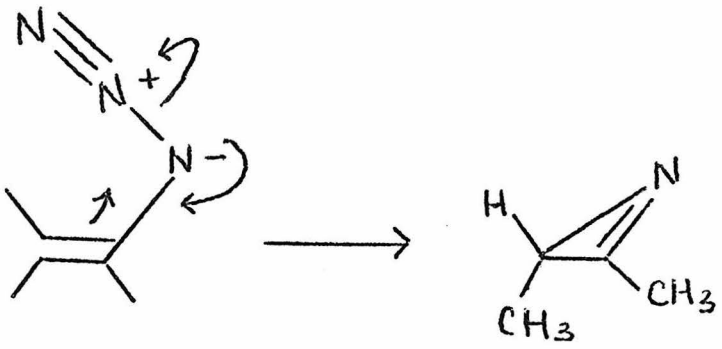


34 35

37 36

Scheme XIII

unsaturated rings, no direct proof for their existence has been reported. Smolinsky (21) originally suggested that nitrogen extrusion from vinyl azides could be envisioned as a concerted process (Scheme XIV).

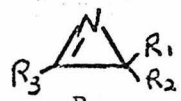


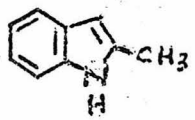
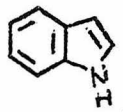
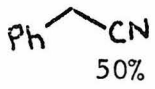
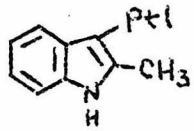
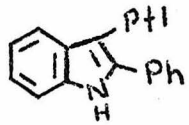
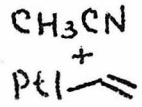
Scheme XIV

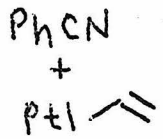
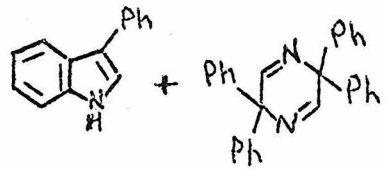
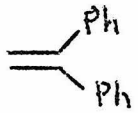
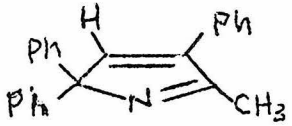
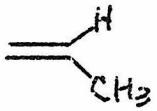
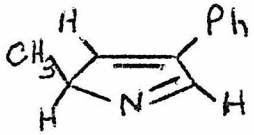
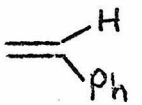
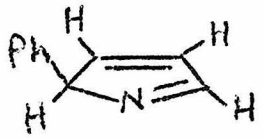
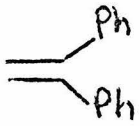
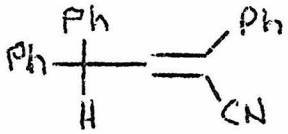
Presently this is a viable alternative. It is indeed ironic that this mechanistic ambiguity so closely parallels the questions raised earlier concerning vinyl nitrene intermediacy versus a carbanion displacement reaction in the Neber rearrangement (Schemes I and II).

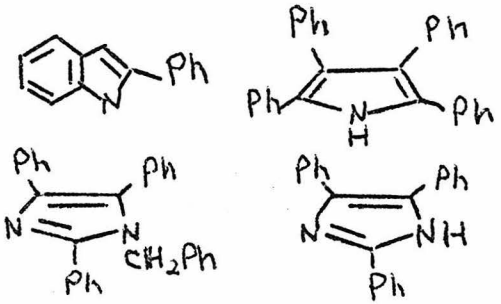
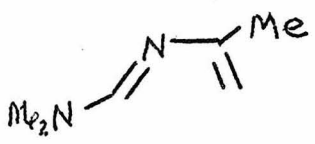
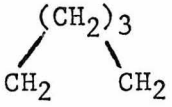
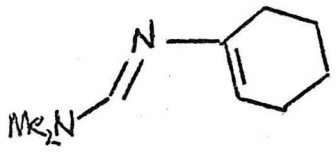
A significant amount of work has been reported which presents a strong case for vinyl carbene formation from the pyrolysis of cyclopropenes (22-25). The list of thermal reactions of 2H-azirines, outlined in Table 2, indicates that azirines behave similarly to their all-carbon analogues and isomerize via vinyl nitrenes. Also, 3-phenyl substituted cyclopropenes rearrange to isoindenes; this reaction parallels the 3-phenyl-2H-azirine to indole conversion (23).

Table 2: Thermal Reactions of Substituted 2H-Azirines.



R_1	R_2	R_3	Rxn Conditions	Products	Reference
H	Ph	CH_3	287° in boiling hexadecane		15
H	Ph	CH_3	287° in boiling hexadecane	 + 50%  50%	15
phthalimido	Ph	CH_3	500° atmospheric flow		17
phthalimido	Ph	Ph	500° atmospheric flow		17
phthalimido	CH_3	CH_3	500° atmospheric flow		17

phthalimido	CH_3	Ph	500° low pressure flow		17
Ph	Ph	H	boiling xylene		26
	Ph	CH_3	boiling hexane		16
	Ph	H	boiling hexane		16
	H	H	boiling hexane		16
	Ph	H	boiling hexane		16

Ph	H	Ph	sealed tube, neat 250°		19
NMe_2	Me	Me	340° .1 Torr		27
NMe_2			400° .1 Torr		27

If vinyl azides decompose in a concerted fashion, while 2H-azirines isomerize via vinyl nitrenes, there is no reason to expect the same products to be formed. However, if both reactions proceed via vinyl nitrenes, possible explanations for different products should be considered. One possibility is that the relatively mild reaction conditions under which vinyl azides are decomposed, supply only enough energy for the vinyl nitrene to cross a barrier leading to azirine. The higher temperatures used for azirine decomposition gives the vinyl nitrene sufficient energy to explore a more extensive energy surface.

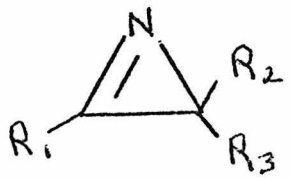
Another explanation involves vinyl nitrenes being formed in different electronic states from vinyl azide decomposition and azirine ring opening. Electronic preferences would then dictate the behavior of the respective nitrenes. Due to the present lack of any experimental or theoretical studies concerning bond-forming preferences of electronic states of vinyl nitrenes, any discussion of this subject would be mere speculation.

As a result of the obvious ambiguities involved with the understanding of vinyl nitrenes, and of our interest in bond-breaking phenomena in small ring compounds (25), we chose to study the thermal decompositions of substituted 2H-azirines. The original intent of this work was to elucidate the nature of the intermediate formed upon C-N bond cleavage in 2H-azirines. However, the formation of unexpected products indicated that we had uncovered the first clear-cut example of carbon-carbon bond cleavage as a major pathway in 2H-azirine thermal decomposition, leading to formation of iminocarbenes.

II. Results

A. Synthesis

In the course of our work, it was necessary to synthesize azirines 33a-d. Compounds 33a and 33b were synthesized via the vinyl azide



33a: R_1 = Ph; R_2 = Me; R_3 = H

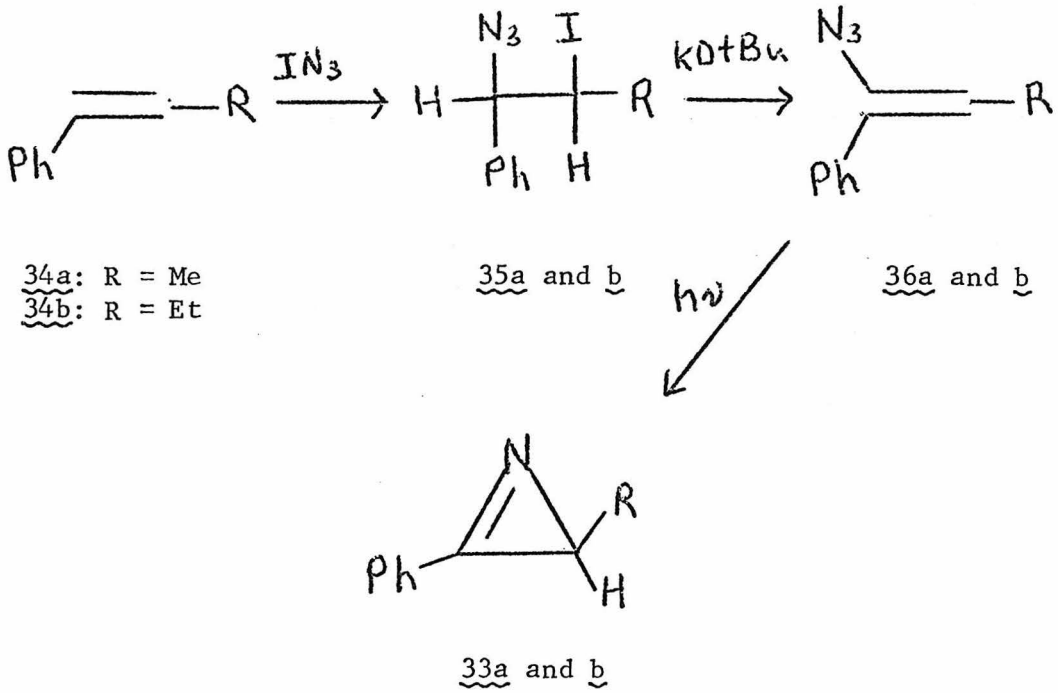
33b: R_1 = Ph; R_2 = Et; R_3 = H

33c: R_1 = Ph; R_2 = Me; R_3 = Me

33d: R_1 = Me; R_2 = Ph; R_3 = Me

route of Hassner (8f, 28), and 33c and 33d were synthesized from the appropriate dimethyl hydrazone methodide (5, 29).

The synthetic route employed for 33a and 33b is depicted in Scheme XV. Both azirines were formed in good overall yields; the pyrolysis samples were vpc purified. The route outlined in Scheme XV was not readily applicable to preparation of 33c and 33d, since mixtures of the iodo-azides (42) and (43) (Scheme XVa) were obtained upon addition of IN_3 to (41). The (43):(42) ratio was $\sim$ 1:3 by nmr. Rather than attempt to optimize reaction conditions, the azirine preparation



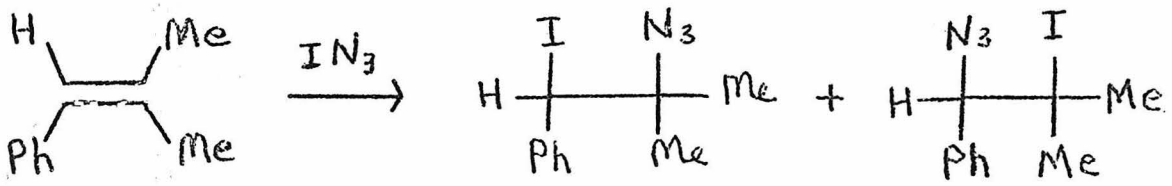
34a: R = Me
34b: R = Et

35a and b

36a and b

33a and b

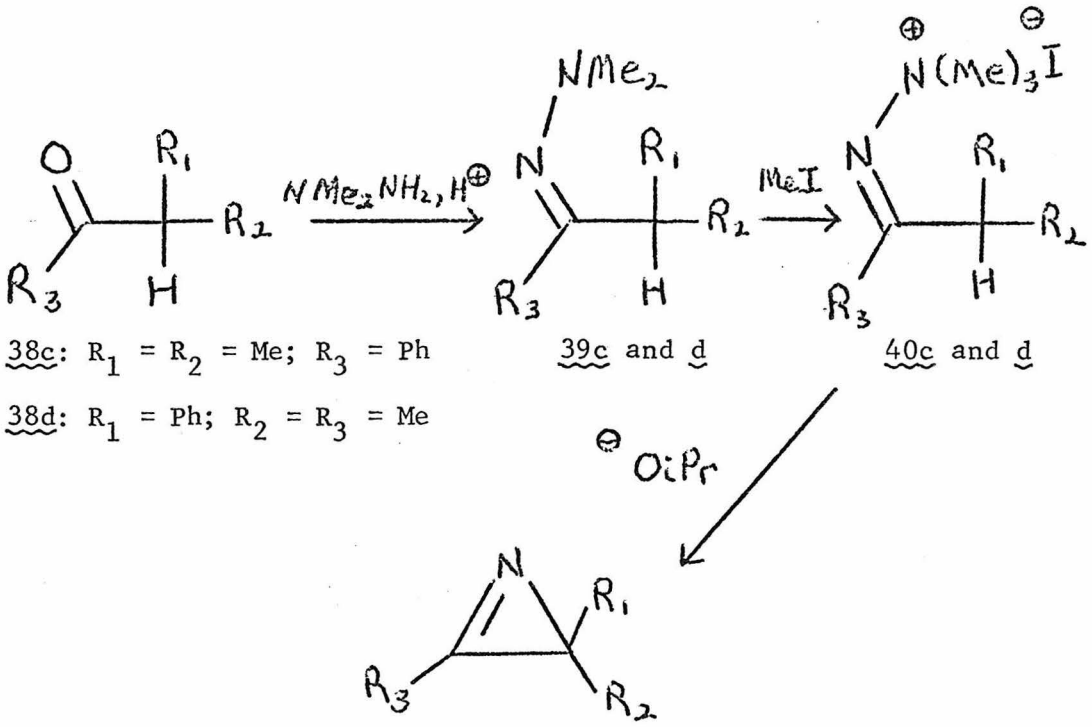
Scheme XV



41 42 43

Scheme XVa

developed by Parcell (5) was utilized (Scheme XVI).



38c: $R_1 = R_2 = Me$; $R_3 = Ph$

38d: $R_1 = Ph$; $R_2 = R_3 = Me$

39c and d

40c and d

33c and d

Scheme XVI

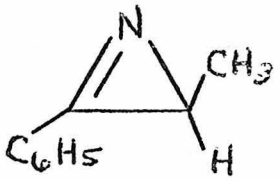
B. Pyrolysis

All pyrolyses were carried out in a quartz flow system at atmospheric pressure using helium as a carrier gas. Typical residence times in the pyrolysis zone were approximately ten seconds. Products were condensed in a double U-tube trap at -196 °C.

Polymerization of some of the pyrolysis products in the collection trap was a troublesome problem in this work. Extensive efforts were made to minimize polymerization; nevertheless 30-40% polymeric material was isolated from every pyrolysis. Even though the yield of polymer varies by as much as 10%, the proportions of apparently nonpolymerizing products remain constant in separate pyrolyses at a given temperature.

Pyrolysis of 3-methyl-2-phenyl-2H-azirine (33a) at 565 °C consumed all the starting material and gave the product distribution displayed in Chart 1. Fragmentation products of styrene comprise 4% of the pyroly-

Chart 1: Products of the 565 °C Pyrolysis of 3- Methyl-2-phenyl-2H-azirine (33a).



33a

$\longrightarrow$ $C_6H_5-CH=CH_2$ + $C_6H_5-C\equiv N$ + Polymer

56% 2% 38%

Other 4%

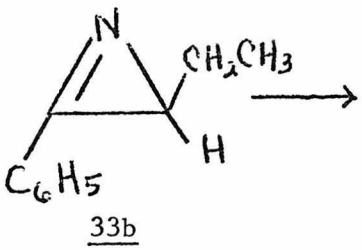
sate and include ethyl benzene, toluene, and benzene. The pyrolysis of 33a at several lower temperatures was monitored by vapor phase chromatography. No buildup of an intermediate was observed at 320°C (0% conversion), 390°C, 466°C, or 523°C.

For atomic conservation it is necessary that one atom of H, C, and N (HCN?) be formed per molecule of styrene produced. The red polymeric material formed is readily soluble in most organic solvents, but infrared analysis of pyrolysis products immediately dissolved in chloroform displayed no C≡N absorbance (other than benzonitrile). A pyrolysis was performed with a bubbler, containing an acidic aqueous solution of $FeSO_4$ and KF, attached to the oven exit. However, the lack of a vivid blue color appearing in the bubbler indicated a negative Prussian Blue test (30). The stability of HCN under the reaction conditions was not determined (this will be discussed later).

The apparent generality of this unexpected fragmentation for 3-alkyl-2-phenyl-2H-azirines was demonstrated by pyrolysis of 33b at 565°C (Chart 2). Fragmentation products of β-methyl styrene include styrene, ethyl benzene, toluene and benzene. Trans and cis β-methyl styrene equilibrate thermally at 565°C; the observed trans:cis ratio of 2:1 is simply the equilibrium mixture at this temperature.

In order to explain the formation of styrenes from 33a and 33b, bonding between C-2 of the azirine ring and the carbon attached to C-3 must occur during the course of reaction. Two possible mechanistic routes which accomplish the observed

Chart 2: Products of the 565°C Pyrolysis of 3-Ethyl-2-phenyl-2H-azirine (33b).



33b

$C_6H_5-CH=CH-CH_3$ + $C_6H_5-CH=CH_2$ + $C_6H_5-C\equiv N$

cis and trans

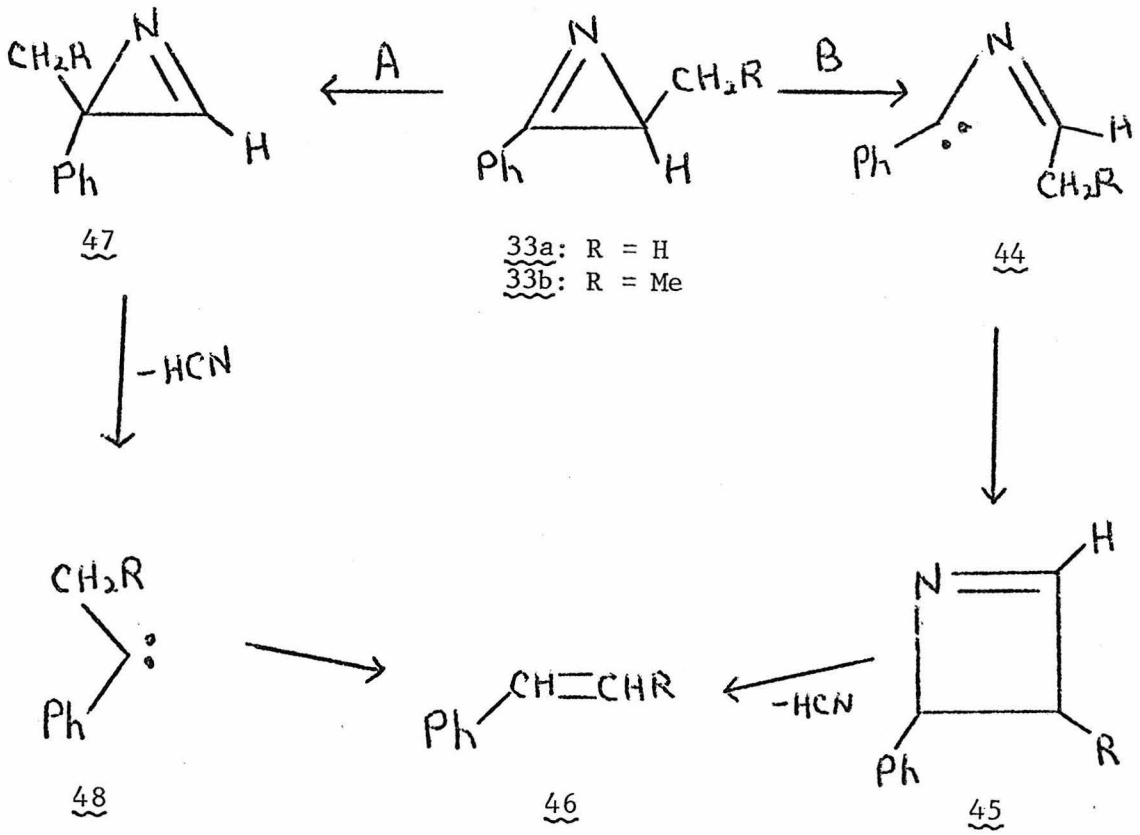
42% 9% 2%

Polymer + Other

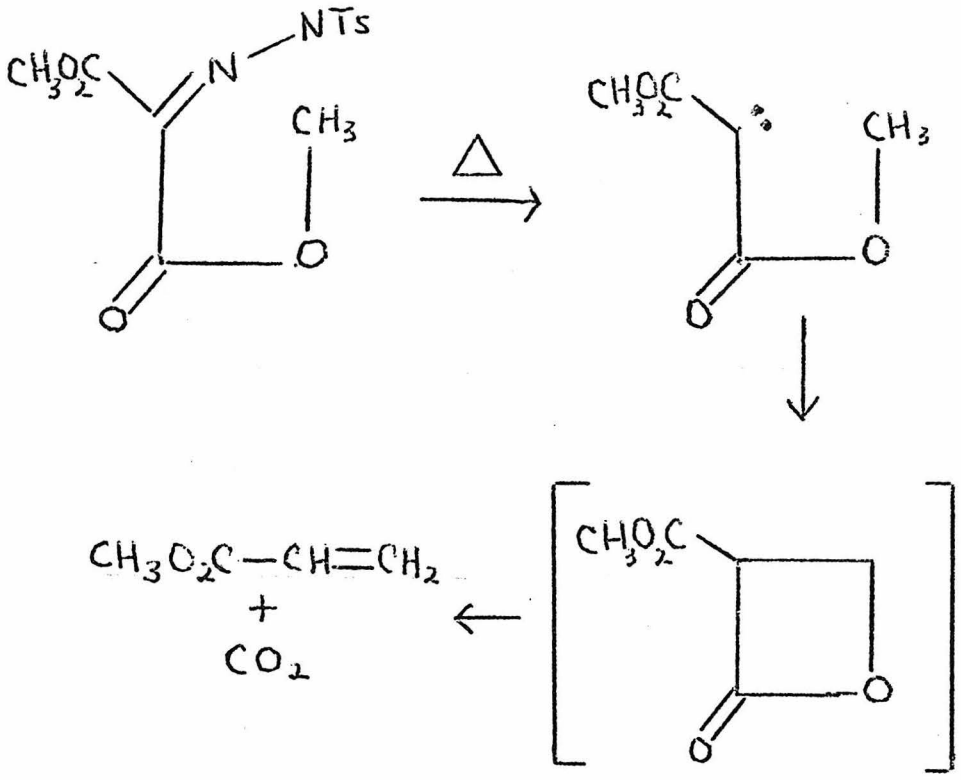
39% 8%

transformation are shown in Scheme XVII; however, neither path is particularly satisfying. Path A involves an unprecedented 1,3-alkyl shift in an unsaturated ring. The fragmentation of (47) is similar to the decomposition mode proposed by Rees (17) for 18c and 18d. 2H-azirines substituted with H at the 2 position are only stable at low temperatures (26); consequently 47 would be expected to rapidly decompose under our reaction conditions.

Path B involves carbon-carbon bond cleavage in azirines and 1,4-carbene insertion into a C-H bond to form azetine (45) (31). Jones (32) does present one case in which a carbene does presumably insert to form a four-membered ring (Scheme XVIII); however, hydrogen abstraction would be expected to be a more facile process than C-H insertion in our system. In 1971 Hassner reported that cyclopropyl azides smoothly

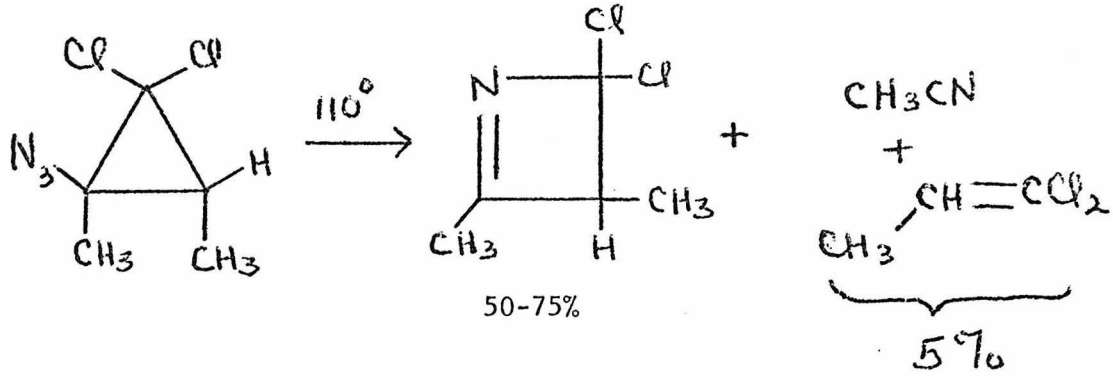


Scheme XVII



Scheme XVIII

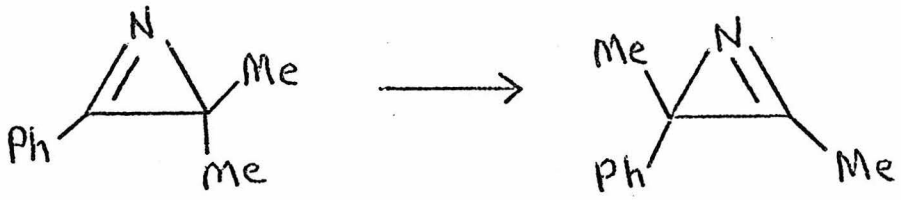
decompose to azetines and olefinic fragmentation products (33). He suggested that the olefins could be coming from azetine decomposition,



but does not rigorously prove it.

Path A is relatively easy to experimentally test. Pyrolysis of 33c should result in formation of 33d (isolable at partial conversion

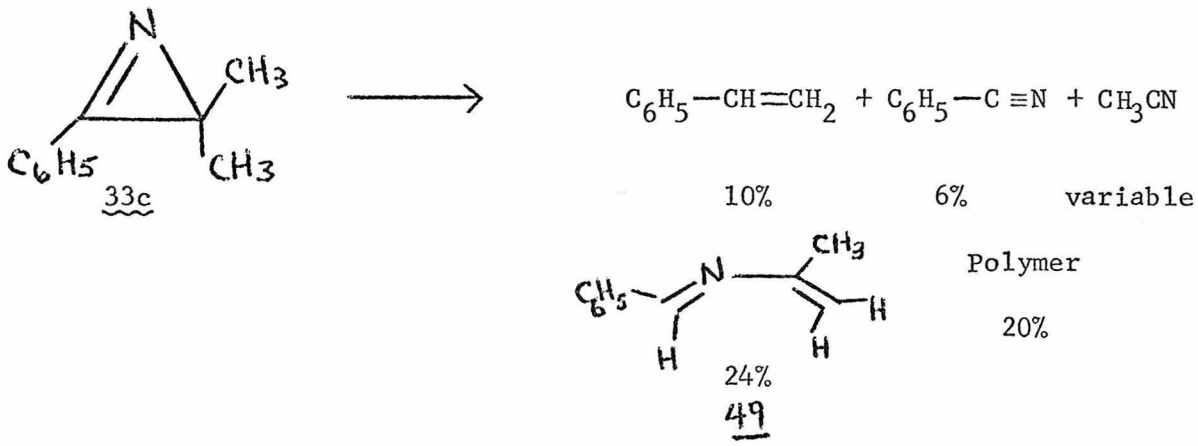
temperatures) if 1,3-alkyl shifts are important in 2H-azirine decomposition. Also, acetonitrile should be the other fragmentation product, analogous to the presumed HCN obtained from decomposition of 33a.



33c 33d

Pyrolysis of 33c at 472°C (60% conversion) did not yield any methyl-shifted azirine 33d; however, an azabutadiene (49), which provided the needed clue for explaining the observed pyrolysis products, was isolated (Chart 3). Acetonitrile in variable amounts

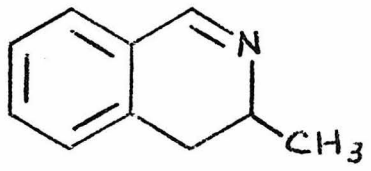
Chart 3: Products of the 472°C Pyrolysis of 3,3-Dimethyl-2-phenyl-2H-azirine (33c).



33c 49

was also detected (see Section III). The spectral data are all consistent with the presented structure for 49. Hydrolysis (34) of 49 in aqueous mineral acid gave two products whose retention times on DEGS and SE-30 analytical vapor phase chromatography columns were identical with authentic samples of benzaldehyde and acetone. The later eluting compound was isolated by preparative vapor phase chromatography and its i.r. spectrum exactly matched an i.r. spectrum of authentic benzaldehyde. The small amount of 49 available for hydrolysis, combined with acetone's solubility in water and tendency to aerosol from vpc collection traps, precluded obtaining its i.r. spectrum.

Pyrolysis of 49 at 545°C (complete conversion temperature of azirine (33c) is 535°C) gave a 14:1 ratio of styrene and 3-methyl-dihydioisoquinoline (51). Pyrolysis of the 2H-azirine (33c) at 545°C gave an

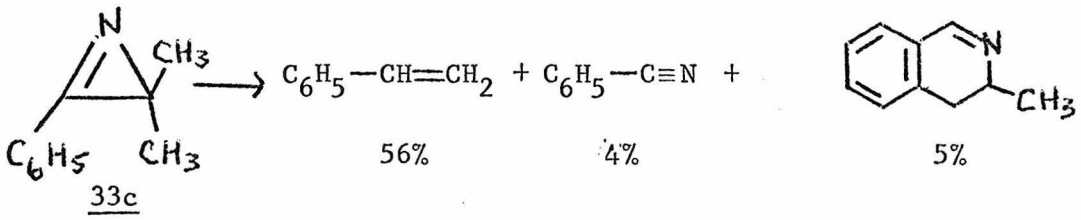


51

~ 11:1 ratio of styrene and (51)(Chart 4). The similar ratios of styrene and 51 in the azirine (33c) and azabutadiene (49) 545°C pyrolyses strongly implicate 49 as the major primary pyrolysis product of 33c.

We were unable to isolate an azabutadiene intermediate from the

Chart 4: Products of the 545°C Pyrolysis of 3,3-Dimethyl-2-phenyl-2H azirine (33c).



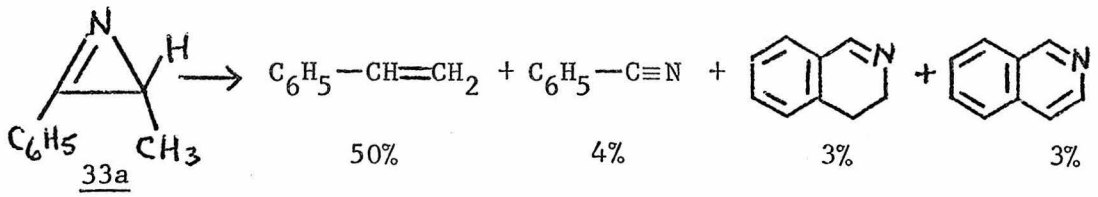
33c

56% 4% 5%

Polymer	Other
32%	3%

pyrolysis of 3-methyl-2-phenyl-2H-azirine (33a). Apparently the azabutadiene is involved in the polymerization process, and its rate for polymerizing or fragmentation to styrene precludes its isolation. Nevertheless, the presumed conversion of azabutadiene (49) to the new product, dihydroisoquinoline (51), provided a possible test for the presence of an azabutadiene in the pyrolysis of 33a. Since formation of (51) became competitive with fragmentation to styrene at higher temperatures, 33a was pyrolyzed at 580°C in anticipation of isolating 3,4-dihydroisoquinoline. Our hopes were realized, as demonstrated in Chart 5. The oxidation of dihydroisoquinoline (56) to isoquinoline (57) at these temperatures is precedented by the high temperature dihydronaphthalene to naphthalene conversion (35). Isolation of the dihydroisoquinoline at higher temperatures strongly suggests that 33a is also isomerizing to an azabutadiene.

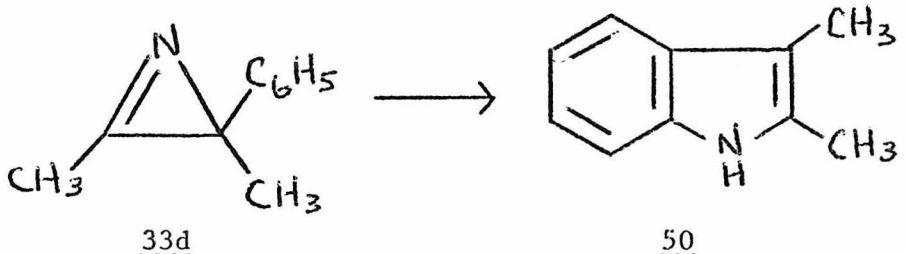
Chart 5: Products of the 580°C Pyrolysis of 3-Methyl-2-phenyl-2H-azirine (33a).



	50%	4%	3%	3%
	Polymer	Other	56	57
	36%	4%		

The intervention of a competing alkyl-shift isomerization path (path A, Scheme XVII) was rigorously ruled out by independent synthesis and pyrolysis of the "alkyl-shifted azirine" (33d) (Chart 6).

Chart 6: Products of the 480°C Pyrolysis of 2,3-Dimethyl-3-phenyl-2H-azirine (33d).



33d 50

100%

Quantitative conversion of 33d to the indole 50 is indicative of ring opening to the vinyl nitrene which then inserts into a phenyl C-H bond (Scheme VIIa).

Our inability to isolate acetonitrile in an amount equivalent to styrene (for the 33c pyrolyses) initially proved disconcerting. Control experiments established that acetonitrile could be recovered quantitatively after passing it through the pyrolysis system at 545°C. However, when an ~5:1 azirine (33c) acetonitrile mixture was pyrolyzed at 470°C, no acetonitrile was isolated. Apparently, acetonitrile is polymerizing under the reaction conditions. Also, the proportion of azabutadiene (49) was reduced from 24% (Chart 3) to 7% in this pyrolysis; it appears that azabutadiene is also involved in the polymerization.

Efforts to retard the polymerization by co-pyrolysis of 33c and a solvent, and also trapping products in solvents were attempted with some success. As a result of acetonitrile's insolubility in volatile hydrocarbons (n-pentane), diethyl ether was utilized as a solvent. A ten-fold excess of diethyl ether was mixed with azirine (33c) in the vapor phase just outside the oven. The product traps contained an additional three-fold excess of frozen diethyl ether prior to pyrolysis. In this manner, acetonitrile was isolated in a 55% yield relative to styrene in one pyrolysis at 470°C. However, these results were not reproducible; recovery of acetonitrile in a 10% yield relative to styrene was a more typical result. Control experiments demonstrated

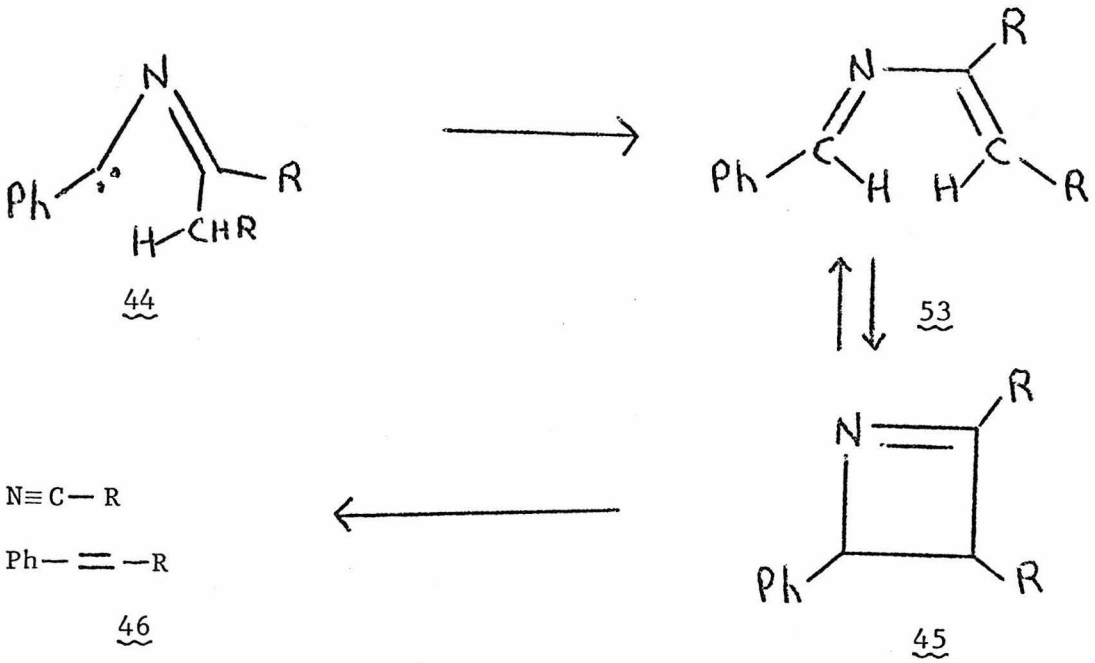
the stability of diethyl ether to the reaction conditions. Attempts at immediate vacuum transfer of volatiles from the pyrolysate met with no success for detection of acetonitrile.

Due to the complex nature of the polymerization process, no further attempts were made at quantitative isolation of the nitrile fragment. While we were not able to rigorously demonstrate the formation of nitriles in an equivalent amount to styrenes, the evidence is strongly suggestive that this is indeed the case. The next section will provide mechanistic discussions based on the preceeding results.

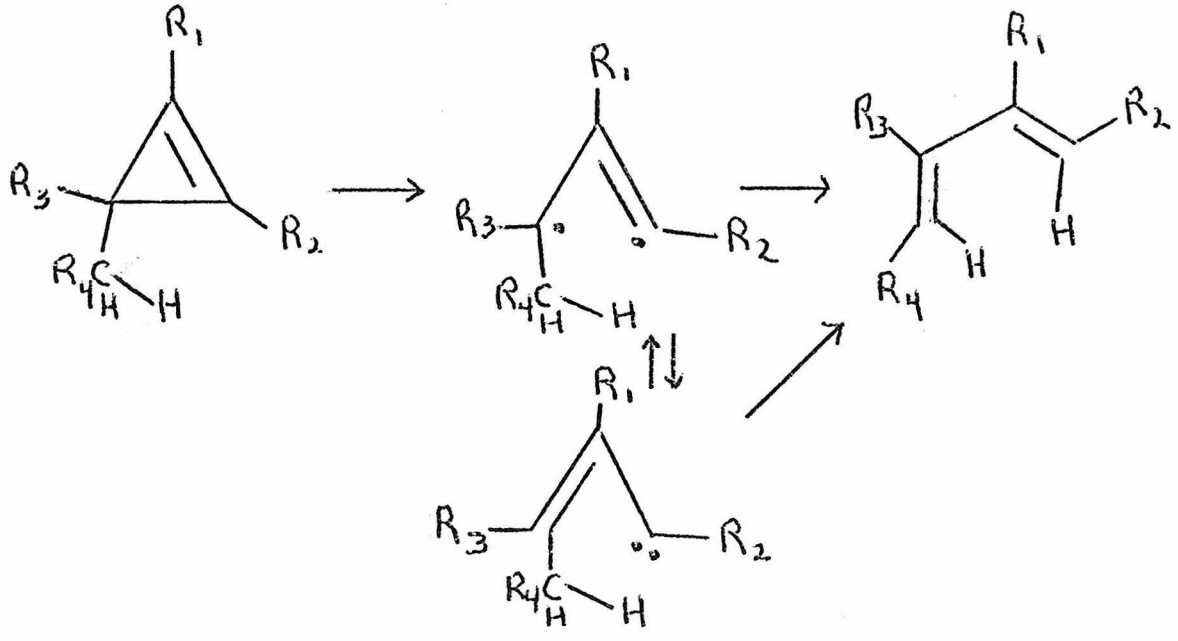
III. Discussion

The results outlined in Section II indicate: 1) carbon-carbon bond cleavage occurs upon thermolysis of 2-phenyl-3-alkyl-2H-azirines, 2) azabutadienes are primary pyrolysis products and precursors to the fragmentation products (styrenes and presumably nitriles), and 3) the azabutadiene to dihydroisoquinoline rearrangement is a competitive process at higher temperatures. Mechanistic questions which we will try to answer include: 1) How do azabutadienes lead to the observed fragmentation products? 2) What is the nature of the species formed upon carbon-carbon bond rupture? 3) Why does this particular family of azirines (33a,b,c) display this behavior? and 4) How does dihydroisoquinoline formation from azabutadienes occur?

The detection of azabutadienes as pyrolysis products, makes reconsideration of path B in Scheme XVII worthwhile. However, rather than postulating C-H insertion by the initially formed carbene (44), hydrogen abstraction occurs to form the imine (49). An endothermic thermal cyclization may then generate a small steady state amount of azetine, which fragments to the observed products (Scheme XIX). 1,4-hydrogen abstraction by vinyl carbene- or 1,3-diradical-like species, generated from thermal ring opening of substituted cyclopropenes, has ample precedence (22-25). 1,3-butadienes comprise a significant portion of the pyrolysis products of alkyl-substituted cyclopropenes and have been postulated as being formed from vinyl carbene or 1,3-diradical species (Scheme XX). Convincing evidence for 1,4-hydrogen

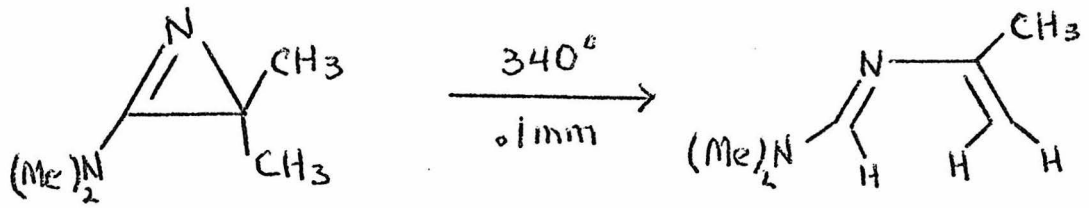


Scheme XIX

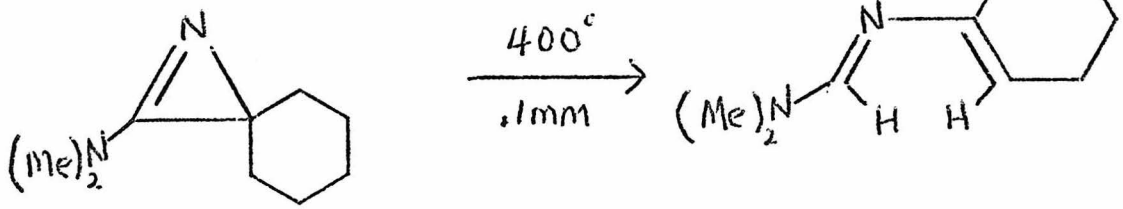


Scheme XX

abstraction by an iminocarbene is provided by work of Ghosez and co-workers in 1975 (27). These workers have shown that 2-amino-3-alkyl-2H-azirines (52a) and (52b) appear to be undergoing a similar C-C bond cleavage with subsequent formation of azabutadienes (53a) and (53b) (Scheme XXI). These authors report no fragmentation products



52a 53a



52b 53b

Scheme XXI

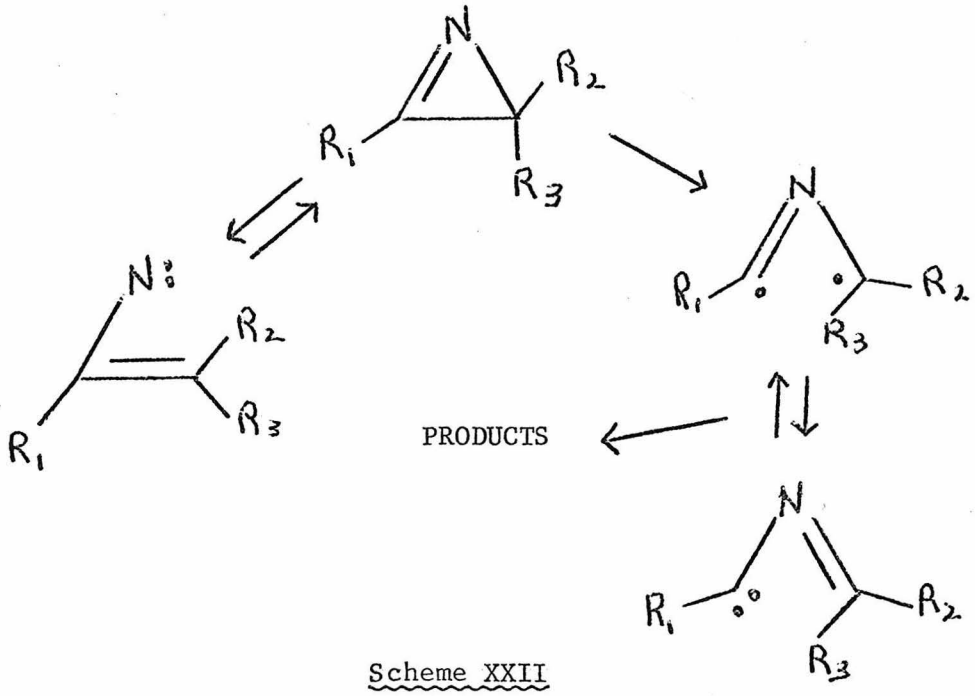
analogous to the ones we observed (27). It is difficult to understand why the possible azetines formed from 52a and 52b would 100% preferentially rearrange to the azabutadienes (53a and b) with no formation of fragmentation products (especially under flash vacuum pyrolysis conditions). This implies initial formation of the azabutadiene. The lack of an azabutadiene-azetine equilibrium in Ghosez' work can be

rationalized by considering the relative bulkiness of the dimethylamino group and the strained bicyclic system formed in the case of (53b). Also, Ghosez' pyrolyses temperatures were 100-200°C lower than in our work (where fragmentation was significant) (27). In light of existing precedent for 1,4-hydrogen shifts in vinyl carbene rearrangements, our isolation of the azabutadiene (49), and similar recent findings reported of Ghosez, we favor a 1,4-hydrogen shift rather than initial C-H insertion to form an azetine.

Our postulated azabutadiene-azetine equilibrium parallels the butadiene-cyclobutene thermal conversion. Brauman and Stephenson (39) have presented strong evidence that butadiene and cyclobutene interconvert at 637°C in the gas phase.

In our system the initial bond-breaking preference (C-N versus C-C) has not been determined. $N(sp^2)$-$C(sp^3)$ bonds are probably 5-10 kcal/mole weaker than $C(sp^2)$-$C(sp^3)$ bonds. This guess is based solely on analogy to sp^3-sp^3 bond dissociation energies (36) in carbon and nitrogen systems. There are no values in the literature for the particular bond strengths in question. For all thermal azirine rearrangements investigated, other than ours and Ghosez (27), carbon-nitrogen bond cleavage to form a vinyl nitrene seems to be the preferred bond-breaking process (Table 2). It is very reasonable that this is also occurring to a large extent in our system; however, no reaction path other than regeneration of azirine is available. By analogy with the work of Rees (17) (18c and 18d, Scheme IX), the

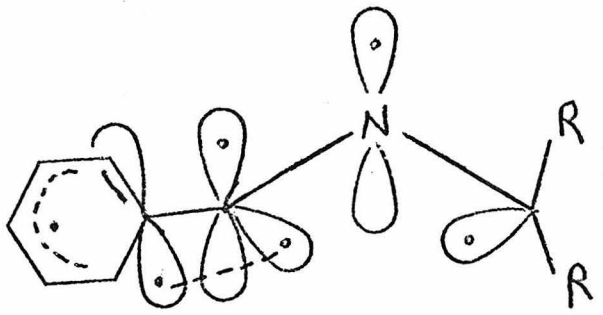
nitrene generated from 33a-c will not undergo 1,4-hydrogen abstractions. The independent work of Isomura (15, 16) and Rees (17) suggests that 1,2-abstraction by the nitrene (to form ketenimines) only occurs when hydrogen is the group being transferred (Schemes VII and IX). Consequently no products indicative of C-N bond cleavage will be observed in our systems. However, when non-preferential carbon-carbon bond cleavage occurs, the observed products are formed (Scheme XXII).



Scheme XXII

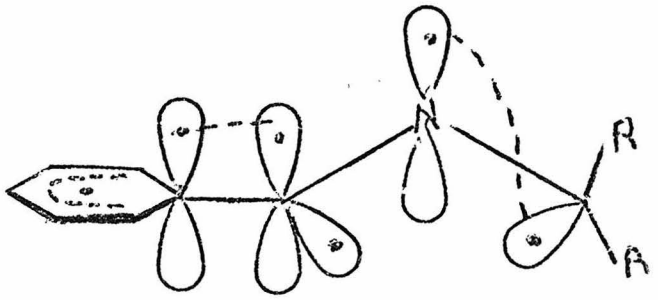
A totally different mechanistic explanation is that the phenyl substituent at the 2-carbon in our azirine systems stabilizes the carbon-carbon bond cleavage relative to carbon-nitrogen bond cleavage. This stabilization can be envisioned as occurring in two different ways.

One explanation is simple resonance stabilization of the σ radical lobe generated by C-C bond cleavage (54). Another possibility is



54

that the phenyl group stabilizes the singly occupied 2-carbon p-orbital while the nitrogen singly occupied p-orbital participates in a bonding interaction with the σ radical lobe at the 3-carbon (55). If the 2-phenyl group is stabilizing carbon-carbon bond cleavage, it



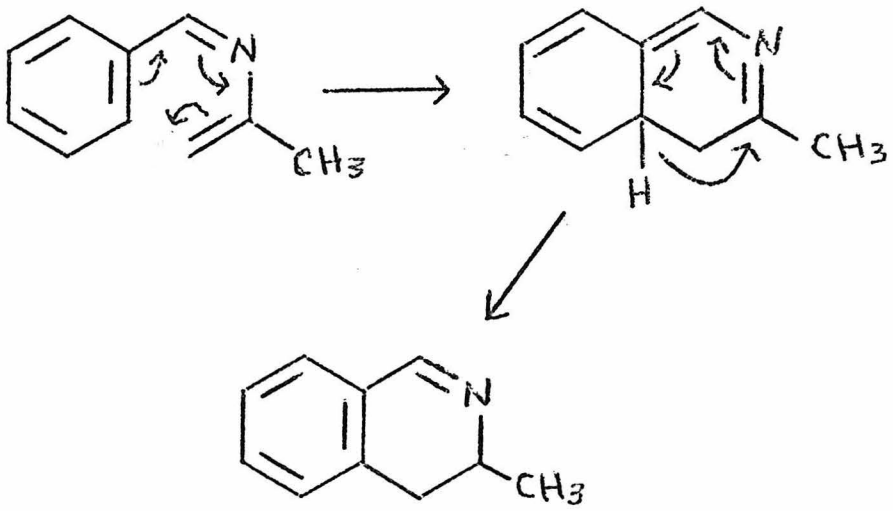
55

is difficult to understand why 2,3-diphenyl-3-phthalimido-2H-azirine

(18b) yielded only indole product (suggestive of C-N bond cleavage) (17). However, Bowie did explain some of the reaction products observed from pyrolysis of 2,3-diphenyl-2H-azirine as arising from initial C-C bond cleavage (Scheme XII) (19).

The substituent effects of phenyl groups on bond-rupture processes in cyclopropenes are not well understood. For example, tetraphenyl-cyclopropene thermally rearranges with an activation energy of 40 kcal/mole (23), while cyclopropene ring opens with an activation energy of 35 kcal/mole (37). By comparison with phenyl-substituted cyclopropanes, a stabilization by even only one phenyl group would be expected to lower the activation energy of tetraphenyl cyclopropene by 12 kcal/mole relative to cyclopropene. In light of such observations it would be premature to rule out preferential carbon-carbon bond cleavage for our phenyl substituted azirines. However, considering the existing precedent for initial carbon-nitrogen bond cleavage for 2H-azirines, we presently favor initial C-N bond cleavage for our azirine systems.

The conversion of the azabutadiene (49) to the dihydroisoquinoline (51) is a novel transformation in its own right. The first step of this process can be viewed as an electrocyclic ring closure of an aza-hexatriene to a 1,3-azacyclohexadiene. The second step simply involves a symmetry allowed, 1,5-suprafacial sigmatropic hydrogen migration (Scheme XXIII). Weber and co-workers have recently confirmed this rearrangement by observing the all-carbon analogue, phenyl-1,3-butadiene



Scheme XXIII

to dihydronaphthalene rearrangement (38).

Our initial goal of studying the vinyl nitrene was not explicitly realized, since unexpected substituent effects shifted our interests to the iminocarbene. This serendipitous turn of events has resulted in the first report of thermal carbon-carbon bond cleavage for 2H-azirines as well as several novel heterocyclic rearrangements. No systematic study of phenyl substituents effects in three-membered unsaturated ring compounds has been reported. We feel that our work suggests the interesting potentials of controlling bond-breaking preferences, and hope that further work in this area will be performed.

IV. Experimental

A. General

Proton nmr spectra were obtained on either an A-60-A, T-60, or 220 Varian Associates Analytical nmr spectrometer. Carbon tetrachloride or deuterochloroform were used as solvents with tetramethyl silane as an internal standard for all proton spectra. Spectra are reported as: chemical shift (in order of increasing δ); multiplicity, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet splitting; relative number of H's; assignment.

Infrared spectra were obtained on a Perkin Elmer 257 Grating Infrared Spectrophotometer using carbon tetrachloride or chloroform as solvent.

All analytical vapor phase chromatography was performed on a Hewlett-Packard 5750 Research chromatograph equipped with a Hewlett-Packard 3370A Digital Integrator. The chromatograph was equipped with a flame ionization detector; maximum sensitivity was maintained at the following gas pressures (lb/in^2): He, 40; H_2, 14; air, 30. 1/8" stainless steel or aluminum columns were utilized for all analytical work.

Preparative vapor phase chromatography was performed on a Varian Airograph 90-P3 chromatograph equipped with a thermal conductivity detector.

VPC Columns

Column A: 10' x 3/8", 20% UCW-98, on 60/80 Chromosorb WAW-DMCS, glass;

Column B: 10' x 1/4", 10% DEGS on 60/80 Chromosorb P-NAW, glass;

Column C: 10' x 1/4", 30% SE-30 on 60/80 Chromosorb WAW-DMCS, glass;

Column D: 20; x 1/8", 20% SE-30 on 100/120 Chromosorb P-NAW, aluminum;

Column E: 8' x 1/8", 10% SE-30 on 100/120 Chromosorb WAW-DMCS, aluminum;

Column F: 12' x 1/8", 15% TCEP on 100/120 Chromosorb WAW-DMCS, aluminum;

Column G: 12' x 1/8", 15% DEGS on 100/120 Chromosorb WAW-DMCS, aluminum.

Mass spectral analyses were performed on a DuPont 21-492B high resolution mass spectrometer. All analyses were performed by the Spang Microanalytical Laboratory, Ann Arbor, Michigan. All boiling points are uncorrected.

B. Synthesis

1-azido-2-iodo-1-phenyl-propane (35a). Hassner's synthetic procedure (28) was utilized for preparation of all azido-iodo-alkanes. To a stirred slurry of 13.0 g (.20 m) sodium azide in 75 ml acetonitrile at 0°C, in a 250 ml three-necked flask, equipped with two addition funnels and a drying tube, was added 24.5 g (.15 m) iodine monochloride

over the course of 40 minutes. After addition was completed, the mixture was stirred for 40 more minutes and warmed to room temperature. 11 g (.09 m) β-methyl styrene was added dropwise over the course of ten minutes and the reaction was stirred for 30 hours at room temperature.

The reaction mixture was filtered through celite into a 150 ml aqueous solution of 50% sodium bisulfite. The product was extracted with diethyl ether and dried over $MgSO_4$. The ether was removed by rotary evaporation to yield 21.0 g of a yellow oil (35a) (73% crude yield). Ir: 2995, 2945, 2890, 2125, 1508, 1464, 1390, 1360, 1295, 1264, 1212, 1180, 1160, 1133, 1092, 1075, 1045, 1010, 945, 713 cm^{-1}. Nmr (CCl_4): δ 0.83 (d, 3H, $-\overset{|}{C}HI-\underline{CH_3}$); 4.25 (five line pattern, 1H, $I-\overset{|}{\underset{|}{C}}-\underline{H}$); 4.70 (d, 1H, $N_3-\overset{|}{\underset{|}{C}}-\underline{H}$); 7.33 (s, 5H, phenyl). The spectra agree exactly with Hassner's data for this compound (8f).

1-azido-2-iodo-1-phenyl-butane (35b). The reaction conditions for (35a) were repeated exactly. 12.31 g (.09 m) trans-1-phenyl butene was the starting olefin and 19.30 g of a yellow oil (35b) (60% yield) were isolated. Nmr (CCl_4): δ 1.02 (t, 3H, $-CH_2-\underline{CH_3}$); 1.80 (five line pattern, 2H, $-\underline{CH_2}-CH_3$); 4.12 (q, 1H, $I-\overset{|}{\underset{|}{C}}-\underline{H}$); 4.88 (d, 1H, $N_3-C-\underline{H}$); 7.32 (s, 5H, phenyl).

1-azido-1-phenyl-1-propene (36a) (28, 8f). To 21.0 g (.07 m) (35a) in 450 ml anhydrous diethyl ether at 0°C was added 9.45 g

(.084 m) potassium t-butoxide. The reaction was allowed to warm to room temperature and was stirred for 15 hrs.

The reaction mixture was washed with cold water and the organic phase was dried over $MgSO_4$. The solvent was removed by rotary evaporation and the product was purified by passage through 80 g of neutral Wollm aluminum oxide activity I with pentane. The solvent was removed by rotary evaporation yielding 10.6 g of the yellow oil (36a) (93% crude yield). Ir: 3150, 2910, 2110, 1665, 1613, 1590, 1450, 1280, 1150, 1120, 1090, 1045, 1020, 963, 954, 023, 875, 850, 825, 780, 745, 715 cm^{-1}. Nmr (CCl_4): δ 1.70 (d, 3H, $-\underline{CH_3}$); 5.45 (q, 1H, vinyl H); 7.40 (s, 5H, phenyl). The spectra correlate exactly with those reported by Fowler for this compound (8f).

1-azido-1-phenyl-1-butene (36b). The procedure used for (36a) was repeated. Product was formed in 90% yield. Nmr (CCl_4): δ 0.85-1.45 (m, 3H, $-CH_2-\underline{CH_3}$); 1.80-2.50 (m, 2H, $-\underline{CH_2}-CH_3$); 5.30 (t, 1H, vinyl H); 7.25 (s, 5H, phenyl).

3-methyl-2-phenyl-2H-azirine (33a). A 5% w/v solution of (36a) in olefin free pentane was placed in a 100 ml quartz reactor equipped with a -15°C condenser and argon inlet. A Hanovia medium pressure, mercury arc lamp was used for photolysis while argon was bubbled through the solution. The course of the reaction was monitored by watching the disappearance of the ca. 2100 cm^{-1} azide band in the ir. A brown

polymer formed on the sides of the reactor; it was necessary to occasionally interrupt the photolysis and scrub off the polymer. After removal of the solvent by rotary evaporation and distillation, the azirine (bp 96°C at 15 mm) was isolated as a faintly yellow liquid in 95% yield. Pyrolysis samples were purified by preparative vpc, column A (130°, 100 ml/min). Spectra correlate exactly with those reported by Fowler for this compound (8f). Ir: 3080, 3040, 1749, 1610, 1410, 1377, 1335, 1315, 1162, 1103, 1085, 993, 954, 778 cm^{-1}. Nmr (CCl_4) δ 1.30 (d, 3H, $\underline{CH_3}$); 2.12 (q, 1H, $CH_3-\underset{|}{\overset{|}{C}}-\underline{H}$); 7.40-8.00 (m, 5H, phenyl).

3-ethyl-2-phenyl-2H-azirine (33b). The photolysis conditions used to prepare (33a) were repeated. After removing the solvent by rotary evaporation, the azirine was vacuum transferred and purified by preparative vpc on column A (130°C, 100 ml/min). Ir: 3090, 3060, 2980, 2960, 2900, 1746, 1615, 1508, 1480, 1470, 1395, 1340, 1321, 1165, 1088, 1045, 1003, 940, 910, 895, 705 cm^{-1}. Nmr (CCl_4) δ 0.92 (t, 3H, $-CH_2\underline{CH_3}$); 1.35-1.90 (m, 2H, $-\underline{CH_2}CH_3$); 2.13 (t, 1H, $-\underline{\underset{|}{CH}}-CH_2$); 7.38-8.00 (m, 5H, phenyl).

Isobutyrophenone dimethylhydrazone methiodide (39c). The synthetic procedure used by Leonard (29) for preparing this compound was followed. 50.0 g (.33 mole) isobutyrophenone and 28.0 g (.47 mole) 1,1-dimethyl hydrazine were reacted to yield a 50:50 mixture of ketone and the

desired hydrazone. 50.0 g of the mixture was reacted with 79.8 g (.56 mole) iodomethane. The resulting solid was recrystallized twice to yield reddish brown crystals after drying for thirty minutes under a heat lamp and for five hours under a .05 mm vacuum (mp 115°-118°C, 36% overall yield from isobutyrophenone). Nmr (DMSO-d_6): δ 1.10 (d, 6H, -CH-($\underline{CH_3}$)$_2$); 2.60-3.10 (seven line pattern, 1H, -$\underline{CH}$-(CH_3)$_2$); 3.31 (s, 9H, -$\overset{+}{N}(CH_3)_3I^{\theta}$); 7.57 (s, 5H, phenyl).

3-phenyl-2-butanone hydrazone methiodide (39d). 3-phenyl-2-butanone (38d) was prepared by adding a solution of 16.6 g (.72 g-atom) Na in 580 ml isopropanol to 90.0 g (.67 m) phenyl acetone in a 1 liter, three-necked flask equipped with 2 addition funnels, a reflux condenser, magnetic stirrer, and drying tube. The reaction mixture was cooled to 0°C, and 142.0 g (.92 m) iodomethane was added dropwise. The reaction was stirred for 90 hrs. at room temperature.

The isopropanol was removed by rotary evaporation. The ketone was taken up in ether and the salts were filtered off. After drying over $MgSO_4$, the ether was removed by rotary evaporation and 37.0 g of the ketone were distilled through a 9" Vigreaux. (bp 108°C at 22 mm). Nmr (CCl_4): δ 1.30 (d, 3H, Ph-C(H)-$\underline{CH_3}$); 1.91 (s, 3H, Ph-CH-$\underline{CH_3}$); 3.70 (q, 3H, -CO-$\underline{CH_3}$); 7.20 (s, 5H, phenyl). The hydrazone (39d) was prepared from the ketone exactly as in the conversion of isobutyrophenone to the dimethyl hydrazone (29). Nmr (CCl_4): δ 1.40 (d, 3H, -C(H)(Ph)-$\underline{CH_3}$); 1.80 (s, 3H, -(CN)-$\underline{CH_3}$); 2.38 (s, 6H, -N($\underline{CH_3}$)$_2$); 3.47 (q, 1H,

(Ph)(CH_3)$\overset{|}{C}$-H); 7.18 (s, 5H, phenyl). Methylation of the dimethyl hydrazone was performed as previously described (29) for isobutyrophenone dimethyl hydrazone to give yellowish-brown crystals of 40d mp. 124-126°C). Nmr (DMSO-d_6) δ 1.30 (d, 3H, (Ph)(H)$\overset{|}{C}$-CH_3); 2.13 (s, 3H, -(CN)-CH_3); 3.45 (s, 9H, $\overset{+}{N}$-$(CH_3)_3I^{\theta}$); 7.30 (s, 5H, phenyl).

3,3-dimethyl-2-phenyl-2H-azirine (33c). The procedure used was exactly as described by Leonard (29) for his preparation of this compound. After distillation through a 10 cm Vigreaux column (bp 100°C at 18 mm) the clear liquid 33c was isolated in 60% yield. Pyrolysis samples were purified by preparative vpc, column A (120°C, 100 ml/min). Ir: 3080, 3050, 2990, 2940, 2880, 1740, 1505, 1475, 1463, 1388, 1225, 1211, 1184, 1085, 1035, 947, 887, 700 cm^{-1}. Nmr (CCl_4): δ 1.38 (s, 6H, $(CH_3)_2$); 7.30-7.90 (m, 5H, phenyl). Spectra correlate exactly with those of Leonard for this compound.

2,3-dimethyl-3-phenyl-2H-azirine (33d). (33d) was synthesized in the same manner as (33c). This azirine could be prepared in 30% yield and was purified by preparative vpc on column A (130°C flow, 100 ml/min). Ir: 3050, 2980, 2960, 2890, 1775, 1615, 1510, 1460, 1445, 1392, 1380, 1279, 1082, 1045, 823, 710 cm^{-1}. Nmr (CCl_4): δ 1.60 (s, 3H, (Ph)$\overset{|}{C}$-CH_3); 2.34 (s, 3H, -(CN)-CH_3); 6.90-7.50 (m, 5H, phenyl). High resolution mass calculated: 145.089145. High resolution mass observed: 145.0888.

B. Pyrolyses

Flow pyrolyses were carried out utilizing a 1.2 cm o.d. quartz tube flow system contained in a Hoskin's tube furnace. Auxilliary heating wires, wrapped with asbestos tape, prevented sample condensation in the flow system at both the inlet and outlet sides. The pyrolyses products were collected in a double U-tube trap filled with pyrex helices and maintained at -196°C. Drying towers attached to the traps prevented condensation of moisture in the traps. The temperature of the quartz tube was monitored by an iron-constantan thermocouple. The neat reactants were introduced into the pyrolysis zone by a flow of helium (200 ml/min).

In a typical pyrolysis, 50-500 mg of vpc purified starting material was carried through the reaction zone over the course of several hours. The pyrolysate was immediately taken up in diethyl ether to minimize polymerization in the collection traps.

Initial pyrolyses were carried out at a temperature where a given azirine was just quantitatively consumed. At these temperatures (typically 500-600°C) monomeric product accounted for 55-65% of the pyrolysate. A reddish polymeric material comprised the remainder of the pyrolysate. Mass balance experiments confirmed that all starting material is accounted for by the trapped monomers and polymer. Relative flame ionization detector sensitivities were determined for all pyrolysis products by analysis of a solution containing known amounts of the products.

The possibility of materials reacting on the surface of the flow system was ruled out by performing a packed-tube pyrolysis. The quartz tube was packed with 1 cm x .2 cm o.d. pieces of quartz tubing. Comparison of open- and packed-tube pyrolyses showed no surface-enhanced reactions to be occurring.

1-phenyl-3-methyl-2-aza-1,3-butadiene (49). (49) was isolated from a concentrated diethyl ether solution of the 472°C flow pyrolysis products of (33c) by preparative vpc on column B (100°, 80 ml/min). Ir: 3040, 3005, 2950, 2900, 2850, 1642, 1616, 1571, 1488, 1447, 1360, 1304, 1257, 1205, 1165, 967, 950, 870, 845, 711, 682 cm^{-1}. Nmr (CCl_4): δ 2.00 (s, 3H, vinyl -$\underline{CH}_3$); 4.48 (s, 1H, vinyl $\underline{H}$); 4.69 (s, 1H, vinyl $\underline{H}$); 7.30-8.90 (m, 5H, phenyl); 8.18 (s, 1H, imino $\underline{H}$).

Analysis calculated: C, 82.76; H, 7.59; N, 9.66

Analysis observed: C, 82.42; H, 7.74; N, 9.84

The structure of (49) was proved by hydrolysis (34) of a solution of .010 g (49) in .100 g 2-butanone with 1.250 ml of a 10% aqueous HCl solution. The reaction was stirred for 48 hrs at room temperature. Workup involved neutralizing with aqueous Na_2CO_3 and extraction into ether. Rigorous spiking experiments on two analytical vpc columns: column G and column E (various temperatures, 80-115°C, 30 ml/min) showed the hydrolysis products to have vpc retention times identical with those of authentic benzaldehyde and acetone samples. The later eluting product was isolated from the hydrolysis extracts by preparative vpc on column B

(70°C and 70 ml/min). This compound's i.r. spectrum correlated exactly with the spectrum of an authentic sample of benzaldehyde. Due to acetone's high solubility in water and its tendency to aerosol from vpc collection traps, no spectral data were obtained for it.

2,3-dimethyl indole (50). The indole was isolated by preparative vpc from an ether solution of the 480°C pyrolysate of (33d). The ir spectrum correlates exactly with IR Spectrum 911G, Aldrich Library for 2,3-dimethyl indole. Ir: 3492, 3060, 2940, 2880, 1625, 1550, 1476, 1346, 1310, 1270, 1253, 1010, 932, 730 cm^{-1}. Nmr (CCl_4): δ 2.19 (s, 3H, 3-$\underline{CH_3}$); 2.32 (s, 3H, 2-$\underline{CH_3}$); 6.50-6.85 (broad, 1H, N-$\underline{H}$); 6.90-7.45 (m, 4H, phenyl).

3,4-dihydroisoquinoline (56). This compound was isolated by preparative vpc of the 580°C pyrolysate of (33a) on column C (100°C, 100 ml/min). Ir: 3100, 3040, 2970, 2920, 2878, 1626, 1576, 1484, 1452, 1443, 1426, 1294, 1272, 1204, 1188, 1113, 1051, 1029, 1000, 951, 918, 873, 857, 683 cm^{-1}. Nmr (CCl_4): δ 2.67 (t, J = 7.1, 2H, N-CH_2-$\underline{CH_2}$); 3.73 (t of d J = 7.1, 2.1, 2H, N-$\underline{CH_2}$-CH_2); 6.95-7.42 (m, 4, aromatic); 8.17 (t, J = 2.1, 1H, imino H). The structure proof was confirmed by oxidation at 530°C over Pd/C in a quartz flow system. Oxidized product spectra correlated exactly with those of authentic isoquinoline.

Isoquinoline (57). The 580°C pyrolysis of 33a produces isoquinoline, presumably from oxidation of 3,4-dihydroisoquinoline (35). This pyrolysis product was isolated by preparative vpc of a concentrated ether solution of the pyrolysate (column C, 100°C, 100 ml/min). Ir: 3080, 3002, 2987, 1628, 1589, 1574, 1505, 1382, 1375, 1270, 1247, 1213, 1136, 1033, 1011, 941, 853, 816 cm^{-1}. Nmr (CCl_4): δ 6.90-8.2 (m, 6H); 5.58 (d, 1H); 6.29 (s, 1H). The spectral data correlate exactly with the spectra of an authentic sample of isoquinoline.

3,4-dihydro-3-methyl-isoquinoline (51). 51 was isolated from a concentrated ether solution of 33c by preparative vpc on column C (100°C, 100 ml/min). Ir: 3078, 3040, 2980, 2943, 2897, 2840, 1670, 1585, 1500, 1468, 1439, 1390, 1368, 1327, 1304, 1227, 1211, 1141, 1130, 1058, 1043, 960, 943, 930, 898, 820, 709 cm^{-1}. Nmr (CCl_4): δ 1.31 (d, J = 6.8, 3H, $-\underline{CH}_3$); 2.68 (d, J = 4.0, 2H, $CH_3-CH-\underline{CH}_2-$); 3.32-4.90 (m, 1H, $-\underline{CH}-CH_3$); 6.90-7.40 (m, 4H, aromatic); 8.18 (d, J = 2.2, 1H, imino H). Low resolution mass spectrum: M+ = m/e 145; 144, 130, 117, 103, 90, 76, 77, 51, 27. This dihydroisoquinoline was oxidized in the same manner as described for 3,4-dihydroisoquinoline (56). In the course of oxidation, the methyl group was cleaved, such that isoquinoline was recovered.

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PROPOSITIONS

Abstract of Propositions

I. Approaches to the preparation of two novel silicon-containing species, the tricyclopropyl silicenium ion and 1,4-disila-Dewarbenzene, are proposed.

II. A sysyematic study to determine the nature of substituent effects on the cyclopropene bond cleavage process is proposed.

III. Approaches to the synthesis of a series of azabenzvalenes are proposed; it is suggested that potential thermal and photochemical processes of these molecules be investigated.

IV. The use of optically active zirconium (IV) complexes as asymmetric reduction agents is suggested.

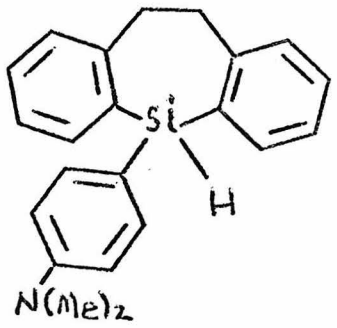
V. Approaches for the isolation of the theoretically-interesting 1H-azirine are proposed.

Proposition 1

A. Tricyclopropyl Silicenium Ion

A problem which has attracted much interest in organosilicon chemistry is the generation of the silicenium ion, the silicon analogue of the carbonium ion (1). By comparison with the stable triphenylmethyl carbonium ion early attempts were aimed at preparation of the triphenyl silicenium ion (2, 3). However, several research groups have reported their complete failures at ionizing triaryl silyl halides or silanols. Careful conductance experiments did not show any appreciable ionization (4).

Very recent work by J. Y. Corey gives evidence for the ionization of 2 by triphenyl carbenium perchlorate (5).

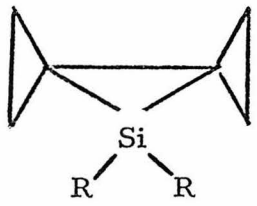


2

Trapping with deuteride and hydroxide provides prima facie evidence for this silicenium ion. The carbon analogue of 2 has a pk_{R+} at least 10^{11} times that of the triphenyl carbenium ion.

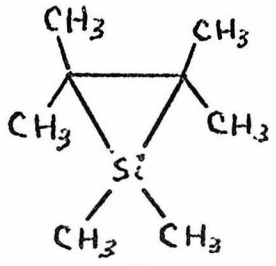
Considering that 1) attempts to stabilize the silicenium ion by Si-C ($p\pi$-$p\pi$) overlap have met largely with no success, and 2) recent evidence that the 3d orbitals of silicon can effectively overlap with filled Walsh orbitals of cyclopropane (d-σ hyperconjugation) (6, 7), it seems reasonable to attempt generation of a tricyclopropyl silicenium ion.

Calculations by Hoffmann suggest that hyperconjugation between the spirocyclopropyl units' filled Walsh orbitals and silicon's unfilled 3d orbitals in 7-siladispiro[2.0.2.1] heptane (3a) lowers the total energy of the system by 17 kcal/mole relative to the carbocyclic analogue (7).



3 a: R = H
b: R = CH_3

Seyforth has recently synthesized 3b and hexamethylsilirane (4) (6). The relative thermal stabilities of 3b and 4 appear to substantiate



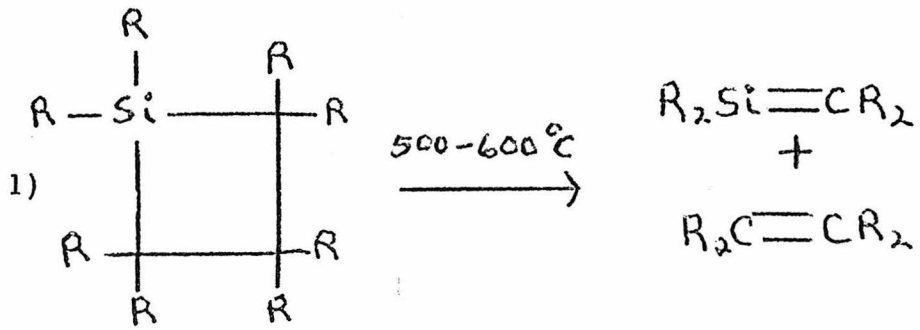
4

the prediction of Hoffmann ($\tau_{\frac{1}{2}}$ = 5 hr at 63°C for 4; $\tau_{\frac{1}{2}}$ = 7 days at 65°C for 3b).

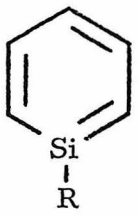
Tricyclopropylsilane 3c or tricyclopropylsilyl chloride 4a would serve as a good precursor to the silicenium ion. 3c and 4a should be readily available from the reaction of cyclopropyl lithium (9) and trichlorosilane and tetrachlorosilane, respectively. Precedence exists for the facile addition of three equivalents of isopropyl lithium to either silane (10). Treatment of 3c with Cl_2 will also result in formation of 4a. Treatment of 3c with carbonium ions or dissociation of 4a in strongly ionizing solvents or with SbF_5 if necessary could produce silicenium ions (2,3,5). Conversion of 4a to the silanol (10) and subsequent treatment with strong acid provides another route to the desired cation.

B. 1,4-Disalabenzene

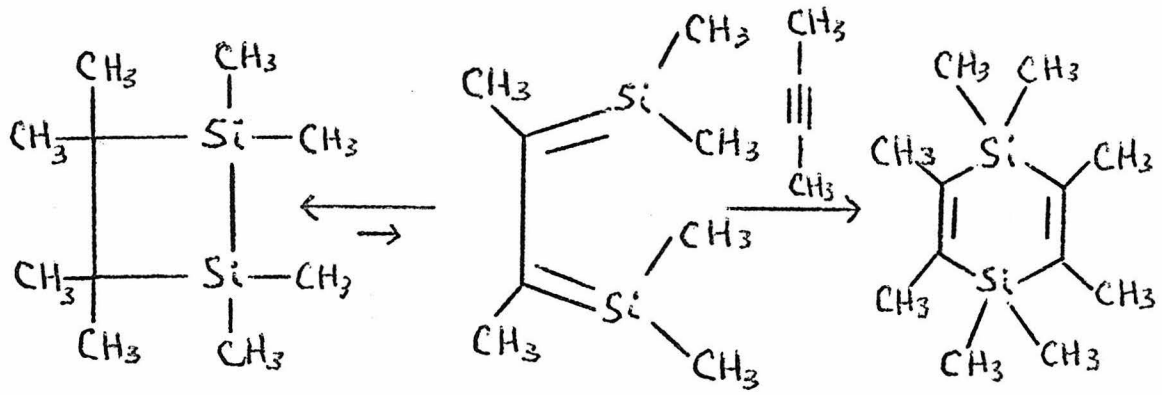
The existence of species utilizing silicon-carbon (pπ-pπ) bonding has been postulated (11). During the past several years significant effort has been directed towards obtaining definitive evidence of the elusive Si-C (pπ-pπ) bond. These efforts have been divided into two main areas: 1) four-electron fragmentation processes (13, 14); 2) incorporation of silicon into an aromatic ring (15).



2)

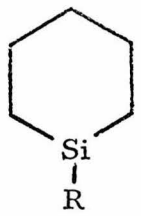


Pyrolysis experiments in which the $\backslash Si{=}C/$ species is trapped by another olefin or a carbonyl compound present convincing evidence for the silicon olefin (13, 14). Barton has recorded a low temperature (-196°C) i.r. spectrum of the thermolysis products of 1, 1-dimethyl-1-silacyclobutane and assigned a band at 1407 cm^{-1} to $Me_2Si{=}CH_2$ (14). Barton has also presented a case for the equilibrium displayed in Scheme II (16).



Scheme II

The research group of West has attempted catalytic oxidation of 5 and 6 in an effort to generate "aromatic" compounds containing the silicon olefinic bond (15). However, this attempt resulted in



5: R = H

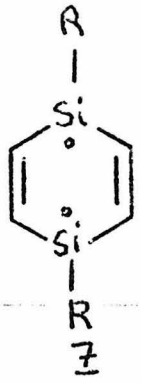
6: R = CH_3

either no reaction or thermal cracking.

Considering the harsh reaction conditions employed for its generation, it should perhaps not be surprising that more definitive evidence for the silicon olefinic bond does not exist. It is our purpose to propose new routes, employing mild reaction conditions for the synthesis and isolation of compounds which will yield valuable information concerning the bonding of silicon.

The synthesis of what could formally be called 1, 4-disila-benzene valence isomer series appears to be an attractive route for the synthesis of silicon olefins (Scheme II). Our initial attempt will involve generation of the 1, 4 diradical 7. It is indicative of the present state of knowledge concerning silicon-bonding that the contribution of any of the structures in Scheme II to a bonding description of 7 is uncertain.

Structure (8) is perhaps a reasonable structure, using existing bonding criteria. The 1, 2-disilacyclobutene has recently been prepared and is thermally stable at room temperature in the absence of oxygen (22). While the Si-Si bond in this system



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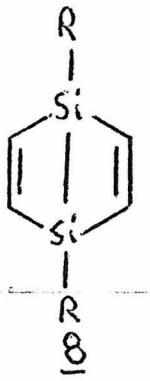

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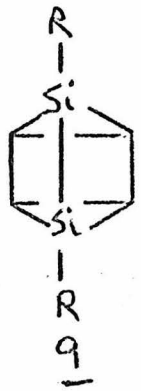

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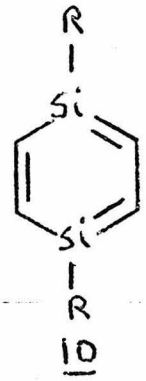


10

11

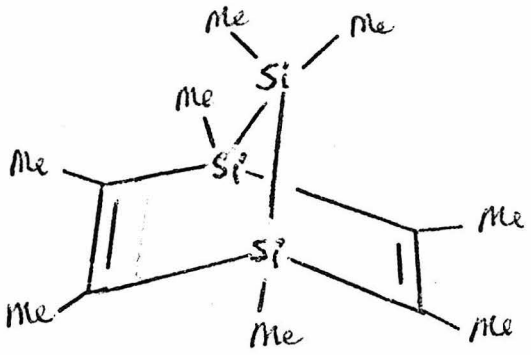
Scheme II

is probably on the order of only 67 kcal/mole (17), the extra length of the Si-Si bond (2.35 Å) (17) will allow reduction of ring strain relative to Dewar benzene, since the sp^2 carbons can more closely assume a C=C-Si bond angle of 120°.

Based on West's (15) lack of success at preparing silabenzene, structure 10 may seem unlikely. However, our synthesis will involve a photochemical extrusion, and bound ground state species, not excessible thermally, may be reached.

Structures 9 and 11 could perhaps be immediately dismissed on strain arguments. However, very recent work by Seyferth (6) and calculations by Hoffmann (7) indicate that filled Walsh orbitals of cyclopropane can effectively overlap with empty silicon 3d orbitals. This results in a greatly enhanced stability of 7-sila-dispiro[2.0.2.1]heptane derivatives relative to hexamethylsilirane. While 9 and 11 are unlikely, they should not too hastily be dismissed.

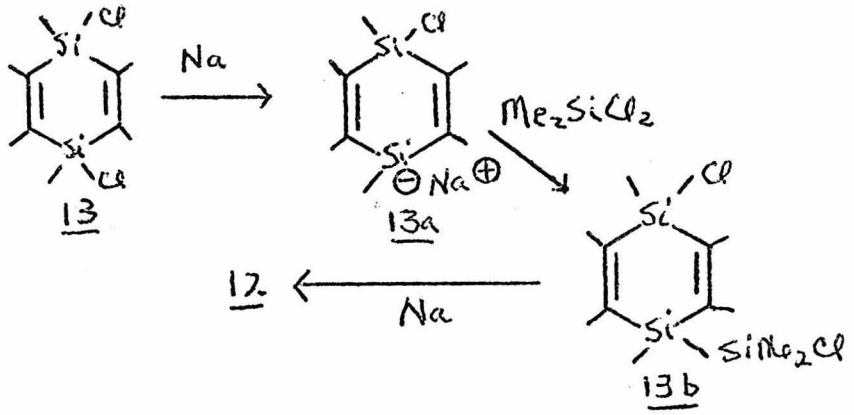
One possible precursor to 7 is the trisilanorbornadiene 12.



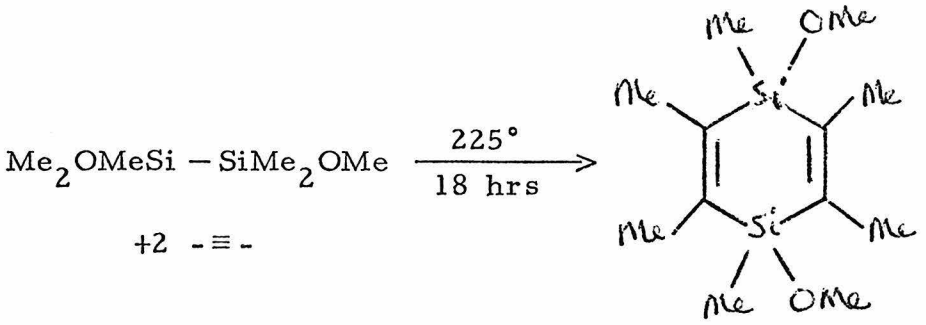
12

Photochemical extrusion of $:SiMe_2$ with concomitant formation of Si-Si bonds has recently been reported for cyclic permethylsilanes (18). 12 probably has less ring strain than the known 7-silanorbornadiene (19); there is no obvious reason to doubt its thermal stability.

One possible synthetic route to 12 involves the reaction of the 1,4-dichloro-1,4-disilahexadiene (13) and Na (10), to form the silanion 13a. Reaction of 13a with excess Cl_2SiMe_2 should lead to 13b. Intramolecular coupling of 13b with Na leads to 12.



It is interesting that treatment of 13 with sodium might directly result in formation of the desired Dewar disilabenzene. This approach, along with electrochemical reduction of 13 offer attractive alternative syntheses. Recently Wiberg has prepared [2.2.2]-propellane by the electrochemical reduction of 1,4-dibromo[2.2.2]-octane (21). The synthesis of 13 has been reported. The 1,4-dimethoxy analogue of 13 has been prepared by Atwell in 49% yield (23). The synthetic sequence employed is shown in Scheme III.



14

Scheme III

Subsequent treatment of 14 with acetyl chloride gave the desired dichloride (13) (23).

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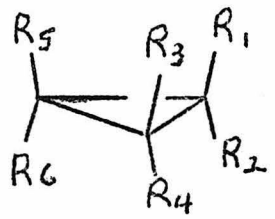
Proposition 2

Despite a significant number of studies concerning bond cleavage and formation processes in small ring, organic compounds, many fundamental questions remain unanswered. Ring cleavage of cyclopropanes has been largely treated as proceeding via 1,3-diradical intermediates (1). Benson has developed thermochemical calculation techniques which describe a bound trimethylene diradical and also predict values for substituent contributions to radical center stabilization (2). Utilizing the Hammond Postulate (3), one can then predict relative activation energies for various substituted cyclopropane ring openings by consideration of the calculated heats of formation of the incipient diradicals. Even though recent theoretical treatments predict no minimum on the parent cyclopropane isomerization energy surface, appropriate substituents could appreciably effect the transition state energy of a continuous process, or actually stabilize formation of a radical species, absent in the parent system. Table 1 lists existing data for cyclopropane isomerization or stereomutation processes consistent with the preceding discussion. Benson attributes the low activation enthalpies of 8 and 9 to allylic and benzylic stabilization energies of ~13 kcal/mol. The low activation entropies for these two cyclopropanes are a result of hindered rotations for vinyl and phenyl groups (2).

In contrast to the relatively consistent picture outlined for cyclopropanes, no general pattern of activation energies for

Table 1

Activation Parameters for Cyclopropane Isomerizations



	R_1	R_2	R_3	R_4	R_5	R_6	E_a (kcal/mol)	log A	Reference
1)	H	H	H	H	H	H	65.5	16.4	4
2)	D	H	D	H	CH_3	H	60.5	15.4	5
3)	H	H	CH_3	H	CH_3	H	59.4	15.1	6
4)	CH_3	CH_3	H	H	H	H	63	15.0	7
5)	CH_3	H	C_2H_5	H	H	H	58.9	15.3	8
6)	CH_3	H	CH_3	H	CH_3	H	61.0	15.8	9
7)	H	CH_3	CH_3	H	CH_3	H	63.0	15.3	9
8)	vinyl	H	H	H	H	H	49.6	13.5	10
9)	C_6H_5	H	H	H	H	H	33.5	11.2	11
10)	C_6H_5	H	C_6H_5	C_6H_5	C_6H_5	H	38.4	14.3	12

substituted cyclopropenes is easily discerned. A tabulation of the available data on cyclopropenes is displayed in Table 2.

The thermochemical data for cyclopropenes must be viewed with some degree of caution since surface effects can be factors in these pyrolyses. However, the values in Table 2 can be accepted with reasonable confidence. Keppel has compared Srinivasan's thermochemical data for 13 with values obtained from a "Walless" reactor and found very close reproducibility (17). Compounds 12, 15, and 16 were all pyrolyzed in a similar manner to 13. Bergman and coworkers went to great lengths to condition their reactor prior to pyrolysis of 14 (15). Cyclopropenes 17 and 18 were pyrolyzed in solution (12).

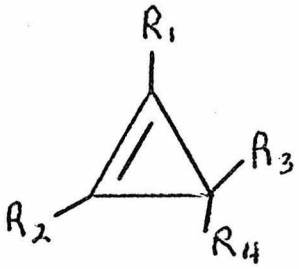
The most striking result from Table 2 is that increasing substitution actually increases the E_a for ring opening. Tetraphenylcyclopropene provides the most dramatic example, having an activation energy of 40.0 kcal/mole while cyclopropene has an activation energy of 35.2 kcal/mole. 1,1,2,2-tetraphenylcyclopropane on the other hand has an activation energy 27.1 kcal/mole lower than the parent cyclopropane.

For cyclopropene ring cleavage of the most highly substituted double bond, the radical-stabilizing ability of the substituent at the unsaturated carbon (R_1, 19) has not been evaluated. However, the substituents at the saturated carbon (R_2 and R_3, 19) might well be expected to show stabilization analogous to the cyclopropane systems.

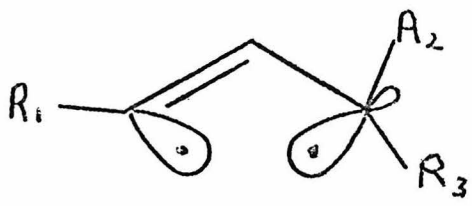
Table 2

Activation Parameters for Cyclopropane Isomerizations

Cyclopropene



	R_1	R_2	R_3	R_4	E_a (kcal/mol)	log A	Reference
11)	H	H	H	H	35.2 ± 1.3	12.1	13
12)	CH_3	H	H	H	34.6 ± 0.7	11.4	13
13)	H	H	CH_3	CH_3	36.6 ± 0.9	13.0	14
14)	C_2H_5	H	C_2H_5	H	32.2	10.2	15
15)	CH_3	H	CH_3	CH_3	39.0 ± 1.4	13.4	14
16)	CH_3	CH_3	CH_3	CH_3	39.7 ± 2.0	12.5	14
17)	t-butyl	H	CH_3	CH_3	29.8	9.0	16
18)	C_6H_5	C_6H_5	C_6H_5	C_6H_5	40.0	14.0	12

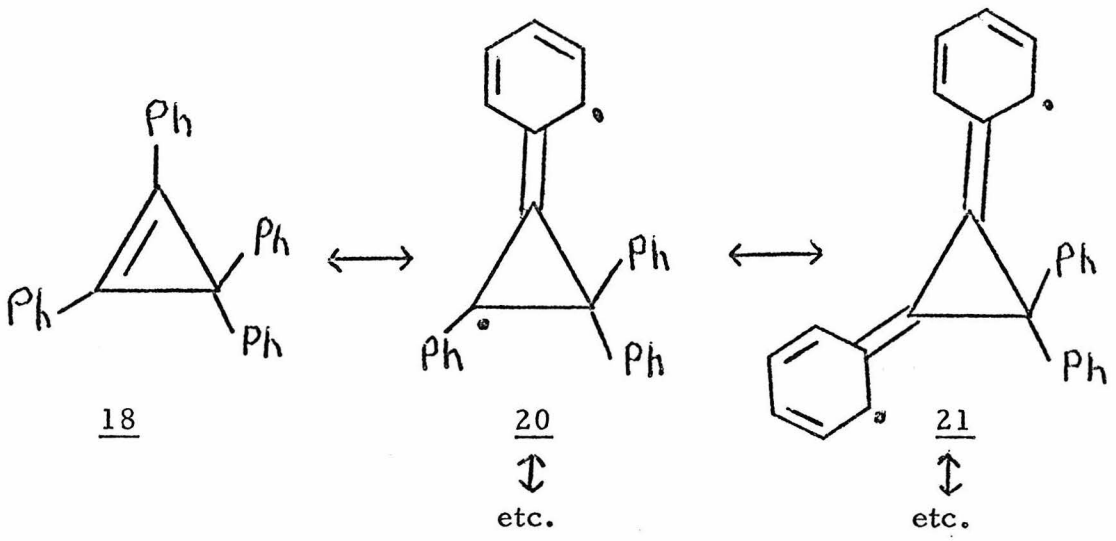


19

Assuming that only one phenyl group at the saturated carbon can offer radical stabilization for tetraphenylcyclopropene (18) [this appears to be the case for cyclopropanes (9) and (10)], either the ground state for (18) is stabilized, or the transition state is destabilized, by ~13 kcal/mole (benzylic resonance) + (40.0 - 35.2) = 17.8 kcal/mole relative to the cyclopropene system. Obviously some combination of ground state stabilization and transition state destabilization will also account for this difference.

One conceivable explanation for transition state destabilization is that different vibrational modes are involved in cyclopropane and cyclopropene bond cleavage. For example, a stretching motion could be important for cyclopropane bond rupture, while a twisting motion could dictate cyclopropene ring opening. The ability of phenyl substituents to stabilize the radical centers generated in these two processes could be very different.

The source of possible ground state reactant stabilization is unclear. Perhaps resonance structures like 20 and 21 are important (Scheme I). Hydrogenation of methylene cyclopropane and methyl cyclopropene suggests respective ring strain energies of



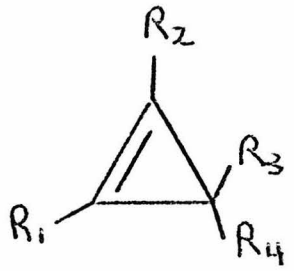
18 20 21

etc. etc.

Scheme I

41.0 kcal/mole and 53.1 kcal/mole (18). No values are known for dimethylene cyclopropane ring strain energies. However, at least structures like 20 could conceivably contribute to ground state stabilization.

A systematic study of a series of phenyl-substituted cyclopropenes could lend considerable insight into the nature of fundamental bond cleavage processes in three-membered ring systems. We propose an initial investigation in which the activation parameters for cyclopropenes 22-24 will be determined. The actual process which will be monitored is conversion of 22-24 to their respective indenes (12).



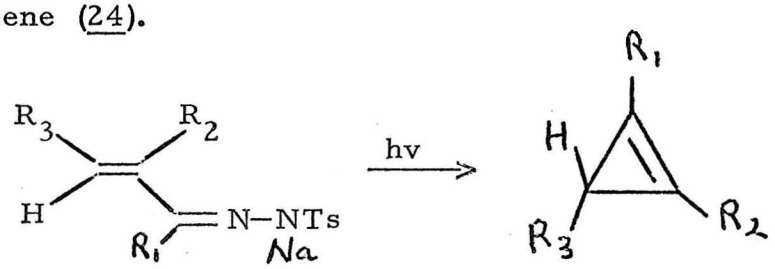
	R_1	R_2	R_3	R_4
22	Ph	H	Ph	H
23	Ph	Ph	Ph	H
24	H	H	Ph	H

Determination of the activation energy for ring opening of 24 will indicate whether benzylic stabilization analogous to that observed for cyclopropanes is important. Knowledge of activation energies of 22 and 23 would allow an evaluation of the effects of phenyl substituents on the unsaturated carbons.

The results of this initial research will determine the direction of future endeavors. For example, if ground state stabilization proved significant, determination of the heats of hydrogenation of the cyclopropene double bonds for 22-24 would allow assessment of the double bond character and indicate any contribution from resonance structures such as 20 or 21. This study could also be expanded to the heterocyclic, phenyl-substituted 2H-azirines.

Synthesis

The synthesis of (22) and (23) in moderate yields has been described by Dürr (19) (Scheme II). The photolysis of the tosyl hydrazone of the appropriate α,β-unsaturated carbonyl compound provides a facile route to the desired cyclopropenes. There is no obvious reason why this method should not provide a good route to cyclopropene (24).



(22): R_1 = Ph, R_2 = H, R_3 = Ph

(23): R_1 = Ph, R_2 = Ph, R_3 = Ph

(24): R_1 = H, R_2 = H, R_3 = Ph

Scheme II

This synthetic approach is suggested since (22) and (23) have actually been prepared in this manner. Other synthetic routes involving carbene addition to olefins or alkynes are also possible (20).

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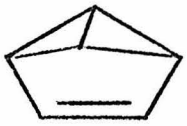
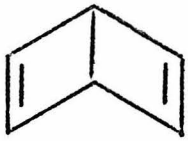
Proposition 3

During the mid-1960's three valence isomers of benzene (or their alkyl-substituted derivatives) were isolated and characterized as benzvalene (1) Dewar benzene (2) and prismane (3) (1-4).



1



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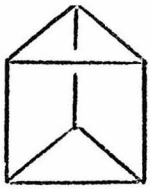


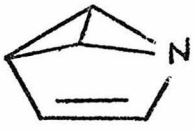
3

Over the past several years these compounds (or their derivatives) have been implicated as being involved in an increasing number of ground- and excited-state reactions (5-8).

We propose investigation of the mono-nitrogen analogues (4, 5 and 6) of benzvalene. These unknown isomers are potentially

4

5

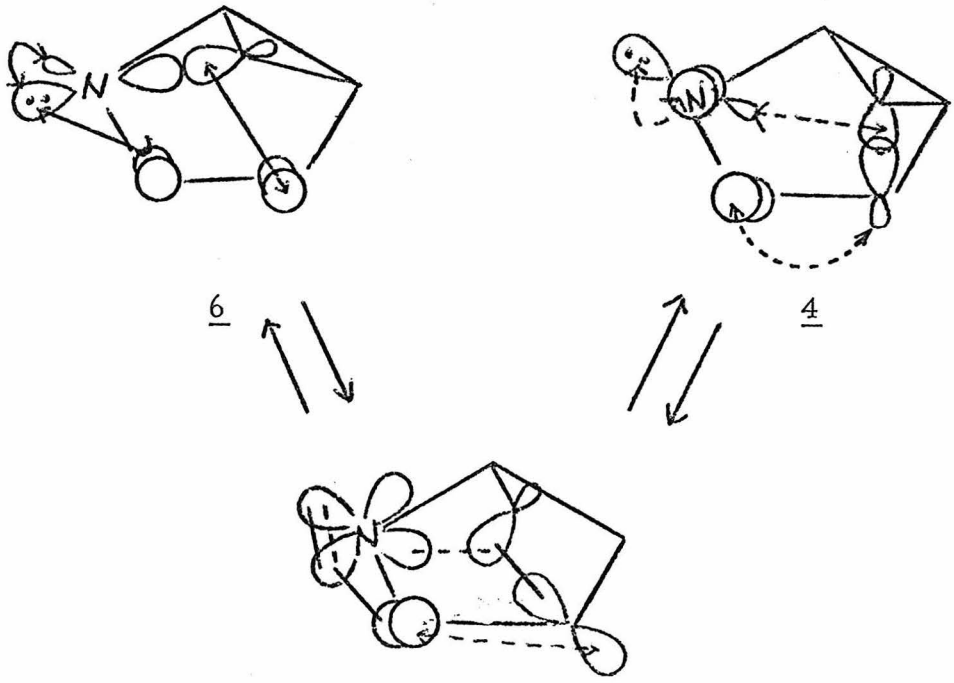


6

capable of displaying behavior similar to benzvalene, as well as undergoing unique reactions due to the electronic structure of

nitrogen. Novel thermal rearrangements are possible for these compounds, and 4 is a potential precursor to tetrahedrane.

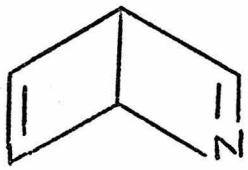
The azabenzvalenes (4) and (6) could conceivably undergo an orbital-symmetry-"allowed" hetero-sigmatropic thermal interconversion ($\sigma^2a + \pi^2a + \omega^2s$) (9) by utilizing the lone pair orbital of the nitrogen atom (Scheme I).



Scheme I

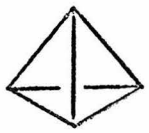
For benzvalene (1), this sort of isomerization is not thermally "allowed" by orbital symmetry considerations. A similar thermally-allowed rearrangement for 5 could only be detected by

distinguishing the carbon atom which changes from sp^2 to sp^3 (6 → 4). This could be done by monitoring the rearrangement with variable temperature ^{13}C nmr. Another interesting possibility unique to the azabenzvalenes is valence isomerization between azabenzvalene and the known Dewar pyridine (7) (prepared as a photolysis product of pyridine) (10).



7

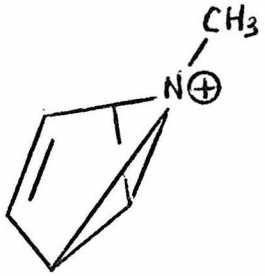
Azabenzvalene 4 can also serve as a novel precursor to tetrahedrane (8).



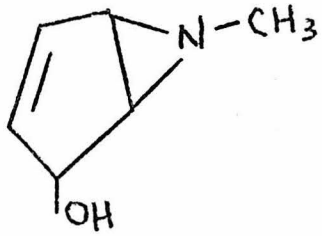
8

Chapman has recently utilized low temperature photolytic extrusion of HCN from pyridine (7) to generate cyclobutadiene. Similar extrusion of HCN from 4 could lead to tetrahedrane. Low temperature i.r. spectroscopy would be used for detection of 8.

The valence isomers of benzene (or their substituted derivatives) have been prepared in low yield by photolysis of benzene (1). Similarly, Dewar pyridine (7) was prepared by photolysis of pyridine (10); however, no azabenzvalenes were detected in the photolysate. 1-Azoniabenzvalene (9) has been suggested as an intermediate to explain the formation of 10 upon photolysis of methylpyridinium chloride in water (11).



9

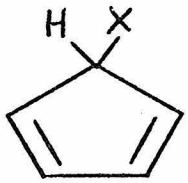


10

The relative stability of the valence isomers of benzene (1), (2), and (3), the isolation of Dewar pyridine (7), and the implication of 1-azoniabenzvalene (9) as a reaction intermediate offer encouragement for the prospect of isolating azabenzvalenes as stable compounds.

We offer two synthetic approaches based on recent innovative precedents. One preparation involves synthesis and the thermal or photochemical decomposition of 5-azido-cyclopentadiene. The other preparation is modeled after Katz' recent synthesis of benzvalene, and involves carbene addition to a pyrrole anion (12).

In 1974, Breslow reported the preparation of the series of 5-halo-cyclopentadienes 11, 12, and 13 (Scheme II) (13, 14).



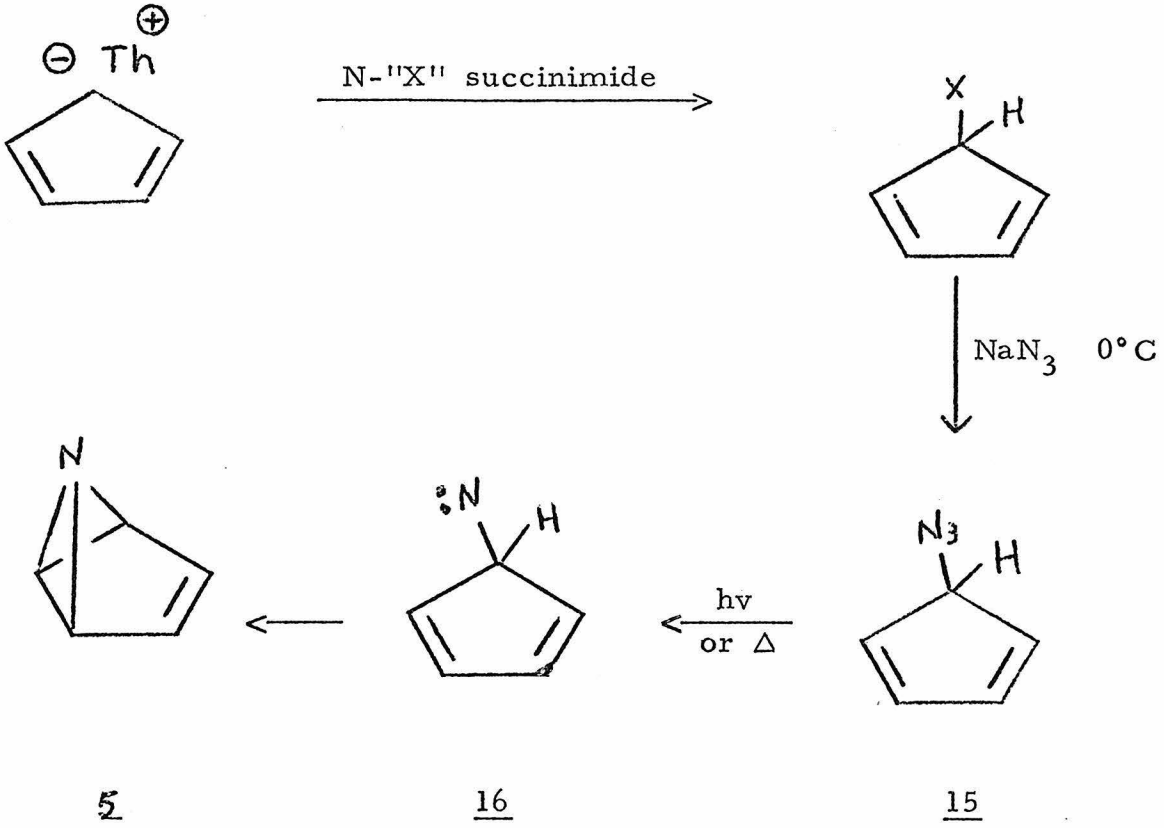
12: X = Cl

13: X = Br

14: X = I

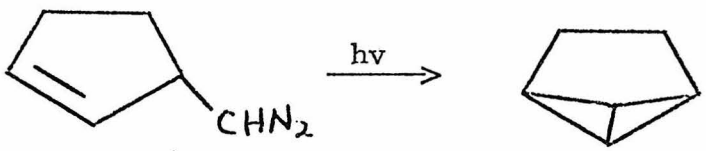
Scheme II

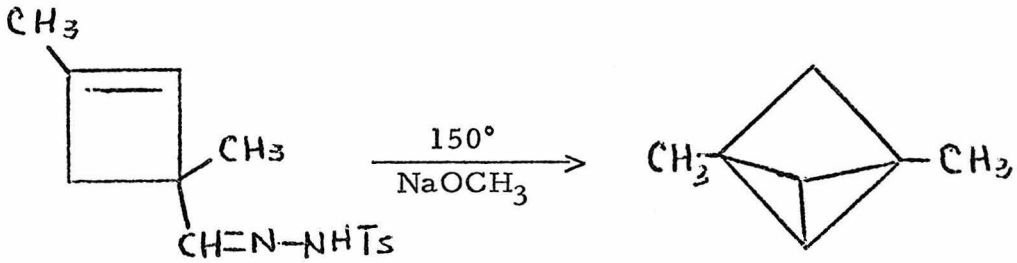
These compounds can be prepared by treatment of thallium cyclopentadienide with the appropriate N-halosuccinimide (15). 12, 13, and 14 show no tendency for isomerization, but will dimerize with heating. Simply treating the halo-cyclopentadiene at 0°C with NaN_3 should be a facile route to the desired 5-azido-cyclopentadiene (15) (Scheme III). The azide can be decomposed by photolysis (low temperature if necessary) or thermolysis to the diallyl nitrene (16) which can insert into either double bond to initially form 6. Intramolecular allyl nitrene insertion into a double bond is precedented by the photolysis of 3-azido-2-phenyl-1-propene to yield 3-phenyl-1-azabicyclobutane (16). Also, numerous examples of allyl carbenes forming strained tricyclic ring systems exist (see Scheme IV) (17, 18).



5 16 15

Scheme III

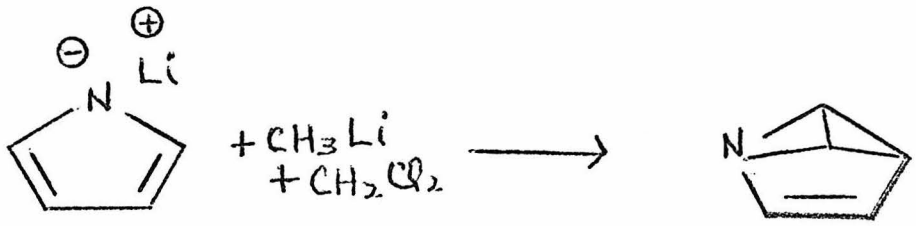




Scheme IV

The synthesis outlined in Scheme III forms only azabenzvalene (5).

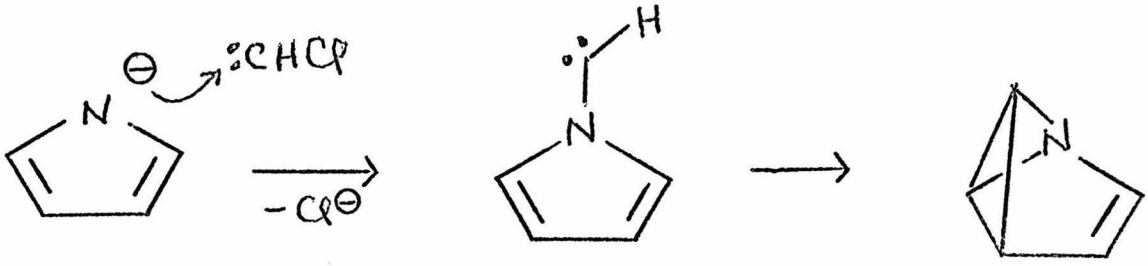
The second approach to the azabenzvalenes is outlined in Scheme V.



17 6

Scheme V

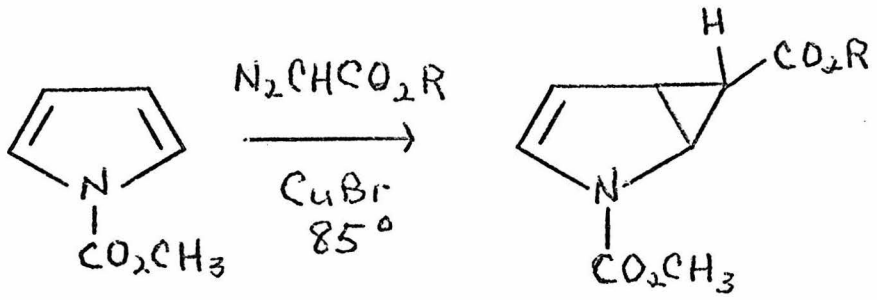
Using the same approach with lithium cyclopentadienide, Katz prepared benzvalene in 18% yield (12). A likely mechanism for this reaction is outlined in Scheme VI.



17 18 6

Scheme VI

The most questionable step is insertion by the carbene moity of 18 into the aromatic pyrrole ring. Encouragement for this step is provided by the example shown in Scheme VII which appears to involve carbene insertion into the double bond of a pyrrole ring (19).



Scheme VII

By analogy to the work of Paquette with azabullvalene (21), where nitrogen showed a strong preference for occupying a double bond position as opposed to a bridgehead position (21), 6 might be expected to readily rearrange to 4, a possible tetrahedrane precursor.

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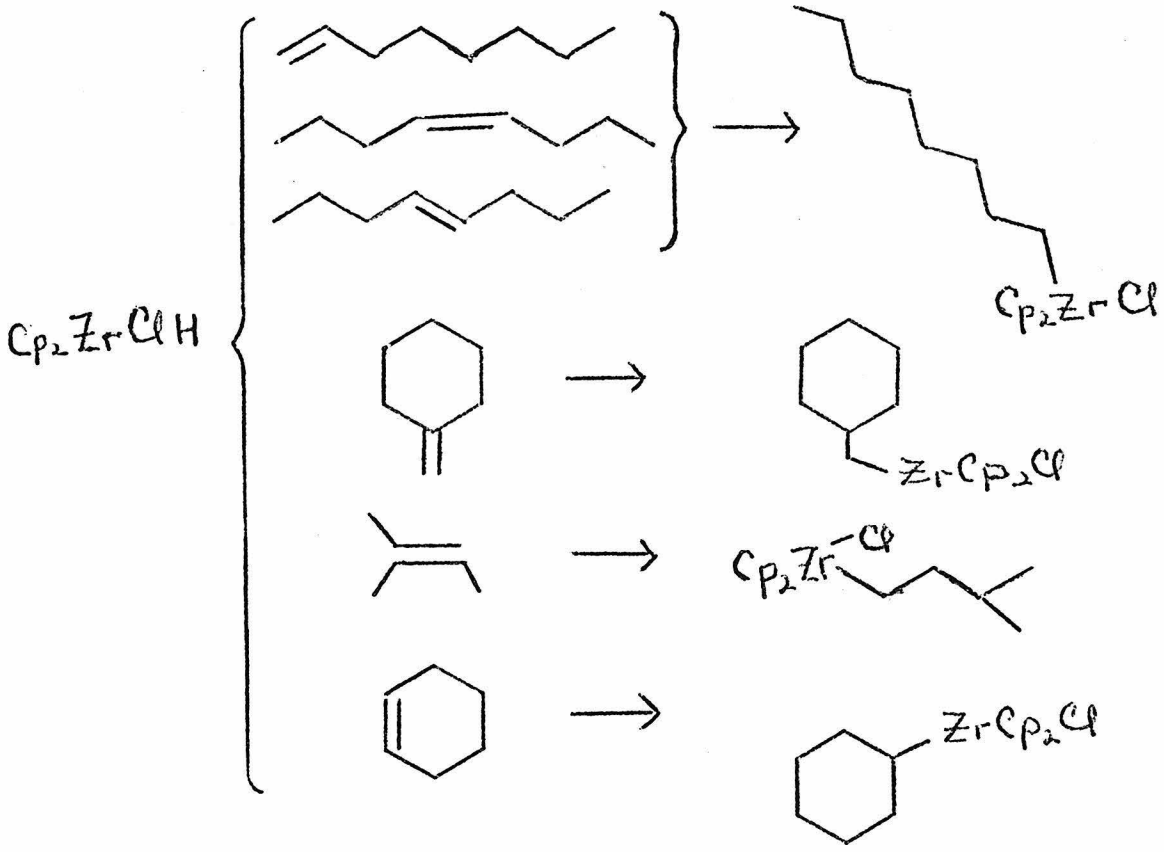
Proposition 4

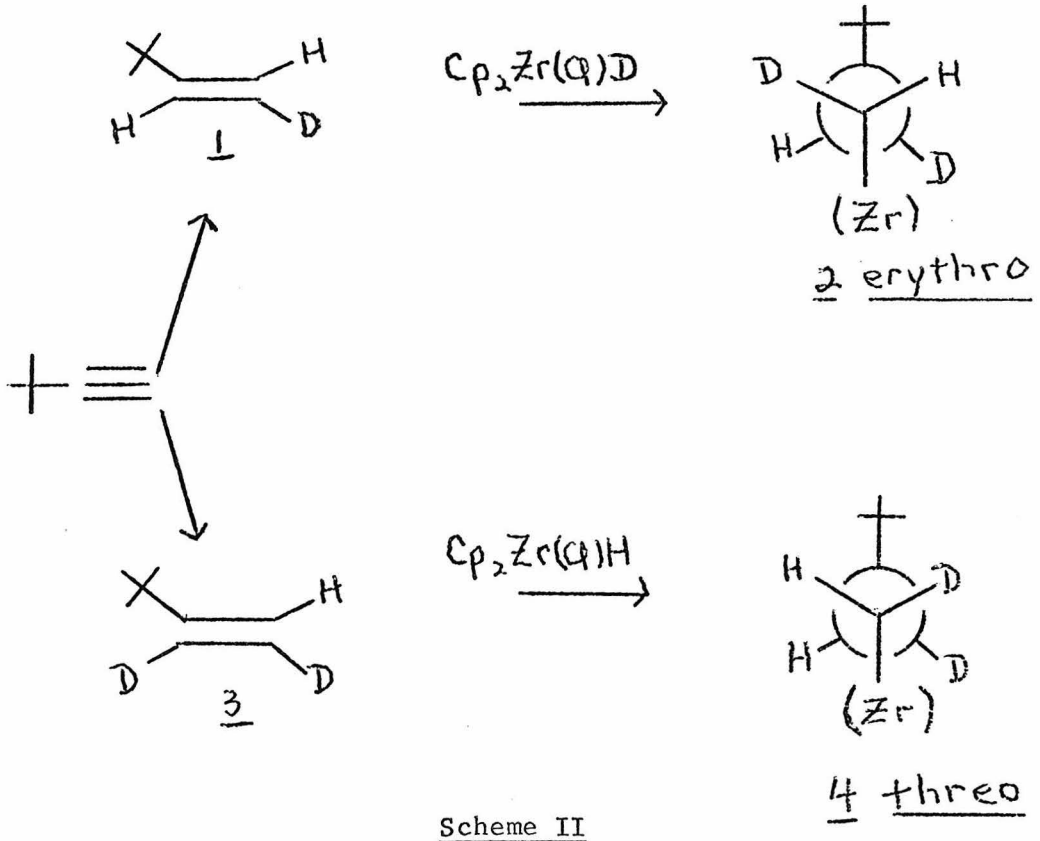
The synthetic potential of biscyclopentadienyl alkylzirconium (IV) complexes has recently been described by Schwartz (1, 2) and coworkers. Reaction of a terminal or internal olefin with $(Cp)_2ZrClH$ occurs regioselectively, yielding the alkylzirconium (IV) complex in which the transition metal moiety occupies the least-sterically hindered accessible position (Scheme I) (1).



Scheme I

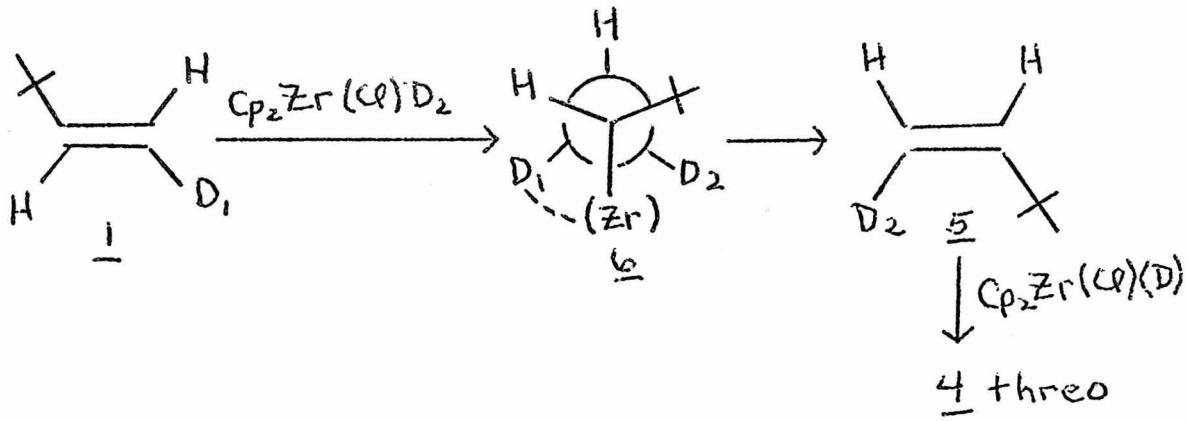
Electrophilic displacement of the zirconium moity by dilute acid or halogens generates alkanes or haloalkanes, respectively. The authors advocate hydrozirconation as an alternative to synthetic procedures employing hydroboration or hydroalumination.

Presently, little work has been explicitly directed towards determining whether the regioselectivity demonstrated in hydrozirconation of alkenes is governed by kinetic or thermodynamic factors. However, a strong case for kinetic control can be constructed from recent work of Schwartz (3). Hydrozirconation of 1 with $Cp_2Zr(Cl)(D)$ produced 90% 2, 10% 4; while treatment of 3 with $Cp_2Zr(Cl)(H)$ gave 90% 4, 10% 2 (Scheme II).



Scheme II

Initial addition of Zr at the t-butyl carbon of 1 followed by elimination of the most accessible D_1 would generate 5 (Scheme III). If conformation 6 is not attained, elimination of Zr and D_2 produces a net "no reaction."



Scheme III

Another addition of $Cp_2Zr(Cl)D$ to 5 would produce the threo 4. Elimination of (Zr)H from 6, followed by hydrozirconation would place two D's on one carbon of the alkyl fragment; this was not observed. Since the mixtures of 2 and 4 are configurationally stable under the reaction conditions, it would appear that the 10% contaminant in 2 and 4 results from impure olefins 1 and 3. Consequently, at least for olefins (1) and (3), the zirconium moiety appears to initially add at the least-hindered carbon.

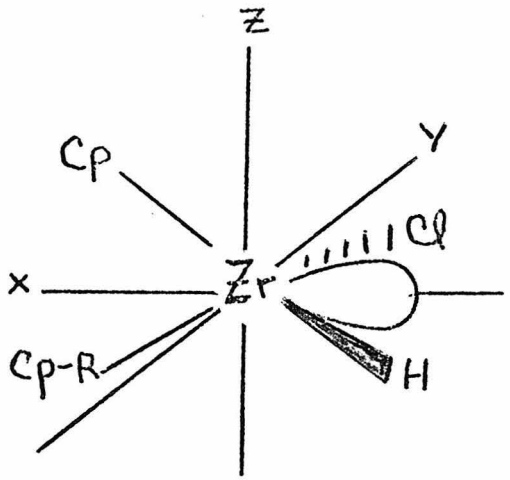
The regioselectivity of hydrozirconation reactions, the deformed tetrahedral geometry of the zirconium hydride, and the lack of dissociative behavior of Zr (IV) complexes (16 electron

complexes) all suggest that chiral zirconium hydrides may be potentially valuable asymmetric reduction agents. The number of available electrophilic cleavage processes of the alkyl zirconium complex makes development of such a reagent even more attractive.

While homogeneous asymmetric hydrogenation utilizing Rh (I) complexes (4), containing chiral phosphine ligands, has been demonstrated to occur with a limited amount of success, no general method for asymmetrically reducing olefins to optically active alkanes, halides or alcohols has been reported. By making the actual site of reduction chiral (as opposed to a chiral ligand), the potential exists for a high degree of optical induction.

To assess the likelihood of asymmetric induction, one must consider possible mechanisms for Zr-H addition across an olefinic bond. For the present discussion, we will consider hydrozirconation using an optically active (Cp)(Cp-R)ZrClH complex. Cp-R represents a substituted cyclopentadienyl ligand (possible synthetic approaches to the Zr complexes will be discussed later).

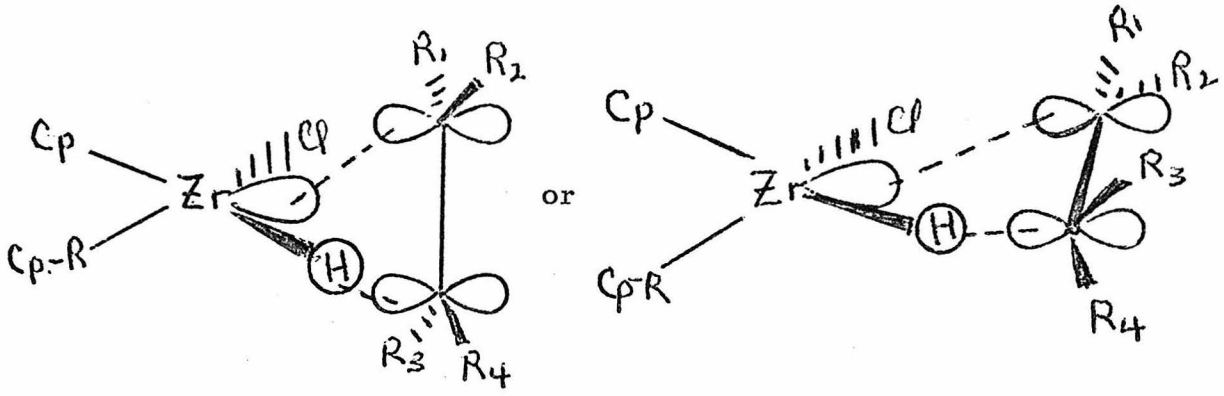
Wailes, Coutts and Weigold (5) have suggested 7 as a reasonable bonding model for bis(cyclopentadienyl) zirconium compounds (6). Nine hybrid orbitals were constructed from the metal 4p, 4d, and 5s orbitals. Six of the hybrid orbitals are directed towards the cyclopentadienyl ligands, with the other three orbitals lying in the x, y plane. For biscyclopentadienyl Zr (IV) complexes, the hybrid orbital directed along the x axis is unoccupied.



empty hybrid orbital

7

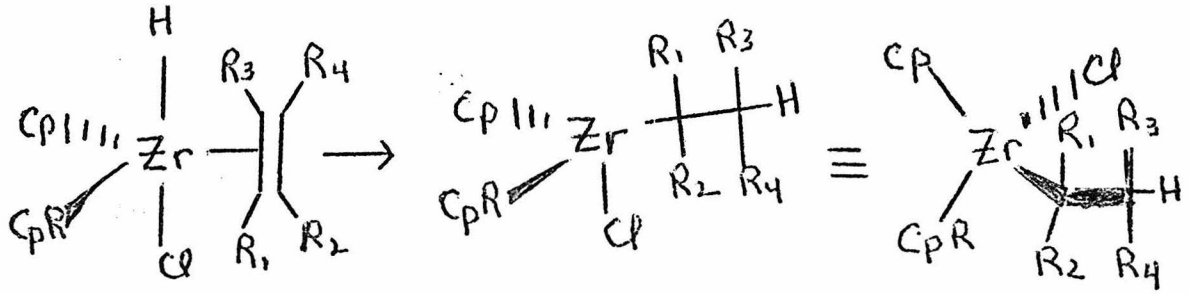
Ruling out initial ligand dissociation of the 16-electron, zirconium hydride complex as unlikely, the formation of the Zr-C bond is best thought of as proceeding via some sort of four-membered transition state (exclusive cis addition of the hydrozirconation process is well established) (3, 7). The π orbital of the approaching olefin may lie in the H-Zr-Cl plane (9) or be perpendicular to this plane (8) (Scheme IV). A short-lived pseudo-trigonal bipyramidal complex (10) with -Cl and -H on the axial positions could also be easily formed from 8 or 9 (Scheme V). Hydrogen transfer from an axial position to an equatorial olefin is well precedented (8). The concomitant formation of the Zr-C bond yields 11 in which the -H of 7 has been replaced with an alkyl group.



8 9

R_1 = H; R_2 = small alkyl or H; R_3 and R_4 = large alkyl

Scheme IV



10 11 12

Scheme V

Transition state 9 perhaps better explains the observed regioselectivity; the steric hindrance between the -Cl and the olefin substituents perhaps dictates the geometry of approach. No such explanation for regioselectivity is obvious for approach via transition state 8.

The elimination of olefin, with regeneration of zirconium hydride, from 11 should be the microscopic reverse of the formation of 11. Consequently, the zirconium hydride should retain its original chirality, even if elimination towards the more-sterically-hindered carbon is an important process. Elimination towards the less-sterically-hindered carbon is more likely, in which case the chiral carbon has no part in the elimination.

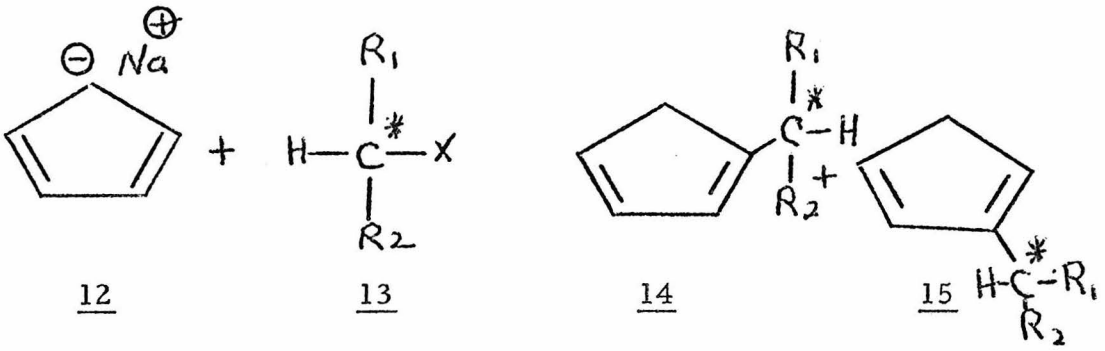
The electrophilic carbon-zirconium complex cleavage has recently been determined (3) to proceed with frontside attack on the carbon atom for H^+ and Br^+ as well as for CO insertion (3) (the stereochemistry of this attack has no effect upon the chiral carbon). If electrophilic cleavage is also stereospecific at the Zr, an optically active Zr complex could be regenerated! Converting the alkyl zirconium complex directly to an alcohol can be accomplished by treatment with dry oxygen followed by acid hydrolysis; however, stereospecific attack at the carbon is not observed. The broad variety of optically active compounds which can be formed from the alkyl- or acyl-zirconium complexes makes investigation of assymetric reduction via chiral zirconium hydrides a very attractive endeavor.

Presently, no reports of zirconium migration past tertiary centers exist. If future work uncovers such a process, chiral zirconium hydrides could also be used to synthesize optically active alkyl-substituted cyclic compounds from mono-unsaturated precursors (i.e., cyclopropanes from cyclopropanes, etc.). It may be possible to reduce cycloalkenes to chiral cycloalkanes, even if the zirconium moiety must remain bonded to a ring carbon. No such studies with racemic complexes have been reported to date.

Synthesis of Chiral Zirconium (IV) Hydrides

Relatively little work has been performed involving chiral organotransition metal compounds. The development of a generalized procedure for resolving the often air- and moisture-sensitive transition metal compounds would be valuable. With this in mind, we suggest the procedure outlined below for resolution of appropriate organotransition metal complexes containing one substituted cyclopentadienyl ligand.

Our approach is to simply synthesize a cyclopentadiene having a chiral substituent. Attachment of this ligand to the Zr (IV), along with three other different substituents produces two diastereomers which should be separable by fractional recrystallization. The general approach to the chiral cyclopentadienyl ligand is outlined in Scheme VI. Initial attempts will use $R_1 = CH_3$; $R_2 = CH_2CH_3$; X = Br or O-tosylate. S_N2 attack of 12 on 13 would produce 14 and 15 with inverted stereochemistry. Ample precedence exists for nucleophilic displacement of secondary halides by



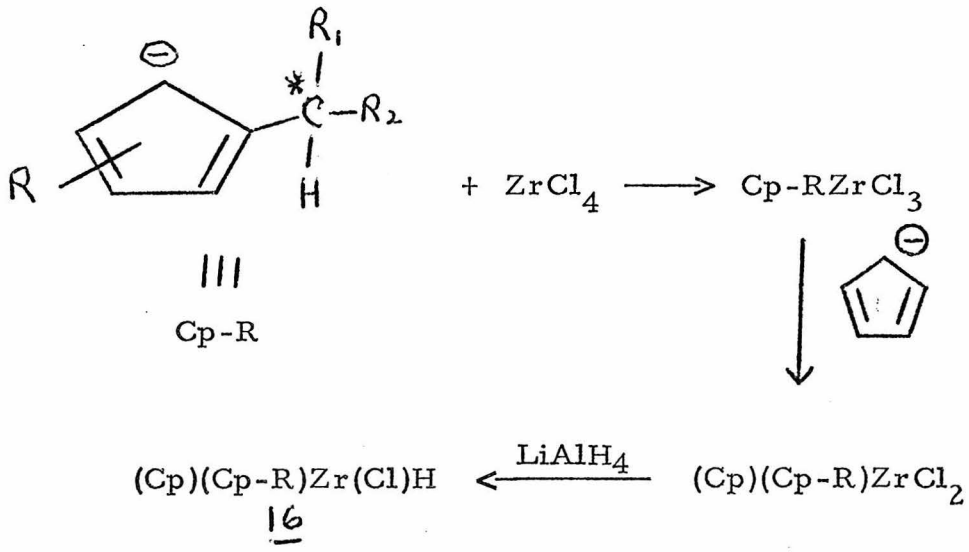
12 13 14 15

Scheme VI

cyclopentadienyl anion (9); the 2- and 3-substituted cyclopentadienes comprise 98% of the product mixture (10). For our purposes, the location of the alkyl group is not important. If it is found that a more bulky ligand is needed to induce optical activity into the olefin, a second alkyl group can be easily added by repeating the sequence shown in Scheme VI. Addition of a second methyl group to a mixture of 2- and 3-methylcyclopentadienes yields 2, 3-; 3, 4-; 2, 4-cyclopentadienes as 90% of the reaction products (10). Obviously, other R_1 and R_2 groups (such as phenyls) can be utilized on 13 if the simple alkyl substituent proves inadequate for inducing fractional recrystallization.

A slight deviation on Scheme VI would be to substitute cyclopentadiene with an amine or alcohol moity capable of chirality. Resolution of this compound with an appropriate optically active acid or base would produce a chiral ligand.

After synthesis of 14, the zirconium hydride can be synthesized by established methods shown in Scheme VII (11, 12).



Scheme VII

The chiral ligand in 16 (after fractional recrystallization) should have no apparent effect on the asymmetric induction process of the zirconium complex.

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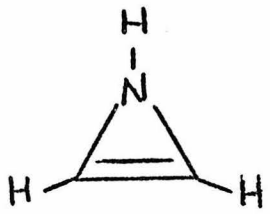
Proposition 5

The synthesis of cyclobutadiene has long been a classical problem in organic chemistry (1). Molecular Orbital theory predicts this 4n π-electron system to be highly unstable and to have no delocalization stabilization energy (1). Isolation of this compound would provide new insight to present theories of reactivity and the nature of chemical bonding.

Another 4n π-electron compound of theoretical interest is 1H-azirine (1a).



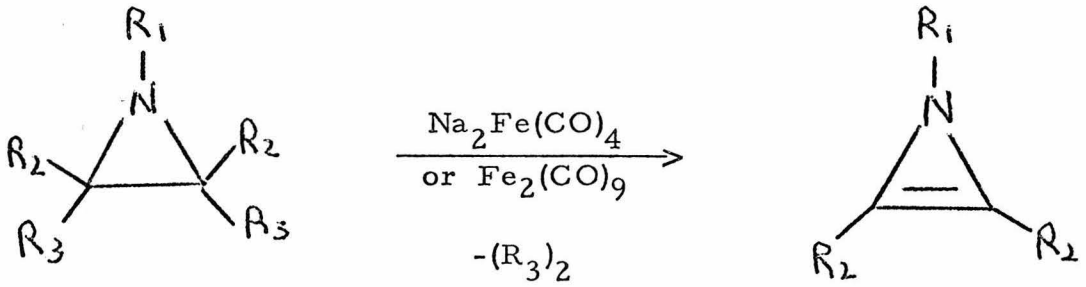
1a

Simple Hückel Molecular Orbital theory calculations predict no π delocalization for the 1H-azirine system (2).

C. W. Rees and coworkers have added phthalimidonitrene to alkynes with the intent of isolating 1H-azirines. Instead, 2H-azirines were isolated which were indicative of a 1H-azirine intermediate, but the intermediate was not isolated (3-5). An attempt to dehydrohalogenate aziridines by Hassner and coworkers (2) also resulted in isolation of 2H-azirines which could conceivably be arising via 1H-azirines.

Both these attempts give indication of the intermediacy of a 1H-azirine; however, no attempts were made at trapping the azirine. Trapping the 1H-azirine as a transition metal complex, or attempting thermal cycloadditions between a diene and the 1H-azirine have not been tried. Furthermore, no effort has been made to generate 1H-azirines photolytically in low temperature matrices. It is our purpose to suggest new precursors to 1H-azirines, and provide definitive evidence for the existence of 1H-azirines.

By analogy with cyclobutadiene formation from 3, 4-dichloro-cyclobutene, reacting an appropriate aziridine with reducing iron carbonyl complexes should result in trapping of the 1H-azirine in the form of the iron tricarbonyl complex (2) (Scheme I) (6).

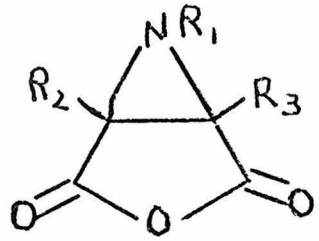


1 2

Scheme I

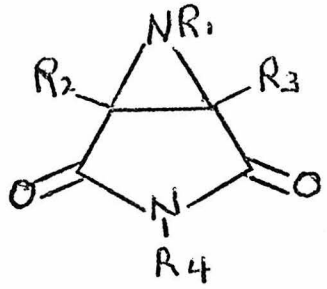
The availability of the appropriate aziridine (1) presents the major obstacle to this approach. However, recent synthesis (7) of 2, 3-dichloro aziridines in 90% yield from the reaction of phthalimido-nitrene with 1, 2-dichloro ethylene provides a reasonable 1H-azirine

precursor [(1): R_1 = phthalimido; R_2 = H; R_3 = Cl]. Another interesting aziridine precursor for reaction with reducing iron carbonyl complexes is 3.



3

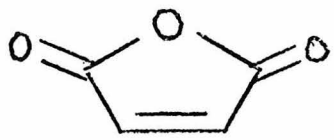
The corresponding aziridines (4) are easily prepared from the pyrolysis of the pyrazolines prepared by the addition of aryl azides and N-arylmaleimides (8, 9).



4

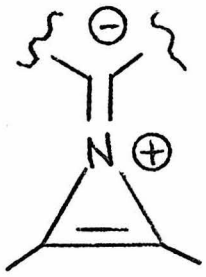
Grubbs has recently reported generation of the iron tricarbonyl complex of cyclobutadiene by reaction of 3, 4-carbonyldioxy cyclobutenes with reducing iron tricarbonyl complexes (10). Reaction

of alkyl, aryl or perhaps silyl azides with the vinyl carbonate (5) should readily produce a variety of 1H-azirine precursors (3).



5

A "push-pull" (11) utilization of substituents may make isolation of an uncomplexed 1H-azirine a possibility. This approach may be carried out in several ways: 1) by making the nitrogen substituent electron withdrawing (6), 2) by making one carbon substituent electron-donating and one electron-withdrawing (7).



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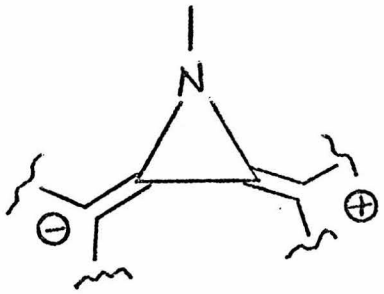
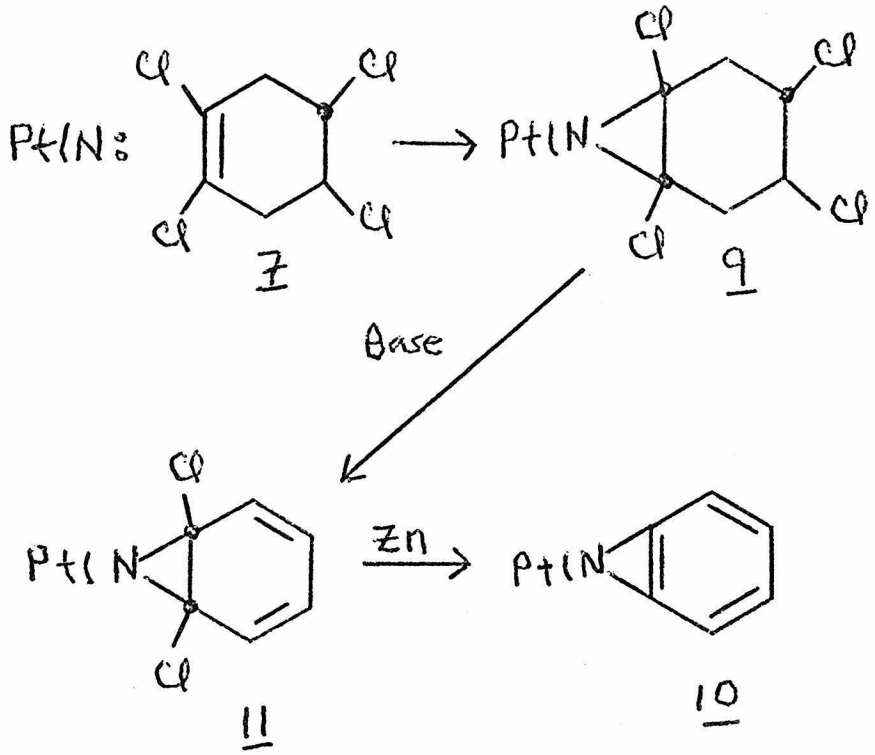


7

Since aziridines (4) can be synthesized with R_1 = p-$NO_2C_6H_4$ (8, 9), it may be possible to synthesize aziridine (3) with R_1 = p-$NO_2C_6H_4$. Oxidative decomposition [with Ce (IV)] (12) of 1H-azirine tricarbonyl iron complexes formed from aziridine (3) with R_1 =

p-$NO_2C_6H_4$ may produce an isolable 1H-azirine like 6. A similar decomposition of the iron complex of a 1H-azirine with p-$NO_2C_6H_4$ and p-$NH_2C_6H_4$ as carbon substituents (formed from 1 or 3) could result in isolation of "push-pull" azirines like 7. Reacting 1 (having appropriate "push-pull" substituents) directly with zinc or NaI could also dechlorinate the aziridine directly to the desired 1H-azirine.

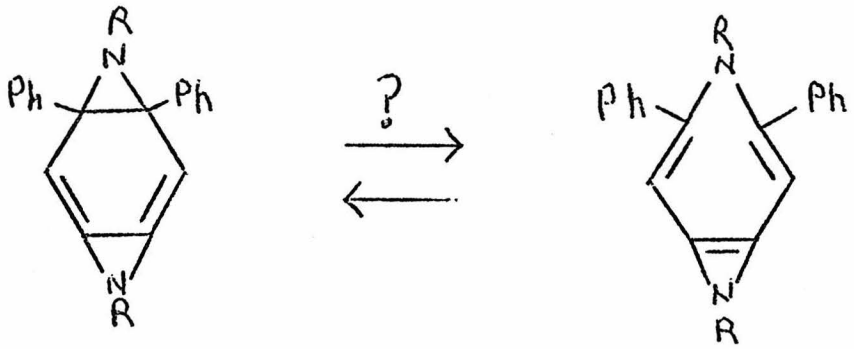
A different approach utilizes the ability of the phthalimido-nitrene to add to deactivated double bonds (7). If the phthalimido-nitrene will add to 7, an attractive precursor to 1H-azirines can be prepared (Scheme II).



Scheme II

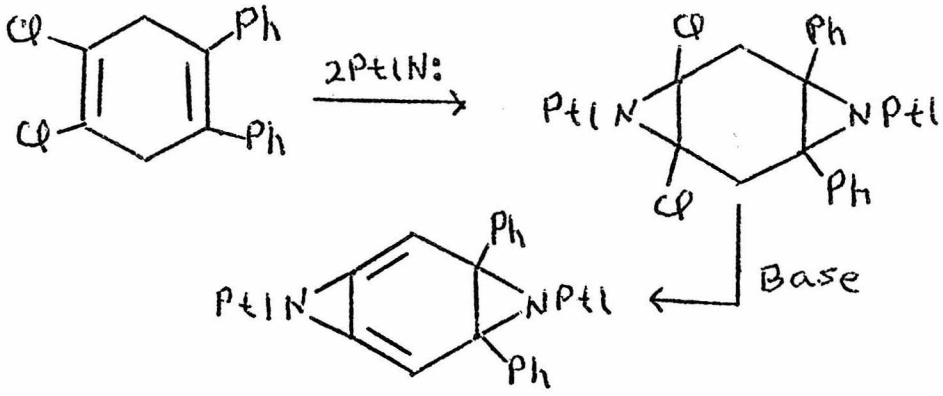
Aromaticity is the obvious driving force for this reaction. The questionable step in this sequence is the stability of 11. 11 might isomerize to an azepine before treatment with zinc.

Another approach along similar lines involves synthesis of the molecule (13).



13a 13b

^{13}C nmr variable temperature studies of the proposed equilibrium should prove very interesting. The synthesis for 13 involves the double addition of phthalimidonitrene to 1,2-dichloro-4,5-diphenyl-1,4-cyclohexadiene, followed by base induced dehydrohalogenation (Scheme III).

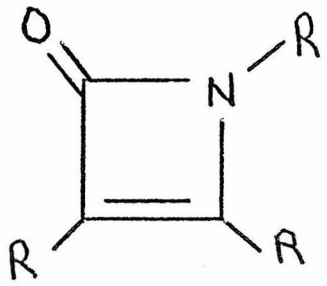


Scheme III

The phthalimidonitrene addition to the highly deactivated cyclohexadiene is questionable, but Rees has reported 90% yields for the nitrene addition to 1,2-dichloro-ethene (7). Analogous dicarbene additions to form tricyclic systems are known (13).

Another approach to the 1H-azirine involves photolysis of a precursor capable of undergoing an extrusion reaction in a low temperature matrix. The product could be characterized by i.r.

spectroscopy. Aziridine (3) is one such precursor; another reasonable approach is via 17.



17

It may be possible to synthesize (17) by the cycloaddition of isocyanates and alkynes. β-lactams may be prepared by the cycloaddition of isocyanates and olefins (14, 15); and cyclobutenones are available from the cycloaddition of ketenes and alkynes (16, 17). Photolysis of cyclobutenones yields cyclopropenes (18).

In addition to spectroscopic characterization of the possible 1H-azirines or their metal complexes, cycloadditions with various dienophiles such as butadienes or cyclopentadienes will be performed. Cycloadditions of the 1H-azirine, generated from oxidation of the metal complexes (12), with various dienophiles also has synthetic potential as a new preparation of aziridines.

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